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Causal Assessment of Pharmaceutical Treatments: Why Standards of Evidence should not be the same for Benefits and Harms?

Barbara Osimani, Fiorenzo Mignini

ABSTRACT

It is increasingly acknowledged both among epidemiologists and regulators that the assessment of pharmaceutical harm requires specific methodological approaches that cannot simply duplicate those developed for testing efficacy. However, this intuition lacks sound epistemic bases and delivers ad hoc advice. This paper explains why the same methods of scientific inference do not fare equally well for efficacy and safety assessment by tracing them back to their epistemic foundations. To illustrate this, Cartwright’s distinction into clinching and vouching methods is adopted and a series of reasons is provided for preferring the latter to the former: (1) the need to take into account all available knowledge and integrate it with incoming data; (2) the awareness that a latent unknown risk may always change the safety profile of a given drug (precautionary principle); (3) cumulative learning over time; (4) requirement of probabilistic causal assessment to allow decision under uncertainty; (5) impartiality; and (6) limited and local information provided by randomised controlled trials. Subsequently, the clinchers/vouchers distinction is applied to a case study concerning the debated causal association between paracetamol and asthma. This study illustrates the tension between implicit epistemologies adopted in evaluating evidence and causality; furthermore, it also shows that discounting causal evidence may be a result of unacknowledged low priors or lack of valid alternative options. We conclude with a presentation of the changing landscape in pharmacology and the trend towards an increased use of Bayesian tools for assessment of harms.

The US Food and Drug Administration-European Medicines Agency Collaboration in Pharmacovigilance: Common Objectives and Common Challenges

Gerald J. Dal Pan, Peter R. Arlett

ABSTRACT

On 19 February 2014, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) announced the formation of a cluster on pharmacovigilance topics. The cluster is designed to complement, and not replace, other international activities in this field. It builds upon years of interactions between the two agencies. The creation of the cluster formalizes this longstanding and productive relationship and facilitates more systematic exchange of information and expertise.

Aristolochic Acid Nephropathy: Epidemiology, Clinical Presentation, and Treatment

Randy L. Luciano, Mark A. Perazella

ABSTRACT

Aristolochic acid (AA) is a compound extracted from the Aristolochia species of herbs. It has been used for centuries as a remedy for various illnesses and diseases. However, in the early 1990s in the setting of a weight loss herbal remedy, AA exposure was associated with a syndrome of kidney injury, termed aristolochic acid nephropathy (AAN). This entity is marked by elevated serum creatinine, significant anemia, and histopathologic changes demonstrating a hypocellular interstitial infiltrate with severe fibrosis. Progression towards end-stage renal disease (ESRD) is rapid, with most patients having chronic kidney disease for less than 2 years. In addition, AAN is associated with a 40–45% prevalence of urothelial carcinomas. Treatment of AAN is limited to glucocorticoids that have been shown to delay progression in non-randomized trials. As most patients progress to ESRD, need for renal replacement therapy, as either dialysis or kidney transplant, usually ensues. However, given the high malignant potential, care must be taken to minimize future development of upper urinary tract cancers by performing prophylactic bilateral nephroureterectomies and aggressive cancer surveillance.
Optimal Glycaemic Control in Elderly People with Type 2 Diabetes: What Does the Evidence Say?
Supriya Mathur, Nicola N. Zammitt, Brian M. Frier

ABSTRACT
The global prevalence of type 2 diabetes mellitus (T2DM) is rising in an ageing population through a combination of lifestyle changes and greater longevity. However, by excluding participants aged over 70 years, most major interventional trials on which current diabetes therapeutic guidelines are based have failed to provide specific evidence to support the prescribed management of diabetes in elderly people. While diabetes per se has a significant impact on the elderly person, the side effects of medications, particularly hypoglycaemia, prevent optimisation of diabetes treatment. Hypoglycaemia is associated with significant morbidity, to which elderly people are often more vulnerable because of factors such as the effects of ageing, progressive renal impairment, frailty, polypharmacy and cognitive decline. T2DM is associated with accelerated cognitive decline in some individuals, and recurrent severe hypoglycaemia has been implicated as a potential contributory factor. Although the evidence for selection of appropriate glycaemic targets in elderly patients is sparse, it is now acknowledged that prevention of hypoglycaemia must influence individualisation of treatment goals in this vulnerable group. This should also be reflected by the choice of anti-diabetes agents that are initiated when diet and lifestyle advice is ineffective. Recently developed international guidelines, which have specifically addressed the management of diabetes in elderly people, highlight the importance of a pragmatic management approach rather than attempting to achieve a generic glycated haemoglobin goal are summarised in this article.

The Comparative Efficacy and Safety of the Angiotensin Receptor Blockers in the Management of Hypertension and Other Cardiovascular Diseases
Hazel Mae A. Abraham, C. Michael White, William B. White

ABSTRACT
All national guidelines for the management of hypertension recommend angiotensin receptor blockers (ARBs) as an initial or add-on antihypertensive therapy. The eight available ARBs have variable clinical efficacy when used for control of hypertension. Additive blood pressure-lowering effects have been demonstrated when ARBs are combined with thiazide diuretics or dihydropyridine calcium channel blockers, augmenting hypertension control. Furthermore, therapeutic use of ARBs goes beyond their antihypertensive effects, with evidence-based benefits in heart failure and diabetic renal disease particularly among angiotensin-converting enzyme inhibitor-intolerant patients. On the other hand, combining renin–angiotensin system blocking agents, a formerly common practice among medical subspecialists focusing on the management of hypertension, has ceased, as there is not only no evidence of cardiovascular benefit but also modest evidence of harm, particularly with regard to renal dysfunction. ARBs are very well tolerated as monotherapy, as well as in combination with other antihypertensive medications, which improve adherence to therapy and have become a mainstay in the treatment of stage 1 and stage 2 hypertension.
Bacillus Calmette-Guérin (BCG) Vaccine Adverse Events in Victoria, Australia: Analysis of Reports to an Enhanced Passive Surveillance System

Hazel J. ClothierEmail authorLaine HoskingNigel W. CrawfordMelissa RussellMee Lee EastonJulie-Ann QuinnJim P. Buttery

ABSTRACT

Background: Bacillus Calmette–Guérin (BCG) vaccine is used worldwide, with high efficacy against childhood Mycobacterium tuberculosis (TB) meningitis and miliary TB. BCG vaccine is considered safe, with serious systematic adverse events following immunization (AEFI) of immunocompetent recipients being rare, although adverse event rates vary between differing BCG strains. In Victoria, Australia, AEFI are reported to SAEFVIC (Surveillance of Adverse Events Following Vaccination In the Community), an enhanced passive surveillance system operational since 2007.

Objective: To describe the epidemiology of reported BCG AEFI in Victoria, Australia, particularly following the 2012 recall of Connaught BCG vaccine, substitution with Denmark-SSI vaccine and subsequent programme delivery adjustments.

Methods: Retrospective analysis of reported BCG AEFI in Victoria, Australia, for the 6-year period 2008–2013. Incidence rates were calculated using available doses-distributed, doses-administered and population data denominators with 95% confidence intervals.

Results: The predominant BCG AEFI reported were abscess and lymphadenopathy, with higher reports for males than for females (p = 0.039). The rates of AEFI per 10,000 doses distributed were similar for the Connaught and Denmark-SSI strains, at 11.6 and 15.4, respectively (p = 0.414). When doses administered rather than doses distributed were considered, the rate of reported Denmark-SSI AEFI was much higher, at 62.8 per 10,000 doses administered. Meaningful result interpretation was hampered by a lack of a BCG vaccination register, multiple disparate providers and absent doses-administered data prior to the recall.

Conclusion: Effective AEFI surveillance is of paramount importance as countries are faced with unplanned vaccine strain changes following the 2012 BCG recall and subsequent global vaccine supply shortages. The Australian experience and lessons learned serve as a timely reminder to BCG vaccination programmes worldwide to review AEFI surveillance systems.
Structured Assessment for Prospective Identification of Safety Signals in Electronic Medical Records: Evaluation in the Health Improvement Network

ABSTRACT

Background: Pharmacovigilance signal detection largely relies on individual case reports, but longitudinal health data are being explored as complementary information sources. Research to date has focused on the ability of epidemiological methods to distinguish established adverse drug reactions (ADRs) from unrelated adverse events.

Objective: The aim of this study was to evaluate a process for structured clinical and epidemiological assessment of temporally associated drugs and medical events in electronic medical records.

Methods: Pairs of drugs and medical events were selected for review on the basis of their temporal association according to a calibrated self-controlled cohort analysis in The Health Improvement Network. Six assessors trained in pharmacovigilance and/or epidemiology evaluated seven drugs each, with up to 20 medical events per drug. A pre-specified questionnaire considered aspects related to the nature of the temporal pattern, demographic features of the cohort, concomitant medicines, earlier signs and symptoms, and possible confounding by underlying disease. This informed a classification of drug–event pairs as known ADRs, meriting further evaluation, or dismissed.

Results: The number of temporally associated medical events per drug ranged from 11 to 307 (median 50) for the 42 selected drugs. Out of the 509 relevant drug–event combinations subjected to the assessment, 127 (25 %) were classified as known ADRs. Ninety-one (24 %) of the remaining pairs were classified as potential signals meriting further evaluation and 291 (76 %) were dismissed. Suggestive temporal patterns and lack of clear alternative explanations were the most common reasons that drug–event pairs were classified as meriting further evaluation. Earlier signs and symptoms and confounding by the underlying disease were the most common reasons that drug–event pairs were dismissed.

Conclusions: Exploratory analysis of electronic medical records can detect important potential safety signals. However, effective signal detection requires that statistical signal detection be combined with clinical and epidemiological review to achieve an acceptable false positive rate.

Volume 38, Issue 2, February 2015

Safety Surveillance of Traditional Chinese Medicine: Current and Future
Shwu-Huey LiuWu-Chang ChuangWing LamZaoli JiangYung-Chi Cheng

ABSTRACT

Herbal medicine, including traditional Chinese medicine, has been used for the prevention, treatment, and cure of disorders or diseases for centuries. In addition to being used directly as therapeutic agents, medicinal plants are also important sources for pharmacological drug research and development. With the increasing consumption of herbal products intended to promote better health, it is extremely important to assure the safety and quality of herbal preparations. However, under current regulation surveillance, herbal preparations may not meet expectations in safety, quality, and efficacy. The challenge is how to assure the safety and quality of herbal products for consumers. It is the responsibility of producers to minimize hazardous contamination and additives during cultivation, harvesting, handling, processing, storage, and distribution. This article reviews the current safety obstacles that have been involved in traditional Chinese herbal medicine preparations with examples of popular herbs. Approaches to improve the safety of traditional Chinese medicine are proposed.
Cancer Chemotherapy and Cardiac Arrhythmias: A Review
Juan TamargoEmail authorRicardo CaballeroEva Delpón

ABSTRACT
Cardiovascular toxicity is a potential complication of cancer chemotherapy (CC) that increases the morbidity and mortality of cancer patients. Cardiac arrhythmias have been reported as an adverse effect of many chemotherapeutic drugs, including novel targeted therapies. The relationship between chemotherapy and arrhythmias has not been well-established and the proarrhythmogenic mechanisms remain uncertain as they can be the result of a direct electrophysiological effect or of changes in cardiac structure and function, including myocardial ischaemia and heart failure, which create an arrhythmogenic substrate. In this review we summarise available evidence of proarrhythmia induced by CC, discuss the possible mechanisms involved in this adverse effect and emphasise the importance of cardiac monitoring for the early diagnosis, intervention and surveillance of those patients more susceptible to develop proarrhythmia in an attempt to reduce the morbidity and mortality. Oncologists should be fully aware of proarrhythmia and the close collaboration between cardiologists and oncologists would result in a better cardiovascular assessment, risk stratification, cardiac monitoring and treatment during CC and during the follow-up. The final objective is to understand the mechanisms of proarrhythmia and evaluate its real incidence and clinical relevance so as to select the safest and most effective treatment for cancer patients.

Specialist Cohort Event Monitoring Studies: A New Study Method for Risk Management in Pharmacovigilance
Deborah LaytonEmail authorSaad A. W. Shakir

ABSTRACT
The evolving regulatory landscape has heightened the need for innovative, proactive, efficient and more meaningful solutions for ‘real-world’ post-authorization safety studies (PASS) that not only align with risk management objectives to gather additional safety monitoring information or assess a pattern of drug utilization, but also satisfy key regulatory requirements for marketing authorization holder risk management planning and execution needs. There is a need for data capture across the primary care and secondary care interface, or for exploring use of new medicines in secondary care to support conducting PASS. To fulfil this need, event monitoring has evolved. The Specialist Cohort Event Monitoring (SCEM) study is a new application that enables a cohort of patients prescribed a medicine in the hospital and secondary care settings to be monitored. The method also permits the inclusion of a comparator cohort of patients receiving standard care, or another counterfactual comparator group, to be monitored concurrently, depending on the study question. The approach has been developed in parallel with the new legislative requirement for pharmaceutical companies to undertake a risk management plan as part of post-authorization safety monitoring. SCEM studies recognize that the study population comprises those patients who may have treatment initiated under the care of specialist health care professionals and who are more complex in terms of underlying disease, co-morbidities and concomitant medications than the general disease population treated in primary care. The aims of this paper are to discuss the SCEM new-user study design, rationale and features that aim to address possible bias (such as selection bias) and current applications.
Treating Severe Malaria in Pregnancy: A Review of the Evidence
Stephanie D. KovacsEmail authorMarcus J. RijkenAndy Stergachis

ABSTRACT
Severe malaria in pregnancy is a large contributor to maternal morbidity and mortality. Intravenous quinine has traditionally been the treatment drug of choice for severe malaria in pregnancy. However, recent randomized clinical trials (RCTs) indicate that intravenous artesunate is more efficacious for treating severe malaria, resulting in changes to the World Health Organization (WHO) treatment guidelines. Artemisinins, including artesunate, are embryo-lethal in animal studies and there is limited experience with their use in the first trimester. This review summarizes the current literature supporting 2010 WHO treatment guidelines for severe malaria in pregnancy and the efficacy, pharmacokinetics, and adverse event data for currently used antimalarials available for severe malaria in pregnancy. We identified ten studies on the treatment of severe malaria in pregnancy that reported clinical outcomes. In two studies comparing intravenous quinine with intravenous artesunate, intravenous artesunate was more efficacious and safe for use in pregnant women. No studies detected an increased risk of miscarriage, stillbirth, or congenital anomalies associated with first trimester exposure to artesunate. Although the WHO recommends using either quinine or artesunate for the treatment of severe malaria in first trimester pregnancies, our findings suggest that artesunate should be the preferred treatment option for severe malaria in all trimesters.

Risk of Anaphylaxis with Repeated Courses of Rasburicase: A Research on Adverse Drug Events and Reports (RADAR) Project
Katherine C. AllenAmanda H. ChamplainJonathan A. CotliarSteven M. BelknapDennis P. WestEmail authorJayesh MehtaSteven M. Trifilio

ABSTRACT
Background: Rasburicase, a recombinant urate oxidase, is used to rapidly metabolize uric acid in patients with hyperuricaemia. Rasburicase is an immunogenic therapeutic protein, which has been shown to elicit antibody response in 64% of healthy volunteers within 1–6 weeks after the initial course, with persistent antibodies for over 1 year. Drug labelling indicates that anaphylaxis rarely occurs (in <1% of patients) after a single course of therapy with rasburicase, but there are no data available on the incidence of anaphylaxis in patients receiving a subsequent rasburicase course.

Objective: The objective of this study was to determine the incidence of anaphylaxis after multiple treatment courses of rasburicase.

Methods: A retrospective chart review was performed on 97 consecutively treated patients who received repeated courses of rasburicase for hyperuricaemia.

Results: None of the 97 patients who were reviewed experienced anaphylaxis during the first rasburicase course; however, six patients (6.2%) experienced anaphylaxis during a subsequent rasburicase treatment course (p = 0.03).

Conclusion: Anaphylaxis after a second course of rasburicase appears to occur more frequently than described in the US Food and Drug Administration-approved package insert for initial treatment courses. Given the serious nature of anaphylactic events, caution is advised when administering repeated courses of rasburicase.
ABSTRACT

Background: The yellow-card scheme continues to be one of the principal methods for signal generation in pharmacovigilance. Nevertheless, under-reporting, one of its disadvantages, delays alert signals and has a negative influence on public health. Educational interventions in pharmacovigilance may have a positive impact on the spontaneous reporting of adverse drug reactions (ADRs).

Objectives: To assess the duration of the effect and effectiveness of an educational intervention in pharmacovigilance designed to improve ADR reporting in a robust pharmacovigilance system.

Methods: A spatial, cluster randomized controlled trial was conducted covering all National Health System physicians in the northwest of Spain and targeting those who were actively engaged in clinical practice (n = 7,498). Of these, 2,120 were assigned in three spatial clusters to the intervention group (six hospitals and 138 primary care centers) and 3,614 in four clusters to the control group (seven hospitals and 267 primary care centers). The educational intervention consisted of two complementary approaches—one active (group sessions), the other passive (educational material, reporting form)—implemented from November 2007 to December 2008, with a follow-up period of 8 months.

Results: Intervention participation was 53.7 % in a hospital setting and 60.5 % in primary care settings. ADR reporting in the intervention group increased by 65.4 % (95 % confidence interval [CI]: 8.2–153.4) across the follow-up. The ADR reporting rate per 1,000 physicians/year in the intervention group rose from 28.1 to 39.6 following the intervention (51.7 and 27.4 in the first and second 4-month period, respectively). For the intervention group, relative risk (RR) was 2.31 (95 % CI: 1.46–3.68) and 1.04 (95 % CI: 0.61–1.77) in the first and second 4-month period, respectively adjusted to baseline values. There was an increase in unexpected ADR reporting (RR 2.06, 95 % CI 1.19–3.55).

Conclusions: Pharmacovigilance educational interventions that have proved effective can be successfully applied in different geographical areas. A high baseline notification rate could account for the educational program having a moderate effect.


ABSTRACT

Background: Healthcare organizations, compendia, and drug knowledgebase vendors use varying methods to evaluate and synthesize evidence on drug–drug interactions (DDIs). This situation has a negative effect on electronic prescribing and medication information systems that warn clinicians of potentially harmful medication combinations.

Objective: The aim of this study was to provide recommendations for systematic evaluation of evidence for DDIs from the scientific literature, drug product labeling, and regulatory documents.

Methods: A conference series was conducted to develop a structured process to improve the quality of DDI alerting systems. Three expert workgroups were assembled to address the goals of the conference. The Evidence Workgroup consisted of 18 individuals with expertise in pharmacology, drug information, biomedical informatics, and clinical decision support. Workgroup members met via webinar 12 times from January 2013 to February 2014. Two in-person meetings were conducted in May and September 2013 to reach consensus on recommendations.

Results: We developed expert consensus answers to the following three key questions. (i) What is the best approach to evaluate DDI evidence? (ii) What evidence is required for a DDI to be applicable to an entire class of drugs? (iii) How should a structured evaluation process be vetted and validated?

Conclusion: Evidence-based decision support for DDIs requires consistent application of transparent and systematic methods to evaluate the evidence. Drug compendia and clinical decision support systems in which these recommendations are implemented should be able to provide higher-quality information about DDIs.
ABSTRACT

Background: Better evidence regarding drug safety in the pediatric population might be generated from existing data sources such as spontaneous reporting systems and electronic healthcare records. The Global Research in Paediatrics (GRiP)–Network of Excellence aims to develop pediatric-specific methods that can be applied to these data sources. A reference set of positive and negative drug–event associations is required.

Objective: The aim of this study was to develop a pediatric-specific reference set of positive and negative drug–event associations.

Methods: Considering user patterns and expert opinion, 16 drugs that are used in individuals aged 0–18 years were selected and evaluated against 16 events, regarded as important safety outcomes. A cross-table of unique drug–event pairs was created. Each pair was classified as potential positive or negative control based on information from the drug’s Summary of Product Characteristics and Micromedex. If both information sources consistently listed the event as an adverse event, the combination was reviewed as potential positive control. If both did not, the combination was evaluated as potential negative control. Further evaluation was based on published literature.

Results: Selected drugs include ibuprofen, flucloxacillin, domperidone, methylphenidate, montelukast, quinine, and cyproterone/ethinylestradiol. Selected events include bullous eruption, aplastic anemia, ventricular arrhythmia, sudden death, acute kidney injury, psychosis, and seizure. Altogether, 256 unique combinations were reviewed, yielding 37 positive (17 with evidence from the pediatric population and 20 with evidence from adults only) and 90 negative control pairs, with the remainder being unclassifiable.

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Computational Approaches for Pharmacovigilance Signal Detection: Toward Integrated and Semantically-Enriched Frameworks

Vassilis G. Koutkias, Marie-Christine Jaulent

ABSTRACT

Computational signal detection constitutes a key element of postmarketing drug monitoring and surveillance. Diverse data sources are considered within the ‘search space’ of pharmacovigilance scientists, and respective data analysis methods are employed, all with their qualities and shortcomings, towards more timely and accurate signal detection. Recent systematic comparative studies highlighted not only event-based and data-source-based differential performance across methods but also their complementarity. These findings reinforce the arguments for exploiting all possible information sources for drug safety and the parallel use of multiple signal detection methods. Combinatorial signal detection has been pursued in few studies up to now, employing a rather limited number of methods and data sources but illustrating well-promising outcomes. However, the large-scale realization of this approach requires systematic frameworks to address the challenges of the concurrent analysis setting. In this paper, we argue that semantic technologies provide the means to address some of these challenges, and we particularly highlight their contribution in (a) annotating data sources and analysis methods with quality attributes to facilitate their selection given the analysis scope; (b) consistently defining study parameters such as health outcomes and drugs of interest, and providing guidance for study setup; (c) expressing analysis outcomes in a common format enabling data sharing and systematic comparisons; and (d) assessing/supporting the novelty of the aggregated outcomes through access to reference knowledge sources related to drug safety.
Meta-analysis has increasingly been used to identify adverse effects of drugs and vaccines, but the results have often been controversial. In one respect, meta-analysis is an especially appropriate tool in these settings. Efficacy studies are often too small to reliably assess risks that become important when a medication is in widespread use, so meta-analysis, which is a statistically efficient way to pool evidence from similar studies, seems like a natural approach. But, as the examples in this paper illustrate, different syntheses can come to qualitatively different conclusions, and the results of any one analysis are usually not as precise as they seem to be. There are three reasons for this: the adverse events of interest are rare, standard meta-analysis methods may not be appropriate for the clinical and methodological heterogeneity that is common in these studies, and adverse effects are not always completely or consistently reported. To address these problems, analysts should explore heterogeneity and use random-effects or more complex statistical methods, and use multiple statistical models to see how dependent the results are to the choice of models.

Benefit–Risk Assessment of Diacerein in the Treatment of Osteoarthritis

Elena Panova, Graeme Jones

ABSTRACT

Osteoarthritis (OA) is the leading musculoskeletal cause of disability. Despite this, there is no consensus on the precise definition of OA and what is the best treatment to improve symptoms and slow disease progression. Current pharmacological treatments include analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase (COX) inhibitors. None of those treatments are disease-modifying agents that target the core pathological processes in OA. Diacerein, a semi-synthetic anthraquinone derivative, inhibits the interleukin-1-beta (IL-1β) cytokine which, according to animal studies, plays a key role in the pathogenesis of OA. Diacerein was synthesized in 1980 and licensed in some European Union and Asian countries for up to 20 years. It has shown modest efficacy and acceptable tolerability in a number of trials of low to moderate quality. Early this year, the European Medicines Agency (EMA) conducted a review and restricted the use of diacerein-containing medicines. This was because of major concerns about the frequency and severity of diarrhoea and liver disorders in OA patients. In addition, the EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) questioned the limited clinical benefits of diacerein, which, in their view, did not outweigh its risks. The aim of this review is to provide a benefit–risk assessment of diacerein in the treatment of OA, based on an systematic evaluation of the published efficacy and safety data. Overall, there is evidence that diacerein is modestly effective for symptoms and possibly for radiographic changes, but this needs to be balanced against higher rates of gastrointestinal toxicity.
Safety and Tolerability Profile of Second-Line Anti-Tuberculosis Medications
Geetha Ramachandran, Soumya Swaminathan

ABSTRACT

Tuberculosis (TB) remains a major public health problem, representing the second leading cause of death from infectious diseases globally, despite being nearly 100 % curable. Multidrug-resistant (MDR)-TB, a form of TB resistant to isoniazid and rifampicin (rifampin), two of the key first-line TB drugs, is becoming increasingly common. MDR-TB is treated with a combination of drugs that are less effective but more toxic than isoniazid and rifampicin. These drugs include fluoroquinolones, aminoglycosides, ethionamide, cycloserine, aminosalicyclic acid, linezolid and clofazimine among others. Minor adverse effects are quite common and they can be easily managed with symptomatic treatment. However, some adverse effects can be life-threatening, e.g. nephrotoxicity due to aminoglycosides, cardiotoxicity due to fluoroquinolones, gastrointestinal toxicity due to ethionamide or para-aminosalicyclic acid, central nervous system toxicity due to cycloserine, etc. Baseline evaluation may help to identify patients who are at increased risk for adverse effects. Regular clinical and laboratory evaluation during treatment is very important to prevent adverse effects from becoming serious. Timely and intensive monitoring for, and management of adverse effects caused by, second-line drugs are essential components of drug-resistant TB control programmes; poor management of adverse effects increases the risk of non-adherence or irregular adherence to treatment, and may result in death or permanent morbidity. Treating physicians should have a thorough knowledge of the adverse effects associated with the use of second-line anti-TB drugs, and routinely monitor the occurrence of adverse drug reactions. In this review, we have compiled safety and tolerability information regarding second-line anti-TB drugs in both adults and children.

Neurodevelopmental Effects of Fetal Antiepileptic Drug Exposure
Naymee J. Velez-Ruiz, Kimford J. Meador

ABSTRACT

Many studies investigating cognitive outcomes in children of women with epilepsy report an increased risk of mental impairment. Verbal scores on neuropsychometric measures may be selectively more involved. While a variety of factors contribute to the cognitive problems of children of women with epilepsy, antiepileptic drugs (AEDs) appear to play a major role. The mechanisms by which AEDs affect neurodevelopmental outcomes remain poorly defined. Animal models suggest that AED-induced apoptosis, altered neurotransmitter environment, and impaired synaptogenesis are some of the mechanisms responsible for cognitive and behavioral teratogenesis. AEDs that are known to induce apoptosis, such as valproate, appear to affect children’s neurodevelopment in a more severe fashion. Fetal valproate exposure has dose-dependent associations with reduced cognitive abilities across a range of domains, and these appear to persist at least until the age of 6. Some studies have shown neurodevelopmental deficiencies associated with the use of phenobarbital and possibly phenytoin. So far, most of the investigations available suggest that fetal exposures to lamotrigine or levetiracetam are safer with regard to cognition when compared with other AEDs. Studies on carbamazepine show contradictory results, but most information available suggests that major poor cognitive outcomes should not be attributed to this medication. Overall, children exposed to polytherapy prenatally appear to have worse cognitive and behavioral outcomes compared with children exposed to monotherapy, and with the unexposed. There is an increase risk of neurodevelopmental deficits when polytherapy involves the use of valproate versus other agents.
Comparative Safety and Tolerability of Anti-VEGF Therapy in Age-Related Macular Degeneration

Yasha S. Modi, Carley Tanchon, Justis P. Ehlers

ABSTRACT

Neovascular age-related macular degeneration (NVAMD) is one of the leading causes of blindness. Over the last decade, the treatment of NVAMD has been revolutionized by the development of intravitreal anti-vascular endothelial growth factor (VEGF) therapies. Several anti-VEGF medications are used for the treatment of NVAMD. The safety and tolerability of these medications deserve review given the high prevalence of NVAMD and the significant utilization of these medications. Numerous large randomized clinical trials have not shown any definitive differential safety relative to ocular or systemic safety of these medications. Intravitreal anti-VEGF therapy does appear to impact systemic VEGF levels, but the implications of these changes remain unclear. One unique safety concern relates drug compounding and the potential risks of contamination, specifically for bevacizumab. Continued surveillance for systemic safety concerns, particularly for rare events, is merited. Overall, these medications are well tolerated and effective in the treatment of NVAMD.

Addressing Limitations in Observational Studies of the Association between Glucose-Lowering Medications and All-Cause Mortality: A Review

Elisabetta Patorno, Elizabeth M. Garry

ABSTRACT

A growing body of observational literature on the association between glucose-lowering treatments and all-cause mortality has been accumulating in recent years. However, many investigations present designs or analyses that inadequately address the methodological challenges involved. We conducted a systematic search with a non-systematic extension to identify observational studies published between 2000 and 2012 that evaluated the effects of glucose-lowering medications on all-cause mortality. We reviewed these studies and assessed the design and analysis methods used, with a focus on their ability to address specific methodological challenges. We described these methodological issues and their potential impact on observed associations, providing examples from the reviewed literature, and suggested possible approaches to manage these methodological challenges. We evaluated 67 publications of observational studies evaluating the association between glucose-lowering treatments and all-cause mortality. The identified methodological challenges included trade-offs associated with the outcome of all-cause mortality, incorrect temporal sequencing in administrative databases, inadequate treatment of time-varying hazards and treatment duration effects, unclear definition of the exposure risk window, improper handling of time-varying exposures, and incomplete accounting for confounding by indication. Most of these methodological challenges may be adequately addressed through the application of appropriate methods. Observational research plays an increasingly important role in assessing the clinical effects of diabetes therapy. The implementation of suitable research methods can reduce the potential for spurious findings, and thus the risk of misleading the medical community about benefits and harms of diabetes therapy.
Evaluation of an Automated Surveillance System Using Trigger Alerts to Prevent Adverse Drug Events in the Intensive Care Unit and General Ward

John P. DiPoto, Mitchell S. Buckley, Sandra L. Kane-Gill

ABSTRACT

Introduction: Adverse events in the intensive care unit (ICU) may be associated with several possible causes, so determining a drug-related causal assessment is more challenging than in general ward patients. Therefore, the hypothesis was that automated trigger alerts may perform differently in various patient care settings. The purpose of this study was to compare the frequency and type of clinically significant automated trigger alerts in critically ill and general ward patients as well as evaluate the performance of alerts for drug-related hazardous conditions (DRHCs).

Methods: A retrospective cohort study was conducted in adult ICU and general ward patients at three institutions (academic, community, and rural hospital) in a health system. Automated trigger alerts generated during two nonconsecutive months were obtained from a centralized database. Pharmacist responses to alerts and prescriber response to recommendations were evaluated for all alerts. A clinical significant event was defined as an actionable intervention requiring drug therapy changes that the pharmacist determined to be appropriate for patient safety and where the physician accepted the pharmacist’s recommendation.

Results: A total of 751 alerts were generated in 623 patients during the study period. Pharmacists intervened on 39.8 and 44.8 % alerts generated in the ICU and general ward, respectively. Overall, the physician acceptance rate of approximately 90 % was comparable irrespective of patient care setting. Therefore, the number of clinically significant alerts was 88.9 and 83.4 % for the ICU and non-ICU, respectively.

Conclusions: The number and type of clinically significant alerts were similar irrespective of patient population, suggesting that the alerts may be equally as beneficial in the ICU population, despite the challenges in drug-related event adjudication. An opportunity exists to improve the performance of alerts in both settings, so quality improvement programs for measuring alert performance and making refinements is needed.

The Monitoring Medicines Project: A Multinational Pharmacovigilance and Public Health Project

Shanthi N. Pal, Sten Olsson, Elliot G. Brown

ABSTRACT

The Monitoring Medicines project (MM), funded by the FP-7 EU framework, was carried out between 2009 and 2013 by a consortium of 11 partners. The objectives were to support and strengthen consumer reporting of adverse drug reactions (ADRs); expand the role and scope of national pharmacovigilance centres concerning medication errors; promote improved use of pharmacovigilance data; and develop methods to complement spontaneous reporting. The work was organised into four themes: patient reporting; medication errors; drug dependence, counterfeit and substandard medicines and clinical risk estimation; and active and targeted spontaneous pharmacovigilance. MM differed from some other major pharmacovigilance initiatives by having participants from developing countries in Asia and Africa and in leaning towards public health and communicable diseases. MM brought together stakeholders including WHO, drug regulators, pharmacovigilance centres, consumers, public health and disease specialists and patient safety networks. Resources and methodologies developed directly by, or with support from, MM include electronic systems/tools for consumer ADR reporting and cohort event monitoring; publication by WHO of handbooks on consumer reporting, medication errors and pharmacovigilance for TB medicines; methodologies for detecting drug dependence and substandard or counterfeit medicines in ADR databases; and a database on HIV treatment risks with a risk assessment tool. MM enabled stakeholders to achieve more than if they had worked alone in pursuit of patient safety.
Empowering Consumers as Contributors for Health Product Safety: Lessons from the Philippines

Kenneth Hartigan-Go

ABSTRACT

Empowering consumers to contribute to adverse drug reaction reporting seems a sensible innovation, particularly when traditional reports emanating from healthcare professionals are neither increasing nor improving. This work, inspired by an EU-FP7-funded project, describes an attempt by the Philippines to introduce a consumer reporting system through education and an online platform for reporting, and the lessons that were captured in the process. While participating consumers did not contribute to the adverse drug reporting process in the traditional sense as originally expected, the reports received by the drug regulatory agency revealed consumers’ concerns regarding health product legitimacy, quality and market claims, as well as the lack of available and accessible information. These reports led regulators to take action. Initial insights on consumer behavior are proposed for regulators and industry to consider in greater depth and how this may impact on consumers providing valued information that will promote other aspects of product safety.

ADR Reporting by the General Public: Lessons Learnt from the Dutch and Swedish Systems

Linda Härmak, Florence van Hunsel, Birgitta Grundmark

ABSTRACT

Consumer reporting of adverse drug reactions (ADRs) has existed in several countries for decades, but throughout Europe the role of consumers as a source of information on ADRs has not been fully accepted until recently. In Europe, The Netherlands and Sweden were among the first countries to implement consumer reporting well before it was mandated by law throughout the EU. Consumer reporting is an integral part of the spontaneous reporting systems in both The Netherlands and Sweden, with yearly numbers of reports constantly increasing. Consumer reporting forms and handling procedures are essentially the same as for healthcare professional reporting; the message in the reports, not the type of messenger, is what is of importance. Studies have established the significant contribution of consumer reporting to ADR signal detection. Combining all reports regardless of reporter type is recommended since it yields the largest critical mass of reports for signal detection. Examples of signals where consumer reports have been of crucial importance for signal detection are electric shock-like sensations associated with the use of duloxetine, and persistent sexual dysfunction after discontinuation of selective serotonin reuptake inhibitors. An example of consumer reporting significantly strengthening a detected signal is Pandemrix® (influenza H1N1 vaccine)-induced narcolepsy. Raising public awareness of ADR reporting is important, but time- and resource-consuming. The minimum effort taken should be to passively inform consumers, e.g. via stakeholders’ homepages and via drug product information leaflets. Another possibility of reaching out to this target group could be through co-operation with other (non-government) organizations. Information from consumer reports may give a new perspective on ADRs via the consumers’ unfiltered experiences. Consumers’ views may change the way the benefit–harm balance of drugs is perceived and assessed today, and, being the ultimate users of drugs, consumers could have a relevant influence in the regulatory decision-making processes for drugs. All stakeholders in pharmacovigilance should embrace this new valuable source of information.
Initiatives to Identify and Mitigate Medication Errors in England
David Cousins, David Gerrett, Natalie Richards, Mitulsinh M. Jadeja

ABSTRACT
In response to the EU Directive on Pharmacovigilance, the National Health Service (NHS) in England and the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK have formed a partnership to work together to simplify and increase medication error reporting, improve data report quality, maximise learning and guide practice to minimise harm from medication errors by sharing incident data. This initiative will facilitate implementation of new requirements for medication error reporting and reduce the need for duplicate data entry by frontline staff. The initiative is also intended to provide new types of feedback from the National Reporting and Learning System run by the NHS England and from the Yellow Card Scheme run by the MHRA and to improve learning at the local level by clarifying medication safety roles and identifying key safety contacts to allow better communication between local and national levels. Finally, the partnership has established a new National Medication Safety Network to provide a forum for discussing potential and recognised safety issues, and for identifying trends and actions to improve the safe use of medicines. This article describes the initiative, the structure of which may act as a template for other countries.

User-Driven Development of a Web-Based Tool for Patient Reporting of Drug-Related Harm
Monica Plöen, Magnus Wallberg, Sten Olsson

ABSTRACT
Commissioned by the Monitoring Medicines project, the Uppsala Monitoring Centre (UMC) led the design and development of a web-based ADR (adverse drug reaction) reporting tool intended for use by patients. The software design was undertaken in close collaboration with representatives of national pharmacovigilance centres (NPCs) and with patient and consumer organizations. The web-based tool was developed by these participants through several telephone conferences, a workshop and site testing. The tool is directly compatible with the UMC’s Individual Case Safety Report (ICSR) data management system VigiFlow® and is also compliant with the ICH-E2B(R2) format. The UMC team benefited by working closely with the end-users during the development process. A major challenge was to balance the need for detailed information required by the NPCs to be able to assess reports with the amount of detail patients are able and willing to provide. Needs, ideas and suggestions from the end users were valuable and were taken into account throughout the process of designing the tool.
Background and Objective: Antiretroviral drugs have well-documented evidence-based favorable benefit–risk ratios. Although various studies have investigated and characterized the safety profile of antiretroviral medicines, there are a limited number of studies evaluating the safety of first-line antiretroviral therapy (ART) in patients with a specific co-morbidity. A cohort event monitoring (CEM) study of the safety and effectiveness of antiretroviral medicines in a target population that has a significant level of co-morbidities (chronic infectious diseases, peripheral blood cytopenias) was implemented. The aim was to evaluate the safety profile of the highly active ART (HAART) in the target population and subpopulations with risk factors, to optimize the monitoring and decision-making procedure for subgroups of patients with specific types of co-morbidity, and to implement a more vigilant approach to therapy management in risk groups of patients.

Methods: Prospective observational CEM was implemented among HAART-naïve HIV-positive patients at four clinical sites from December 2012. Eligible patients were those starting first-line HAART. Close medical supervision of all enrolled patients, with regular clinical and laboratory monitoring, was provided by healthcare professionals within 1 year after commencement of therapy. Standardized forms were used for data collection on initial and subsequent visits. All objective or subjective deviations in condition (events) were assessed for a causal relationship with ART, and for severity, seriousness, reversibility, preventability, and pre-existing risk factors in the case of adverse drug reactions (ADRs).

Results: A total of 518 HAART-naïve HIV-positive patients were enrolled in the CEM study. Of these patients, 65% (337) experienced one or several ADRs related to one or more components of HAART. Most of the ADRs reported were non-serious, expected, common (very common), transient (correctable), or reversible. The most common were hematotoxic, hepatotoxic, and neurotoxic adverse reactions. In several cases, some types of toxicities, associated with zidovudine, efavirenz, and nevirapine, had a high level of severity, necessitating hospitalization and drug regimen or single-agent substitution. Severe cases of hematological, hepatobiliary, and psychiatric toxicities were associated with pre-existing risk factors.

Conclusion: CEM is an effective tool for safety and effectiveness monitoring and could be successfully implemented for intensive study of important safety issues and for overcoming knowledge gaps regarding safety. In order to achieve a favorable benefit–risk ratio for HAART in the specific sections of the population with pre-existing risk factors for development of ART toxicities, more vigilant consideration and careful assessment before therapy is commenced and further regular monitoring of key laboratory parameters is required.
ABSTRACT

Background: Substandard medicines, whether the result of intentional manipulation or lack of compliance with good manufacturing practice (GMP) or good distribution practice (GDP), pose a significant potential threat to patient safety. Spontaneous adverse drug reaction reporting systems can contribute to identification of quality problems that cause unwanted and/or harmful effects, and to identification of clusters of lack of efficacy. In 2011, the Uppsala Monitoring Centre (UMC) constructed a novel algorithm to identify reporting patterns suggestive of substandard medicines in spontaneous reporting, and applied it to VigiBase®, the World Health Organization’s global individual case safety report database. The algorithm identified some historical clusters related to substandard products, which were later able to be confirmed in the literature or by contact with national centres (NCs). As relevant and detailed information is often lacking in the VigiBase reports but might be available at the reporting NC, further evaluation of the algorithm was undertaken with involvement from NCs.

Objective: To evaluate the effectiveness of an algorithm that identifies clusters of potentially substandard medicines, when these are assessed directly at the NC concerned.

Methods: The algorithm identifies countries and time periods with disproportionally high reporting of product inadequacy. NCs with at least 20 clusters were eligible to participate in the study, and six NCs—those in the Republic of Korea, Malaysia, Singapore, South Africa, the UK and the USA—were selected, taking into account the geographical spread and prevalence of recent clusters. The clusters were systematically assessed at the NCs, following a standardized protocol, and then compiled centrally at the UMC. The clusters were classified as ‘confirmed’, ‘potential’ or ‘unlikely’ substandard products; or as ‘confirmed not substandard’ when confirmed by an investigation; or as ‘indecisive’ when the information available did not allow a sound assessment even at the NC.

Results: The assessment of a total of 147 clusters resulted in 8 confirmed, 12 potential and 51 unlikely substandard products, and a further 19 clusters were confirmed as not substandard. Reflecting the difficulty of evaluating suspected substandard products retrospectively when additional information from the primary reporter, as well as samples, are no longer available, 57 clusters were classified as indecisive.

Conclusion: While application of the algorithm to VigiBase allowed identification of some substandard medicines, some key prerequisites have been identified that need to be fulfilled at the national level for the algorithm to be useful in practice. Such key factors are fast handling and transfer of incoming reports into VigiBase, detailed information on the product and its distribution channels, the possibility of contacting primary reporters for further information, availability of samples of suspected products and laboratory capacity to analyse suspected products.
Assessment of a New Instrument for Detecting Preventable Adverse Drug Reactions

Raja Benkirane, Rachida Soulaymani-Bencheikh, Asmae Khattabi

ABSTRACT

Background: Pharmacovigilance centres (PVCs) in the World Health Organization (WHO) Programme for International Drug Monitoring have demonstrated their ability to detect preventable adverse drug reactions (ADRs) in their databases. In this field, there is no gold-standard method for detecting medication errors and evaluating ADR preventability. Therefore, we developed, from existing tools, a preventability assessment method: the ‘P Method’ (PM).

Objective: To present the PM and to evaluate its inter-rater reliability.

Methods: The PM includes 20 explicit criteria for assessing ADR preventability. This approach is based on identification of any potentially preventable risk factor that increases the likelihood of ADR occurrence. The outcome of the preventability assessment results in one of three possible scores: ‘preventable’, ‘non-preventable’ or ‘not assessable’. The PM was tested in a multicentre study involving nine national PVCs. Two experienced reviewers at each participating PVC independently analysed the preventability of 183 ADRs, applying the PM.

Results: The overall agreement between all reviewers for assessment of ADR preventability was ‘fair’, with a kappa value of 0.27 [95 % confidence interval (CI) 0.21–0.40]. The level of agreement between reviewer pairs ranged from ‘slight’, with a kappa value of 0.12 (95 % CI –0.03 to 0.27), to ‘substantial’, with a kappa value of 0.69 (95 % CI 0.48–0.89).

Conclusion: The analysis of the agreements and disagreements between reviewers highlighted where improvements might be made. Given that no standard assessment tool exists in the WHO Programme, the transparency of the assessment process in this method provides a substantial basis for further development and for support in signalling possible preventability.
Targeted Spontaneous Reporting of Suspected Renal Toxicity in Patients Undergoing Highly Active Anti-Retroviral Therapy in Two Public Health Facilities in Uganda

Helen Ndagije, Victoria Nambasa, Elizabeth Namagala, Huldah Nassali

ABSTRACT

Background: Although the national HIV control programme in Uganda has a well-established system for monitoring disease progression and treatment outcomes, monitoring of adverse drug reactions (ADRs) is inadequate. In order to address under-reporting of ADRs, the National Pharmacovigilance Centre, in collaboration with the HIV control programme, piloted a targeted spontaneous reporting (TSR) system as a complementary method to traditional spontaneous reporting.

Methods: From April 2012 to March 2014, all cases of suspected renal toxicity in 10,225 patients on tenofovir-based regimens were monitored in the regional pharmacovigilance centres of Masaka and Mbale. The identification of renal toxicity was performed using serum creatinine, urinalysis, and other signs and symptoms of kidney injury.

Results: There was one suspected renal toxicity reported for every 200 patients on a tenofovir-based regimen. Some of the serious reactions reported were death in two cases and bone demineralisation in five patients. Most of patients had been on treatment for 2 years. Those that had been on tenofovir for more than 4 years had raised serum creatinine levels, emphasising the importance of monitoring for the risk of renal damage for longer. We also found that the reporting rate of suspected ADRs for all medicines in the two sites increased almost fivefold during the implementation period.

Conclusion: Although the occurrence of suspected tenofovir renal toxicity of HIV patients is low, there is need to monitor those at risk so as to prevent irreversible kidney injury. TSR can complement spontaneous reporting for collecting safety data on particular drugs and increase ADR reporting rates.

Organ-On-A-Chip: Development and Clinical Prospects toward Toxicity Assessment with an Emphasis on Bone Marrow

Jeehye Kim, Hanna Lee, Šeila Selimović, Robert Gauvin, Hojae Bae

ABSTRACT

Conventional approaches for toxicity evaluation of drugs and chemicals, such as animal tests, can be impractical due to the large experimental scale and the immunological differences between species. Organ-on-a-chip models have recently been recognized as a prominent alternative to conventional toxicity tests aiming to simulate the human in vivo physiology. This review focuses on the organ-on-a-chip applications for high-throughput screening of candidate drugs against toxicity, with a particular emphasis on bone-marrow-on-a-chip. Studies in which organ-on-a-chip models have been developed and utilized to maximize the efficiency and predictability in toxicity assessment are introduced. The potential of these devices to replace tests of acute systemic toxicity in animals, and the challenges that are inherent in simulating the human immune system are also discussed. As a promising approach to overcome the limitations, we further focus on an in-depth analysis of the development of bone-marrow-on-a-chip that is capable of simulating human immune responses against external stimuli due to the key roles of marrow in immune systems with hematopoietic activities. Owing to the complex interactions between hematopoietic stem cells and marrow microenvironments, precise control of both biochemical and physical niches that are critical in maintenance of hematopoiesis remains a key challenge. Thus, recently developed bone-marrow-on-a-chip models support immunogenicity and immunotoxicity testing in long-term cultivation with repeated antigen stimulation. In this review, we provide an overview of clinical studies that have been carried out on bone marrow transplants in patients with immune-related diseases and future aspects of clinical and pharmaceutical application of bone-marrow-on-a-chip.
Comparative Safety and Tolerability of Endothelin Receptor Antagonists in Pulmonary Arterial Hypertension
Meghan Aversa, Sandra Porter, John Granton

ABSTRACT
Pulmonary arterial hypertension (PAH) is a condition that leads to progressive right heart failure and death unless recognized and treated early. Endothelin, a potent endogenous vasoconstrictor, has been identified as an important mediator of PAH. Endothelin receptor antagonists (ERAs) have been associated with an improvement in exercise capacity and time to clinical worsening in patients with Group 1 PAH, and three different ERAs are currently approved for use in this population: bosentan, ambrisentan, and macitentan. While all three ERAs are generally well-tolerated, they each have important adverse effects that need to be recognized and monitored. In particular, they may cause anemia, peripheral edema, and mild cardiac, respiratory, neurologic, and gastrointestinal adverse effects to varying degrees. Although bosentan increases a patient’s risk of developing liver transaminitis, ambrisentan and macitentan do not appear to confer the same risk of hepatotoxicity at this time. Important drug–drug interactions, particularly involving other drugs metabolized via the cytochrome P450 pathway, are important to recognize when prescribing ERAs. In this review, we provide a brief overview of the current state of knowledge as it relates to the adverse effect profiles, tolerability, and drug–drug interactions of this class of medication as informed by the results of randomized clinical trials, drug surveillance programs, and regulatory agencies.

Epidemiology of Adverse Drug Reactions in Europe: A Review of Recent Observational Studies
Jacoline C. Bouvy, Marie L. De Bruin, Marc A. Koopmanschap

ABSTRACT
Adverse drug reactions (ADRs) cause considerable mortality and morbidity but no recent reviews are currently available for the European region. Therefore, we performed a review of all epidemiological studies quantifying ADRs in a European setting that were published between 1 January 2000 and 3 September 2014. Included studies assessed the number of patients who were admitted to hospital due to an ADR, studies that assessed the number of patients who developed an ADR during hospitalization, and studies that measured ADRs in the outpatient setting. In total, 47 articles were included in the final review. The median percentage of hospital admissions due to an ADR was 3.5 %, based on 22 studies, and the median percentage of patients who experienced an ADR during hospitalization was 10.1 %, based on 13 studies. Only five studies were found that assessed ADRs occurring in the outpatient setting. These results indicate that the occurrence of ADRs in the European hospital setting—both ADRs that result in hospitalization and ADRs that occur during the hospital stay—is significant. Furthermore, the limited number of studies that were performed in the outpatient setting identify a lack of information regarding the epidemiology of ADRs in this setting.
Chimeric Fusion Proteins Used for Therapy: Indications, Mechanisms, and Safety

Brian A. Baldo

ABSTRACT

Chimeric fusion proteins, produced by genetic engineering, are currently made up of effector peptides, for example, a ligand-binding portion of a cytokine or growth factor, extracellular domains of lymphocyte antigens, or a toxin linked to a suitable fusion partner. This review covers eight fusion proteins that have received regulatory approval for human therapy: etanercept, belatacept, abatacept, alefacept, rilonacept, romiplostim, aflibercept, and denileukin-diftitox. Important requirements for an effective fusion protein are effective targeting and binding, cytotoxicity, and a stable molecule with an extended half-life. The Fc region of human IgG1 is generally chosen as the fusion partner for the effector molecule(s) because it extends the fusion protein half-life by recycling via the salvage neonatal FcRn receptor and protects the molecule from lysosomal degradation. Each of the fusion proteins has IgG1 Fc as a fusion partner except denileukin-diftitox, which employs a modified diphtheria toxin effector peptide linked to interleukin-2. For six of the Fc fusion proteins, the effector peptide(s) is linked to the N-terminus of the Fc piece but for the thrombopoietin-mimetic romiplostim, linkage is through the C-terminus. Although some clear type I and IV hypersensitivities are known to be induced by fusion protein therapy, the pathomechanisms underlying many adverse hematologic, respiratory, renal, and cutaneous events have generally not been investigated. Assessment of immunogenicity risk is important because a number of immune-based or influenced, adverse reactions such as anaphylaxis, cutaneous manifestations, infusion, and injection-site reactions, and cytokine release syndrome can occur. Features of many reactions, some autoimmune in nature, suggest type II, III, or IV hypersensitivities. Clinical findings with the anti-arthritis anti-psoriasis biologic etanercept provide the largest body of current knowledge of fusion protein-induced adverse events. For most fusion proteins, little information is available on appropriate diagnostic and desensitization procedures for hypersensitivity and other adverse responses, although skin test concentrations and some successful desensitization protocols have been published for etanercept.

Risks and Benefits of Triple Oral Anti-Thrombotic Therapies after Acute Coronary Syndromes and Percutaneous Coronary Intervention

Joakim Alfredsson, Matthew T. Roe

ABSTRACT

The key pathophysiological process underlying symptomatic coronary artery disease, including acute coronary syndromes (ACS), is usually a rupture or an erosion of an atherosclerotic plaque, followed by platelet activation and subsequent thrombus formation. Early clinical trials showed benefit with long-term aspirin treatment, and later—based on large clinical trials—dual anti-platelet therapy (DAPT), initially with clopidogrel, and more recently with prasugrel or ticagrelo, has become the established treatment in the post-ACS setting and after percutaneous coronary intervention (PCI). Treatment with DAPT is recommended for both ST-elevation myocardial infarction and non-ST-elevation ACS, as well as after PCI with stenting, in American and European clinical guidelines. Notwithstanding the benefits observed with DAPT, including third-generation P2Y12 receptor inhibitors plus aspirin, ACS patients remain at high risk for a recurrent cardiovascular event, suggesting that other treatment strategies, including the addition of a third oral anti-platelet agent or a novel oral anticoagulant (NOAC) to standard DAPT regimens, may provide additional benefit for post-ACS patients and for patients undergoing PCI. Adding a third anti-thrombotic agent to DAPT after an ACS event or a PCI procedure has been shown to have modest benefit in terms of ischemic event reduction, but has consistently been associated with increased bleeding complications. Therefore, the quest to optimize anti-thrombotic therapies post-ACS and post-PCI continues unabated but is tempered by the historical experiences to date that indicate that careful patient and dose selection will be critical features of future randomized trials.
Skin atrophy is an adverse effect of topical corticosteroids (TCs) which, as an established non-life-threatening effect, has been poorly reported by trials involving these drugs. Atopic dermatitis and psoriasis are example of disorders that require repeated therapies with TCs; however, assessing the atrophogenic activity of TCs is still an issue. This study aims to review clinical data on skin atrophy induced by TCs. Searches of the PubMed, EMBASE, and Cochrane (Central) databases from 1965 to May 2013 were undertaken using the keywords ‘corticosteroid’, ‘skin’, and ‘atrophy’. Skin and epidermal thickness values were retrieved from trials on healthy skin, and studies including skin atrophy as a safety endpoint in trials testing the efficacy of TCs were analyzed. Overall, 60 articles were retrieved. Whole skin and epidermal thickness were relevant parameters to measure early skin atrophy on healthy skin before it becomes clinically obvious. Epidermis thickness also seems to be more sensitive than whole skin thickness in detecting early atrophy; however, measuring skin atrophy still requires standardization. Further clinical trials on the atrophic effects of each TC are required to better evaluate their respective atrophic risks and their risk/benefit ratios. However, measuring epidermal or whole skin thickness will not be relevant in acute phases of inflammatory skin disorders treated with TCs because of the thickening induced by inflammation. In addition, skin atrophy seems to be induced by chronic TC use rather than by acute treatments. Long-term safety studies may be more relevant to evaluate atrophic activity.

Relationship Between Structural Alerts in NSAIDs and Idiosyncratic Hepatotoxicity: An Analysis of Spontaneous Report Data from the WHO Database

Naomi Jessurun, Eugene van Puijenbroek

Background: Idiosyncratic drug reactions such as hepatotoxicity and blood dyscrasias represent one of the major causes of drug withdrawal from the market. According to the reactive metabolite (RM) concept, this may be due to the metabolic activation of structural alerts (SAs), functionalities in the drug molecule that are susceptible to bioactivation resulting in RMs. The relationship, however, between metabolic activation of SAs in drugs with in vivo toxicity measured as disproportionate reporting of adverse drug reactions (ADRs) to the WHO VigiBase™ database has never been studied.

Objective: The objective of this study was to investigate whether reported associations of hepatotoxicity between NSAIDs with SAs and NSAIDs with mitigated SAs are disproportionately present in the ADR reporting VigiBase™ database of the WHO collaborating center (the Uppsala Monitoring Centre). The extent of disproportionality of these associations is compared with associations of NSAIDs and hemorrhage, an ADR not associated with the forming of RMs.

Methods: We calculated the reporting odds ratios for five NSAIDs [bromfenac (withdrawn), lumiracoxib (withdrawn), diclofenac, ibuprofen, and naproxen] associated with the MedDRA preferred terms: hepatic failure, hepatic function abnormal, hepatic necrosis, and hepatitis. The disproportionality of the association of these ADRs is compared with associations of NSAIDs and hemorrhage, an ADR not associated with the forming of RMs.

Results: The results show that hepatotoxicity is more disproportionately reported in the WHO database for NSAIDs with SAs (bromfenac, lumiracoxib, diclofenac) than for NSAIDs where SAs are mitigated (ibuprofen and naproxen). This difference in reporting between NSAIDs with SAs and with mitigated SAs is not observed for the ADR hemorrhage, an ADR not associated with the forming of RMs.

Conclusions: This study shows that although spontaneous reports have many limitations, the findings are in line with previous research on the reactive metabolite concept. Whether SAs and the number of SAs in the NSAIDs actually play a role in the observed hepatotoxicity must be investigated in future studies.
ABSTRACT
Proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors are a novel class of medications that greatly lower low-density lipoprotein cholesterol (LDL-C) by upregulating LDL receptor availability. In early 2014, the US Food and Drug Administration (FDA) directed developers of PCSK9 inhibitors to monitor neurocognitive adverse effects and consider neurocognitive testing in at least a subset of participants in ongoing late-stage trials. Available trial evidence indicates that neurocognitive adverse events may occur more commonly in individuals receiving an antibody to PCSK9, but these events are uncommon and have not been associated with on-treatment LDL-C levels. Moreover, it is unclear to what extent closer monitoring of trial participants allocated to PCSK9 inhibitors has led to an ascertainment bias. Regardless, further trial data are needed, and long-term outcomes trials are ongoing, with at least one including a neurocognitive substudy. Considering lessons learned from the statin experience, high-quality prospective cohort studies and randomized trials may not be enough to allay concerns or settle debate since the focus of effect in these studies is the group average. Therefore, we suggest that n-of-1 trials could be considered to bring the focus to the individual while retaining the benefits of blinding and randomization in evidence generation. Ultimately, any neurocognitive adverse effects that might exist with PCSK9 inhibition and lipid lowering must be weighed against potential benefits of therapy, including avoidance of myocardial infarction and stroke, and a reduced risk of dementia due to neurovascular benefits from long-term lipid lowering.

Oral Anticoagulants and Risk of Nephropathy
Vinay Narasimha Krishna, David G. Warnock, Nakshatra Saxena, Dana V. Rizk

ABSTRACT
Anticoagulant-related nephropathy, a recently recognized entity, manifests as unexplained acute kidney injury in the setting of excessive anticoagulation with oral agents. Histologic findings in warfarin-related nephropathy include glomerular hemorrhage and renal tubular obstruction by red blood cells. Affected patients are at increased risk of mortality as well as irreversible kidney injury. Patients with chronic kidney disease are particularly vulnerable to this complication. Similar case reports of anticoagulant-related nephropathy have been linked to the more novel oral anticoagulant, dabigatran. Anticoagulant-related nephropathy has been successfully reproduced in rat models. These animal models shed light on the pathogenesis of the disease including the potential role of direct thrombin and protease-activated receptor-1 inhibition.

Drug-Induced Renal Damage in Preterm Neonates: State of the Art and Methods for Early Detection
Anna Girardi, Emanuel Raschi, Silvia Galletti, Elisabella Poluzzi

ABSTRACT
Only a small fraction of drugs widely used in neonatal intensive care units (NICU) are specifically authorized for this population. Even if unlicensed or off-label use is necessary, it is associated with increased adverse drug reactions, which must be carefully weighed against expected benefits. In particular, renal damage is frequent among preterm babies, and is considered a predisposing factor for the development of chronic kidney disease in adulthood. Apart from specific conditions affecting premature neonates (e.g. respiratory distress syndrome, perinatal asphyxia), drugs play an important role in impairing renal function because of well-known nephrotoxicity and/or interaction with renal developmental factors. From a review of the available studies on drug use in NICU patients, we identified and described the most commonly administered drugs that are correlated to renal damage. Early detection of kidney injury is becoming an essential aspects for clinicians because of the limited number of biomarkers applicable in the neonatal population. Postnatal changes of biochemical processes that influence pharmacokinetic and pharmacodynamic aspects need to be further investigated in order to better understand the mechanisms of drug toxicity in this population. The most promising strategies for dose adjustment and therapeutic schemes are discussed.

Bianca Blanch, Nicholas A. Buckley, Leigh Mellish, Andrew H. Dawson

ABSTRACT

Background: Prescription drug misuse is a growing public health concern globally. Routinely collected data provide a valuable tool for quantifying prescription drug misuse.

Objective: To synthesize the global literature investigating prescription drug misuse utilizing routinely collected, person-level prescription/dispensing data to examine reported measures, documented extent of misuse and associated factors.

Methods: The MEDLINE, EMBASE, CINAHL, MEDLINE an aim/method investigating prescription drug misuse in adults and a measure of misuse derived exclusively from prescription/dispensing data.

Results: Four proxies of prescription drug misuse were commonly used across studies: number of prescribers, number of dispensing pharmacies, early refills and volume of drugs dispensed. Overall, 89 unique measures of misuse were identified across the 52 studies, reflecting the heterogeneity in how measures are constructed: single or composite; different thresholds, cohort definitions and time period of assessment. Consequently, it was not possible to make definitive comparisons about the extent (range reported 0.01–93.5 %), variations and factors associated with prescription drug misuse.

Conclusions: Routine data collections are relatively consistent across jurisdictions. Despite the heterogeneity of the current literature, our review identifies the capacity to develop universally accepted metrics of misuse applied to a core set of variables in prescription/dispensing claims. Our timely recommendations have the potential to unify the global research field and increase the capacity for routine surveillance of prescription drug misuse.

Methodological Approaches to Evaluate the Impact of FDA Drug Safety Communications

Aaron S. Kesselheim, Eric G. Campbell, Sebastian Schneeweiss, Paula Rausch

ABSTRACT

Background: When the US FDA approves a new prescription drug there is still a great deal remaining to be learned about the safe and proper use of that product. When new information addressing these topics emerges post-approval, the FDA may issue a Drug Safety Communication (DSC) to alert patients and physicians. The effectiveness of the communication—how drug safety messaging conveyed in FDA DSCs changes patient or prescriber behavior—may depend on multiple factors, including the way physicians and patients learn about the information, their understanding of the issues conveyed, and their perception of the importance of the information. In 2013, the FDA issued two DSCs addressing critical new warnings related to products containing the sedative/hypnotic zolpidem.

Objective: In this article, we describe a core set of research initiatives that can be used to study how zolpidem-related DSCs affected subsequent physician and patient decision making.

Methods: These research initiatives include analyzing drug utilization patterns and related health outcomes; comparing zolpidem-containing products against a comparator with similar indications [eszopiclone (Lunesta)] not covered by the 2013 DSCs; and surveying patients and qualitatively evaluating the dissemination of information regarding these drugs in traditional and social-media channels.

Conclusions: Using an integrated, multidisciplinary approach, we can obtain information that can be used to optimize regulatory communications by seeking to understand the impact of the information contained in FDA risk communications.
Comparison of Statistical Signal Detection Methods within and Across Spontaneous Reporting Databases

Gianmario Candore, Kristina Juhlin, Katrin Manlik, Bharat Thakrar…

ABSTRACT

Background: Most pharmacovigilance departments maintain a system to identify adverse drug reactions (ADRs) through analysis of spontaneous reports. The signal detection algorithms (SDAs) and the nature of the reporting databases vary between operators and it is unclear whether any algorithm can be expected to provide good performance in a wide range of environments.

Objective: The objective of this study was to compare the performance of commonly used algorithms across spontaneous reporting databases operated by pharmaceutical companies and national and international pharmacovigilance organisations.

Methods: 220 products were chosen and a reference set of ADRs was compiled. Within four company, one national and two international databases, 15 SDAs based on five disproportionality methods were tested. Signals of disproportionate reporting (SDRs) were calculated at monthly intervals and classified by comparison with the reference set. These results were summarised as sensitivity and precision for each algorithm in each database.

Results: Different algorithms performed differently between databases but no method dominated all others. Performance was strongly dependent on the thresholds used to define a statistical signal. However, the different disproportionality statistics did not influence the achievable performance. The relative performance of two algorithms was similar in different databases. Over the lifetime of a product there is a reduction in precision for any method.

Conclusions: In designing signal detection systems, careful consideration should be given to the criteria that are used to define an SDR. The choice of disproportionality statistic does not appreciably affect the achievable range of signal detection performance and so this can primarily be based on ease of implementation, interpretation and minimisation of computing resources. The changes in sensitivity and precision obtainable by replacing one algorithm with another are predictable. However, the absolute performance of a method is specific to the database and is best assessed directly on that database. New methods may be required to gain appreciable improvements.
ABSTRACT

Introduction: The Premier Perspective hospital billing database provides a promising data source for studies of inpatient medication use. However, in-hospital recording of confounders is limited, and incorporating linked healthcare claims data available for a subset of the cohort may improve confounding control. We investigated methods capable of adjusting for confounders measured in a subset, including complete case analysis, multiple imputation of missing data, and propensity score (PS) calibration.

Methods: Methods were implemented in an example study of adults in Premier undergoing percutaneous coronary intervention (PCI) in 2004–2008 and exposed to either bivalirudin or heparin. In a subset of patients enrolled in UnitedHealth for at least 90 days before hospitalization, additional confounders were assessed from healthcare claims, including comorbidities, prior medication use, and service use intensity. Diagnostics for each method were evaluated, and methods were compared with respect to the estimates and confidence intervals of treatment effects on repeat PCI, bleeding, and in-hospital death.

Results: Of 210,268 patients in the hospital-based cohort, 3240 (1.5 %) had linked healthcare claims. This subset was younger and healthier than the overall study population. The linked subset was too small for complete case evaluation of two of the three outcomes of interest. Multiple imputation and PS calibration did not meaningfully impact treatment effect estimates and associated confidence intervals.

Conclusions: Despite more than 98 % missingness on 24 variables, PS calibration and multiple imputations incorporated confounders from healthcare claims without major increases in estimate uncertainty. Additional research is needed to determine the relative bias of these methods.

Electronic Health Data for Postmarket Surveillance: A Vision Not Realized

Thomas J. Moore, Curt D. Furberg

ABSTRACT

What has been learned about electronic health data as a primary data source for regulatory decisions regarding the harms of drugs? Observational studies with electronic health data for postmarket risk assessment can now be conducted in Europe and the US in patient populations numbering in the tens of millions compared with a few hundred patients in a typical clinical trial. With standard protocols, results can be obtained in a few months; however, extensive research published by scores of investigators has illuminated the many obstacles that prevent obtaining robust, reproducible results that are reliable enough to be a primary source for drug safety decisions involving the health and safety of millions of patients. The most widely used terminology for coding patient interactions with medical providers for payment has proved ill-suited to identifying the adverse effects of drugs. Directly conflicting results were reported in otherwise similar patient health databases, even using identical event definitions and research methods. Evaluation of some accepted statistical methods revealed systematic bias, while others appeared to be unreliable. When electronic health data studies detected no drug risk, there were no robust and accepted standards to judge whether the drug was unlikely to cause the adverse effect or whether the study was incapable of detecting it. Substantial investment and careful thinking is needed to improve the reliability of risk assessments based on electronic health data, and current limitations need to be fully understood.
ABSTRACT
Pharmacovigilance of herbal medicines relies on the product label information regarding the ingredients and the adherence to good manufacturing practices along the commercialisation chain. Several studies have shown that substitution of plant species occurs in herbal medicines, and this in turn poses a challenge to herbal pharmacovigilance as adverse reactions might be due to adulterated or added ingredients. Authentication of constituents in herbal medicines using analytical chemistry methods can help detect contaminants and toxins, but are often limited or incapable of detecting the source of the contamination. Recent developments in molecular plant identification using DNA sequence data enable accurate identification of plant species from herbal medicines using defined DNA markers. Identification of multiple constituent species from compound herbal medicines using amplicon metabarcoding enables verification of labelled ingredients and detection of substituted, adulterated and added species. DNA barcoding is proving to be a powerful method to assess species composition in herbal medicines and has the potential to be used as a standard method in herbal pharmacovigilance research of adverse reactions to specific products.

Adverse Drug Reactions and Clinical Outcomes in Patients Initiated on Antiretroviral Therapy: A Prospective Cohort Study from Ethiopia
Woldesellassie M. Bezabhe, Luke R. Bereznicki, Leanne Chalmers, Peter Gee

ABSTRACT
Introduction: In Ethiopia, the use of antiretroviral therapy (ART) has been scaled up for HIV/AIDS over the past decade. Adverse drug reactions (ADRs) associated with ART pose a unique challenge in the treatment of the infection in this resource-limited setting.

Objectives: The aims of this study were to examine the incidence and nature of ADRs, identify the risk factors associated with the development of ADRs, and assess their impact on treatment outcomes.

Methods: A prospective cohort study was conducted in adult patients (≥18 years of age) with HIV/AIDS who commenced ART. All ADRs in the first 12 months of therapy were recorded, and the severity, causality, and preventability assessed. The impact of severe ADRs on self-reported adherence, immunological, and body mass index (BMI) outcomes were assessed.

Results: Of the 211 patients included in the analysis, 181 (85.7 %) experienced at least one ADR and 66 (31.3 %) experienced at least one severe ADR within 12 months of commencing ART (incidence rates for any ADR and severe ADR of 14.8 and 3.2 per 100 person-months, respectively). Logistic regression analysis indicated that taking zidovudine-containing regimens (odds ratio [OR] 4.2, 95 % confidence interval [CI] 2.1–8.4) or being unemployed (OR 2.2, 95 % CI 1.1–4.3) were independent predictors of experiencing severe ADRs. Patients who experienced a severe ADR were less likely (OR 0.4, 95 % CI 0.2–0.9) to be ≥90 % adherent to ART. The mean gain in BMI was significantly lower in patients with severe ADRs after 3 and 12 months of therapy.

Conclusions: ADRs were common within the first 3 months in patients initiated on ART. Severe ADRs were negatively associated with self-reported adherence and gain in BMI. Measures need to be implemented to routinely monitor for severe ADRs to improve ART adherence and treatment outcomes.
**Atypical Antipsychotics and the Risk of Hyperlipidemia: A Sequence Symmetry Analysis**

Yoshinori Takeuchi, Kazuhiro Kajiyama, Chieko Ishiguro, Yoshiaki Uyama

**ABSTRACT**

**Introduction:** Although hyperlipidemia is a well known adverse event of atypical antipsychotic (AAP) medication, there are few studies that have quantitatively compared the risks of various AAPs.

**Objective:** Our aim was to comparatively evaluate the risk of hyperlipidemia associated with the use of AAPs approved in Japan through a consecutive epidemiological study.

**Methods:** We conducted a sequence symmetry analysis (SSA) using health insurance claims data to analyze the following nine AAPs approved for use in Japan: risperidone, paliperidone, perospirone hydrochloride hydrate, blonanserin, clozapine, olanzapine, quetiapine fumarate, aripiprazole, and zotepine. Exposed cases were identified from drug dispensing records as those who had been administered both AAPs and antihyperlipidemic drugs. The adjusted sequence ratio (ASR) and 95 % confidence interval (CI) for each individual AAP and for all AAPs were calculated while controlling for time trends in dispensing patterns.

**Results:** Olanzapine was significantly associated with increased hyperlipidemia occurrence (ASR 1.56; 95 % CI 1.25–1.95). The ASRs obtained for risperidone (1.01; 95 % CI 0.80–1.27), perospirone hydrochloride hydrate (0.93; 95 % CI 0.63–1.39), blonanserin (0.83; 95 % CI 0.52–1.33), quetiapine fumarate (0.93; 95 % CI 0.73–1.18), and aripiprazole (1.02; 95 % CI 0.82–1.26) were approximately 1.0. Unstable estimates (wide CIs) were obtained for paliperidone and zotepine due to the small sample sizes.

**Conclusions:** Among the AAPs used in Japan, only olanzapine was found to have an elevated risk of hyperlipidemia. In contrast, risperidone, perospirone hydrochloride hydrate, blonanserin, quetiapine fumarate, and aripiprazole had relatively low risks.

**P-Glycoprotein-Mediated Drug Interactions in Pregnancy and Changes in the Risk of Congenital Anomalies: A Case-Reference Study**

Aizati N. A. Daud, Jorieke E. H. Bergman, Marian K. Bakker, Hao Wang

**ABSTRACT**

**Introduction:** Drug use in pregnancy is very common but may cause harm to the fetus. The teratogenic effect of a drug is partly dependent on the drug level in the fetal circulation, which is associated with the transport across the placenta. Many drugs are substrates of P-glycoprotein (P-gp), an efflux transporter that acts as a protective barrier for the fetus. We aim to identify whether drug interactions associated with P-gp promote any changes in fetal drug exposure, as measured by the risk of having children with congenital anomalies.

**Methods:** In this study, cases (N = 4634) were mothers of children with congenital anomalies registered in the EUROCAT Northern Netherlands registry, and the reference population were mothers of children (N = 25,126) from a drug prescription database (IADB.nl).

**Results:** Drugs that are associated with P-gp transport were commonly used in pregnancy in cases (10 %) and population (12 %). Several drug classes, which are substrates for P-gp, were shown to have a higher user rate in mothers of cases with specific anomalies. The use of this subset of drugs in combination with other P-gp substrates increased the risk for specific anomalies (odds ratio [OR] 4.17, 95 % CI 1.75–9.91), and the addition of inhibitors further increased the risk (OR 13.03, 95 % CI 3.37–50.42). The same pattern of risk increment was observed when the drugs were analyzed separately according to substrate specificity.

**Conclusions:** The use of drugs associated with P-gp transport was common during pregnancy. For several drug classes associated with specific anomalies, P-gp-mediated drug interactions are associated with an increased risk for those specific anomalies.
ABSTRACT

Introduction: Information technology (IT) has the potential to prevent medication errors. While many studies have analyzed specific IT technologies and preventable adverse drug events, no studies have identified risk factors for errors still occurring that are not preventable by IT.

Objectives: The objective of this study was to categorize reported or trigger tool-identified errors and adverse events (AEs) at a pediatric tertiary care institution. Also, we sought to identify medication errors preventable by IT, determine why IT-preventable errors occurred, and to identify risk factors for errors that were not preventable by IT.

Methods: This was a retrospective analysis of voluntarily reported or trigger tool-identified errors and AEs occurring from 1 July 2011 to 30 June 2012. Medication errors reaching the patients were categorized based on the origin, severity, and location of the error, the month in which they occurred, and the age of the patient involved. Error characteristics were included in a multivariable logistic regression model to determine independent risk factors for errors occurring that were not preventable by IT. A medication error was defined as a medication-related failure of a planned action to be completed as intended or the use of a wrong plan to achieve an aim. An IT-preventable error was defined as having an IT system in place to aid in prevention of the error at the phase and location of its origin.

Results: There were 936 medication errors (identified by voluntarily reporting or a trigger tool system) included and analyzed. Drug administration errors were identified most frequently (53.4%), but prescribing errors most frequently caused harm (47.2% of harmful errors). There were 470 (50.2%) errors that were IT preventable at their origin, including 155 due to IT system bypasses, 103 due to insensitivity of IT alerting systems, and 47 with IT alert overrides. Dispensing, administration, and documentation errors had higher odds than prescribing errors for being not preventable by IT [odds ratio (OR) 8.0, 95% CI 4.4–14.6; OR 2.4, 95% CI 1.7–3.7; and OR 6.7, 95% CI 3.3–14.5, respectively; all p < 0.001]. Errors occurring in the operating room and in the outpatient setting had higher odds than intensive care units for being not preventable by IT (OR 10.4, 95% CI 4.0–27.2, and OR 2.6, 95% CI 1.3–5.0, respectively; all p ≤ 0.004).

Conclusions: Despite extensive IT implementation at the studied institution, approximately one-half of the medication errors identified by voluntarily reporting or a trigger tool system were not preventable by the utilized IT systems. Inappropriate use of IT systems was a common cause of errors. The identified risk factors represent areas where IT safety features were lacking.
**Primary Care Medication Safety Surveillance with Integrated Primary and Secondary Care Electronic Health Records: A Cross-Sectional Study**

Artur Akbarov, Evangelos Kontopantelis, Matthew Sperrin, Susan J. Stocks…

**ABSTRACT**

**Introduction:** The extent of preventable medication-related hospital admissions and medication-related issues in primary care is significant enough to justify developing decision support systems for medication safety surveillance. The prerequisite for such systems is defining a relevant set of medication safety-related indicators and understanding the influence of both patient and general practice characteristics on medication prescribing and monitoring.

**Objective:** The aim of the study was to investigate the feasibility of linked primary and secondary care electronic health record data for surveillance of medication safety, examining not only prescribing but also monitoring, and associations with patient- and general practice-level characteristics.

**Methods:** A cross-sectional study was conducted using linked records of patients served by one hospital and over 50 general practices in Salford, UK. Statistical analysis consisted of mixed-effects logistic models, relating prescribing safety indicators to potential determinants.

**Results:** The overall prevalence (proportion of patients with at least one medication safety hazard) was 5.45% for prescribing indicators and 7.65% for monitoring indicators. Older patients and those on multiple medications were at higher risk of prescribing hazards, but at lower risk of missed monitoring. The odds of missed monitoring among all patients were 25% less for males, 50% less for patients in practices that provide general practitioner training, and threefold higher in practices serving the most deprived compared with the least deprived areas. Practices with more prescribing hazards did not tend to show more monitoring issues.

**Conclusions:** Systematic collection, collation, and analysis of linked primary and secondary care records produce plausible and useful information about medication safety for a health system. Medication safety surveillance systems should pay close attention to patient age and polypharmacy with respect to both prescribing and monitoring failures; treat prescribing and monitoring as different statistical processes, rather than a combined measure of prescribing safety; and audit the socio-economic equity of missed monitoring.

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**Evaluating AE Reporting of Two Off-Patent Biologics to Inform Future Biosimilar Naming and Reporting Practices**

Stella Stergiopoulos, Kenneth Getz

**ABSTRACT**

Historical studies of voluntary, spontaneous drug reports show poor attribution of adverse events to generic versions of commonly prescribed medications. As biosimilars enter the market place, it may be similarly difficult to accurately attribute adverse events to their respective reference products. At this time, lack of global consensus with regard to biosimilar naming conventions may result in drug reporting confusion, misattribution of adverse events and insufficient active monitoring of safety signals. Now, with the first biosimilar approval in the USA and many biosimilars expected to be launched globally in the near future, US Food and Drug Administration (FDA) guidance on biosimilar naming conventions will be essential. To inform the FDA and the global drug development community, the Tufts Center for the Study of Drug Development (Tufts CSDD) examined primary suspect reports sent to the FDA’s Adverse Event Reporting System (FAERS) from US reporters for two biologics that have lost patent exclusivity—somatropin and human insulin—and extracted 4703 insulin reports and 6487 somatropin reports from FAERS. The results show that reporting practices are inconsistent between the two biologics that were evaluated and that manufacturer identifiability and traceability are lacking. Ways to improve biosimilar naming conventions and improve reporting practices are suggested.
Update on Cardiovascular Safety of Tyrosine Kinase Inhibitors: With a Special Focus on QT Interval, Left Ventricular Dysfunction and Overall Risk/Benefit

Rashmi R. Shah, Joel Morganroth

ABSTRACT

We previously reviewed the cardiovascular safety of 16 tyrosine kinase inhibitors (TKIs), approved for use in oncology as of 30 September 2012. Since then, the indications for some of them have been widened and an additional nine TKIs have also been approved as of 30 April 2015. Eight of these nine are indicated for use in oncology and one (nintedanib) for idiopathic pulmonary fibrosis. This report is an update on the cardiovascular safety of those 16 TKIs, including the post-marketing data concerning their pro-arrhythmic effects, and reviews the cardiovascular safety of the nine new TKIs approved since (afatinib, cabozantinib, ceritinib, dabrafenib, ibrutinib, lenvatinib, nintedanib, ponatinib, and trametinib). As before, we focus on specific aspects of cardiovascular safety, namely their potential to induce QT interval prolongation, left ventricular (LV) dysfunction and hypertension but now also summarise the risks of arterial thromboembolic events (ATEs) associated with these agents. Of the newer TKIs, cabozantinib and ceritinib have been shown to induce a mild to moderate degree of QTc interval prolongation while cardiac dysfunction has been reported with the use of afatinib, dabrafenib, lenvatinib, ponatinib and trametinib. The label for axitinib was revised to include a new association with cardiac dysfunction. Hypertension is associated with cabozantinib, lenvatinib, nintedanib, ponatinib and trametinib. Ponatinib, within 10 months of its approval in December 2012, required voluntary (temporary) suspension of its marketing until significant safety revisions (restricted indication, additional warnings and precautions about the risk of arterial occlusion and thromboembolic events and amended dose) were made to its label. Compared with the previous 16 TKIs, more of the recently introduced TKIs are associated with the risk of LV dysfunction, and fewer with QT prolongation. Available data on morbidity and mortality associated with TKIs, together with post-marketing experience with lapatinib and ponatinib, emphasise the need for effective pharmacovigilance and ongoing reassessment of their risk/benefit after approval of these novel agents. If not adequately managed, these cardiovascular effects significantly decrease the quality of life and increase the morbidity and mortality in a population already at high risk.

Hepatotoxicity of New Oral Anticoagulants (NOACs)

Evangelia Liakoni, Alexandra E. Rätz Bravo, Stephan Krähenbühl

ABSTRACT

Case reports and analyses of clinical studies and of pharmacovigilance data suggest that new oral anticoagulants (NOACs) are associated with a small risk for hepatotoxicity. The objective of this publication is to summarize the current data about this subject, with a special emphasis on pharmacovigilance data in the World Health Organization (WHO) Global Individual Case Safety Reports (ICSR) database and on potential mechanisms of hepatotoxicity. For that, all available case reports as well as published analyses of clinical studies were obtained with a detailed search in PubMed. In addition, pharmacovigilance data from VigiBase®, the WHO Global ICRS database, were extracted and analyzed. The data show that liver injury associated with NOACs was reported in clinical studies and in pharmacovigilance databases. Several case reports described potentially life-threatening hepatotoxicity in patients treated with rivaroxaban or dabigatran. For rivaroxaban, most affected patients were symptomatic and liver injury was most often hepatocellular or mixed. The frequency was between 0.1 and 1 % in clinical studies and was by trend lower than for comparators (mostly enoxaparin or warfarin). Comparing the pharmacovigilance reports for the individual NOACs, more hepatic adverse events were reported for rivaroxaban than for dabigatran or apixaban. With the exception of edoxaban, for which only few reports are available, patients with acute liver failure have been reported for every NOAC, but most patients had concomitant drugs or diseases. So far, there are no clear mechanisms explaining the hepatotoxicity of these drugs. We conclude that hepatotoxicity appears to be associated with all NOACs currently on the market. Hepatotoxicity associated with NOACs is idiosyncratic; it appears at therapeutic doses, is rare and the mechanism is not related to the pharmacological action of these drugs. Prescribers should inform patients about possible symptoms of hepatotoxicity and stop these drugs in patients presenting with severe liver injury.
Changes in Side Effect Risk Communication in Patient Information Leaflets over the Past Decade: Results of a Survey
Katherine Harris, Rebecca Dickinson, David K. Raynor, Jan MacDonald

ABSTRACT

Introduction: Patients’ perceptions of side effect risks are important influences on their medicine-taking behaviour. A previous survey of Patient Information Leaflets (PILs) showed considerable variation in the terms used to communicate risks.

Objective: Our objective was to assess the methods used to describe risk of side effects in recent PILs and to compare them with PILs sampled in 2006.

Method: We sampled PILs for the 50 most frequently dispensed medicines in England and Wales in 2012 and PILs for the 50 most recently licensed medicines. We assessed the use of risk frequency terms or numbers, and the use of the risk format recommended by the European Medicines Agency (EMA).

Results: A majority (76%) of PILs for the most frequently dispensed medicines included a risk frequency descriptor, with 66% using the recommended format. No difference was seen between PILs for branded and generic medicines. All 50 PILs for the most recently licensed medicines used the EU recommended risk format. PILs from the 2012 sample were much more likely than those from the 2006 sample to include risk descriptors and to use a consistent approach.

Conclusion: The increased use and consistency of risk descriptors in PILs should benefit patients, particularly those using multiple medicines produced by different market authorisation holders. A need remains for further research evaluating the risk format recommended by the EMA. There is also a need for research evaluating spoken information and other sources of printed risk information about medicines that is available to patients.

Accidents and Incidents Related to Intravenous Drug Administration: A Pre–Post Study Following Implementation of Smart Pumps in a Teaching Hospital
Aurélie Guérin, Julien Tourel, Emmanuelle Delage, Stéphanie Duval…

ABSTRACT

Introduction: Smart pumps are expected to prevent and reduce medication errors. The implementation of smart pumps requires a significant effort and collaboration of physicians, nurses, pharmacists, and other stakeholders.

Objectives: The main objective of this study was to evaluate the impact of new smart pumps on reported drug-related accidents and incidents (AIs).

Method: This is a descriptive retrospective pre–post study conducted at a women’s and pediatric hospital with 500 beds. A strong multidisciplinary team (nurse, pharmacist, pharmacy resident, physician, biomedical technician, information technology technician, patient safety officer, manager) was involved in the planning, implementation, and monitoring technology implementation. A total of 1045 smart pumps were implemented in 2011 in our hospital. The reported number of AIs related to intravenous drug administration (AIIV) before and after the implementation of 1045 smart pumps were collected.

Results: A total of 2911 AI events related to medications, devices, and equipment were self-reported by clinical staff in the pre-phase (Y0), 3523 in the post-phase (Y1), and 2788 in the post-phase (Y2). The total AIIV increased from 1432 in Y0 to 1834 in Y1 and decreased to 1389 in Y2.

Conclusions: We observed no risk reduction associated with the implementation of smart pumps in a 500 bed mother–child hospital. Further studies are required to explore the details of the potential risk reduction associated with the use of smart pumps.
Actual Use of Medications Prescribed During Pregnancy: A Cross-Sectional Study Using Data from a Population-Based Congenital Anomaly Registry

Linda de Jonge, Hermien E. K. de Walle, Lolkje T. W. de Jong-van den Berg…

ABSTRACT

Introduction and Aim: Data from prescription databases are increasingly being used to study associations between maternal medications used in pregnancy and congenital anomalies. We therefore investigated the extent to which prescriptions reflect the actual use of medication during pregnancy, and whether medicines used during pregnancy are taken according to the prescribed dosage and duration.

Methods: We performed a cross-sectional study in a population-based congenital anomaly register (EUROCAT Northern Netherlands). We included 202 women who had at least one prescription during their pregnancy and who gave birth between 2009 and 2011. Compliance with the prescribed medication was verified by telephone interview. We calculated the compliance rates for several medication groups by dividing the number of mothers who confirmed they had taken the medication by the total number to whom it had been prescribed. Compliance was positive if the mother confirmed she took the medication, even if she only took one of several prescriptions from the same medication group. For each prescription taken, we also determined whether her use conformed to the prescribed dosage and duration.

Results: During the first trimester, the compliance rates ranged from 0.84 (for chronic diseases) to 0.92 (for pregnancy-related symptoms). Most of the medications actually taken were used at the prescribed dosage or lower. More than half of the medications actually taken were used for the duration prescribed or shorter.

Conclusion: Prescription records are generally a relatively reliable source of data for research into associations between medication use in pregnancy and congenital anomalies compared with other data sources. Pharmacy records of medication use in pregnancy might represent an overestimation, which should be taken into account. However, our results show that, except for ‘corticosteroids, dermatological preparations’; ‘ear, eye, nose and throat preparations’; and ‘anxiolytics, hypnotics and sedatives’, this overestimation generally seems minimal.
A Comparative Assessment of Observational Medical Outcomes Partnership and Mini-Sentinel Common Data Models and Analytics: Implications for Active Drug Safety Surveillance

Yihua Xu, Xiaofeng Zhou, Brandon T. Suehs, Abraham G. Hartzema…

ABSTRACT

Introduction: An often key component to coordinating surveillance activities across distributed networks is the design and implementation of a common data model (CDM). The purpose of this study was to evaluate two drug safety surveillance CDMs from an ecosystem perspective to better understand how differences in CDMs and analytic tools affect usability and interpretation of results.

Methods: Humana claims data from 2007 to 2012 were mapped to Observational Medical Outcomes Partnership (OMOP) and Mini-Sentinel CDMs. Data were described and compared at the patient level by source code and mapped concepts. Study cohort construction and effect estimates were also compared using two different analytical methods—one based on a new user design implementing a high-dimensional propensity score (HDPS) algorithm and the other based on univariate self-controlled case series (SCCS) design—across six established positive drug-outcome pairs to learn how differences in CDMs and analytics influence steps in the database analytic process and results.

Results: Claims data for approximately 7.7 million Humana health plan members were transformed into the two CDMs. Three health outcome cohorts and two drug cohorts showed differences in cohort size and constituency between Mini-Sentinel and OMOP CDMs, which was a result of multiple factors. Overall, the implementation of the HDPS procedure on Mini-Sentinel CDM detected more known positive associations than that on OMOP CDM. The SCCS method results were comparable on both CDMs. Differences in the implementation of the HDPS procedure between the two CDMs were identified; analytic model and risk period specification had a significant impact on the performance of the HDPS procedure on OMOP CDM.

Conclusions: Differences were observed between OMOP and Mini-Sentinel CDMs. The analysis of both CDMs at the data model level indicated that such conceptual differences had only a slight but not significant impact on identifying known safety associations. Our results show that differences at the ecosystem level of analyses across the CDMs can lead to strikingly different risk estimations, but this can be primarily attributed to the choices of analytic approach and their implementation in the community-developed analytic tools.

Implications of the IQ-CSRC Prospective Study: Time to Revise ICH E14

Borje Darpo, Christine Garnett, James Keirns, Norman Stockbridge

ABSTRACT

Exposure-response (ER) analysis has evolved as an important tool to evaluate the effect of a drug on cardiac repolarization, as reflected in the QTc interval. It has been suggested that careful electrocardiogram (ECG) evaluation in ‘first-in-human’ studies using ER analysis could replace or serve as an alternative to the E14 ‘thorough QT’ study. This commentary shares and discusses the results of a recently conducted study with the objective to evaluate this approach. Six drugs with a well-characterized QT effect, five of which are known QT prolongers, were evaluated in a study design similar to a conventional single-ascending-dose study. Each drug was given to nine healthy subjects (six for placebo) in two dose levels, which for the positive drugs (ondansetron, quinine, dolasetron, moxifloxacin, and dofetilide) were chosen with the intent to cause 10–12 ms and 15–20 ms QTc prolongation. Replicate 12-lead ECGs were extracted from continuous recordings pre-dose and serially after dosing and paired with drug concentration determinations. The ER criteria for the identification of a QT effect, a statistically significant positive ER slope and an effect above 10 ms, were met with all five positive drugs, and an effect exceeding 10 ms could be excluded at the supratherapeutic dose of the negative drug, levocetirizine. The study results thereby provided evidence to support that careful QT assessment in early phase clinical studies can be used as an alternative to the thorough QT study. Clinical and regulatory implications, as well as limitations of this approach, are discussed in the commentary.
Vaccination–Drug Interactions: Cytokines, Cytochromes, and Molecular Mechanisms
Paolo Pellegrino, Cristiana Perrotta, Emilio Clementi, Sonia Radice

ABSTRACT

Vaccinations are recommended throughout life to reduce the risk of vaccine-preventable diseases and their sequelae. Vaccines are often administered in patients with chronic diseases who are likely to be treated with several drugs. A growing number of clinical observations have indicated the possibility of interactions between vaccines and drugs, leading to changes in drug metabolism after vaccination. These interactions represent a significant concern because of the increasing use of vaccines in older patients who are likely to be treated with several drugs. Because of the possible implications of adverse reactions in terms of public health, several studies were performed to verify the risk posed by these interactions and to clarify the biologic mechanisms that drive these events. Of the several mechanisms proposed to be at the basis of vaccine–drug interactions, the most convincing evidence suggests a role of inflammatory cytokines on the regulation of specific cytochrome P450 enzymes in the liver. Differences in the cytochrome P450 enzymes involved in the metabolism of these drugs could explain these contrasting results and provide important insights to fully understand the clinical importance of these events. Further studies are required to verify whether vaccine–drug interactions may occur in other clinical settings, especially the ones for which patients are required to be vaccinated against specific diseases.

Indigenous Medicine Use for Sex Selection during Pregnancy and Risk of Congenital Malformations: A Population-Based Case-Control Study in Haryana, India
Sutapa Bandyopadhyay Neogi, Preeti H. Negandhi, Navraj Sandhu

ABSTRACT

Introduction: Congenital malformations (CMFs) are a major public health problem in India. Consanguineous marriages, infections during pregnancy, folic acid deficiency during the periconceptional period, exposure to pesticides and a history of intake of drugs during pregnancy have been hypothesized as risk factors. Drugs include oral contraceptive pills, progesterone analogues, medications for ailments and indigenous drugs to bear male offspring. It is important to analyze the risk factors in order to implement preventive measures. The prime objective of this study was to study the risk factors of visible structural CMFs, with a focus on indigenous medicines for sex selection.

Methods: A population-based, case-control study was undertaken in Haryana state. Cases included children (0–18 months) with any apparent structural deformity as reported by various Government sources. A consecutive birth from the same area as the case was labelled and included as the control. The sample size calculated was 175 in each group. Mothers of every case and control were interviewed at their respective homes using a structured tool. Descriptive analysis, bivariate analysis, followed by logistic regression was conducted to establish the association between risk factors and CMFs.

Results: The sociodemographic profiles of the cases and controls were similar. Among the various risk factors studied, more than two living children (unadjusted odds ratio [OR] 1.6, 95 % CI 1.04–2.4) and intake of sex-selection drugs (unadjusted OR 2.8, 95 % CI 1.6–5.1) were significant risk factors on bivariate and regression analyses. The risk of having a child with CMFs was threefold more among mothers with a history of intake of indigenous medicines for sex selection (adjusted OR 3; 95 % CI 1.7–5.6).

Conclusions: The intake of indigenous drugs during pregnancy increased the risk of CMFs almost threefold. This has social as well as economic implications, and hence needs further investigation.
Detection of Drug–Drug Interactions Inducing Acute Kidney Injury by Electronic Health Records Mining

Yannick Girardeau, Claire Trivin, Pierre Durieux, Christine Le Beller

ABSTRACT

**Background and Objective:** While risk of acute kidney injury (AKI) is a well documented adverse effect of some drugs, few studies have assessed the relationship between drug–drug interactions (DDIs) and AKI. Our objective was to develop an algorithm capable of detecting potential signals on this relationship by retrospectively mining data from electronic health records.

**Material and methods:** Data were extracted from the clinical data warehouse (CDW) of the Hôpital Européen Georges Pompidou (HEGP). AKI was defined as the first level of the RIFLE criteria, that is, an increase ≥50 % of creatinine basis. Algorithm accuracy was tested on 20 single drugs, 10 nephrotoxic and 10 non-nephrotoxic. We then tested 45 pairs of non-nephrotoxic drugs, among the most prescribed at our hospital and representing distinct pharmacological classes for DDIs.

**Results:** Sensitivity and specificity were 50 % [95 % confidence interval (CI) 23.66–76.34] and 90 % (95 % CI 59.58–98.21), respectively, for single drugs. Our algorithm confirmed a previously identified signal concerning clarithromycin and calcium-channel blockers (unadjusted odds ratio (ORu) 2.92; 95 % CI 1.11–7.69, p = 0.04). Among the 45 drug pairs investigated, we identified a signal concerning 55 patients in association with bromazepam and hydroxyzine (ORu 1.66; 95 % CI 1.23–2.23). This signal was not confirmed after a chart review. Even so, AKI and co-prescription were confirmed for 96 % (95 % CI 88–99) and 88 % (95 % CI 76–94) of these patients, respectively.

**Conclusion:** Data mining techniques on CDW can foster the detection of adverse drug reactions when drugs are used alone or in combination.

The Risk of Opioid Intoxications or Related Events and the Effect of Alcohol-Related Disorders: A Retrospective Cohort Study in German Patients Treated with High-Potency Opioid Analgesics

K. Jobski, B. Kollhorst, T. Schink, Edeltraut Garbe

ABSTRACT

**Introduction:** Intoxications involving prescription opioids are a major public health problem in many countries. When taken with opioids, alcohol can enhance the effects of opioids, particularly in the central nervous system. However, data quantifying the impact of alcohol involvement in opioid-related intoxications are limited.

**Methods:** Using claims data from the German Pharmacoepidemiological Research Database (GePaRD), we conducted a retrospective cohort study based on users of high-potency opioid (HPO) analgesics during the years 2005–2009. HPO use was classified as extended-release, immediate-release or both. We calculated incidence rates (IRs) for opioid intoxications or related events as well as adjusted IR ratios (aIRR) comparing HPO-treated patients with alcohol-related disorders (ARDs) to those without ARDs overall and within each HPO category.

**Results:** During the study period, 308,268 HPO users were identified with an overall IR of 340.4 per 100,000 person-years [95 % confidence interval (CI) 325.5–355.7]. The risk was highest when patients received concomitant treatment with extended- and immediate-release HPOs (IR 1093.8; 95 % CI 904.6–1310.9). ARDs increased the risk during HPO use by a factor of 1.7 and the highest aIRR was seen when comparing patients simultaneously exposed to extended- and immediate-release HPOs with ARDs to those without ARD also after excluding patients with potential improper/non-medical HPO use.

**Conclusions:** Physicians should be aware of these elevated risks in HPO patients with ARDs. Active patient education by healthcare providers regarding the risk of opioid intoxications or related events due to alcohol in conjunction with HPOs is warranted.
Variation in Association between Thiazolidinediones and Heart Failure across Ethnic Groups: Retrospective analysis of Large Healthcare Claims Databases in Six Countries
Elizabeth E. Roughead, Esther W. Chan, Nam-Kyong Choi, Michio Kimura

ABSTRACT

Introduction: The prevalence of polymorphisms among the metabolising enzymes and pharmacodynamic receptors relevant for the thiazolidinediones differs by ethnic group, a factor that may modify risk of adverse drug events.

Objective: The aim of the study was to determine if the risk of oedema or heart failure associated with the thiazolidinediones varies in populations in Australia, Canada, Hong Kong, Japan, Korea and Taiwan.

Methods: Sequence symmetry analyses were undertaken to investigate the risk of peripheral oedema, as measured by incident furosemide dispensing, and risk of hospitalisations for heart failure. Results were pooled, with Australia and Canada representing predominantly Caucasian population and all other countries contributing to Asian population estimates.

Results: Pooled estimates of risk for furosemide initiation in the Caucasian populations were significantly increased for pioglitazone [adjusted sequence ratio (ASR) 1.47; 95 % confidence interval (CI) 1.14–1.91] and rosiglitazone (ASR 1.65; 95 % CI 1.58–1.72), while in the Asian populations, the pooled risk estimates were lower (ASR 1.11; 95 % CI 0.93–1.32 and ASR 1.21; 95 % CI 1.01–1.45 for pioglitazone and rosiglitazone, respectively).

Conclusion: The risk of both oedema and heart failure with thiazolidinediones was higher in predominantly Caucasian countries than in the Asian countries assessed. Assessment of adverse events by ethnicity may support safer medicine use.

Prevalence, Nature, Severity and Risk Factors for Prescribing Errors in Hospital Inpatients: Prospective Study in 20 UK Hospitals
Darren M. Ashcroft, Penny J. Lewis, Mary P. Tully, Tracey M. Farragher

ABSTRACT

Introduction: It has been suggested that doctors in their first year of post-graduate training make a disproportionate number of prescribing errors.

Objective: This study aimed to compare the prevalence of prescribing errors made by first-year post-graduate doctors with that of errors by senior doctors and non-medical prescribers and to investigate the predictors of potentially serious prescribing errors.

Methods: Pharmacists in 20 hospitals over 7 prospectively selected days collected data on the number of medication orders checked, the grade of prescriber and details of any prescribing errors. Logistic regression models (adjusted for clustering by hospital) identified factors predicting the likelihood of prescribing erroneously and the severity of prescribing errors.

Results: Pharmacists reviewed 26,019 patients and 124,260 medication orders; 11,235 prescribing errors were detected in 10,986 orders. The mean error rate was 8.8 % (95 % confidence interval [CI] 8.6–9.1) errors per 100 medication orders. Rates of errors for all doctors in training were significantly higher than rates for medical consultants. Doctors who were 1 year (odds ratio [OR] 2.13; 95 % CI 1.80–2.52) or 2 years in training (OR 2.23; 95 % CI 1.89–2.65) were more than twice as likely to prescribe erroneously.

Conclusion: The problem of prescribing errors in hospitals is substantial and not solely a problem of the most junior medical prescribers, particularly for those errors most likely to cause significant patient harm. Interventions are needed to target these high-risk errors by all grades of staff and hence improve patient safety.
Product-Specific Regulatory Pathways to Approve Generic Drugs: The Need for Follow-up Studies to Ensure Safety and Effectiveness

Aaron S. Kesselheim, Joshua J. Gagne

ABSTRACT

Generic drugs possessing the same active ingredients, dosage form, strength, route of administration, and labeling can be approved by the US Food and Drug Administration (FDA) as interchangeable with a brand-name drug without needing to repeat the formal Phase I, II, and III clinical trials conducted by the original manufacturers. In recent years, the FDA has approved several generic drugs using product-specific testing to determine therapeutic equivalence in accordance with the unique features of the particular drug. These have been used in two primary situations: (1) cases for which certain bioequivalence studies were not relevant; and (2) cases of complex molecules that may require specially tailored pharmaceutical equivalence studies. Examples include venlafaxine extended release, acarbose, vancomycin capsules, sodium ferric gluconate, salmon calcitonin nasal spray, and enoxaparin. Product-specific approaches to demonstrating therapeutic equivalence are essential to avoid delays in low-cost generic drug availability but can have important clinical implications; yet, currently, there is no formal process in place to monitor the safety and effectiveness of generic drugs approved using modified regulatory pathways. Several strategies can be used to monitor the safety and effectiveness of generic drugs approved via product-specific determinations of therapeutic equivalence.

Pharmacogenetics of Drug-Induced QT Interval Prolongation: An Update

Maartje N. Niemeijer, Marten E. van den Berg, Mark Eijgelshiem

ABSTRACT

A prolonged QT interval is an important risk factor for ventricular arrhythmias and sudden cardiac death. QT prolongation can be caused by drugs. There are multiple risk factors for drug-induced QT prolongation, including genetic variation. QT prolongation is one of the most common reasons for withdrawal of drugs from the market, despite the fact that these drugs may be beneficial for certain patients and not harmful in every patient. Identifying genetic variants associated with drug-induced QT prolongation might add to tailored pharmacotherapy and prevent beneficial drugs from being withdrawn unnecessarily. In this review, our objective was to provide an overview of the genetic background of drug-induced QT prolongation, distinguishing pharmacokinetic and pharmacodynamic pathways. Pharmacokinetic-mediated genetic susceptibility is mainly characterized by variation in genes encoding drug-metabolizing cytochrome P450 enzymes or drug transporters. For instance, the P-glycoprotein drug transporter plays a role in the pharmacokinetic susceptibility of drug-induced QT prolongation. The pharmacodynamic component of genetic susceptibility is mainly characterized by genes known to be associated with QT interval duration in the general population and genes in which the causal mutations of congenital long QT syndromes are located. Ethnicity influences susceptibility to drug-induced QT interval prolongation, with Caucasians being more sensitive than other ethnicities. Research on the association between pharmacogenetic interactions and clinical endpoints such as sudden cardiac death is still limited. Future studies in this area could enable us to determine the risk of arrhythmias more adequately in clinical practice.
Safety Profile of Certolizumab Pegol in Patients with Immune-Mediated Inflammatory Diseases: A Systematic Review and Meta-Analysis

Alice Capogrosso Sansone, Stefania Mantarro, Marco Tuccori, Elisa Ruggiero

ABSTRACT

Introduction: Certolizumab pegol (CZP), an anti-tumor necrosis factor PEGylated Fab’ fragment of a humanized monoclonal antibody, is currently approved for treatment of some immune-mediated inflammatory diseases (IMIDs). To our knowledge, no systematic review and meta-analysis evaluating the overall safety profile of CZP has been performed.

Objective: The objective of this systematic review was to assess the adverse event (AE) patterns of CZP versus a control in patients with IMIDs.

Methods: A systematic literature search was performed using PubMed/MEDLINE, EMBASE, the Cochrane Library, and the FDA database for clinical trials up to March 2014. Eligible studies were those that compared the safety profile of CZP to a control group in patients with IMIDs. The following data were extracted: number of patients experiencing AEs, serious AEs (SAEs), adverse drug reactions (ADRs), withdrawals due to AEs, fatal AEs, infectious AEs and SAEs, upper respiratory tract infections, injection-site reactions, neoplasms, and tuberculosis.

Results: A total of 2023 references were identified and 18 randomized controlled trials were included. The main pooled risk ratios of CZP-treated versus control patients were as follows: AEs 1.09 (95% confidence interval, CI 1.04–1.14), SAEs 1.50 (95% CI 1.21–1.86), ADRs 1.20 (95% CI 1.03–1.39), infectious AEs 1.28 (95% CI 1.13–1.45), infectious SAEs 2.17 (95% CI 1.36–3.47), and upper respiratory tract infections 1.34 (95% CI 1.15–1.57).

Conclusion: Safety data on CZP suggest an overall favorable tolerability profile, with infections being the most common AE. However, CZP-treated patients had a twofold higher risk of infectious SAEs than control patients. Large observational studies and data from national registries are needed to detect rare AEs, which might occur after long-term exposures to CZP.
ABSTRACT

Background: Angiotensin II receptor blockers (ARBs) are widely used to treat hypertension and heart failure. Photosensitivity reactions are cutaneous adverse events due to exposure to a drug and either ultraviolet or visible radiation. Among the ARB class, this type of adverse drug reaction is labeled only for losartan.

Objective: The aim of this study was to provide a descriptive evaluation of photosensitivity reports with ARBs in the World Health Organization Global Individual Case Safety Report database, VigiBase®.

Methods: All reports of photosensitivity reported with ARBs were identified from VigiBase®. All variables contained in the reports were analyzed. Information component (IC) and its lower limit of a 95% credibility interval (IC025) values were considered as measures of disproportionality for the assessment of photosensitivity cases reported with ARBs. VigiGrade completeness score (C) was used as a measure of quality of each report. Well-documented reports (C > 0.8) were fully described and analyzed.

Results: Up to December 2014, a total of 203 reports on photosensitivity reported with ARBs and submitted by 25 different countries had been recorded in VigiBase®. Among them, 25.1% involved losartan, 23.1% involved irbesartan, and 21.7% involved valsartan. In 126 cases, the ARB was the only suspected drug and in 10% of them the reaction was serious. IC and IC025 values indicated a possible positive correlation between photosensitivity and both irbesartan and losartan. A focus on well-documented reports, after excluding those with a co-prescription of other drugs known to cause photosensitivity, showed that out of 18 cases, six were related to losartan, four to olmesartan, three to irbesartan, two to valsartan and to candesartan, and one to telmisartan. Causality assessment was ‘probable’ in ten cases and ‘possible’ in eight cases. Moreover, positive dechallenge was reported in ten cases and positive rechallenge in one case.

Conclusions: Photosensitivity reactions have been reported with almost all ARBs in VigiBase® with a positive disproportionality for irbesartan and losartan. Considering that ARBs share the same chemical structure, which may have the same response to sunlight, it is plausible to consider photosensitivity as a possible class effect. Physicians and patients should be aware of potentially serious photosensitivity reactions related to treatment with ARBs.
ABSTRACT

Introduction: Observational healthcare data contain information useful for hastening detection of adverse drug reactions (ADRs) that may be missed by using data in spontaneous reporting systems (SRSs) alone. There are only several papers describing methods that integrate evidence from healthcare databases and SRSs. We propose a methodology that combines ADR signals from these two sources.

Objectives: The aim of this study was to investigate whether the proposed method would result in more accurate ADR detection than methods using SRSs or healthcare data alone.

Research Design: We applied the method to four clinically serious ADRs, and evaluated it using three experiments that involve combining an SRS with a single facility small-scale electronic health record (EHR), a larger scale network-based EHR, and a much larger scale healthcare claims database. The evaluation used a reference standard comprising 165 positive and 234 negative drug–ADR pairs.

Measures: Area under the receiver operator characteristics curve (AUC) was computed to measure performance.

Results: There was no improvement in the AUC when the SRS and small-scale HER were combined. The AUC of the combined SRS and large-scale EHR was 0.82 whereas it was 0.76 for each of the individual systems. Similarly, the AUC of the combined SRS and claims system was 0.82 whereas it was 0.76 and 0.78, respectively, for the individual systems.

Conclusions: The proposed method resulted in a significant improvement in the accuracy of ADR detection when the resources used for combining had sufficient amounts of data, demonstrating that the method could integrate evidence from multiple sources and serve as a tool in actual pharmacovigilance practice.
Benzodiazepine Use and Risk of Developing Alzheimer’s Disease or Vascular Dementia: A Case–Control Analysis

Patrick Imfeld, Michael Bodmer, Susan S. Jick, Christoph R. Meier

ABSTRACT

Introduction: Previous observational studies have associated benzodiazepine use with an increased risk of dementia. However, limitations in the study methods leave questions unanswered regarding the interpretation of the findings.

Methods: A case–control analysis was conducted using data from the UK-based Clinical Practice Research Datalink (CPRD). A total of 26,459 patients aged ≥65 years with newly diagnosed Alzheimer’s disease (AD) or vascular dementia (VaD) between 1998 and 2013 were identified and matched 1:1 to dementia-free controls on age, sex, calendar time, general practice, and number of years of recorded history. Adjusted odds ratios (aORs) were calculated with 95 % confidence intervals (CIs) of developing AD or VaD in relation to previous benzodiazepine use, stratified by duration and benzodiazepine type.

Results: The aOR (95 % CI) of developing AD for those who started benzodiazepines <1 year before diagnosis was 2.20 (1.91–2.53), and fell to the null for those who started between 2 and <3 years before [aOR 0.99 (0.84–1.17)]. The aOR (95 % CI) of developing VaD for those who started benzodiazepines <1 year before diagnosis was 3.30 (2.78–3.92), and fell close to the null for those who started between 3 and <4 years before [aOR 1.16 (0.96–1.40)]. After accounting for benzodiazepine use initiated during this prodromal phase, long-term use of benzodiazepines was not associated with an increased risk of developing AD [aOR 0.69 (0.57–0.85)] or VaD [aOR 1.11 (0.85–1.45)].

Conclusion: After taking a prodromal phase into consideration, benzodiazepine use was not associated with an increased risk of developing AD or VaD.
Evaluating Social Media Networks in Medicines Safety Surveillance: Two Case Studies
Preciosa M. Coloma, Benedikt Becker, Miriam C. J. M. Sturkenboom

ABSTRACT

Introduction: There is growing interest in whether social media can capture patient-generated information relevant for medicines safety surveillance that cannot be found in traditional sources.

Objective: The aim of this study was to evaluate the potential contribution of mining social media networks for medicines safety surveillance using the following associations as case studies: (1) rosiglitazone and cardiovascular events (i.e. stroke and myocardial infarction); and (2) human papilloma virus (HPV) vaccine and infertility.

Methods: We collected publicly accessible, English-language posts on Facebook, Google+, and Twitter until September 2014. Data were queried for co-occurrence of keywords related to the drug/vaccine and event of interest within a post. Messages were analysed with respect to geographical distribution, context, linking to other web content, and author’s assertion regarding the supposed association.

Results: A total of 2537 posts related to rosiglitazone/cardiovascular events and 2236 posts related to HPV vaccine/infertility were retrieved, with the majority of posts representing data from Twitter (98 and 85 %, respectively) and originating from users in the US. Approximately 21 % of rosiglitazone-related posts and 84 % of HPV vaccine-related posts referenced other web pages, mostly news items, law firms’ websites, or blogs. Assertion analysis predominantly showed affirmation of the association of rosiglitazone/cardiovascular events (72 %; n = 1821) and of HPV vaccine/infertility (79 %; n = 1758). Only ten posts described personal accounts of rosiglitazone/cardiovascular adverse event experiences, and nine posts described HPV vaccine problems related to infertility.

Conclusions: Publicly available data from the considered social media networks were sparse and largely untrackable for the purpose of providing early clues of safety concerns regarding the prespecified case studies. Further research investigating other case studies and exploring other social media platforms are necessary to further characterise the usefulness of social media for safety surveillance.

A Note on the Validity and Reliability of Multi-Criteria Decision Analysis for the Benefit–Risk Assessment of Medicines
Alberto Garcia-Hernandez

ABSTRACT

The comparative evaluation of benefits and risks is one of the most important tasks during the development, market authorization and post-approval pharmacovigilance of medicinal products. Multi-criteria decision analysis (MCDA) has been recommended to support decision making in the benefit–risk assessment (BRA) of medicines. This paper identifies challenges associated with bias or variability that practitioners may encounter in this field and presents solutions to overcome them. The inclusion of overlapping or preference-complementary criteria, which are frequent violations to the assumptions of this model, should be avoided. For each criterion, a value function translates the original outcomes into preference-related scores. Applying non-linear value functions to criteria defined as the risk of suffering a certain event during the study introduces specific risk behaviours in this prescriptive, rather than descriptive, model and is therefore a questionable practice. MCDA uses weights to compare the importance of the model criteria with each other; during their elicitation a frequent situation where (generally favourable) mild effects are directly traded off against low probabilities of suffering (generally unfavourable) severe effects during the study is known to lead to biased and variable weights and ought to be prevented. The way the outcomes are framed during the elicitation process, positively versus negatively for instance, may also lead to differences in the preference weights, warranting an appropriate justification during each implementation.
Comparative Safety of Vaccine Adjuvants: A Summary of Current Evidence and Future Needs

Nikolai Petrovsky

ABSTRACT

Use of highly pure antigens to improve vaccine safety has led to reduced vaccine immunogenicity and efficacy. This has led to the need to use adjuvants to improve vaccine immunogenicity. The ideal adjuvant should maximize vaccine immunogenicity without compromising tolerability or safety. Unfortunately, adjuvant research has lagged behind other vaccine areas such as antigen discovery, with the consequence that only a very limited number of adjuvants based on aluminium salts, monophosphoryl lipid A and oil emulsions are currently approved for human use. Recent strategic initiatives to support adjuvant development by the National Institutes of Health should translate into greater adjuvant choices in the future. Mechanistic studies have been valuable for better understanding of adjuvant action, but mechanisms of adjuvant toxicity are less well understood. The inflammatory or danger-signal model of adjuvant action implies that increased vaccine reactogenicity is the inevitable price for improved immunogenicity. Hence, adjuvant reactogenicity may be avoidable only if it is possible to separate inflammation from adjuvant action. The biggest remaining challenge in the adjuvant field is to decipher the potential relationship between adjuvants and rare vaccine adverse reactions, such as narcolepsy, macrophagic myofasciitis or Alzheimer’s disease. While existing adjuvants based on aluminium salts have a strong safety record, there are ongoing needs for new adjuvants and more intensive research into adjuvants and their effects.

Selective Serotonin Reuptake Inhibitor Use and Perioperative Bleeding and Mortality in Patients Undergoing Coronary Artery Bypass Grafting: A Cohort Study

Joshua J. Gagne, Jennifer M. Polinski, Jeremy A. Rassen, Michael A. Fischer

ABSTRACT

Introduction: Several small studies have reported inconsistent findings about the safety of selective serotonin reuptake inhibitors (SSRIs) among patients undergoing coronary artery bypass grafting (CABG). We sought to investigate post-CABG bleeding and mortality outcomes related to antidepressant exposure.

Methods: We identified patients who underwent CABG between 2004 and 2008 in the Premier Perspective Comparative Database. We determined whether they received SSRIs, other antidepressants, or no antidepressants on any pre-CABG hospital day and used Cox proportional hazards models to compare bleeding and mortality rates among the exposure groups while adjusting for potential confounders based on administrative data, pre-CABG charge codes, and discharge diagnosis codes.

Results: We identified 132,686 eligible patients: 7112 exposed to SSRIs, 1905 exposed to other antidepressants, and 123,668 unexposed. As compared with no exposure, neither SSRIs (hazard ratio [HR] 0.98; 95% confidence interval [CI] 0.90–1.07) nor other antidepressants (HR 1.11; 95% CI 0.96–1.28) increased major bleeds, and neither SSRIs (HR 0.93; 95% CI 0.80–1.07) nor other antidepressants (HR 0.84; 95% CI 0.62–1.14) increased mortality. Both SSRIs (HR 1.14; 95% CI 1.10–1.18) and other antidepressants (HR 1.11; 95% CI 1.03–1.19) were associated with a slight increase in receipt of one or more packed red blood cell (pRBC) units, but neither were associated with substantial increases in receipt of three or more pRBC units (HR 1.06; 95% CI 0.96–1.17 for SSRIs; HR 1.09; 95% CI 0.91–1.31 for other antidepressants).

Conclusion: In this large cohort study, neither SSRIs nor other antidepressants were associated with elevated rates of major bleed, or in-hospital mortality.
Improving Information on Maternal Medication Use by Linking Prescription Data to Congenital Anomaly Registers: A EUROmediCAT Study
Linda de Jonge, Ester Garne, Rosa Gini, Susan E. Jordan, Kari Klungsøyr

ABSTRACT

Introduction: Research on associations between medication use during pregnancy and congenital anomalies is significant for assessing the safe use of a medicine in pregnancy. Congenital anomaly (CA) registries do not have optimal information on medicine exposure, in contrast to prescription databases. Linkage of prescription databases to the CA registries is a potentially effective method of obtaining accurate information on medicine use in pregnancies and the risk of congenital anomalies.

Methods: We linked data from primary care and prescription databases to five European Surveillance of Congenital Anomalies (EUROCAT) CA registries. The linkage was evaluated by looking at linkage rate, characteristics of linked and non-linked cases, first trimester exposure rates for six groups of medicines according to the prescription data and information on medication use registered in the CA databases, and agreement of exposure.

Results: Of the 52,619 cases registered in the CA databases, 26,552 could be linked. The linkage rate varied between registries over time and by type of birth. The first trimester exposure rates and the agreements between the databases varied for the different medicine groups. Information on anti-epileptic drugs and insulins and analogue medicine use recorded by CA registries was of good quality. For selective serotonin reuptake inhibitors, anti-asthmatics, antibacterials for systemic use, and gonadotropins and other ovulation stimulants, the recorded information was less complete.

Conclusion: Linkage of primary care or prescription databases to CA registries improved the quality of information on maternal use of medicines in pregnancy, especially for medicine groups that are less fully registered in CA registries.

Modelling Hospitalisation Ratios for Febrile Convulsions and Severe Varicella under Combined Measles, Mumps, Rubella, and Varicella (MMRV—Priorix-Tetra™) Compared to Separate MMR + V Vaccination
Vincent Bauchau, Lionel Van Holle, Carine Cohen

ABSTRACT

Introduction: Measles, mumps, rubella, and varicella combination vaccines (MMRV) facilitate varicella vaccination uptake compared with separate administration of measles, mumps, and rubella vaccine (MMR) with varicella vaccine (V). However, the risk of developing febrile convulsions (FC) is higher in children vaccinated with MMRV.

Objectives: The aim was to demonstrate how to put the increased FC risk associated with MMRV into perspective by comparing it with the lower V-coverage risk associated with MMR + V.

Methods: FC and varicella burdens were measured by total numbers or duration of hospitalisations. A model, based on several assumptions and integrating parameters from heterogeneous data sources relevant to Germany, was developed to evaluate hospitalisation ratios (HRs; ratios between yearly numbers of varicella-related hospitalisation days prevented by MMRV and yearly numbers of FC-related hospitalisation days attributed to MMRV, both compared with MMR + V). A sensitivity analysis estimated HR under different scenarios beyond the German experience.

Results: For parameter values compatible with the German experience, where MMRV (Priorix-Tetra™, GSK, Belgium) was introduced in 2006, the model predicted that transitioning from MMR + V to MMRV would induce 225 vaccine-related FC hospitalisation days whilst preventing 1976 varicella-related hospitalisation days per year. The HR estimated by Monte Carlo simulations was 8.5 (95 % confidence interval: 1.99–25.22). A sensitivity analysis on two key parameters suggested that transitioning from MMR + V to MMRV would be favourable in situations where MMRV use would significantly impact varicella vaccination uptake.

Conclusions: MMRV use instead of MMR + V can substantially reduce the number of hospitalisation days, despite increased FC risk when MMRV is used as a first dose of measles-containing vaccine.
Clinical Pattern of Tolvaptan-Associated Liver Injury in Subjects with Autosomal Dominant Polycystic Kidney Disease: Analysis of Clinical Trials Database


ABSTRACT

Introduction: Subjects with autosomal dominant polycystic kidney disease (ADPKD) who were taking tolvaptan experienced aminotransferase elevations more frequently than those on placebo in the TEMPO 3:4 (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and its Outcomes) clinical trial.

Methods: An independent, blinded, expert Hepatic Adjudication Committee re-examined data from TEMPO 3:4 and its open-label extension TEMPO 4:4, as well as from long-term (>14 months) non-ADPKD tolvaptan trials, using the 5-point Drug-Induced Liver Injury Network classification.

Results: In TEMPO 3:4, 1445 subjects were randomized 2:1 (tolvaptan vs. placebo) and 1441 had post-baseline assessments of hepatic injury. Sixteen patients on tolvaptan and one on placebo had significant aminotransferase elevations judged to be at least probably related to study drug. No association with dose or systemic exposure was found. Two of 957 subjects taking tolvaptan (0.2%) and zero of 484 taking placebo met the definition of a Hy’s Law case. One additional Hy’s Law case was identified in a TEMPO 4:4 subject who had received placebo in the lead study. The onset of a hepatocellular injury occurred between 3 and 18 months after starting tolvaptan, with gradual resolution over the subsequent 1–4 months. None of the events were associated with liver failure or chronic liver injury/dysfunction. No imbalance in hepatic events was observed between tolvaptan and placebo in lower-dose clinical trials of patients with hyponatremia, heart failure, or cirrhosis.

Conclusions: Although hepatocellular injury following long-term tolvaptan treatment in ADPKD subjects was infrequent and reversible, the potential for serious irreversible injury exists. Regular monitoring of transaminase levels is warranted in this patient population.
Experiences and Lessons From Implementing Cohort Event Monitoring Programmes for Antimalarials in Four African Countries: Results of a Questionnaire-Based Survey

Comfort Kunak Suku, Geraldine Hill, George Sablah, Mimi Darko

ABSTRACT

**Introduction**: Cohort event monitoring (CEM) is an intensive method of post-marketing surveillance for medicines safety. The method is based on prescription event monitoring, which began in the 1970s, and has since been adapted by WHO for monitoring the safety of medicines used in Public Health Programmes. CEM aims to capture all adverse events that occur in a defined group of patients after starting treatment with a specific medicine during the course of routine clinical practice.

**Objective**: The aims of this study were to describe the experiences of National Pharmacovigilance Centres (NCs) that have used CEM to monitor artemisinin-based combination therapy (ACT) for uncomplicated malaria in the African setting, to raise awareness of some of the challenges encountered during implementation and to highlight aspects of the method that require further consideration.

**Method**: A questionnaire-based survey was conducted to capture the experiences of NCs that have implemented CEM for active post-marketing surveillance of antimalarial medicines in sub-Saharan Africa. Six NCs were identified as having implemented CEM programmes and were invited to participate in the survey; five NCs indicated willingness to participate and were sent the questionnaire to complete.

**Results**: Four NCs responded to the survey—Ghana, Kenya, Nigeria and Zimbabwe—providing information on the implementation of a total of six CEM programmes. Their experiences indicate that CEM has helped to build pharmacovigilance capacity within the participating NCs and at the monitoring sites, and that healthcare providers (HCPs) are generally willing to participate in implementing the CEM method. All of the programmes took longer than expected to complete: contributing factors included a prolonged enrolment period and unexpectedly slow data entry. All of the programmes exceeded their budget by 11.1–63.2%. Data management was identified as a challenge for all participating NCs.

**Conclusions**: The reported experiences of four NCs that have undertaken CEM studies on ACTs indicate that CEM has helped to build pharmacovigilance capacity within NCs and monitoring sites and that HCPs are willing to participate in CEM programmes; however, the method was found to be labour intensive and data management was identified as a challenge. Reducing the workload associated with CEM, particularly in relation to data management, and integrating the method into the routine work of HCPs and NCs should be considered for future implementation.
Safety of Perflutren Ultrasound Contrast Agents: A Disproportionality Analysis of the US FAERS Database
Manfred Hauben, Eric Y. Hung, Kelly C. Hanretta, Sripal Bangalore

ABSTRACT

Introduction: Perflutren microbubble/microsphere ultrasound contrast agents have a black-box warning based on case reports of serious cardiopulmonary events. There have been several subsequent observational safety studies. Large spontaneous reporting databases may help detect/refine signals of rare adverse events that elude other data sources/study designs.

Objective: The objective of this study was to supplement existing knowledge of the reported safety of perflutren using statistical analysis of spontaneous reports.

Methods: We analyzed information from the US Food and Drug Administration Adverse Event Reporting System using a disproportionality analysis. Analysis of overall reporting for perflutren was supplemented by subset (age, indication) analysis. A signal of disproportionate reporting (SDR) was defined as EB05 >2.

Results: Overall, 18/380 Preferred Terms and 1/83 Standardized Medical Queries had SDRs. Most were small (EB05 = 2–4). Back pain and flank pain were the largest SDRs followed by events compatible with signs/symptoms of hypersensitivity. The general pattern of SDRs in the subset analysis was consistent with the overall analysis. Almost all events with SDRs were literally or conceptually labeled. Except for chest pain (higher in the age <65 years subgroup) and back pain (higher in the age ≥65 years subgroup), there were no statistically significant differences between age subsets. Except for the Preferred Terms Pruritus and Urticaria and the narrow Standardized Medical Queries Ventricular tachyarrhythmia, Angioedema, Oropharyngeal allergic conditions, and Hypersensitivity (higher in the stress test subgroup), there were no statistically significant reporting differences between indication subsets. There were no SDRs associated with the major cardiovascular events of death, myocardial infarction/ischemia, angina, arrhythmias, or convulsions in any analysis.

Conclusions: Our combined signal detection/evaluation analysis did not identify SDRs of novel adverse events or major cardiovascular events associated with perflutren ultrasound contrast agents. The negative results for major cardiovascular events extend previous signal evaluation exercises supporting the relative cardiovascular safety of these agents.
Impact on Drug Safety of Variation in Adherence: The Need for Routinely Reporting Measures of Dose Intensity in Medication Safety Studies Using Electronic Health Data

Elizabeth E. Roughead, Nicole L. Pratt

ABSTRACT

Randomized controlled trials always report the dose assessed and usually include a measure of adherence. By comparison, observational studies assessing medication safety often fail to report the dose used and rarely report any measure of adherence to therapy. This limits the ability to control for differences in doses used when undertaking meta-analyses. Non-adherence with therapy is common in the practice setting and varies across countries and settings. Inter-country differences in the registration of medicines may also result in different product strengths being available in different countries. These two factors combined means that observational studies undertaken for the same medicine in different settings may be assessing the same medicine but in circumstances where quite different dosages are used. Given that many adverse drug effects are dose dependent, differences in dosages used could be a factor explaining differences in risk estimates observed across studies. We argue that dose intensity, which can be defined as a product of the dose prescribed and adherence to the dose prescribed over the course of treatment, should be routinely reported in observational studies of medication safety. We illustrate the issue with the example of dabigatran. The randomized controlled trial evidence underpinning dabigatran’s marketing authorization resulted in uncertainty about the appropriate dose for efficacy versus safety. As a result, different dosages of dabigatran were registered in the USA and Europe. The USA registered the 150- and 75-mg dabigatran products, while the 150- and 110-mg dabigatran products were registered in Europe. Among five observational studies subsequently undertaken to resolve the safety question concerning dabigatran and risk of bleeding, only one stratified results by dose. None of the US studies stratified results by the 75-mg dabigatran dose, despite this dose not being assessed in the original trial. None of the five studies reported adherence measures, despite three separate observational studies finding between 25 and 40 % of patients were non-adherent to dabigatran. The STROBE and RECORD statements should consider adding the requirement for reporting measures of dose intensity and its component products to improve observational study reports.

Drug-Induced Hyperglycaemia and Diabetes

Neila Fathallah, Raoudha Slim, Sofien Larif, Houssem Hmouda

ABSTRACT

Drug-induced hyperglycaemia and diabetes is a global issue. It may be a serious problem, as it increases the risk of microvascular and macrovascular complications, infections, metabolic coma and even death. Drugs may induce hyperglycaemia through a variety of mechanisms, including alterations in insulin secretion and sensitivity, direct cytotoxic effects on pancreatic cells and increases in glucose production. Antihypertensive drugs are not equally implicated in increasing serum glucose levels. Glycaemic adverse events occur more frequently with thiazide diuretics and with certain beta-blocking agents than with calcium-channel blockers and inhibitors of the renin–angiotensin system. Lipid-modifying agents may also induce hyperglycaemia, and the diabetogenic effect seems to differ between the different types and daily doses of statins. Nicotinic acid may also alter glycaemic control. Among the anti-infectives, severe life-threatening events have been reported with fluoroquinolones, especially when high doses are used. Protease inhibitors and, to a lesser extent, nucleoside reverse transcriptase inhibitors have been reported to induce alterations in glucose metabolism. Pentamidine-induced hyperglycaemia seems to be related to direct dysfunction in pancreatic cells. Phenytoin and valproic acid may also induce hyperglycaemia. The mechanisms of second-generation antipsychotic-associated hyperglycaemia, diabetes mellitus and ketoacidosis are complex and are mainly due to insulin resistance. Antidepressant agents with high daily doses seem to be more frequently associated with an increased risk of diabetes. Ketoacidosis may occur in patients receiving beta-adrenergic stimulants, and theophylline may also induce hyperglycaemia. Steroid diabetes is more frequently associated with high doses of glucocorticoids. Some chemotherapeutic agents carry a higher risk of hyperglycaemia, and calcineurin inhibitor-induced hyperglycaemia is mainly due to a decrease in insulin secretion. Hyperglycaemia has been associated with oral contraceptives containing high doses of oestrogen. Growth hormone therapy and somatostatin analogues may also induce hyperglycaemia.
Clinicians should be aware of medications that may alter glycaemia. Efforts should be made to identify and closely monitor patients receiving drugs that are known to induce hyperglycaemia.

Association of Attorney Advertising and FDA Action with Prescription Claims: A Time Series Segmented Regression Analysis

Elizabeth C. Tippett, Brian K. Chen

ABSTRACT

Introduction: Attorneys sponsor television advertisements that include repeated warnings about adverse drug events to solicit consumers for lawsuits against drug manufacturers. The relationship between such advertising, safety actions by the US Food and Drug Administration (FDA), and healthcare use is unknown.

Objectives: To investigate the relationship between attorney advertising, FDA actions, and prescription drug claims.

Methods: The study examined total users per month and prescription rates for seven drugs with substantial attorney advertising volume and FDA or other safety interventions during 2009. Segmented regression analysis was used to detect pre-intervention trends, post-intervention level changes, and changes in post-intervention trends relative to the pre-intervention trends in the use of these seven drugs, using advertising volume, media hits, and the number of Medicare enrollees as covariates. Data for these variables were obtained from the Center for Medicare and Medicaid Services, Kantar Media, and LexisNexis.

Results: Several types of safety actions were associated with reductions in drug users and/or prescription rates, particularly for fentanyl, varenicline, and paroxetine. In most cases, attorney advertising volume rose in conjunction with major safety actions. Attorney advertising volume was positively correlated with prescription rates in five of seven drugs, likely because advertising volume began rising before safety actions, when prescription rates were still increasing. On the other hand, attorney advertising had mixed associations with the number of users per month.

Conclusion: Regulatory and safety actions likely reduced the number of users and/or prescription rates for some drugs. Attorneys may have strategically chosen to begin advertising adverse drug events prior to major safety actions, but we found little evidence that attorney advertising reduced drug use. Further research is needed to better understand how consumers and physicians respond to attorney advertising.
**ABSTRACT**

**Introduction:** Eltrombopag and romiplostim are thrombopoietin receptor agonists (TPO-RAs) marketed for immune thrombocytopenia (ITP). Thrombotic events have been reported with both drugs. This study was aimed at assessing whether there is a signal for differential risks of thrombosis between these two TPO-RAs.

**Methods:** We carried out a disproportionality analysis in the World Health Organization global individual case safety report (ICSR) database (VigiBase®). We selected all ICSRs with exposure to a TPO-RA between January 2011 and December 2014. We searched for exposures to eltrombopag or romiplostim in thrombosis reports as compared with other ICSRs, and we calculated adjusted reporting odds ratios (aRORs).

**Results:** We identified 5850 ICSRs, including 764 cases of thrombosis. In multivariate analyses, there was a signal for an increased risk of thrombosis (venous or arterial; aROR 1.72, 95 % confidence interval [CI] 1.47–2.02), venous thrombosis (aROR 1.88, 95 % CI 1.53–2.31), arterial thrombosis (aROR 1.54, 95 % CI 1.18–2.00), ischaemic stroke (aROR 1.65, 95 % CI 1.13–2.42) and myocardial infarction (aROR 1.50, 95 % CI 1.05–2.13) with eltrombopag as compared with romiplostim. Restriction to ICSRs reported by physicians led to similar results. However, worldwide dispensing data for romiplostim and eltrombopag were not accessible, so the rates of thrombosis with both drugs were not normalized by the daily defined doses and the generalizability of the results is limited.

**Conclusion:** This study suggests the presence of a signal for an increased risk of thrombosis with eltrombopag compared with romiplostim. These results must be confirmed and quantified by large aetiological pharmacoepidemiological studies.
Risk of Out-of-Hospital Sudden Cardiac Death in Users of Domperidone, Proton Pump Inhibitors, or Metoclopramide: A Population-Based Nested Case-Control Study

Alejandro Arana, Catherine B. Johannes, Lisa J. McQuay

ABSTRACT

Introduction: Epidemiological studies have linked domperidone use with serious cardiac arrhythmias, including sudden cardiac death, but data on age, dose, and duration of use are limited.

Objectives: The aim of this study was to assess the risk of out-of-hospital sudden cardiac death associated with domperidone use versus proton pump inhibitors (PPIs), metoclopramide, or non-use of all three medications, and to evaluate the risk of sudden cardiac death in relation to age and domperidone dose.

Methods: This was a population-based case-control study nested in a cohort of subjects aged ≥2 years in the Clinical Practice Research Datalink with one or more prescriptions for domperidone, any PPI, or metoclopramide from 2005 to 2011. Out-of-hospital sudden cardiac death was assessed by linkage with Hospital Episode Statistics and death certificates. Controls were matched on age, sex, and medical practice. The risk of sudden cardiac death in domperidone users versus risk in users of PPIs or metoclopramide was evaluated with multivariable conditional logistic regression; case-crossover analysis addressed possible residual confounding.

Results: From the study cohort (n = 681,104), 3239 sudden cardiac death cases were matched to 12,572 controls. The adjusted odds ratio (95% confidence interval) for sudden cardiac death with current use of domperidone alone was 1.71 (0.92–3.18) versus non-use of study medications, 1.26 (0.68–2.34) versus current PPI use, and 0.40 (0.17–0.94) current metoclopramide use. The adjusted odds ratio (95% confidence interval) relative to exposure to no study drug for domperidone >30 mg/day (eight cases, five controls) was 3.20 (0.59–17.3) and 1.65 (0.89–3.07) for age ≥61 years (27 cases, 49 controls). The odds ratio (95% confidence interval) was 3.17 (1.72–5.83) for within-person periods of domperidone use versus non-use in the case-crossover analysis.

Conclusions: Compared with non-use of any study drug, current domperidone use was associated with sudden cardiac death in nested case-control and case-crossover analyses, with a suggestion of higher risk in older persons and users of higher daily doses.
ABSTRACT

Background and Objective: Spontaneous reporting systems (SRSs) remain the cornerstone of post-marketing drug safety surveillance despite their well-known limitations. Judicious use of other available data sources is essential to enable better detection, strengthening and validation of signals. In this study, we investigated the potential of electronic healthcare records (EHRs) to be used alongside an SRS as an independent system, with the aim of improving signal detection.

Methods: A signal detection strategy, focused on a limited set of adverse events deemed important in pharmacovigilance, was performed retrospectively in two data sources—(1) the Exploring and Understanding Adverse Drug Reactions (EU-ADR) database network and (2) the EudraVigilance database—using data between 2000 and 2010. Five events were considered for analysis: (1) acute myocardial infarction (AMI); (2) bullous eruption; (3) hip fracture; (4) acute pancreatitis; and (5) upper gastrointestinal bleeding (UGIB). Potential signals identified in each system were verified using the current published literature. The complementarity of the two systems to detect signals was expressed as the percentage of the unilaterally identified signals out of the total number of confirmed signals. As a proxy for the associated costs, the number of signals that needed to be reviewed to detect one true signal (number needed to detect [NND]) was calculated. The relationship between the background frequency of the events and the capability of each system to detect signals was also investigated.

Results: The contribution of each system to signal detection appeared to be correlated with the background incidence of the events, being directly proportional to the incidence in EU-ADR and inversely proportional in EudraVigilance. EudraVigilance was particularly valuable in identifying bullous eruption and acute pancreatitis (71 and 42 % of signals were correctly identified from the total pool of known associations, respectively), while EU-ADR was most useful in identifying hip fractures (60 %). Both systems contributed reasonably well to identification of signals related to UGIB (45 % in EudraVigilance, 40 % in EU-ADR) but only fairly for signals related to AMI (25 % in EU-ADR, 20 % in EudraVigilance). The costs associated with detection of signals were variable across events; however, it was often more costly to detect safety signals in EU-ADR than in EudraVigilance (median NNDs: 7 versus 5).

Conclusion: An EHR-based system may have additional value for signal detection, alongside already established systems, especially in the presence of adverse events with a high background incidence. While the SRS appeared to be more cost effective overall, for some events the costs associated with signal detection in the EHR might be justifiable.
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): A National Analysis of Data from 10-Year Post-marketing Surveillance

Francesca Renda, Giovanni Landoni, Renato Bertini Malgarini

ABSTRACT

Introduction: Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare, severe and potentially fatal cutaneous adverse drug reaction (the mortality rate is up to 10 %) associated with numerous and apparently heterogeneous drugs. The aetiology is unknown.

Objective: To report Italian cases of DRESS over a 10-year period.

Methods: We searched the National Pharmacovigilance Network (NPN) for the term ‘drug reaction with eosinophilia and systemic symptoms’ from 1 January 2004 to 1 January 2014, to identify all reports of DRESS. Each case was checked to avoid duplication.

Results: In the NPN, we identified 91 serious cases of DRESS: 68 were spontaneous, still-unpublished reports, while 23 additional cases were derived from screening of the scientific literature, performed by marketing authorization holders. Notably, the single common element linking all cases of DRESS was intake of a drug containing an aromatic ring.

Conclusion: Thanks to the largest national DRESS case series ever reported, we were able to hypothesize, for the first time, that there is an association between use of drugs containing an aromatic ring in their chemical structure and DRESS. This might aid understanding of the aetiology of DRESS and facilitate diagnosis.

Statistical Signal Detection as a Routine Pharmacovigilance Practice: Effects of Periodicity and Resignalling Criteria on Quality and Workload

Magnus Lerch, Peter Nowicki, Katrin Manlik, Gabriela Wirsching

ABSTRACT

Introduction: The goal of signal detection in pharmacovigilance (PV) is to detect unknown causal associations between medicines and unexpected events. Statistical methods serve to detect signals and supplement traditional PV methods. Statistical signal detection (SSD) requires decisions about various settings that influence the quality and efficiency of SSD, as shown in several studies. To our knowledge, the effects of SSD periodicity and resignalling criteria on the quality and workload of routine SSD have not been published before.

Objective: To analyse the effects of different periodicities and resignalling criteria on signal detection quality and signal validation workload, and to test the impact of changing the signal threshold for number of cases.

Methods: We calculated signals of disproportionate reporting (SDRs) using thresholds of number of cases (N) ≥3, proportional reporting ratio ≥2 and Chi2 ≥ 4. We retrospectively simulated recurrent SDR calculation and validation with varying periodicity (quarterly vs. monthly), resignalling criteria, and N ≥ 3 vs. N ≥ 5.

Results: Changing the periodicity from quarterly to monthly increased the workload by 46.6 % (0 % signal loss). More restrictive resignalling criteria reduced the workload between 36.3 % (0 % signal loss) and 74.1 % (50 % signal loss). For N ≥ 3, the most efficient monthly SSD resignalling criterion reduced the workload by 36.3 % and detected all true signals earlier than quarterly SSD. N ≥ 5 reduced the workload between 13.8 and 21.4 % (0 % signal loss).

Conclusions: In real-life PV practice, signal detection and validation are recurrent periodic activities. Some true signals are only discovered upon resignalling. Our results demonstrate resignalling criteria with high signal detection quality and high efficiency. We found potential earlier detection of true signals using monthly SSD. Additional studies about resignalling should be performed to complement our findings.

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