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Comedications alter drug-induced liver injury reporting frequency: Data mining in the WHO VigiBase™

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ABSTRACT

Polypharmacy is common, and may modify mechanisms of drug-induced liver injury. We examined the effect of these drug–drug interactions on liver safety reports of four drugs highly associated with hepatotoxicity. In the WHO VigiBase™, liver event reports were examined for acetaminophen, isoniazid, valproic acid, and amoxicillin/clavulanic acid. Then, we evaluated the liver event reporting frequency of these 4 drugs in the presence of co-reported medications. Each of the 4 primary drugs was reported as having more than 2000 liver events, and co-reported with more than 600 different medications. Overall, the effect of 2275 co-reported drugs (316 drug classes) on the reporting frequency was analyzed. Decreased liver event reporting frequency was associated with 245 drugs/122 drug classes, including anti-TNFα, opioids, and folic acid. Increased liver event reporting frequency was associated with 170 drugs/82 drug classes; in particular, halogenated hydrocarbons, carboxamides, and bile acid sequestrants. After adjusting for age, gender, and other co-reported drug classes, multiple co-reported drug classes were significantly associated with decreased/increased liver event reporting frequency in a drug-specific/unspecific manner. In conclusion, co-reported medications were associated with changes in the liver event reporting frequency of drugs commonly associated with hepatotoxicity, suggesting that comedications may modify drug hepatic safety.

1. Introduction

Drug-related adverse events are a critical public health problem. In the US, serious and fatal adverse drug events (ADE) increased nearly 3-fold between 1998 and 2005, with most events due to a minority of important drugs (Moore et al., 2007). In the UK, 6.5% of adult hospital admissions were due to adverse drug reactions, resulting in an estimated $700 million annual cost (Pirmohamed et al., 2004). Drug-induced liver injury (DILI) is one of the most common adverse drug reactions, and can result in drug non-approvals, withdrawals and warnings (Senior, 2007). Drug-induced liver injury is the top cause of acute liver failure resulting in transplantation in the US (5,6) and is associated with significant mortality (Carey et al., 2008). In the US, the drugs most frequently associated with acute liver failure include: acetaminophen, antimicrobials, anti-epileptics, psychotropics, and antimetabolites (Reuben et al., 2010). However, most drug classes can cause drug-induced liver injury (Suzuki et al., 2010).

In parallel with rising adverse drug events, the use of prescription medications, over-the-counter products and dietary supplements have also increased (Qato et al., 2008). The average elderly

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ADE, adverse drug events; AERS, adverse event reporting system; APAP, acetaminophen; ATC classification, Anatomical Therapeutic Chemical Classification; ATIIA, angiotensin II receptor antagonist; BSEP, bile salt export pump; COX, cyclooxygenase; DILI, drug induced liver injury; EBGM, Empirical Bayes Geometric Mean of Relative Reporting Frequency; FDA, Food and Drug Administration; ICSR, individual case safety report; INTSS, interaction signal score; MedDRA, Medical Dictionary for Regulatory Activity; NSAID, non-steroidal anti-inflammatory drug; OTC, over the counter; SSRI, selective serotonin reuptake inhibitor; 2D, two-dimensional; 3D, three-dimensional; TNF, Tumor Necrosis Factor; WHO, World Health Organization.

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outpatient consumes 4 medications or more daily (Gurwitz et al., 2003; Hauben, 2003; Argikar and Remmel, 2009; Aleo et al., 2014; Chalasani et al., 2014), and most (63%) use complementary and alternative medications (Cheung et al., 2007), which have been increasingly associated with liver injury (Navarro et al., 2014). This polypharmacy contributes to adverse drug reactions (Gurwitz et al., 2003); large population studies reveal a sixfold increased injury risk with coadministration of medications associated with hepatotoxicity (de Abajo et al., 2004). Therefore, it is helpful to understand potential drug–drug interactions, which may contribute to drug-induced liver injury.

While drug-induced liver injury is clinically important, it is relatively uncommon, with symptomatic injury affecting approximately 1 in 10,000 patients annually (Sgro et al., 2002). In those with symptomatic drug-induced liver injury followed for 6 months, 1 in 14 will progress to liver transplant or liver-related death and nearly 1 in 5 of those remaining develop evidence of chronic injury (Fontana, 2014). With increasing polypharmacy potentially increasing the frequency of drug interactions and the likelihood of drug induced liver injury, it is imperative to examine the effect of concomitant medications on drug-induced liver injury in very large datasets. Therefore, we investigated the effect of comedications on selected drug-induced liver injury events using the largest global spontaneous adverse event reporting system, with over 8 million case reports. While analysis of this dataset does not enable causality assessment, it identifies new hypotheses on the effects of comedications on drug-induced liver injury.

Using this large global dataset, we applied quantitative signal detection methods to identify liver adverse events reported for 4 drugs commonly associated with hepatotoxicity: acetaminophen, isoniazid, valproic acid, and amoxicillin/clavulanic acid. These four drugs were chosen to illustrate different types of hepatotoxicity: acetaminophen causes direct dose-related toxicity, as well as hepatocellular injury at therapeutic doses (Watkins et al., 2006); isoniazid exhibits hepatocellular injury due to metabolic and epigenetic factors (Murata et al., 2007) which increases with aging (Uetrecht and Naisbitt, 2013); amoxicillin/clavulanic acid is associated with an hepatocellular, mixed and cholestatic injury with immunologic manifestations (Lucena et al., 2011) and is the most frequently identified drug causing drug-induced liver injury in Western registries (Chalasani et al., 2014); and valproate acid causes mitochondrial toxicity, particularly in infants and young children (Uetrecht and Naisbitt, 2013). Furthermore, antibiotics and antiepileptics account for >60% of drug-induced liver injury in a prospective US registry (Chalasani et al., 2014). We systematically investigated the impact of comedications on liver event reporting frequency, to identify drugs and drug classes, which were associated with increased or decreased liver event reporting frequency. We then examined the identified comedications and constructed a plausible conceptual framework to explain mechanisms by which they might alter liver injury caused by the 4 primary drugs, in order to provide testable hypotheses for future empirical research and structure future investigations of human drug-induced liver injury.

2. Methods

2.1. Study design

This data-mining study used the released version of the large global VigiBase™ database, a spontaneous adverse event reporting system. We performed data-mining analyses to quantify liver event reports for 4 primary drugs, which are known human hepatotoxicants: acetaminophen, isoniazid, valproic acid, and amoxicillin/clavulanic acid. We then explored the potential impact of concomitant medications on liver event reporting frequency using individual comedications as well as drug classes, as outlined below.

This study did not breach the confidentiality or anonymity of reported cases. The study was conducted using only coded data, without accessing identifiable private information, and therefore did not involve human subjects [45 CFR 46.102(f)].

2.2. Data source

We used the WHO global individual case safety report database (VigiBase™, the fourth quarter issue of 2010), which is broadly utilized in pharmacovigilance research (Bjornsson and Olsson, 2006; Suzuki et al., 2010). VigiBase™ is the world's largest spontaneous adverse event reporting system, with more than 8.4 million reports from 104 countries compiled since the WHO International Drug Monitoring Programme started in 1968 (Caster et al., 2014). The majority of database reports were received from Europe and North America; both regulatory and voluntary sources are included.

2.3. Primary study drugs

We investigated four drugs commonly associated with clinical hepatotoxicity: acetaminophen, isoniazid, valproic acid, and amoxicillin/clavulanic acid (Suzuki et al., 2010). Acetaminophen, isoniazid, and valproic acid predominantly cause hepatocellular injury (Chalasani et al., 2014). Amoxicillin/clavulanic acid causes both hepatocellular and cholestatic injury, with cholestatic injury predominant in the elderly (Lucena et al., 2006). We used a single compound as a reference drug for acetaminophen, isoniazid, and valproic acid, and combined two drugs 'Amoxicillin and Clavulanic Acid' and 'Amoxicillin and Clavulanate Potassium' as a pooled reference for amoxicillin/clavulanic acid. For these four drugs, known drug: drug interactions were searched in Drug Bank (Law et al., 2014) and the Indiana University Division of Clinical Pharmacology P450 Drug Interaction Table website (Indiana University, 2015). These known interactions were then compared to potential drug: drug interactions identified through our data mining analysis.

2.4. Drug dictionary and classification

In the individual drug analyses, we used generic/abridged drug names, which are available in a pharmacovigilance application used for the analyses (Empirica™ Signal, Oracle, Waltham, MA, USA). In the drug class analyses, we classified co-reported medications (comedications, hereafter) using the fourth category of the Anatomical Therapeutic Chemical Classification (ATC4) of the WHO Drug Dictionary, which describes chemical subgroups (Dictionary, 2014). Drug classes were excluded when indicated only for skin, eye, or ears.

2.5. Liver events

Two custom liver event terms were created for data mining, combining groups of 'Preferred Terms' (codes from the Medical Dictionary for Regulatory Activity, MedDRA) indicating different types of drug-induced liver injury: 'hepatocellular injury' and 'cholestatic injury'. Supplemental Table 1 summarizes the lists of 'Preferred terms' used to define the two custom terms (26 terms for 'hepatocellular injury' and 16 terms for 'cholestatic injury').

2.6. Analytical methods

The data were computed using the Empirica™ Signal application (Oracle, Waltham, MA, USA). A relative reporting ratio (RRR)

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