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Drug interactions involving antiepileptic drugs: Assessment of the consistency among three drug compendia and FDA-approved labels

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ABSTRACT

Interactions of antiepileptic drugs (AEDs) with other substances may lead to adverse effects and treatment failure. To avoid such interactions, clinicians often rely on drug interaction compendia. Our objective was to compare the concordance for twenty-two AEDs among three drug interaction compendia (Micromedex, Lexi-Interact, and Clinical Pharmacology) and the US Food and Drug Administration-approved product labels. For each AED, the overall concordance among data sources regarding existence of interactions and their classification was poor, with less than twenty percent of interactions listed in all four sources. Concordance among the three drug compendia decreased with the fraction of the drug excreted unchanged and was greater for established inducers of hepatic drug-metabolizing enzymes than for the drugs that are not inducers (R-square = 0.83, $P < 0.01$). For interactions classified as contraindications, major, and severe, concordance among the four data sources was, in most cases, less than 30%. Prescribers should be aware of the differences between drug interaction sources of information for both older AEDs and newer AEDs, in particular for those AEDs which are not involved in hepatic enzyme-mediated interactions.

1. Introduction

Antiepileptic drugs (AEDs)[1] are the treatment of choice for the majority of people with epilepsy (PWE). Antiepileptic drugs are often used for lifelong treatment and are given as polytherapy in approximately one-fifth of patients [1–6]. Furthermore, many PWE receive additional drugs for the treatment of concomitant medical conditions [7]. For example, in the US, 13% of patients treated with enzyme-inducing AEDs (EIAEDs) were newly prescribed a statin [8]. Patients with drug-resistant epilepsy and psychiatric comorbidity were reported to be treated with two to eight concomitant CNS-active drugs [9]. As AEDs are highly prone to pharmacokinetic (PK) and pharmacodynamic (PD) interactions [10–14], PWE under polytherapy are at risk of adverse drug reactions, loss of seizure control, and loss of control of other diseases [12–14]. Among AEDs, newer compounds, such as levetiracetam and pregabalin, are overall known to be associated with fewer interactions compared with older drugs (e.g., phenobarbital, phenytoin, and carbamazepine). This has been attributed to both lesser propensity of the newer AEDs to be involved in PK interactions and shorter duration in routine clinical practice [12]. Nevertheless, the same reasons may also minimize the information available on interactions involving newer AEDs and lead to disagreement among data sources.

Past studies have demonstrated substantial differences between drug compendia in terms of the total number of potential interactions and interaction severity for several drugs, including warfarin [15–17], oral anticancer agents [18], and hepatotoxic medications [19]. Given the serious potential adverse outcomes of such interactions for patients, it is important that clinicians become aware of those differences relating to the existence, the nature, and the severity of such interactions. The aim of this study was to compare sources of information regarding interactions with older and newer AEDs by assessing three drug information compendia and the AED product labels approved by the US Food and Drug Administration (FDA).

2. Methods

We compared the most recent AED product labels approved by the FDA (Supplementary Table 1) and the three major drug information

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[1] AED, antiepileptic drug; EIAED, enzyme-inducing AED; FDA, US Food and Drug Administration; FE, the drug fraction excreted unchanged in urine; P-gp, P-glycoprotein; PD, pharmacodynamic; PK, pharmacokinetic; PWE, people with epilepsy.

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compendia with respect to whether and how interactions of other products with AEDs were reported. The compendia included Micromedex [20], Clinical Pharmacology [21], and Lexi-Interact [22] and were selected because they are commonly used by US health-care practitioners and by drug interaction services [15,23,24]. Micromedex and Clinical Pharmacology have been officially recognized by the US Centers for Medicare and Medicaid Services as drug compendia for determining the appropriate use of drugs and biologics for patients with cancer [25]. All drug monographs were reviewed based on their electronic versions. We studied the available information on 22 older (phenobarbital, phenytoin, primidone, ethosuximide, carbamazepine, valproic acid, and clonazepam) and newer (vigabatrin, lamotrigine, oxcarbazepine, felbamate, gabapentin, topiramate, tiagabine, levetiracetam, zonisamide, pregabalin, rufinamide, lacosamide, eslicarbazepine, retigabine/ezogabine, and perampanel) AEDs [12,26], including both EIAEDs [1] and non-EIAEDs. In addition, we searched Clinical Pharmacology for each interaction that was identified in the other compendia. The total number of interactions for each of the newer AEDs was the sum of all the PK and PD interactions with AEDs and with drugs used to treat disorders other than epilepsy, as previously described [12,13]. For phenobarbital, only three sources were accessed because pre-1938 drugs are not included in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations list. Stiripentol was excluded from analysis because it was listed in two sources of information (Micromedex and Lexi-Interact) only.

Data from the four sources were collected by a clinical pharmacist, and interactions were assigned degrees of severity and quality in accordance with the listing in the database. Entries with the lowest degree of risk ("no known interaction") in Lexi-Interact were excluded from the analysis. For the purpose of comparing the four sources, each drug or product was transformed into a binary variable (present and absent), as previously described [15]. The binary variable was used to assess the overall concordance among data sources using percentage of agreement. We also reviewed information on the severity ranking of the interactions. All the interactions of a given drug pair were considered one entry. For interactions that were assigned within a database into two classifications with different degrees of risk, severity, or documentation, we used the greater value of the classification. Our analysis included only individual compound entries and not product classes (e.g., beta blockers). Information on the number of that AEDs were clinically available was from a recent review by Löscher et al. [26], and the fraction excreted unchanged (FE) in urine of AEDs was from Patsalos and Bourgeois [27]. We also used data from the literature on the renal elimination of metformin [28,29], sitagliptin [30], warfarin [15], and rifampin [31]. These drugs were selected because they represent both older drugs and newer drugs with various degrees of renal elimination versus hepatic elimination. For example, metformin is an older drug, but, in contrast to the older AEDs, its elimination is almost exclusively renal without metabolism [28,29]. In contrast, warfarin is almost completely metabolized [15]. Sitagliptin is a newer drug which is highly excreted unchanged in urine [30]. Rifampin is a well-established hepatic enzyme inducer [31].

Statistical analysis was performed using the two-tailed Mann–Whitney test, the Pearson correlation (GraphPad Instat 3, La Jolla, CA), and linear regression (SAS 8, Cary, NC, USA). The significance level was set at $P < 0.05$. Based on the regression analysis, we constructed linear models which describe the concordance among the sources of information for all four sources, any three sources, and the three drug compendia. Following initial inspection of several models, we used the logarithmic transformed values of the drug FE for the regression analysis. We also used the linear models to predict the concordance for metformin, sitagliptin, and rifampin, for which data were extracted from the four data sources and analyzed as described above for the AEDs. The values of concordance for warfarin, as previously reported [15], were also aligned with the model.

3. Results

3.1. Number of interactions

Antiepileptic drugs were listed as having potential interactions with other small molecule drugs (including other AEDs), ethanol, food, dietary supplements and herbal compounds (Supplementary Table 2), and biologicals. The number of interactions per AED in the three drug compendia further exceeded that of the FDA drug labels and the listings in recent comprehensive reviews of drug interactions with the newer AEDs (data not shown) [12,13].

In accordance with the presumed contributors to the propensity of AEDs to interact with other compounds [12,32], we further evaluated to what extent the total number of interactions is affected by the following factors: the AED's duration in use, its tendency to be an object of PK interactions (as inversely reflected by the FE, the fraction of the drug not subjected to interactions based on enhanced or inhibited metabolism), and its tendency to be a perpetrator of PK interactions (being an EIAED). We did not include enzyme inhibition in the analysis because only two AEDs (valproic acid and felbamate) are considered potent enzyme inhibitors, whereas others may inhibit drug-metabolizing enzymes to various extents [10,12,13]. Older AEDs were overall associated with greater numbers of entries compared with newer AEDs in each of the three drug interactions compendia but not in the drug labels (Fig. 1). The fraction of the AED dose excreted unchanged did not significantly correlate with the number of interaction entries into the databases ($P > 0.05$; data not shown). Greater numbers of interactions were recorded in the three compendia for EIAEDs than for non-AEDs ($P < 0.01$; data not shown).

3.2. Mechanism of interactions

Lexi-Interact and, to a lesser extent, Micromedex listed several classes of mechanistic-based interactions. These included interactions with CNS depressants, QT prolonging agents, P-glycoprotein (P-gp) substrates, and a variety of cytochrome P450 isoenzyme substrates, inducers, and inhibitors (Supplementary Fig. 1). However, not only were the characterized classes of interactions different, but the assignment of specific interactions into such classes differed between these two databases as well. For example, categories for cytochrome P450 isoform substrates existed in Micromedex for carbamazepine and perampanel only, whereas, in Lexi-Interact, 8 other AEDs were also listed as substrates (Supplementary Fig. 1a). Likewise, in Lexi-Interact, 17 AED lists contained categories for "CNS depressants" (PD interactions), whereas the only AED potentially interacting with a similar class of compounds in Micromedex was perampanel, for which CNS depressants accounted for 71% of all Micromedex interactions (Supplementary Fig. 1b). Lexi-Interact CNS depression-based interactions were 91%, 91%, and 84% of all entries for vigabatrin, pregabalin, and gabapentin, respectively. Furthermore, the assignment of interactions did not appear to be consistent even within the same database. Since individual drug interactions could be both listed within specific categories or identified independently, the absence of categorization did not necessarily exclude the listing of an interaction in a compendium.

3.3. Classification of severity and documentation

Sources utilized different classification systems for interaction severity and documentation (Supplementary Table 3). For example, Micromedex used five terms for severity classification compared with four terms in Clinical Pharmacology and three terms in Lexi-Interact. Based on this classification, several mechanistic-based AED interactions were assigned severity rankings by default. For example, the severity of most carbamazepine's interactions with CYP3A4 substrates was ranked major in both Lexi-Interact and Micromedex. However, the CYP3A4 substrate lists differed between the two compendia.