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Concordance rate amongst electronic databases about drug interactions between warfarin and antimicrobials: a descriptive analysis.

Concordância entre bases de dados sobre interações medicamentosas entre varfarina e antimicrobianos: uma análise descritiva.

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ABSTRACT

Drug interactions (DI) are adverse events that may compromise therapeutic effectiveness and patient safety. Warfarin is associated with relevant DI with several drugs, including antimicrobials (AM). **Objective:** to analyze the degree of agreement between information on the probable mechanism, classification of severity and suggested management of potential DI between warfarin and AM present in the Municipal List of Medications of Porto Alegre (REMUME/POA), in the electronic databases (EDB) UpToDate®, Drugs.com®, Medscape® and Micromedex®. **Methodology:** descriptive analysis in accordance with the *Guidelines for Reporting Reliability and Agreement Studies*. **Results:** Of the fifteen AM, 13 had reported DI with warfarin in at least one of the four EDB. For the DI classification, the total concordance rate obtained in the four consulted EDB was 33%; Partial agreement between two EDB was 33% and between three, 33% either, and the EDB most in agreement with each other were UpToDate® and Drugs.com® (87%). As for the probable mechanism of the DI, there was no complete agreement between the four BDE; partial agreement between two EDB was 38% and between three, 23%, and the EDB that most agreed with each other were UpToDate® and Medscape® (38%). For the suggestion of clinical management, the total agreement was 23%; partial agreement between two EDB was 38%, and between three, 38%. The most concordant EDB were UpToDate® and Drugs.com® (85%). **Conclusions:** Total concordance rates between the EDB are relatively low; however, partial agreement is higher.
Keywords: Drug-drug interactions; electronic databasis; warfarin; Essential Drugs; National Drug Policy; Single Health System.

RESUMO

Interações medicamentosas (IM) são eventos adversos que podem comprometer a efetividade terapêutica e a segurança do paciente. A varfarina está associada à IM relevantes com diversos medicamentos, incluindo antimicrobianos (AM). **Objetivo:** analisar concordância entre informações sobre mecanismo provável, classificação de gravidade e manejo sugerido de IM potenciais entre varfarina e AM presentes na Relação Municipal de Medicamentos de Porto Alegre (REMUME/POA), nas bases de dados eletrônicas (BDE) UpToDate®, Drugs.com®, Medscape® e Micromedex®. **Metodologia:** análise descritiva de acordo com os *Guidelines for Reporting Reliability and Agreement Studies*. **Resultados:** Dos 15 AM, 13 apresentaram IM com varfarina em ao menos 01 das 04 BDE. Para a classificação da IM, a taxa de concordância total obtida nas 04 BDE consultadas foi de 33%; a concordância parcial entre 02 BDE foi de 33% e entre 03, também de 33%, e as BDE mais concordantes entre si foram UpToDate® e Drugs.com® (87%). Quanto ao mecanismo provável da IM, não houve concordância total entre as 04 BDE; a parcial entre 02 BDE foi de 38% e entre 03, de 23%, e as BDE mais concordantes entre si foram UpToDate® e Medscape® (38%). Para a sugestão de manejo clínico, a concordância total foi de 23%; a parcial entre 02 BDE foi de 38%, e entre 03, também de 38%. As BDE mais concordantes entre si foram UpToDate® e Drugs.com® (85%). **Conclusões:** As taxas de concordância total entre as BDE são relativamente baixas, mas a parcial é maior.
Palavras-chave: Interações medicamentosas; bases de dados eletrônicas; varfarina; Medicamentos Essenciais; Política Nacional de Medicamentos; Sistema Único de Saúde.

Introduction

Several countries, including Brazil, adopt lists of essential medicines, which are, by definition, those that meet the priority health care needs of a population, selected considering efficacy, safety, and cost-effectiveness in certain health conditions and their relevance to public health[1-3].

Drug interactions (DI) are classified as Drug-Related Problems (DRP)[4] and are characterized as clinical events in which a drug has its action or effect increased, reduced, or modified due to the presence of another drug when used concomitantly[5]. They can be broadly classified into pharmacodynamic drug interactions (PD-DI) and pharmacokinetic drug interactions (PK-DI). PD-DIs occur at the sites of drug action, where the effect results from the action of drugs related to the same receptor or enzyme, or to different receptors or enzymes, producing either similar or opposite effects. PK-DIs, which are usually more frequent than PD-DIs, occur when one drug alters the rate or extent of absorption, distribution, metabolism, or excretion of another drug[5].

The oral anticoagulant available in the Brazilian National List of Essential Medicines (RENAME) is warfarin, one of the most prescribed and widely used worldwide[6]. Its mechanism of action is based on the inhibition of vitamin K–dependent clotting factors (II – prothrombin –, VII, IX, and X). It is indicated for the prophylaxis and treatment of prothrombotic disorders, and its effect is monitored through the International Normalized Ratio (INR), a ratio calculated between the prothrombin time of the anticoagulated patient and the normal average prothrombin time[7].

Warfarin is a drug with a narrow therapeutic index and, in primary health care, is among the drugs most associated with fatal medication errors[8]. In many cases, these errors result from inadequate laboratory monitoring, undetected or neglected clinically relevant DIs, gaps in the technical knowledge of professionals, and failures in patient counseling regarding treatment[9]. The risk of death increases proportionally with the INR value[10], therefore patients using warfarin require clinical and laboratory follow-up with multidisciplinary team evaluation[11]. Warfarin interacts with several drugs, including antimicrobials (AM), with which it presents significant interactions through different mechanisms: inhibition or induction of cytochrome P450 isoenzymes, competition for protein-binding sites, or reduced vitamin K absorption due to changes in intestinal microbiota. Such interactions can lead to therapeutic failure or toxicity[7,12].

The clinical pharmacist is a professional capable of preventing, detecting, and managing DRPs[13,14]. One of the tools employed in clinical pharmacy practice are electronic databases (EDB), which are considered reliable sources of information on medicines and diseases to support clinical decision-making, conveniently accessed via computer or mobile applications[15]. Some of the most commonly used EDBs to identify potential DIs, through the theoretical analysis of the pharmacokinetic and pharmacodynamic profiles of each drug in use, include UpToDate®[16], Drugs.com Drug Interactions Checker®[17], Medscape Drug Interaction Checker®[18], and Micromedex® Drug Interactions[19]. A potential DI may or may not result in a real DI, which is identified from signs and symptoms presented by the patient. In the literature, the prevalence of real DIs is consistently lower than that of potential DIs[20,21].

One of the challenges in using EDBs is the discrepancy between the results provided by different databases, often due to the use of different evidence sources, which are not always reliable, robust, or up to date. In 2021, de Oliveira and collaborators published a systematic review that found prevalence rates of DIs in hospitalized older adults ranging from 8.34% to 100%. Among the possible causes raised by the authors to explain such wide variation was, among other factors, the use of different methods and EDBs for DI detection[22], which may compromise the reliability of the data obtained for appropriate clinical decision-making. Although more studies on databases and drug interactions have been published in recent years, few studies compare the presence of DIs across two or more EDBs[23]. Thus, we understand that studies comparing the information provided on DIs among three or more EDBs are necessary.

Objective

To analyze the agreement rates of information on drug interactions between warfarin and antimicrobials listed in the Municipal List of Medicines of Porto Alegre (REMUME/POA) across different electronic databases, regarding the presence of potential drug interactions, the probable mechanism of interaction, classification by severity and risk, and the suggested management.

Methodology

Descriptive analysis conducted in accordance with the Guidelines for Reporting Reliability and Agreement Studies[24], assessing the degree of agreement across information on the presence of potential drug interactions, the likely mechanism of interaction, the classification of severity and risk, and the suggested management for potential interactions between warfarin and antimicrobials listed in the Municipal List of Medicines of Porto Alegre (REMUME/POA), using the version revised on 09/30/2020. Inclusion criteria for the antimicrobials evaluated were: availability in oral or injectable form (i.e., systemic use); indication primarily for acute infections, generally without a main indication for conditions requiring long-term treatment; and indication for adult use, given that warfarin is predominantly prescribed to and used by adult patients (Table 1).

Table 1. Antimicrobial drugs listed in the REMUME/POA evaluated

Antimicrobial medication
Aciclovir 200 mg, tablet
Amoxicillin 250 mg + Potassium Clavulanate 62.5 mg / 5 mL, oral suspension
Amoxicillin 500 mg + Potassium Clavulanate 125 mg, tablet
Amoxicillin 250 mg / 5 mL, oral suspension
Amoxicillin 500 mg, capsule
Azithromycin 500 mg, tablet
Azithromycin 600 mg / 15 mL, oral suspension
Benzathine Benzylpenicillin 1,200,000 IU, powder for injectable solution
Benzylpenicillin G Procaine + Potassium 300,000 + 100,000 IU, powder for injectable solution
Cephalexin 50 mg/mL, oral suspension
Cephalexin 500 mg, capsule
Ceftriaxone 500 mg + IM diluent
Ciprofloxacin 500 mg, tablet
Doxycycline Hydrochloride 100 mg, tablet
Erythromycin Estolate 250 mg / 5 mL, oral suspension
Fluconazole 150 mg, capsule
Metronidazole 400 mg, tablet
Benzoilmetronidazole 40 mg/mL, oral suspension
Nitrofurantoin 100 mg, capsule
Sulfamethoxazole 400 mg + Trimethoprim 80 mg, tablet
Sulfamethoxazole 40 mg + Trimethoprim 8 mg/mL, oral suspension

The electronic databases (EDBs) used for evaluating potential drug interactions (DIs) between warfarin and antimicrobials (AMs) listed in the REMUME/POA were: UpToDate®[16], Drugs.com Drug Interactions Checker®[17], Medscape Drug Interaction Checker®[18], and Micromedex® Drug Interactions[19].

These EDBs were selected for their specific features: UpToDate® is one of the first-choice tools for students and healthcare professionals[25]; Micromedex® is considered a "gold standard" for drug information and provides some of the most robust literature[26]; Medscape® is freely available to any healthcare professional; and Drugs.com® is also free and supplies relevant information both to healthcare professionals and to patients.

From these EDBs, the following data were compiled and analyzed: a) classification of interaction severity, b) the likely interaction mechanism, and c) suggested clinical management. These items were entered into a dedicated spreadsheet between March 2021 and November 2021. The classifications of DIs among the EDBs were assumed and interpreted as equivalent, based on the validation conducted by Shariff et al. (2021), as described in Table 2[27].

Fifteen systemically administered antimicrobials listed in the REMUME/POA were included. Data on the presence of potential drug interactions, probable interaction mechanism, severity and risk classification, and suggested management were collected by a pharmacist with two years of clinical experience (RTM) and reviewed by a pharmacist with fifteen years of clinical experience and six years in BDE evaluation (LMO). We defined a total agreement rate as the scenario in which all four BDEs used provided convergent results for the same parameter (presence or absence of drug interaction, classification, and corresponding management of the interaction). A partial agreement rate was defined as concordance in results for the same parameter between two or three BDEs, but not among all databases tested.

Results

Thirteen drug interactions were reported by the BDEs UpToDate®, Drugs.com Drug Interactions Checker®, and Micromedex® Drug Interactions, respectively. The Micromedex® Drug Interactions BDE reported nine interactions.

Thirteen antimicrobials showed interactions with warfarin in at least one of the BDEs tested (Table 3). The antimicrobials acyclovir and nitrofurantoin did not have any reported interactions with warfarin in any of the four BDEs. Five out of fifteen (33%) tested antimicrobial–warfarin combinations demonstrated total agreement among the databases regarding interaction classification. Another five out of fifteen (33%) combinations showed agreement on interaction classification between only two databases; a notable example is the interaction between azithromycin and warfarin, where classification agreement was found between UpToDate® and Drugs.com Drug Interactions Checker®, and separately between Medscape Drug Interaction Checker® and Micromedex® Drug Interactions. For the remaining five out of fifteen tested combinations, there was agreement on interaction classification among three of the four BDEs consulted (33%).

Regarding interaction classification, the BDEs with the highest agreement were UpToDate® and Drugs.com Drug Interactions Checker® (87%), while the pair with the lowest agreement was UpToDate® and Medscape Drug Interaction Checker® (40%).

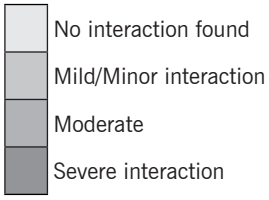
Table 2. Interpretation of equivalence for DI classifications among the BDEs used.

Classification/ Database	UpToDate®	Drugs.com Drug Interactions Checker®	Medscape Drug Interaction Checker®	Micromedex® Drug Interactions
No interaction found	A	No drug interactions found	No interactions found	No interactions have been identified for this selected drug list
Mild/minor interaction	B	Minor	Minor	Minor
Moderate interaction	C	Moderate	Monitor Closely	Moderate
Severe interaction	D	Major	Serious/Use Alternative	Major

Table 3. Classification of drug interactions between warfarin and antimicrobials.

Medication	UpToDate®	Drugs®	Medscape®	Micromedex®
Amoxicillin/Potassium Clavulanate				
Amoxicilin				
Azithromycin				
Benzathine Benzylpenicillin				
Benzylpenicillin G Procaine + Potassium				
Cephalexin				
Ceftriaxone				
Ciprofloxacin				
Doxycycline				
Erythromycin				
Fluconazole				
Metronidazole				
Sulfamethoxazole/Trimethoprim				

Legend:



Significant discrepancies were observed in the classification of drug interactions across the different electronic databases (EDBs): for the same combination of antimicrobial (AM) and warfarin, one database might report no identified interaction, while another reports a severe interaction. Disagreements were also noted in the severity classification of interactions between warfarin and AMs belonging to the same pharmacological class. Beta-lactams, such as amoxicillin, benzylpenicillin, and cephalexin, by inhibiting the intestinal flora, can potentially reduce vitamin K synthesis, leading to increased INR. The results obtained from the databases varied. Table 4 describes the probable mechanism(s) by which the interaction between AMs and warfarin occurs, if provided. The evaluated EDBs proposed interaction mechanisms for thirteen of the fifteen AM–warfarin combinations. Regarding the description of the probable interaction mechanism between AMs and warfarin, there was no complete agreement among all four EDBs for any of the tested combinations. Partial agreement was observed in 38% of cases between two of the four tested databases and in 23% of cases between three of the four EDBs. The databases that showed the highest level of agreement regarding the probable mechanism of interaction were UpToDate® and Medscape Drug Interaction Checker® (38%).

The overall agreement rate for the proposed clinical management of drug interactions was 23%. Agreement between two of the four databases tested was 38% , and the same percentage was found for agreement among three of the four electronic databases (EDBs). The databases that showed the highest level of agreement with each other were UpToDate® and Drugs.com Drug Interactions Checker® (85%), while the lowest agreement for the management of drug interactions was observed between UpToDate® and Medscape Drug Interaction Checker® (30%).

Table 4. Description of the probable mechanism of drug interactions between antimicrobials and warfarin.

Medication	UpToDate®	Drugs®	Medscape®	Micromedex®
Amoxicillin/Potassium Clavulanate	1;3	5	0	1
Amoxicilin	1;3	5	0	1
Azithromycin	3	7	3	1
Benzathine Benzylpenicillin	1;3	5	0	1
Benzylpenicillin G Procaine + Potassium	1;3	5	0	1
Cephalexin	1;5	1;5	0	1
Ceftriaxone	1;5	1;5	1;5	7
Ciprofloxacin	7	3;5	3	1
Doxycycline	7	1;5	5	7
Erythromycin	3	7	3	1;3
Fluconazole	3	3	3	1;3
Metronidazole	3	3	3	5
Sulfamethoxazole/Trimethoprim	1;2;5	2;3	2;3	1;3

Legend:
0: no interaction found
1: pharmacokinetic interaction – absorption
2: pharmacokinetic interaction – distribution
3: pharmacokinetic interaction – metabolism
5: pharmacodynamic interaction – agonism
7: unknown interaction mechanism

Table 5. Suggested management strategies for drug interactions between antimicrobials and warfarin

Medication	Uptodate®	Drugs®	Medscape®	Micromedex®
Amoxicillin/Potassium Clavulanate				
Amoxicilin				
Azithromycin				
Benzathine Benzylpenicillin				
Benzylpenicillin G Procaine + Potassium				
Cephalexin				
Ceftriaxone				
Ciprofloxacin				
Doxycycline				
Erythromycin				
Fluconazole				
Metronidazole				
Sulfamethoxazole/Trimethoprim				

Legend:
No interaction found
No action is necessary
Monitor INR
Consider alternative antimicrobial

Discussion

Information on drug interactions (DIs) in EDBs should be interpreted as potential, characterizing a risk to the patient, and not as a statement that, once described, will inevitably occur. In general, the occurrence of a DI depends, among other factors, on the patient's metabolism, health condition, exposure to the drugs involved, age, and also on other equally important factors, such as the prescribed dosage, including administration times, dose, and duration of use[28]. For warfarin, in addition to these factors, genetic polymorphisms that determine the drug's effect[29], diet, and nutritional status[30] must also be considered.

Several EDBs for the analysis and screening of DIs are commercially available. The algorithms employed allow interconnectivity between different knowledge sources, which can be easily expanded and updated, extracting information between selected drug pairs[31]. EDBs provide information on whether the identified DI occurred due to a PK or PD mechanism, severity classification, and management, in addition to providing reference literature. However, some EDBs do not contain all of these components[15].

UpToDate® is widely used by many professionals and institutions in Brazil and worldwide, with information published based on drug manufacturer specifications and package inserts, data from regulatory agencies, and primary medical literature[16]. The information provided by Drugs.com® comes from several independent drug information providers, such as the American Society of Health-System Pharmacists and Micromedex®[17]. Medscape® was developed by clinical specialists who compile drug monographs and drug interaction data, based mainly on U.S. drug approvals and applications, and is periodically updated[18] Micromedex® has a well-defined and documented editorial process, based on critical evaluation of primary me2dical literature, including classifications to support clinical decision-making as well as the robustness of the evidence[19].

Discrepancies in DI information are possibly the result of the complexity of sources, published literature, regulatory documents, drug package inserts, and case reports[32]. More studies on the agreement, accuracy, and robustness of information provided by EDBs are needed. It can be inferred that the greater the agreement between EDBs regarding classification, description, and management of DIs, the higher the reliability of the information provided, since the data presented by an EDB should reflect the consistency of the literature data on the described DI. In this study, for example, the suggested management strategies in the four EDBs are directly related to the classification of DIs, so similar rates would be expected.

In our study, we found considerable differences among the four EDBs evaluated regarding classification, mechanism description, and clinical management of DIs between AMs and warfarin. Most DIs between warfarin and antimicrobials were described as PK DIs at the metabolism level, through enzymatic inhibition of the CYP450 enzyme complex, leading to a possible increase in warfarin serum levels and, consequently, hemorrhagic events due to elevated INR[10,33]. Pharmacokinetic interactions at the absorption level are also quite common, as well as pharmacodynamic agonist interactions.

The antimicrobials with the greatest ability to significantly affect INR are sulfamethoxazole/trimethoprim, metronidazole, and fluconazole; ciprofloxacin and azithromycin may also clinically impact INR[34]. Ceftriaxone, widely used for treating urinary tract infections, also interacts significantly with warfarin, leading to INR elevation in anticoagulated patients[33]. Regarding amoxicillin/clavulanate, at high doses in anticoagulated patients, there is an increased risk of hemorrhagic events; however, the risk of INR alteration may also be associated with polypharmacy, since the greater the number of concomitant medications, the higher the chances of potential DIs[35]. Thus, the results found in the EDBs regarding the classification of DIs between warfarin and antimicrobials are consistent with previously described data in the literature.

It should be noted that antimicrobial treatment is generally short-term, ranging from 3 to 14 days, usually for acute infections. Treatment duration is normally established according to clinical trial results evaluating this variable for a given infection; dose and administration intervals, as well as distribution and elimination, also affect duration[36]. Treatment

duration therefore allows estimation of whether a DI will occur. One study that evaluated the implementation of a guide for managing DIs between warfarin and AMs in a hospital setting (inpatient and care transition) excluded patients on warfarin whose antimicrobial treatment lasted fewer than three days[6]. Another study suggests monitoring INR within three to five days of starting AM therapy and again three to five days after AM discontinuation[7].

Another important aspect is the scarcity of antimicrobial therapeutic alternatives, partly due to the AM's spectrum of activity, but also due to microbial resistance and the difficulty of developing and producing new antimicrobials[36].

In primary healthcare, INR monitoring is not performed at the health unit itself, so patients must return for exam result evaluation during consultation. This aspect, when combined with the patient's lack of understanding of their health condition, as well as the lack of training of professionals in the multidisciplinary team for oral anticoagulation management and indications, leads to difficulty in adequate INR monitoring of warfarin-anticoagulated patients[9].

In addition to the wide discrepancies between EDBs and the lack of information on DI classification, mechanism, and management, an important limitation of EDBs is that they report a large number of DIs of low clinical relevance, which can lead to alert fatigue and mask clinically significant DIs[23]. Inconsistencies among different EDBs are numerous: although an EDB can increase the capacity to detect clinically significant DIs, these systems are far from flawless, often alerting to clinically irrelevant DIs, which results in a higher number of false-positive alerts, or, occasionally, failure to identify clinically significant DIs[23]. Patient-specific characteristics and peculiarities are not considered, which may be a risk factor for excessive alerts[38]. According to studies in the literature, the only characteristic highly correlated with DI detection accuracy is the pharmacist's years of experience[39]. The assessment of clinical pharmacists would therefore be considered paramount, with the EDB serving as a tool for recognizing potential DIs, thereby aiming to increase DI detection, clinical interpretation, and appropriate management.

As suggestions to support the safe prescription of AMs for patients anticoagulated with warfarin, we highlight: searching at least three different EDBs; otherwise, discrepancies tend to be ignored[23]; elderly patients require special attention, particularly due to changes in hepatic and renal metabolism, as well as polypharmacy[23]; in the case of an identified and moderate DI, INR should be monitored; in the case of a severe DI, consider replacing the antimicrobial or evaluating possible medication administration strategies to minimize DI risk, depending on its mechanism; and monitor INR within three to five days of initiating antimicrobial therapy and again three to five days after discontinuation[7].

This study analyzed the agreement among EDBs regarding the presence of potential DIs involving antimicrobials listed in a municipal formulary of a Brazilian city and the anticoagulant warfarin, which is a drug with significant drug interactions with multiple medications. It demonstrated variability in the information obtained from EDBs, and considering the discrepancies among the data provided, it is possible to evaluate strategies to mitigate this problem. A limitation of this study is the inclusion of only four EDBs, although few comparative studies include more than two or three EDBs in their analyses. Different practice settings adopt different sources of consultation, and this study chose to evaluate the most widely used. Furthermore, this study aimed to analyze discrepancies among EDBs regarding potential DIs, not to determine whether the data are correct or incorrect.

Conclusion

The use of drug databases (DDs) is widespread, as they provide quick and concise information on DI mechanisms and management; however, significant inconsistencies were identified in the results they provide. Our study revealed that the total agreement rate for DI classification was relatively similar to the partial agreement rates. For the other two evaluated aspects, the description of the probable DI mechanism and the suggested DI management, the total agreement rate was relatively lower. Partial agreement rates for the parameters describing the DI mechanism and suggesting DI mana-

gement were higher than the total agreement rates. This highlights the importance of consulting three or more different DDs to obtain consistent information that can support clinical decision-making. Furthermore, more studies are needed to assess not only agreement among databases but also the robustness of the evidence used by DDs.

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