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Comparison of two databases to detect potential drug–drug interactions between prescriptions of HIV/AIDS patients in critical care

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SUMMARY

What is known and objective: **Adverse drug events (ADE), common and underestimated in ICU patients, have direct consequences on length of stay, mortality and hospital costs. Critically ill patients with HIV/AIDS are at a high risk of ADE because of their need for multiple drug therapies. ADE can be prevented, especially by the identification of potentially harmful drug–drug interactions (DDIs). Electronic databases are useful tools for the investigation of DDIs to avoid potential ADEs, thereby increasing patient safety. The purpose of this study was to compare the classification and severity rating of potential adverse drug interactions seen in the prescriptions for patients with HIV/AIDS in two databases, one with free access (Drugs.com™) and another requiring payment for access (Micromedex®).**

Methods: **A cross-sectional retrospective study of the prescriptions issued for 40 ICU HIV/AIDS patients on mechanical ventilation, admitted for more than 48 h, in a referral hospital for infectious diseases in Rio de Janeiro, Brazil, was undertaken. One prescription was reviewed each week for each patient from the second day after admission. A list of all drug–drug interactions was generated for each patient using the two drug–drug interactions databases. The weighted kappa index was estimated to assess the agreement between the classifications of DDIs identified by both databases and qualitative assessment made of any discordant classification of recorded drug–drug interactions.**

Results and discussion: **Of the 106 prescriptions analysed, Micromedex® and Drugs.com identified 347 and 615 potential DDIs, respectively. A predominance of moderate interactions and pharmacokinetic interactions was observed. The agreement between the databases regarding the severity rating was only 68·3%. The weighted kappa of 0·44 is considered moderate. Better agreement (82·4%) was observed in the classification of mechanism of interaction, with a weighted kappa of 0·61.**

What is new and Conclusion: **DDIs are common between the prescriptions of patients with HIV/AIDS admitted to the ICU. Although both databases were able to identify the clinically relevant DDIs, we observed a significant discrepancy in the classification of the severity of DDIs in the two bases. The free access database could serve as an alternative to the identification of DDIs in resource-limited settings; however, there is a need for better evidence-based assessments for your use on clinical management of more serious DDIs.**

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WHAT IS KNOWN AND OBJECTIVE

The long-term survival of patients with human immunodeficiency virus (HIV) has improved markedly since the introduction of highly active antiretroviral therapy (HAART).[1,2] UNAIDS/WHO estimated that around 34 million of people were living with HIV worldwide at the end of 2010.[3] This number is expected to continue to grow, in particular in third-world urban centres. This setting presents multiple challenges in establishing acceptable, efficacious and minimally toxic regimens, especially in the treatment of patients with HIV/AIDS with severe infections.[4]

Patients with HIV/AIDS presenting acute and severe illnesses can require multiple therapeutic schemes simultaneously, predisposing them to significant drug interactions and adverse drug events (ADE).[5] These events can affect patient's outcome and hinder clinical management, increasing hospital stay and costs.[6,7] Additionally, patients with HIV have a much greater rate of ADE to many drug classes, such as antimicrobials and anticonvulsants, including severe and life-threatening hypersensitivity reactions.[8] Therefore, critically ill patients with HIV/AIDS are prone to ADE, and their drug prescriptions should be monitored.

ADE can be prevented through the identification of relevant drug–drug interactions (DDIs). The term DDIs refers to the presence of a second drug altering the effectiveness or toxicity of the first drug. Clinically relevant DDIs can be predicted from the drug's properties, the method of drug administration and patient-specific parameters. Electronic databases are useful tools for to investigate and to prevent potential ADE, increasing patient safety.[9] Severely ill patients are especially susceptible to potential interactions, and the estimated incidence of potential interactions in the ICU is as high as 287·5 per 100 admissions.[10] However, many of the reference databases in pharmacovigilance, such as Micromedex® and Lexi-Interact™, require payment for access, restricting their use to a limited number of institutions. Therefore, we propose free access to electronic tools as an alternative for the management of DDIs in healthcare facilities with limited resources, especially in lower-income countries.

Therefore, the aim of this study was to compare the identification and classification of potential DDIs between prescriptions for patients with HIV/AIDS in the ICU using two databases, one with free access (Drugs.com™) and another requiring payment for access (Micromedex®).

METHODS

This cross-sectional retrospective study included patients with HIV/AIDS who were 18 years or older, using mechanical ventilation, and admitted for more than 48 h to the ICU of the Evandro Chagas Clinical Research Institute from November 2006 to September 2008. A non-probabilistic sample of 40 patients was selected from 75 eligible patients.

One prescription per week for the length of stay in the ICU was reviewed for each patient from the second day after admission. We considered only the drugs effectively administered and excluded prescribed drugs that were not administered.

We collected data on the prescription drugs, ICU length of stay, and demographic and clinical information from medical records. The Simplified Acute Physiology Score (SAPS II) was calculated to assess the severity of acute illness.[11]

This study was approved by the Evandro Chagas Clinical Research Institute Review Board and was registered in the National System of Information on Ethics in Research.

Drug Interaction Identification

Thomson Reuters Micromedex®[12] and Drug Information Database™ (Drugs.com™)[13] databases were used to identify potential drug–drug interactions. The overall study design is shown in Fig. 1.

Micromedex® is a registered database requiring payment that offers information related to references for drug management, diseases and conditions, as well as toxicology and patient education. This software identifies potential interactions and provides information regarding the mechanisms of potential adverse reactions and their clinical consequences.[12]

Drugs.com™ is a free database powered by four independent leading medical information suppliers: Wolters Kluwer Health, American Society of Health-System Pharmacists, Cerner Multum and Micromedex®.[13]

A list of all drug–drug interactions was generated for each patient according to each database. Both databases classify DDIs according severity. Micromedex classifies DDIs in four categories: contraindicated, major, moderate and minor. Drugs.com classifies severity into three categories: major, moderate and minor. For the database comparisons, the DDIs specified as contraindicated by Drugs.com were placed in a separate category (the complete database classifications are presented in Table S1). Additionally, Micromedex®[12] classifies the documentation (excellent, good and fair) and the onset of the event (rapid, delayed and not specified). The interaction mechanism was classified as pharmacokinetic or pharmacodynamic, through the use of the information provided by the databases. For pharmacokinetic interactions, the researchers identified the process involved (absorption, distribution, metabolism or excretion).

Each specific pair of drug–drug interaction was counted only once per patient. The drugs were classified in therapeutic classes according to the third level of the anatomical therapeutic chemical (ATC) classification.[14]

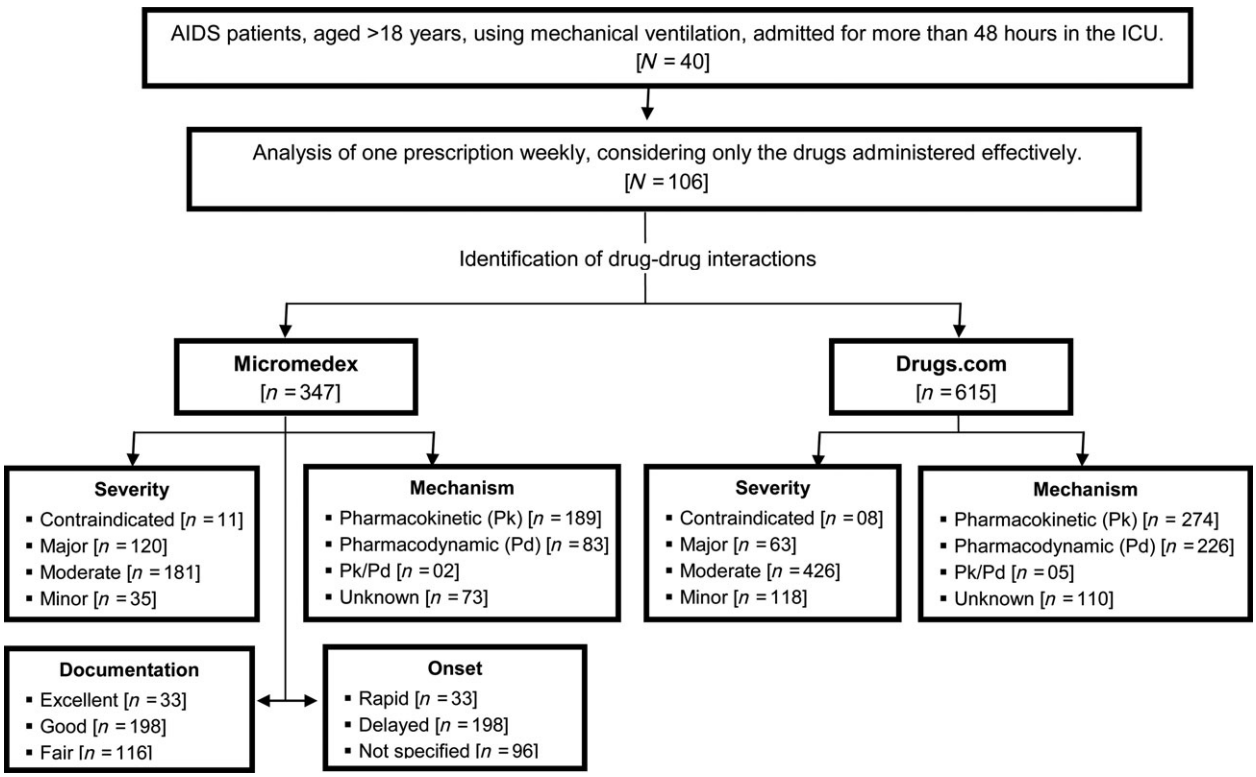

Fig. 1. Flowchart of the study: critically ill patients with AIDS, aged > 18 years, using mechanical ventilation, admitted for more than 48 h in the ICU.

Data analysis

Data were entered into EPIDATA 3.1 (http://www.epidata.dk) and were analysed with SPSS for Windows version 16.0 (SPSS Inc, Chicago, IL, USA). Exploratory analyses of demographic data and DDIs were performed using frequencies, medians and ranges. All tests were stratified for a comparison of the two bases.

The weighted kappa index was estimated to assess agreement between the classifications of DDIs identified by both databases and qualitative assessment made of any discordant classification of recorded drug–drug interactions. The kappa value was interpreted according to Landis and Koch[15] using qualitative descriptors: intraclass correlation values >0·80 are 'almost perfect'; 0·61–0·80, 'substantial'; 0·41–0·60, 'moderate'; 0·21–0·40, 'fair'; 0·00–0·20, 'slight'; and <0·00, 'poor'.

RESULTS

The study population comprised 40 patients and 106 prescriptions. The median age of patients was 36 years, with a male predominance (70%). The median SAPS II was 57 (range 31–87) points, and the length of stay in the ICU ranged from 2 to 52 days, with a median of 12 days. A median of 9 (range 3–18) drugs was prescribed for each patient.

Of the 106 prescriptions analysed, the Micromedex® database identified 347 potential DDIs, and the Drugs.com™ database identified 615 potential DDIs. A total of 307 DDIs were described in both of the databases. We observed a predominance of moderate interactions and pharmacokinetic mechanism in both databases. The Micromedex® database identified a predominance of DDIs with a delayed onset time (59·7%) and good scientific documentation (57·1%) (Table 1).

The most frequent DDI was Midazolam × Omeprazole, which was present in 55% of the prescriptions. Among the therapeutic classes, both databases identified Opioids × Hypnotics/Sedatives as the most common DDI of the therapeutic classes. However, 8·3% (Drugs.com™) and 15·3% (Micromedex®) of these DDIs are regarded as expected interactions resulting from institutional clinical protocols.

Regarding the severity of DDIs, Micromedex classified 37·6% of DDIs as contraindicated or major, whereas Drugs.com identified only 11·3%. DDIs classified as moderate were more frequent in both bases, 52·2% and 69·3%, respectively. The agreement between the two databases regarding severity was 68·3% with a moderate-weighted kappa (κ = 0·44) (Table 1). Micromedex detected six contraindicated DDIs. However, one of them was classified as moderate (Amitriptyline × Metoclopramide) by Drugs.com (Table 2). Efavirenz × Midazolam interaction was the most frequent (4/11) contraindicated DDIs. There were also differences in the severity classification of major DDIs detected between Micromedex and Drugs.com. Twenty-two major DDIs detected by Micromedex were classified by Drugs.com as moderate or minor in severity, whereas six major DDIs identified by Drugs.com were classified as minor and moderate by Micromedex database (Table S2).

Regarding the classification of the mechanism of action, we observed a predominance of pharmacokinetic DDIs. They represent 54·5% and 44·6% of DDIs identified by Micromedex and Drugs.com databases, respectively. The correlation between the databases was 82·4% with a substantially weighted kappa of 0·61.

Among the 347 DDIs identified by the Micromedex database, 9·5% (33) were classified as having an excellent documentation, being mostly of moderate severity (Table S3).

Table 1. Comparison of drug–drug interactions characteristics between the Micromedex and Drugs.com databases

	Micromedex (n = 347)	Drugs.com (n = 615)
Severity, n (%)[a]		
Contraindicated	11 (3·2)	8 (1·3)
Major	120 (34·6)	63 (10·2)
Moderate	181 (52·2)	426 (69·3)
Minor	35 (10·1)	118 (19·2)
Mechanism, n (%)[b]		
Unknown	73 (21·0)	110 (17·9)
Pharmacokinetic	189 (54·5)	274 (44·6)
Pharmacodynamic	83 (23·9)	226 (36·7)
Pharmacokinetic/ Pharmacodynamic	2 (0·6)	5 (0·8)
Onset, n (%)[c]		
Rapid (until 24 h)	44 (12·7)	–
Delayed (after 24 h)	207 (59·7)	–
Not Specified	96 (27·7)	–
Documentation, n (%)[c]		
Excellent	33 (9·5)	–
Good	198 (57·1)	–
Fair	116 (33·4)	–

[a]Weighted kappa for severity: 0·44.
[b]Weighted kappa for mechanism: 0·61.
[c]Information about the onset and documentation is only present in the Micromedex database.

Table 2. Comparison of contraindicated drug–drug interactions between the Micromedex and Drugs.com databases

	MICROMEDEX	DRUGS.COM
Efavirenz × Midazolam	Contraindicated	Contraindicated
Midazolam × Ritonavir	Contraindicated	Contraindicated
Amitriptyline × Metoclopramide	Contraindicated	Moderate
Haloperidol × Metoclopramide	Contraindicated	Contraindicated
Metoclopramide × Risperidone	Contraindicated	Contraindicated
Atazanavir × Midazolam	Contraindicated	Contraindicated

DISCUSSION

In this population of severely ill patients with HIV/AIDS, we demonstrated a high frequency of DDIs between prescriptions. Both databases were able to identify DDIs, and both showed a higher frequency of observations related to moderate interactions and pharmacokinetic mechanism. The agreement between the databases regarding severity and mechanism of action was considered moderate (κ = 0·44) and substantial (κ = 0·61), respectively.

The most prevalent drug interaction between therapeutic classes in the two databases was Opioids × Hypnotics/Sedatives. Among the DDIs related to these classes, stands out Midazolam × Fentanyl, a common combination frequently used for patients sedation during mechanical ventilation. The combination of these two drugs can be characterized as a

pharmacodynamic interaction, mainly by the additive effects on the central nervous system (CNS). The high frequency of DDIs among these classes was also observed by Reis and Cassiani.[16] In their study, Fentanyl × Midazolam was the most identified DDI. However, the combination of Opioids × Hypnotics/Sedatives is used in intensive care in clinical protocols with therapeutic goals,[17] and the high prevalence of this interaction in our sample of severely ill patients was expected. Among the unexpected DDIs, Midazolam × Omeprazole was the most detected in both databases. Their mechanism of action is pharmacokinetic and involves reduction of metabolism and excretion of midazolam with the potential increase in the CNS depressant effects.

Stratifying the interactions according severity and comparing the findings from both databases, we found that the base Drugs.com tends to be less stringent than the Micromedex. Among the contraindicated DDIs, we observed discrepancy between Amitriptyline × Metoclopramide classified as moderate by Drugs.com. The same trend was observed between the major interactions, which may influence the relevance and appropriate clinical management against these interactions.

We observed a significant agreement between the two databases regarding the identification of DDIs. We also observed a moderate and substantial agreement for severity and mechanism of action, respectively. However, the Drugs.com™ interaction database identified a greater number of DDIs than Micromedex®.

This difference in the number of interactions identified can be explained by the fact that the Drugs.com™ database is powered by four independent leading medical information suppliers, including Micromedex®. However, individual drug information in the Drugs.com™ database can be misleading because it is compiled from these sources in its complete and unaltered format. Alternatively, the Micromedex® database screens published data on evidence-based concepts, using peer-review scientific journals and providing an assessment of the quality of documentation. This approach avoids the problem of identifying a large number of drug–drug interactions with no clear presentation of clinical significance or relevance, which can lead to fatigue to clinical alerts.[18]

The present study has limitations. First, a retrospective data collection can generate a bias due to an incomplete patient record. However, the analysis of this study only considered drugs that were effectively administered. Second, this study was developed in a specialized ICU, thus limiting the ability to generalize the results. Moreover, as the Drugs.com database is also fuelled by the Micromedex database, data concordance may be overestimated.

WHAT IS NEW AND CONCLUSIONS

In conclusion, both databases were able to identify DDIs. However, we observed a significant discrepancy in the classification of the severity of DDIs in the two bases. The free access database could serve as an alternative to the identification of DDIs in resource-limited settings, but there is a need for better evidence-based assessments for your use on clinical management of more serious DDIs. Besides, to understand the connection between potential DDIs in prescriptions and ADEs arising from DDIs, future studies are needed to quantify and characterize DDIs and their consequences.

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AUTHORS CONTRIBUTIONS

All authors made substantial contribution to the study design and methods. GVR, LG, AMJ and FAB conceived of the study. GVR and AMJ collected clinical data. All authors performed the data analysis. The authors thanks Dr Raquel de Vasconcellos Carvalhaes de Oliveira for the statistical support. GVR, LG, and FAB drafted the manuscript, and AMJ critically revised it for important intellectual content. All authors read and approved the final version of the manuscript. The authors have not disclosed any potential conflicts of interest.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 Severity classification according the Micromedex and Drugs.com databases.

Table S2 Comparison of major drug-drug interactions between the Micromedex and Drugs.com databases.

Table S3 Drug-Drug interactions with excellent documentation according severity, detected by Micromedex database.

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