RBFHSS
Revista Brasileira de Farmácia Hospitalar e Serviços de Saúde

Original Paper

Open Access

Dosage adjustment in renal insufficiency: comparison between databases

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Submitted: 01-03-2023 Resubmitted: 30-01-2024 Accepted: 08-03-2024

Peer review: blind reviewer and Paula Pimenta

Abstract

Objective: To compare the information provided by three databases regarding dosage adjustment in renal failure of standardized drugs in a Brazilian teaching hospital in the Midwest region. **Method:** This is a documentary, descriptive and analytical study with a qualitative approach based on the analysis of information on standardized drugs in that hospital. The main variables collected were: whether the medication requires dose adjustment based on renal function, whether it is dialyzable or not. Agreement between databases was analyzed by calculating Cohen's kappa (k) coefficient, which measures agreement between two observers. The agreement regarding the information on whether there was a dosage adjustment and whether the drug would be removed during hemodialysis was evaluated. **Results:** A total of 262 drugs were included (81.9% of the standardized in the institution). UpToDate® presented information for a greater number of medications, 228 medications (87%) for renal adjustment and 185 medications (70.6%) for behavior during dialysis. Micromedex® was the basis with information for the smallest quantity of drugs. Regarding the comparison between the databases regarding dosage adjustment, a moderate agreement was observed between UptoDate® and Micromedex® (k=0.474) and a fair agreement between UpToDate® and Whitebook® (k=0.379). In the comparative analysis regarding the behavior of drugs during dialysis, both UpToDate® and Micromedex® and UpToDate® and Whitebook® showed slight agreement (k=0.188 and k=0.187, respectively). **Conclusion:** This study found variability between the UpToDate®, Micromedex® and Whitebook® databases regarding information on dosage adjustment in renal failure and suggests considering more than one source for clinical decision-making.

Keywords: dosage; acute kidney injury; chronic renal failure; renal replacement therapy; data base

Ajuste posológico na insuficiência renal: comparação entre bases de dados

Resumo

Objetivo: Comparar as informações fornecidas por três bases de dados referentes ao ajuste posológico na insuficiência renal dos medicamentos padronizados em um hospital de ensino brasileiro da região Centro-Oeste. **Método:** Trata-se de um estudo documental, descritivo e analítico com abordagem qualitativa a partir da análise de informações dos medicamentos padronizados no referido hospital. As principais variáveis coletadas foram: (i) necessidade de ajuste da dose do medicamento com base na função renal; (ii) informação quanto a dialisação do medicamento. A concordância entre as bases foi analisada calculando o coeficiente kappa (*k*) de Cohen que mede a concordância entre dois observadores. Foi avaliada a concordância da informação quanto ao ajuste posológico e se o medicamento seria removido na hemodiálise. **Resultados:** Foram incluídos 262 medicamentos (81,9% dos padronizados na instituição). O *UpToDate®* apresentou informação para um número maior de medicamentos, sendo 228 medicamentos (87%) para ajuste renal e 185 medicamentos (70,6%) para o comportamento durante diálise. O *Micromedex®* foi a base com informação para a menor quantidade de medicamentos. Com relação a comparação entre as bases de dados referente ao ajuste posológico, observou-se uma concordância moderada entre *UptoDate®* e *Micromedex®* (*k*=0,474) e uma concordância razoável entre *UpToDate®* e *Whitebook®* (*k*=0,379). Na análise comparativa quanto ao comportamento dos medicamentos durante diálise, tanto *UpToDate®* e *Micromedex®* quanto *UpToDate®* e *Whitebook®* apresentaram concordância fraca (*k*=0,188 e *k*=0,187, respectivamente). **Conclusão:** Este estudo encontrou variabilidade entre as bases *UpToDate®, Micromedex®* e *Whitebook®* em relação às informações sobre ajuste posológico na insuficiência renal e sugere considerar mais de uma fonte para a tomada de decisões clínicas.

Palavras-chave: posologia; injúria renal aguda; insuficiência renal crônica; terapia de substituição renal; base de dados

Introduction

Renal Insufficiency (RI) or Renal Disease (RD) occurs when the kidneys lose or are unable to perform their regulatory, exocrine and endocrine functions[1], and can be Acute (ARF) or Chronic (CRF). According to the Brazilian Society of Nephrology[2], ARF is caused by the sudden loss of the kidneys' ability to filter waste produced by our metabolism, which can include food, medication, blood fluids and salts. Hospitalized patients, depending on their clinical condition and the worsening of the case, can develop ARF[2] with the highest incidence in intensive care units and the lowest incidence in wards[3-4]. ARF can occur progressively or rapidly, and its course will depend on the patient's state of health. It may be reversible, but this does not rule out the need for intensive treatment, as ARF can be fatal. Some of the possible causes of ARF and actions to be taken are the need to restore blood flow to the kidneys, de-prescribing medications that can be nephrotoxic or removing an obstruction in the urinary tract[2]. As this condition can be reversible, hemodialysis (HD), if necessary, is carried out until the body's homeostasis is re-established.

Chronic Kidney Disease (CKD) or Chronic Renal Failure (CRF) is an initially asymptomatic, progressive, and irreversible condition in which there is a renal metabolic imbalance, with biochemical and hydroelectrolytic disorders[5-6]. Toxic substances present in the blood are retained in the body due to loss of kidney function[7]. According to Oliveira et al[8], the disorders caused by CRF are directly or indirectly responsible for high rates of hospitalization, morbidity, and mortality, as well as impacting on patients' quality of life.

Due to the progression of kidney damage, in most cases renal replacement therapy (RRT) is required, which can include intermittent hemodialysis, peritoneal dialysis, hemofiltration, prolonged intermittent renal replacement therapy and continuous renal replacement therapy[9-10]. Intermittent hemodialysis is chosen in the vast majority of cases[11]. Patients with acute or chronic kidney disease have other associated comorbidities, and their presence requires the use of medications to control them. In addition, patients undergoing dialysis and using polypharmacy may have a greater potential for medication interactions[12-13]. The accumulation of these substances due to renal dysfunction affects their elimination, increasing the risk of nephrotoxicit[14]. The risk of adverse reactions in these patients is related to the excretion of the medications via the kidneys and the Glomerular Filtration Rate (GFR) in debt. The medications used require a dose adjustment based on the GFR calculation, to avoid adverse reactions and toxicity[13,15].

Hospitalized patients use antimicrobials, antifungals, antivirals, and other medications to manage the disease, in addition to treating their underlying illnesses and other disorders that can affect critically ill patients. It is therefore of great importance to know which drugs are used, whether they are dialyzable or not and whether they need to be adjusted based on renal function[16], as well as knowing about nephrotoxicity, monitoring the patient's renal function from the start of treatment, and making dose adjustments[14]. When undergoing RRT, dosage adjustment must be carried out, post-HD scheduling or dose replacement, if necessary[17], in order not to jeopardize the patient's treatment, guaranteeing their safety and avoiding excessive spending on medication. In clinical practice, this information is obtained by consulting various sources such as institutional guides, reference books, scientific articles, websites, and databases. The use of apps for mobile devices has become increasingly common, given the practicality and constant updating that many offer. Some health institutions provide their professionals with access to these tools.

Studies have shown that databases differ in the information they provide. Kheshti et al.[18] compared the ability of programs to detect clinically important medication interactions and concluded that all the programs evaluated were deficient in detecting medication interactions. McConachie et al.[19] compared the presentation of adverse drug reactions in medication information programs, and identified variations between them that could impact clinical decisions.

Despite the importance of knowing the behavior of medications in patients with renal dysfunction, we found no studies in the scientific literature on which tool is most suitable for consultation. Therefore, this study aimed to compare the information provided by three databases regarding the dosage adjustment in renal failure of standardized medications in a teaching hospital in the Midwest region.

Methods

This is a documentary, descriptive and analytical study with a qualitative approach based on the analysis of standardized medications at a university hospital in the Midwest region. The hospital under study is a state reference in infectious diseases, cardiovascular surgery, hemodialysis, high-risk pregnancy, renal therapy, among others, and has 228 beds for adult and pediatric hospitalization.

The medications to be analyzed were selected based on the items standardized at the institution and included in the pharmacotherapeutic guide, version 2020. All medications with a systemic action, regardless of the route of absorption, used in surgical or diagnostic procedures were included. For medications with more than one route of administration, only those with predominantly systemic absorption were considered.

The databases used in this study were UpToDate®, Whitebook® and Micromedex®, which are commonly used by health professionals at the institution, mainly physicians and pharmacists. These databases help in making therapeutic decisions through information such as adverse effects, medication interactions, toxicity, administration precautions, preparations, among other important information in day-to-day clinical practice.

The American database UpToDate® is available in English to residents and collaborators at the hospital where the study was carried out. It can be accessed via the website or mobile app, and contains up-to-date medication monographs, as well as various scientific articles on a wide range of subjects; it also provides medication interactions to be analyzed and their severity reported. The Brazilian database Whitebook® is a privately-accessible mobile application in Portuguese with free features, which provides information such as buliaries, treatments, imaging tests, dilutions, calculators and scores, guides, laboratory tests and other information for health professionals. Like Whitebook®, Micromedex® is a database available as a paid mobile application, which is only available in English, as it is an American database, where you can also access information on medications, adverse reactions, and medication incompatibilities. Both the Whitebook® and Micromedex® are not available on the institution's intranet.

The main variables collected were, as follows: whether the medication is dialyzable or not; whether there is a dose adjustment based on renal function and hemodialysis. The information was collected manually by consulting the selected databases and recorded in a Microsoft® Excel 2016 spreadsheet between March and October 2022 by the researchers. The results were then systematized and subjected to simple descriptive analysis. Absolute and relative frequencies were calculated for the qualitative variables. To compare the databases, UpToDate® was used as a reference because it is available to all collaborators. Agreement between the databases was analyzed by calculating Cohen's kappa coefficient (k), which measures agreement between two observers. Agreement was assessed in relation to information on whether there was a dosage adjustment and whether the drug would be removed during RRT. The kappa values were interpreted using the Landis and Koch[20] criteria. Kappa values: between 0.00 - 0.20 indicate weak agreement; between 0.21 - 0.40, reasonable agreement; between 0.41 - 0.60, moderate agreement; between 0.61 - 0.80, substantial agreement; and between 0.81 - 1.0, almost perfect agreement. The statistical analyses were carried out using the IBM® SPSS Statistics program, version 20. The tables were structured to show the medications that were adjusted for renal function or not, dialyzable medications or not, and those not found/not informed (NF/NI) in the databases. In addition, there was a comparison between agreement on dose adjustment and whether or not the medication was dialyzable.

Table 1. Absolute and relative frequency of medications evaluated according to the need for dosage adjustment in renal failure and database consulted (n=262)

	UPTODATE®	MICROMEDEX®	WHITEBOOK®
WITH dosage adjustment	85 (32.4%)	83 (31.7%)	91 (34.7%)
WITHOUT dosage adjustment*	143 (54.6%)	80 (30.5%)	122 (46.6%)
Total medications found	228 (87%)	163 (62.2%)	213 (81.3%)
NF / NI **	34 (13%)	99 (37.8%)	49 (18.7%)
Total	262 (100%)	262 (100%)	262 (100%)

NF/NI: not found or not informed. *Medications without adjustment or with observations, but without objective and clear guidelines. **Medications that were not included in the databases and medicines that had no information on adjustment.

Table 2. Distribution of medications studied according to behavior during renal replacement therapy procedures and database consulted

	UPTODATE®	MICROMEDEX®	WHITEBOOK®
Dialyzable	49 (18.7%)	2 (0.7%)	13 (5.0%)
Non-dialyzable	136 (51.9%)	62 (23.7%)	96 (36.6%)
Total medications found	185 (70.6%)	64 (24.4%)	109 (41.6%)
NF / NI	77 (29.4%)	198 (75.6%)	153 (58.4%)
Total	262 (100%)	262 (100%)	262 (100%)

NE/NI: não encontrado ou não informado

Results

In the hospital's pharmacotherapeutic guide, version 2020, 320 different medications were standardized. According to the inclusion and exclusion criteria, 58 (18.1%) medications were excluded, and 262 (81.9%) of the standardized medications were analyzed in the databases.

Antimicrobials and antifungals accounted for 20.6% of the medications evaluated (54 drugs). Regarding renal adjustment or dialysis behavior, in Micromedex® 9 (16.7%) antimicrobials were not found or not reported. In Whitebook® there were 7 (12.9%) and in UptoDate® there were 2 (3.7%) antimicrobials.

Of the 262 medications evaluated in relation to the need for dosage adjustment in renal failure, 5 (1.9%) medications were not found or did not have this information on any database. Table 1 shows the absolute and relative frequencies of the medications evaluated according to renal adjustment. UpToDate® was the database where information was found for the largest number of medications (87%), followed by Whitebook® (81.3%). The Micromedex® platform had the highest number of NF/NI medications with a total of 99 (37.8%).

In relation to behavior during dialysis (Table 2), UpToDate® provided information on the largest number of medications (185 medications, 70.6%), followed by Whitebook® (109 medications, 41.6%) and Micromedex® (64 medications, 24.4%).

Regarding the comparison between the databases for dosage adjustment, Cohen's kappa value was higher than 0.41 (kappa = 0.474; p<0.001) between UptoDate® and Micromedex®, indicating moderate agreement, according to Landis and Coch's criteria[20]. On the other hand, agreement between UpToDate® and Whitebook® was reasonable (kappa = 0.379; p<0.001). Table 3 shows the data from the analysis of agreement regarding dosage adjustment. The Micromedex® and UpToDate® databases disagreed on the need to adjust 19 medications (7.3%). Whitebook® and UpToDate® disagreed on 26 medications (9.9%).

In the comparative analysis of medication behavior during RRT, both UpToDate® and Micromedex® as well as UpToDate® and Whitebook® showed kappa values of less than 0.20, indicating poor agreement (Table 4). The kappa values found in the UpToDate® and Micromedex® comparison were 0.188 (p<0.001) and between UpToDate® and Whitebook® were 0.187 (p<0.001). There was disagreement on whether or not it should be removed during HD in 6 medications (2.3%) in the UpToDate® and Micromedex® comparison and in 4 medications (1.5%) between UpToDate® and Whitebook®.

Discussion

This study compared three databases in relation to their differences in information on the need for dose adjustment in patients with kidney failure and/or undergoing HD. There were differences in the information on renal adjustment and dialyzable medications. The UpToDate® database provided information on a greater number of medications than the other databases. Therapeutic management and patient safety require access to and analysis of this information. As well as informing whether or not dose replacement is necessary. The platforms also presented discordant data in relation to these results, which shows the need for double-checking information on the medications to be administered to patients undergoing RRT.

Table 3. Agreement between databases regarding dosage adjustment in renal failure (n=262)

	MICROMEDEX® - Adjustment				
	NF / NI	**Yes**	**No**	**Total**	**kappa**
UPTODATE® - Adjustment	NF / NI	29 (11.1%)	2 (0.8%)	3 (1.1%)	34 (13%)	0.474 p<0.001
	Yes	11 (4.2%)	68 (26%)	6 (2.3%)	85 (32.4%)	
	No	59 (22.5%)	13 (5%)	71 (27.1%)	143 (54.6%)	
	Total	99 (37.8%)	83 (31.7%)	80 (30.5%)	262 (100%)	
	WHITEBOOK® - Adjustment				
	NF / NI	**Yes**	**No**	**Total**	**kappa**
	NF / NI	5 (1.9%)	7 (2.7%)	22 (8.4%)	34 (13%)	0.379 p<0.001
	Yes	9 (3.4%)	67 (25.6%)	9 (3.4%)	85 (32.4%)	
	No	35 (13.4%)	17 (6.5%)	91 (34.7%)	143 (54.6%)	
	Total	49 (18.7%)	91 (34.7%)	122 (46.6%)	262 (100%)	

NF/NI: not found or not informed. Kappa values: between 0.0- 0.20 are considered weak; between 0.21- 0.40 are reasonable; between 0.41- 0.60 are moderate; between 0.61- 0.80 are substantial; between 0.81- 1.00 are almost perfect.

Table 4. Agreement between the databases regarding the behavior of medications during the renal replacement therapy procedure (n=262)

	MICROMEDEX® - Dialysis				
	NE / NI	**Sim**	**Não**	**Total**	**kappa**
UPTODATE® - Dialysis	NE/NI	71 (27.1%)	0 (0%)	6 (2.3%)	77 (29.4%)	0.188 p<0.001
	Sim	43 (16.4%)	1 (0.4%)	5 (1.9%)	49 (18.7%)	
	Não	84 (32.1%)	1 (0.4%)	51 (19.5%)	136 (51.9%)	
	Total	198 (75.6%)	2 (0.8%)	62 (23.7%)	262 (100%)	
	WHITEBOOK® - Dialise				
	NE / NI	**Sim**	**Não**	**Total**	**kappa**
	NE/NI	50 (19.1%)	1 (0.4%)	26 (9.9%)	77 (29.4%)	0.187 p<0.001
	Sim	33 (12.6%)	12 (4.6%)	4 (1.5%)	49 (18.7%)	
	Não	70 (26.7%)	0 (0%)	66 (25.2%)	136 (51.9%)	
	Total	153 (58.4%)	13 (5%)	96 (36.6%)	262 (100%)	

NF/NI: not found or not informed. Kappa values: between 0.0- 0.20 are considered weak; between 0.21- 0.40 are reasonable; between 0.41- 0.60 are moderate; between 0.61- 0.80 are substantial; between 0.81- 1.00 are almost perfect.

The literature presents several studies on the occurrence of kidney problems in Brazilian patients. Inda-Filho et al.[21] analyzed the epidemiological profile of patients with ARF admitted to Intensive Care Units (ICUs) in the Federal District, Brazil. They found that 21.3% of the 8,131 patients developed ARF and mortality in this group of patients was higher than in those without ARF (25.7% against 4.9%). Other authors have reported drug-related problems (DRPs) in hospitalized patients undergoing RRT[16,22-23]. Moreira et al.[23] identified in their study that approximately 40% of hospitalized patients using antimicrobial therapy and undergoing RRT had a greater chance of medication interactions, most of which were identified as serious or potentially serious, mainly adverse events related to the cardiovascular system and changes in plasma glucose.

The study by Spanevello et al.[13] showed that 54 to 61.4% of the 88 medications used by hemodialysis patients required dose adjustment, using the Micromedex® database as a source of information. They also reported that the most commonly interacting medications were furosemide, anlodipine and enalapril. In relation to the severity of these interactions, 32.3% of the patients had an interaction between anlodipine and simvastatin. The author also pointed out that the main MI of moderate severity found was with enalapril and furosemide, which can result in postural hypotension, which is aggravated in HD patients.

Carvalho et al.[24] highlight the need to administer medications at a different time to HD, in order to avoid possible interferences, such as their elimination or metabolization, and recommend that they be administered before or after dialysis. Patients in the ICU who are treated with antimicrobials and undergo RRT need special care, as dialysis alters the bioavailability of the antimicrobial, impairing the effectiveness of the treatment. This was demonstrated by Oliveira[25] who compared the pharmacokinetics of meropenem and vancomycin in terms of the percentage that were dialyzable, where meropenem showed 78% clearance compared to vancomycin, with 41%. Despite the difference, both medications suffer a great loss with dialysis, requiring their administration after the dialysis process and the need to check for possible dose supplementation if administered pre-dialysis.

Many drugs are nephrotoxic and can induce ARF or aggravate CRF[5,26]. In particular, antimicrobials in the aminoglycoside class have the greatest potential for nephrotoxicity, since when concentrated they produce damage to proximal tubular cells. Their administration should be carried out with caution, with constant monitoring and necessary dose adjustments, the factors related to aminoglycoside nephrotoxicity being those reported by Rosenberg[5]. Like aminoglycosides, non-steroidal anti-inflammatory drugs (NSAIDs) can induce different forms of kidney damage, as well as electrolyte disturbances, nephrotic syndrome, and other reactions. NSAIDs may have an increased risk of inducing Acute Kidney Injury (AKI) when combined with diuretics, Angiotensin Converting Enzyme Inhibitors (ACEIs), Angiotensin Receptor Blockers (ARBs) and Calcineurin Inhibitors (CNIs)[27].

In the scientific literature, no study was found that compared databases in relation to dosage adjustment in renal failure. Several authors have evaluated the performance or capacity of these sources in terms of detecting drug interactions or providing information on medications. Shareef et al.[28] compared the evidence between six databases regarding the drug interaction of psychotropic medications and COVID-19 therapies and concluded that the reliability or agreement is variable and that there are important divergences between the sources. Kheshti et al.[18] compared 5 drug interaction screening programs, identifying variations and deficiencies in the programs, suggesting an evaluation of interactions in two programs or more, to compare their results. McConachie et al.[19] compared the formatting of the frequency of adverse reactions of 20 medications between 7 databases, showing that the formatting was different between them, due to the variation in information, such as references, severity, and other parameters that can influence clinical decisions. In our study, when comparing the databases, we also observed a difference between them, both in the number of medications with data on adjustment and dialysis and in the agreement between these databases. The kappa coefficient used to measure agreement showed a moderate and reasonable value in relation to dosage adjustment and a weak value in relation to behavior during dialysis. This shows that clinical decisions should be made considering more than one source of information and individualized to the patient's profile and clinical conditions.

There are limitations to the study. The databases studied differ in the organization or presentation structure of the available data, often valuing certain aspects of medication behavior to the detriment of others, which can influence the identification of information. The difficulty of accessing paid platforms, the correct interpretation of those in another vernacular, as well as infrequent updating in some cases, were also limitations encountered.

Conclusion

The importance of knowing whether the medication is dialyzable or not, as well as the necessary adjustment to be made in patients with renal insufficiency, serves to properly manage the patient, reduce medication-related problems, and not harm the treatment, aiming for better treatment efficacy. Databases are excellent sources for quick consultations and to aid decision-making, but this study concluded that no matter how much information a database can provide, more than one source should be considered, due to the variability of information between them, whether it is due to medications not being registered, or the absence or different information on whether the medication is dialyzable or not.

Funding sources

This research did not receive funding.

Collaborators

IFM, EAMD and EOA conceived the project; IFM and EAMD collected the data; IFM, EAMD and EOA analyzed and interpreted the data; IFM, EAMD and EOA drafted the article; IFM, EAMD and EOA critically reviewed the article and approved the final version. All authors are responsible for all aspects of the work in ensuring the accuracy and integrity of any part of the paper.

Acknowledgements

The authors would like to thank the Maria Aparecida Pedrossian University Hospital (HUMAP) and the Federal University of Mato Grosso do Sul (UFMS) for their support in carrying out this study.

Conflict of interest statement

The authors declare that they have no conflicts of interest.

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