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Causality assessment of adverse drug reactions by applying a global introspection method in a high complexity hospital

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ABSTRACT

Background: Causality assessment of adverse drug reactions (ADRs) is an essential approach in pharmacovigilance. The World Health Organization-Uppsala Monitoring Center (WHO-UMC) system has been considered one of the most adequate method for establishing causal relationship in hospitalized patients.
Objective: To describe the causality of potential ADRs in hospitalized patients assessed by the WHO-UMC system and by different healthcare professionals.
Methods: Three healthcare professionals, with different backgrounds, acted as judges to adjudicate the causality categories for potential ADRs according to WHO-UMC system, in a Brazilian high complexity hospital. Judges' agreement was evaluated by using Fleiss' and Cohen's kappa coefficients.
Results: Ninety potential ADRs identified in 300 participants were adjudicated by each judge, comprising a total of 270 assessments. Most potential ADRs were classified as probable or possible (77.8%). Fleiss´ kappa revealed slight concordance among judges (k = 0.096;CI:95%;0.01–0.18).
Conclusions: Diverse backgrounds may have influenced the results for causality assessment of ADRs by employing the WHO-UMC system. Despite the slight concordance found for the method, this result suggests potential opportunity to enrich the ADRs management by engaging multiprofessional teams in the process. Further studies should be considered to investigate the performance of methods for ADRs assessment in hospitalized patients in low- and middle-income countries.

1. Introduction

The causality assessment of adverse drug reactions (ADRs) is an essential and complex approach in pharmacovigilance, as an attempt to investigate the connection between the suspected ADR and the use of a certain drug. An adequate causality classification of ADRs, especially in institutions providing high complexity assistance, may contribute to their early recognition, prevention of recurrence and optimization of drug therapy, thus improving the quality of patient care.[1] There are some available tools with applicability for this classification, as algorithms, probabilistic approaches and global introspection methods. For the latter, clinical experience prints a relevant subjective value in the causality assessment of ADRs, not covered by algorithms or probabilistic methods.[2] In this context, experts` judgement becomes a fundamental stage to identify and to establish a causal relationship between ADR and a drug treatment.[1,3]

The World Health Organization-Uppsala Monitoring Center (WHO-UMC) system is a global introspection method, used for causality assessment, based on expert judgement, though delimited by specific criteria.[3,4] Despite the lack of consensus about a gold standard method, a comparative study, using ten different methods suggested the WHO-UMC system as the most consistent for establishing causal relationship between drug usage and the occurrence of ADR in hospitalized patients.[1] Once this method allows the evaluation of the quality of the report, the WHO-UMC system is considered a convenient and planned tool for individual case reports and due to its good performance, global introspection methods are being preferable over statistical methods.[1,2,5] Thereby, considering the current state of art, expert judgement remains as a decisive factor in causality evaluation of ADR.[1,2] However, some limitations of global introspection methods have been raised, such as the poor reproducibility among judges.[3] Individual experience or different backgrounds could lead to a tendency of attributing

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discrepant results for causal relationship of ADRs.[6] In contrast, the assessment performed by multiprofessional teams can be essential to validate ADR categorization.

Pharmacovigilance practices, including causality assessment of ADRs, are well documented in high-income countries. However, there are few investigations describing this process in low- and middle-income countries (LMICs).[7] Despite the recent progress, these practices are still considered immature in LMIC.[7] Poor quality reports, lack of investments and innovative approaches, as well as a fragile notification culture have been raised as contributing factors for this scenario.[2,7] In Brazil, a middle-income country, the use of WHO-UMC is recommended by the Brazilian Health Regulatory Agency (Agência Nacional de Vigilância Sanitária – Anvisa) for an individual categorization of ADR.[8] To date, results for the employment of WHO-UMC system has not been described for causality assessment of ADRs in hospitalized patients in LMIC with the participation of healthcare professionals with different backgrounds. Thus, this study sought to describe the causality assessment of potential ADRs in hospitalized Brazilian patients applying the WHO-UMC system and to calculate the interrater agreement among healthcare professionals.

2. Methods

This is a sub-study of an observational prospective investigation of adverse drug events conducted in a general 500-bed public university hospital in Belo Horizonte, Southeastern Brazil.[9] This facility is a region referral center of high complexity with approximately 16,000 hospital admissions a year. A total of 300 hospitalized adults ($\geq$18 years) were consecutively recruited in surgical and medical units. Patients in respiratory isolation, with communication difficulties or without a responsible caregiver were not considered eligible to be enrolled in this study. All study participants or their respective legal guardians signed a written consent form.

The occurrence of adverse drug events was primarily assessed from patients´ clinical alterations by a pharmacist, a nurse and a physician acting independently as judges. Detailed methods for ADRs screening are available elsewhere.[9] Then, candidate ADRs were extracted from database and assessed independently by another team, also including a pharmacist, a nurse and a physician. It is noteworthy that they were not involved in providing care to the study participants. The WHO definition for ADR was adopted herein comprising a noxious and unintended response to a medicinal product which occurs at doses normally used in man (www.who.int).

For each potential ADR, three healthcare professionals with different backgrounds acted as judges to adjudicate, independently, the causality categories for potential ADRs. These professionals were selected due to their experience in clinical practice, in research and in pharmacovigilance programs, including ADR assessment. They were indicated in this study, as follows: Judge A (nurse), Judge B (pharmacist) and Judge C (physician). A training session was offered to these judges with the purpose of standardizing the use of the WHO-UMC system for analysis of the causality assessment of potential ADR. Expert adjudication process involved the record of ADR causality assessment in a form developed specifically for this study. ADRs were classified into six categories (certain, probable, possible, unlikely, conditional, unassessable), according to WHO-UMC criteria.[4] Additionally, the judge was required to register the suspected drug(s) to have caused ADR. For certain, probable and possible categories a link with a drug was required. According to the methodology, ADR is classified as unlikely when an "event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) or when disease or other drugs provide plausible explanations", and a suspected drug could be assigned for this category. For those reports classified as unassessable, no suspected drug was attributed to potential ADR due to insufficient or contradictory information indicated by the judge during the adjudication.[4]

The judges reviewed standardized forms containing patients' data (age, sex, diagnosis, type of comorbidities, laboratory data, daily clinical data and drug therapy) and ADR information (onset/end of clinical manifestation, history of allergies, administered doses, drug interactions, suspected drugs and length of drug treatment).

Table 1
Descriptive data of patients identified with ADR by WHO-UMC system.

Characteristics	Value
Age *(years)* [median, (IQR)]	63 (51.0–70.8)
Sex [n, (%)]	
Female	33 (51.6)
Male	31 (48.4)
Admission	
Emergency	60 (93.8)
Elective	4 (6.2)
Type of treatment	
Clinical	47 (73.4)
Surgical	17 (26.6)
Underlying disease	
Circulatory disease	30 (46.9)
Neoplasm	9 (14.1)
External causes	5 (7.8)
Other diagnosis	20 (31.2)
ADR length *(days)* [mean, (SD)]	3.0 (2.9)
ADR per patient [n, (%)]	
1	45 (70.3)
2	13 (20.3)
3	5 (7.8)
4	1 (1.6)
ADR [n, (%)]	
Hypotension	19 (21.1)
Constipation	17 (18.9)
Bleeding	11 (12.2)
Hyperglycemia	10 (11.1)
Renal Injury	10 (11.1)
Somnolence	6 (6.7)
Others ADR[a]	17 (18.9)
Main suspect drugs [n, (%)]	
Morphine	10 (11.1)
Tramadol	8 (8.9)
Captopril	5 (5.6)
Clonazepam	5 (5.6)
Enoxaparin	5 (5.6)
Furosemide	5 (5.6)
Warfarin	5 (5.6)
Carvedilol	3 (3.3)
Enalapril	3 (3.3)
Prednisone	3 (3.3)
Vancomycin	3 (3.3)
Others drugs[b]	35 (38.8)

ADR: Adverse drug reaction; IQR, interquartile range, SD: Standard deviation.
[a] Others ADRs included: nausea/vomiting, diarrhea, changing in respiratory pattern, hypoglycemia, rash and tachycardia.
[b] Others drugs included 19 drugs with frequency of use $\leq$2: Atenolol, bisacodyl, codein/acetominophen, ciclosporin, insulin, sinvastatim, amiodarone, cefepime, dexamethasone, dobutamine, phenytoin, fenoterol, heparin, hydralazine, gentamicin, hydrocortisone, methylprednisolone, mycophenolate mofetil, rifampicin/isoniazid/pyrazinamide/ethambutol

Descriptive statistics were employed for numerical and categorical variables. Numerical variables were presented using measures of central tendency and dispersion (mean, median, standard deviation and interquartile range, as appropriate). Absolute and relative frequencies were presented for categorical variables. The overall interrater agreement among the three judges was calculated using Fleiss' kappa coefficient[10] with 95% confidence interval (CI). Cohen's kappa coefficient with linear weighting was used to measure pairwise judge concordance.[11] Potential ADRs classified as unassessable by at least one judge were not considered to calculate Fleiss´ and Cohen's kappa coefficient. The assessment of concordance was based on the quantitative scale proposed by Landis and Koch[12]: <0 = poor, 0.00–0.20 = slight, 0.21–0.40 = fair, 0.41–0.60 = moderated, 0.61–0.80 = substantial, 0.81–0.99 = almost perfect and 1.00 = perfect.

3. Results

From 300 participants, 64 presented at least one potential ADR (median age = 63 years;51.6% women). Overall, 90 potential ADRs were forwarded to be assessed by the judges, comprising the total of 270 assessments.

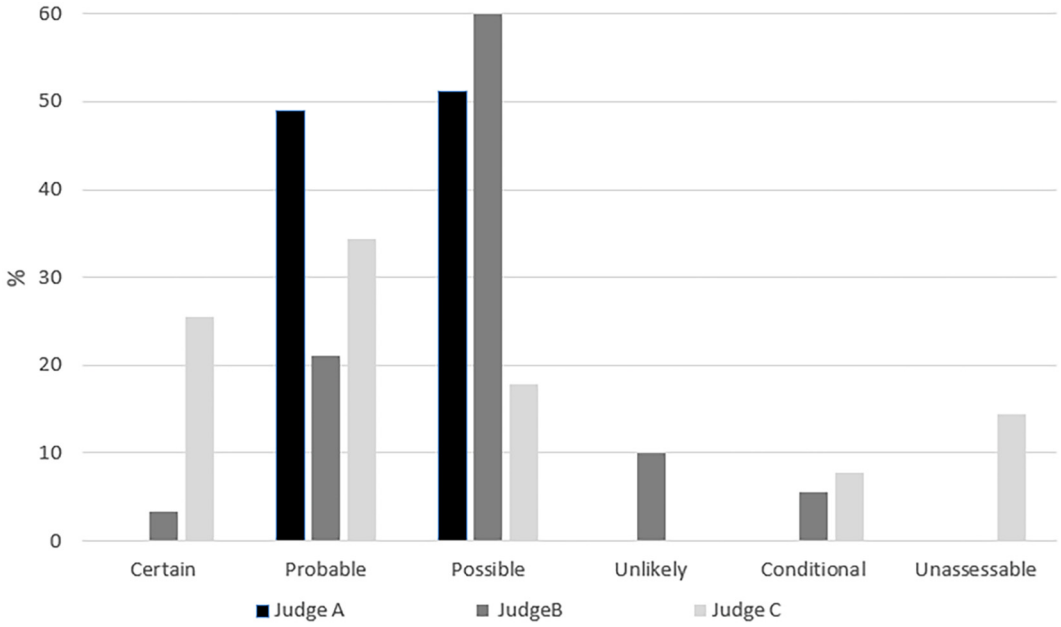

Fig. 1. Distribution of causality categories by judges using WHO. Judge A: Nurse; Judge B: Pharmacist; Judge C: Physician.

Emergency admissions ($n = 60$; 93.8%) were the main type of hospitalization and 73.4% of patients ($n = 47$) received clinical treatment. The underlying diagnosis of almost half patients ($n = 30$; 46.9) was related to circulatory system diseases. Most patients ($n = 45$;70.3%) presented only one potential ADR. The mean length of potential ADRs was 3.0 ± 2.9 days and 13 potential ADRs (14.4%) lasted for more than five days. The main clinical manifestation was hypotension, found in 19 (21.1%) cases. The main suspected drugs involved were morphine (11.1%), followed by tramadol (8.9%). Descriptive data are presented in Table 1.

Most potential ADRs were categorized as possible (116;43.0%) and 26 (9.6%) as certain. The physician attributed more certain causality assessment than the others judges and the nurse classified potential ADRs only in probable and possible categories. Distribution of adjudicated causality categories by each judge is presented in Fig. 1. Distribution of the main suspected drugs by three judges, according to the categories of causality from the WHO-UMC system are depicted in Table 2. Slight agreement was found in the comparison of all judges in the pairwise analysis, and also for the overall interrater agreement, indicating poor reproducibility of WHO-UMC system. Thirteen cases were classified as unassessable by at least one judge and excluded from kappa analysis (Table 3).

Table 2
Distribution of suspected drugs by three judges according to the categories of causality from the WHO-UMC system indicated.

Drugs[a,b]	Judge[c]	WHO-UMC categories (%)				
		Certain	Probable	Possible	Unlikely	Conditional
Morphine	Judge A	0	7	3	0	0
	Judge B	0	6	3	0	1
	Judge C	5	3	2	0	0
Tramadol	Judge A	0	3	5	0	0
	Judge B	1	3	3	0	0
	Judge C	1	6	1	0	0
Captopril	Judge A	0	5	5	0	0
	Judge B	0	0	2	1	1
	Judge C	0	2	2	0	1
Clonazepam	Judge A	0	4	2	0	0
	Judge B	0	2	1	1	0
	Judge C	2	2	1	0	0
Enoxaparin	Judge A	0	5	2	0	0
	Judge B	0	2	1	1	1
	Judge C	1	1	0	0	2
Furosemide	Judge A	0	1	2	0	0
	Judge B	0	1	4	1	0
	Judge C	0	2	3	0	1
Warfarin	Judge A	0	2	1	0	0
	Judge B	0	2	3	0	0
	Judge C	3	2	0	0	0

ADR: Adverse drug reaction
[a] Drugs with frequency of ADR categorization ≥5
[b] The total of classifications performed for each drug may vary among judges due to the classification of potential ADR as unassessable or the divergent indication of the potential ADR to another drug in use.
[c] Judge A: nurse; Judge B: pharmacist; Judge C:physician

Table 3
Categories of causality assessment of ADR using WHO-UMC system and results for interrater agreement.a

Characteristics	Value	*p*-value
WHO-UMC system categories [n, (%)]		
Certain	26 (9.6)	
Probable	94 (34.8)	
Possible	116 (43.0)	
Unlikely	9 (3.3)	
Conditional	12 (4.5)	
Unassessable	13 (4.8)	
Interrater agreement		
Exactly agreement proportion		
Judge A x Judge B	0.53	
Judge B x Judge C	0.24	
Judge A x Judge C	0.33	
Multiple Judges	0.19	
Extreme disagreement proportion		
Judge A x Judge B	0.19	
Judge B x Judge C	0.33	
Judge A x Judge C	0.31	
Multiple Judges	0.29	
Kappa[a]; CI (95%)		
Judge A x Judge B	0.180 (0.04–0.32)	0.011
Judge B x Judge C	0.168 (0.05–0.29)	0.007
Judge A x Judge C	0.113 (0.01–0.22)	0.035
Multiple Judges	0.096 (0.01–0.18)	0.013

ADR: Adverse drug reaction; CI: Confidence interval
[a] Cohen's kappa was used to assess pairwise agreement and Fleiss' kappa overall agreement

4. Discussion

This study described the causality assessment of potential ADRs based on WHO-UMC system and the performance of healthcare professionals in the adjudication process. Among the drugs in use, opioid analgesics and antihypertensive drugs were the main suspect drugs involved in ADRs causality. Their effects are compatible with the main clinical presentations found in this study represented by hypotension and constipation. In pharmacovigilance, most ADRs have been classified as probable or possible, and rarely as certain.[4] The findings are in line with the literature, considering that 77.8% of the cases were classified as possible or probable.[3,6] Individual assessment performed by the pharmacist and the nurse in this study followed this trend, however the physician had a tendency to attribute more certain category, similarly to the results demonstrated by Davies et al.[6] Warfarin and morphine were the drugs with greater proportion with classification as certain by the judge C. It is worth mentioning that the certain category often involves a rechallenge, which is rare and could imply ethical issues.[6] All categories indicated by judge A were probable and possible, with enoxaparin and morphine presenting the largest proportions of causal relationship. Morphine was mostly categorized as probable by judge B and as certain by judge C. These results could reflect more comfortability with this drug by the professionals, given its extensive use in clinical practice.

The interrater agreement was slight for WHO-UMC, according to Lands and Koch scale.[12] Dependence on individual judgement and different backgrounds of healthcare professionals could explain the weak reproducibility and slight interrater agreement among judges. Previous studies have reported concordance ranging from fair to substantial in the ADRs causality assessment in hospitals,[1,6] and the lowest interrater agreement was demonstrated between physicians and nurses,[6] similarly to this study. A concordance slightly greater was found when the pharmacist was involved. These differences suggest a potential opportunity to enrich the ADRs assessment and management by engaging multiprofessional teams in the process and improving effectiveness and safety of drug therapies. This becomes especially important in the context of high complexity assistance, whose ADRs classification is particularly difficult by the presence of many risk factors, such as polypharmacy and comorbidities.

Pharmacovigilance services are unevenly distributed in LMICs. Although there are few data available, investments in pharmacovigilance are hypothesized to be scarce in LMICs with particular restriction for human resources.[7,13] Regarding the Brazilian pharmacovigilance system, 259 sentinel hospitals (https://www.gov.br/anvisa) are the main source for ADRs report to Anvisa. The notification system has been recently adapted to a new version, including the WHO-UMC system as an option for ADRs causality assessment. In this scenario, pharmacists are traditionally the main healthcare professionals involved in the pharmacovigilance process.[13] Nevertheless, there are remarkable challenges for Brazilian pharmacists, as low scientific production and dissemination of information, poor patient safety culture, insufficient support to healthcare professionals involved in this practice, mainly direct to human resources that hinder the imputation of causality and the communication with other healthcare professionals.[13]

This is not the first study in the literature on the ADRs causality assessment. However, to date there is no previous study designed to compare their causality assessment performed by different healthcare professionals in hospitalized patients of a middle-income country. Some limitations should be addressed. The small number of judges involved in this preliminary study may have reinforced the slight agreement among judges. Besides, the study did not compare how much better for clinical practice would be the evaluation by professionals from different areas *versus* professionals from the same area. Additional investigation applying multiple algorithms and the participation of larger numbers of professionals could help expanding knowledge in this field.

5. Conclusion

The adjudication process for the causality of potential ADRs, assessed by the WHO-UMC system, demonstrated different imputation when evaluated by a nurse, a pharmacist and a physician, presenting slight agreement among the judges. The results could reflect the influence of background and clinical experience in causality assessment. An integration of different healthcare professionals could enrich and improve the quality of this evaluation. Further studies investigating the ADR assessment performed by multiprofessional should be considered as a strategy to strengthen the management process of ADRs in hospitalized patients from LMICs.

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Ethics approval

The research project was approved by the Research Ethics Committee of the Universidade Federal de Minas Gerais (code number CAAE 28222514.3.0000.5149). Informed consent was obtained from all individual participants included in the study.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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