Rev Soc Bras Med Trop 49(6):763-767, November-December, 2016
doi: 10.1590/0037-8682-0238-2016

Short Communication

Adverse drug reactions among patients admitted with infectious diseases at a Brazilian hospital

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Abstract

Introduction: Despite the therapeutic benefits of drugs, adverse drug reactions (ADRs) occur. **Method:** We assessed a series of suspected ADRs identified from notifications and intensive monitoring of inpatients from March 2013 to March 2014. **Results:** Skin reactions predominated (31%). Systemic anti-infective agents were implicated in 16 (72%) reactions. Fifteen (68%) ADRs were classified as *possible.* The implicated drug was not correctly identified by the healthcare team in 12 cases. **Conclusions:** Some reactions were not correctly attributed to the causative drug(s), suggesting that the use of a validated evaluation method can promote successful identification of causal links between ADRs and drugs.

Keywords: Adverse drug reactions. Pharmacovigilance. Hospitals.

Drugs are crucial therapeutic tools, and ensuring access to their use is a global priority. However, drugs also carry the risk of adverse reactions. Since the thalidomide tragedy in 1960, countries have sought to implement pharmacovigilance systems and have conducted studies to prevent or minimize adverse drug reactions (ADRs), thereby reducing the huge impact these events can have on morbidity and mortality rates and on healthcare costs[1] [2]. Questions on whether responses to drugs and the occurrence of ADRs are influenced by factors such as ethnicity remain unanswered, calling for local pharmacoepidemiologic studies to feed the World Health Organization (WHO) notification system in Uppsala. Furthermore, national or regional level data have educational value and can guide the formulation of national level regulatory measures[3] [4].

In 2013, the Brazilian Health Surveillance Agency [*Agência Nacional de Vigilância Sanitária* (ANVISA)] issued regulations to improve patient safety in healthcare services, decreeing that adverse event notifications and monitoring be employed to reduce risks among inpatients[5]. By detecting and evaluating ADR causality − a key procedure in pharmacovigilance − risk-benefit assessment of drugs can be conducted for specific populations, triggering warnings from global pharmacovigilance systems and ultimately reducing exposure risks by adjusting drug dosages[6]. The present study sought to describe the occurrence of ADRs in adults hospitalized with infectious diseases at a Brazilian teaching hospital and to establish causal links with the drugs administered.

Adverse drug reactions identification was based on data collected from suspected ADR notification forms, drug-therapy follow-up reports, medical records, laboratory tests, and hospital prescriptions. The patients included in the study were adults treated by the infectology team of the *Universidade de Brasília* teaching hospital between 1 March 2013 and 31 March 2014. Patients hospitalized for less than 48h and those with no medical records available were excluded. The following data were collected: patient identification; description of suspected ADR; onset and duration of the event; daily dose, administration route, administration period, and rationale for prescription of the implicated drug; other drugs prescribed; protocol followed for ADR management; clinical evolution; and information on re-exposure to the implicated drug. ADR diagnosis was based on the definition proposed by the World Health Organization (WHO), i.e., any harmful or undesirable and unintended response occurring with drugs in dosages typically used in humans for prophylaxis, diagnosis, or treatment of diseases or for altering physiologic functions[1].

The Naranjo algorithm[6] was employed to establish causal links between suspected ADRs and drugs. The descriptions of suspected ADRs were harmonized with the WHO Adverse Drug Reaction Terminology. The approaches adopted by the

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Received 10 June 2016
Accepted 26 August 2016

multiprofessional team were categorized as drug withdrawal followed by no reaction improvement, drug withdrawal followed by reaction improvement, continued drug administration, dosage modification, and need for symptomatic treatment. Identification of suspected events drew on the following sources: Brazilian National Formulary (*Formulário Terapêutico Nacional 2010)*[7], Micromedex Solutions (Truven Health Analytics) [8], and Meyler's Side Effects of Drugs: The International Encyclopedia of Adverse Drugs Reactions and Interactions [9]. Investigation of causal links was not limited to the drug initially identified, but extended to other drugs having a possible temporal relationship with the suspected ADR. The organs and physiologic systems affected were identified and all suspected ADRs were categorized as type A or B, according to Rawlins and Thompson [10]. The Anatomical Therapeutic Chemical (ATC) classification[11] was applied to categorize the drugs implicated in suspected events.

The study included 113 patients: 67% (n = 76) were men; the mean age was 43 years; and 44% (n = 50), were human immunodeficiency virus (HIV) infected. The mean length of hospital stay was 12 days (**Table 1**). Fourteen (12%) patients were hospitalized more than once, 15 (13%) had changes in the level of treatment complexity, and four (3.5%) died during the study period. Twenty-two suspected ADRs were identified in 13 (12%) patients (1.7 ADR per patient). The mean length of hospital stay for these patients was 25 days (**Table 1**). Skin (31%), hepatobiliary (18%), and gastrointestinal reactions (18%) predominated. Pruritus (22%), changes in liver function (13%), and nausea/vomiting (13%) were the most common symptoms experienced. Twenty-one 95%) of the events (were Type A ADRs; one reaction (cutaneous hyperpigmentation related to polymyxin B) was categorized as type B.

The suspected drug was withdrawn in 14 (63%) cases and continued in six (27%); information on ADR management was lacking for two events. Symptomatic treatment was initiated in seven cases (after drug withdrawal in four). Three events required intensive monitoring using laboratory tests. Of the patients affected, 11 (84%) recovered without sequelae and two died of unrelated causes. Fifteen drugs were implicated, ten (66%) of which were systemic anti-infectives (J01, J02, J05) and four (26%) were drugs acting on the central nervous system (N02, N03). Among the anti-infective agents, polymyxin B and sulfamethoxazole-trimethoprim were each connected with four events. Among exposed patients, polymyxin B accounted for most suspected cases (**Table 2**).

Causal links with the drug initially implicated were established as suspected in 22 events, probable in six (27%), possible in 15 (68%), and uncertain in one (5%). In the six cases having a probable causal link with the drug initially reported (Naranjo scores of 5 or higher), the additional drugs administered had lower scores (possible ADR) (**Table 3**). In the 15 events with possible causal links, 99 other drugs were administered. The drug initially reported scored higher than the other drugs administered in only one event. In all remaining cases, the other drugs scored the same or higher than that initially reported as causing the reaction.

Fourteen (64%) reactions were identified from notification forms and eight (36%) from clinical records, indicating underreporting of ADRs. Employing both strategies allows ADR frequencies to be more accurately estimated, and entails the surveying of cases during patient follow-up by professionals with pharmacovigilance training. Intensive monitoring and review of medical records were also employed by Menezes et al.[12] Lobo et al.[13] used incentives to promote spontaneous notification, associated with intensive monitoring of medical records and laboratory tests. Miguel et al.[14] compared intensive monitoring with retrospective searching of databases, finding the latter method to be less costly.

In the present study, the ADR incidence was 11.5%. In a systematic review of 29 studies, Cano et al.[2] observed that ADRs occurred in 1.6-41.4% of inpatients, with rates of 1.7-51.8 events per 100 hospitalizations. In another systematic review, Miguel et al.[14] found that ADRs occurred in 16.9% of inpatients, but this rate may have been biased by population heterogeneity and the methods employed. Secondary data from the Brazilian Hospital Information System revealed an ADR prevalence

TABLE 1

Characteristics of patients hospitalized for infectious diseases at the *Universidade de Brasília* teaching hospital between March 2013 and March 2014.

Characteristics	All patients	Patients with ADRs
Patients enrolled	113	13
Males n (%)	76 (67)	9 (69)
Age (years: mean ± SD)	43 ± 17.1	37 ± 14.3
>60 years (n)	16	1
HIV-infected (n)	50	5
On ART (n)	40	3
Length of hospital stay (days: mean ± SD)	12 ± 10.2	25 ± 21.7
Length of hospital stay (days: median, range)	9 (2–81)	19 (2–77)

ADR: adverse drug reaction; **SD:** standard deviation; **HIV:** human immunodeficiency virus **ART:** antiretroviral therapy.

TABLE 2

Drugs implicated in suspected ADRs among patients hospitalized for infectious diseases at the *Universidade de Brasília* teaching hospital between March 2013 and March 2014.

Drug	ATC	ADRs	Patients affected	Patients exposed	ADRs per exposed patient (× 100)
Sulfamethoxazole + trimethoprim	J01EE01	4	4	36	11.1
Polymyxin B	J01XB02	4	2	2	200.0
Ceftriaxone	J01DD04	1	1	31	3.2
Sulfadiazine	J01EC02	1	1	9	11.1
Oxacillin	J01CF04	1	1	8	12.5
Fluconazole	J02AC01	1	1	30	3.3
Liposomal amphotericin B	J02AA01	1	1	7	14.3
Ganciclovir	J05AB06	1	1	4	25.0
Atazanavir	J05AE08	1	1	7	14.3
Ritonavir	J05AE03	1	1	26	3.8
Tramadol	N02AX02	2	1	16	12.5
Paracetamol	N02BE01	1	1	14	7.1
Carbamazepine	N03AF01	1	1	5	20.0
Gabapentin	N03AX12	1	1	2	50.0
Lactulose	A06AD11	1	1	8	12.5

ADR: adverse drug reaction; **ATC:** anatomical therapeutic chemical classification.

TABLE 3

Evaluation of ADR causality in patients hospitalized for infectious diseases at the *Universidade de Brasília* teaching hospital between March 2013 and March 2014.

Adverse drug reaction	Suspected drug	Naranjo score	Causality	Other drugs	Naranjo score	Causality
Elevated serum creatinine	Polymyxin B	7	Probable	Meropenem	3	Possible
				Tigecycline	2	Possible
				Heparin	2	Possible
				Promethazine	2	Possible
Paresthesia	Polymyxin B	7	Probable	Amlodipine	3	Possible
				Tigecycline	2	Possible
				Heparin	2	Possible
				Meropenem	2	Possible
				Promethazine	2	Possible
Pruritus	Polymyxin B	5	Probable	Amlodipine	3	Possible
				Meropenem	3	Possible
				Promethazine	3	Possible
				Tigecycline	2	Possible
				Heparin	2	Possible
Anemia	Sulfamethoxazole + trimethoprim	5	Probable	Prednisone	3	Possible
				Omeprazole	3	Possible
				Fluconazole	2	Possible
Nausea and vomiting	Ritonavir	7	Probable	-	-	-
Diarrhea	Lactulose	7	Probable	Meropenem	3	Possible
				Vancomycin	3	Possible
				Ranitidine	3	Possible
				Liposomal amphotericin B	2	Possible

of 1.8 per 1,000 hospitalizations. According to the investigators, all inpatients in the sample were at risk, given the widespread use of drug therapy in hospitals[15].

In the present study, 31% of suspected ADRs affected the skin, while 18% impacted hepatobiliary functions and another 18% altered gastrointestinal functions. Similarly, Menezes et al.[12] found a predominance of cutaneous rash (20%), pruritus (13%), and hyperemia (12%) among ADRs, while Rozenfeld et al.[15] reported ADRs predominantly affecting the gastrointestinal tract (55%) and central nervous system (22%). Dermatologic reactions are described as the most frequent type in a number of studies, partially because these ADRs are more promptly identified[16]. In the present study, type A reactions accounted for 95% of the suspected cases. Similar results have been reported elsewhere[13] [17]. The only reaction classified as type B in the present study was a case of skin hyperpigmentation associated with polymyxin B – a rarely reported ADR[18].

Of the patients with suspected ADRs, 84% recovered without sequelae and two (16%) died of other causes. Similar results were obtained elsewhere in Brazil. In a study by Noblat et al.[17], the outcomes of ADRs included 90.6% recoveries, 6.1% deaths from other causes, 2.8% unknown outcomes, and 0.5% deaths from ADRs. In an investigation by Rozenfeld et al[15], 84.1% of patients with ADRs were discharged.

In the present study, an association was found between length of hospital stay and ADR occurrence: patients with longer stays had a greater number of reactions. Involvement of anti-infective agents in the majority of suspected ADRs was an expected feature, as all patients had an infectious disease and there was a high prevalence of immunosuppression. This pattern, however, was not observed for drugs acting on the central nervous system, prescribed for few patients in the present study. A number of studies have reported an association between ADRs and anti-infective agents[12] [13] [17], as well as between ADRs and drugs acting on the central nervous system[12] [13].

Using the Naranjo algorithm, most reactions described in the present study were classified as possible. Similar results were found by other investigators. Causality was investigated for all drugs having a temporal relationship with the reaction. Few studies, however, have applied the Naranjo algorithm to additional medications given to patients. In a study by Danza et al.[19], nearly half of ADRs were related to drug interactions, a factor that increases the risks of type A reactions. The Naranjo algorithm proved highly specific, establishing causal links when causality criteria were clearly met – i.e., the algorithm correctly identified patients with high scores (who developed ADRs) and those with very low scores (without ADRs). However, when criteria were not readily met or when variables could not easily be distinguished, the algorithm displayed low sensitivity, failing to clearly distinguish causal links. Categorization of a reaction as possible indicated that the healthcare team failed to identify the drugs responsible for the reaction, since the drug initially suspected had a lower score than other medications administered.

In most studies, the number of ADRs identified from notification system databases tends to be low, but can be enhanced by additional techniques, such as intensive monitoring or use of ADR surveillance software. Encouraging healthcare professionals to record iatrogenic events is crucial for obtaining valid data. In a review of ADR prevention methods, Rommers[20] found that participation of a clinical pharmacist in patient visits and use of computer-based prescribing are among the most employed strategies. The relevance of engaging pharmacists in ADR prevention has also been emphasized by other investigators.

The ADR profile identified in the present study and the finding that some of these reactions failed to be correctly attributed to the causative drugs suggest that employing a validated evaluation method promotes the successful identification of causal links between adverse reactions and drugs.

Ethical considerations

The study was approved by the Research Ethics Committee of the School of Health Sciences of the *Universidade de Brasília* (permit 278.787). All data concerning patients and prescribers were kept confidential.

Conflict of Interest

The authors declare that there is no conflicts of interest.

Financial Support

This study is part of a subproject funded by the Brazilian Health Ministry (bidding process 133/2013).

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