Adverse events to antibiotics in inpatients of a university hospital

ABSTRACT

OBJECTIVE: Antibiotics are the most common drugs causing adverse events and they lead to problems to patients and additional costs of the health system. The aim of the study was to evaluate the occurrence of adverse events to antibiotics in inpatients of a hospital.

METHODS: An extensive drug monitoring was conducted in adult inpatients taking antibiotics in the city of Maringá, Southern Brazil, from September 2002 to February 2003. Variables related to medications used, especially those related to antibiotic use and adverse events, were studied. Based on criteria for adequate antibiotic use, the observed events were classified as adverse events, medication errors and near-misses. For the analysis of causality between drug administration and event occurrence Naranjo algorithm was used.

RESULTS: A total of 87 patients were studied and 91 adverse events were identified: three (3.3%) adverse drug reactions; seven (7.7%) medication errors; and 81 (89.0%) medication near-misses. Adverse drug reactions were related to the use of quinolones and likely according to Naranjo algorithm. The seven medication errors were associated to four inadequately prescribed doses and three drug interactions.

CONCLUSIONS: The study results indicate that an inadequate knowledge on antibiotics or lack of information about the patient at the time of prescription were the major factors involved in the occurrence of adverse events.


INTRODUCTION

Adverse drug reactions (ADRs) are defined by the World Health Organization (WHO) as “any noxious, unintended effect to the use of a drug, which occurs at doses usually used in humans for prophylaxis, diagnosis or therapy or for modifying a physiological action”. This definition assumes the correct use of a drug and reflects the intrinsic risk to its use. Therefore, these are non-preventable events.

In contrast, medication errors (MEs) are defined as “any preventable event that may cause patient harm or lead to inappropriate medication use while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, procedures, and systems, including prescribing, order communication, product labeling, packaging,
nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use”.*

WHO defines an adverse event as any untoward medical effect that occurs during drug therapy but not necessarily with a causal relationship with this treatment.²¹ Therefore, from the occurrence’s perspective, ADRs and MEs can be considered adverse drug events.

Adverse drug events in hospitalized patients are an emerging condition associated to significantly increased hospital stay, costs, and morbidity.¹⁶ In the United States, health service costs due to drug-related morbidity and mortality were estimated in more than $76.6 billion in 1995.⁹ Bates et al.³ estimated in about $2,000 the additional cost associated to patients admitted to a hospital due to an adverse event and an increase of about 1.9 days in hospital stay.

Antibiotics are among the most commonly prescribed drugs in hospitals and they account for 20% to 50% of drug costs.¹⁹ Its use is estimated to be inappropriate in about 50% of cases¹⁹ and several studies showed antibiotics as one of the drug groups causing more adverse events.²,⁷,¹³

Adverse drug events are a public health concern because of its high occurrence incurring in additional costs to health services. Knowing their actual rate and classification will allow to intervening in the process of drug use in hospitals. Thus, the purpose of the present study was to assess the rate of adverse events due to antibiotic use in hospitalized patients, to describe these events and determine the associated factors involved in their occurrence.

METHODS

Intensive monitoring of adverse events to antibiotics was conducted in hospitalized patients of a university hospital in the city of Maringá, Southern Brazil, from September 2002 to February 2003. The study was conducted in a 114-bed hospital serving a population of about 300,000 inhabitants, which provides services in several different clinical and surgical specialties. The Internal Medicine department provides care to patients aged 15 years of age and more and has 15 beds with an average occupancy rate of 85%.

Intensive drug monitoring in hospitals is an active approach to pharmacovigilance. It comprises medical record reviews and interviews with patients and/or prescribers for collecting information on patient demographics, therapy indications, duration of treatment, dos-

es, and medical events.¹¹ The study monitoring consisted of reviewing medical records and information reported in a standardized chart. The following variables were investigated: a) patient-related: gender, age, diagnosis, length of hospital stay and length of study participation; b) drug-related: antibiotics and other drugs prescribed; and c) those related to antibiotic use: indication, purpose of use, dose, route of administration, dosage, treatment duration, association of antibiotics, and culture and antibiogram test results. The use of protocols for the treatment of pneumonias was also investigated.

There were included in the study medical records of all patients admitted to the Internal Medicine department who were treated with antibiotics for bacterial infections. The following medical records were excluded: patients coming from the intensive care unit; patients staying less than 48 hours in the hospital; and those who received antibiotics for the treatment of fungal or protozoan infections.

In regard to drug adverse events, there were investigated patients’ signs and symptoms and potential drug interactions; possible indications of events such as antibiotic replacement or discontinuation, abnormal laboratory tests, and use of drugs acting as antidotes. Data were collected and validated by pharmacists and an infectious disease specialist involved with hospital infection control who contributed to the differential diagnoses.

Criteria for the assessment of appropriate antibiotic use were compiled from the Micromedex** database which provided information on the antibiotics used in the hospital. Based on these criteria, the events found were classified as adverse reactions, medication errors, and near-miss errors.

Adverse reactions were those which occurred despite appropriate patient indication and prescription. It was sought to establish a causality relationship between drug administration and event occurrence using Naranjo algorithm.¹⁴ Rawlins & Thompson¹⁸ proposed criteria were used to classify adverse reaction by drug action mechanism.

Medication errors were those events which caused harm to the patient but that could have been prevented with appropriate antibiotic prescription and administration.

Near-miss errors were failures which did not result in either injury or harm to the patient. Such events can help identify failures in the medication system that could potentially cause harm to patients, which is essential for preventing injuries. They are also known as potential

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adverse drug events, although they do not cause any harm and do not match the proposed WHO definition for adverse events.

Drugs were classified based on the Anatomical Therapeutic Chemical Classification Index (ATC), developed by WHO Collaborating Center for Drug Statistics Methodology. * Diagnoses were classified according to the International Classification of Diseases (ICD-10). ** Micromedex database was also used to ascertain whether suspected adverse events were known and described in the literature.

The study was approved by the Research Ethics Committee of Faculdade de Saúde Pública of Universidade de São Paulo and Permanent Human Research Ethics Committee of Universidade Estadual de Maringá.

### RESULTS

A total of 87 patients who met the inclusion criteria during the study period were monitored. Of them, 54 (62.0%) were males and 33 (38.0%) were females aged between 15 and 92 years; 58.6% were over 60.

Patient monitoring time ranged between two and 39 days. Antibiotic therapy duration ranged between two and 37 days. Mean diagnoses per patient were 3.5 (1-6). The most common diagnoses requiring antibiotic therapy based on ICD-10 were: respiratory (44.2%); genitourinary (25.6%); and infectious diseases (12.4%).

A total of 23 different antibiotic agents were prescribed. Only one antibiotic was prescribed to 62 (71.3%) patients. The most common antibiotics prescribed were: ciprofloxacin (20%), norfloxacin (18%), and clindamycin (16%).

### Table 1. Adverse reactions to antibiotics in hospitalized patients. Maringá, Southern Brazil, 2002–2003.

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Antibiotic</th>
<th>Patient/diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epigastric pain with nausea, sweating and tachycardia after drug administration</td>
<td>Ciprofloxacin 200 mg IV replaced with ciprofloxacin 250 mg PO</td>
<td>38-year-old female/pyelonephritis and repetitive urinary tract infection</td>
</tr>
<tr>
<td>Epigastric pain after drug administration</td>
<td>Norfloxacin 400 mg PO</td>
<td>15-year-old male/urinary tract infection and diabetes mellitus type 1</td>
</tr>
<tr>
<td>Epigastric pain after drug administration</td>
<td>Norfloxacin 400 mg PO</td>
<td>36-year-old female/acute pyelonephritis and anemia</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Observed error</th>
<th>Prescription</th>
<th>Patient’s age/diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated serum creatinine</td>
<td>Incorrect dose of amicacycin due to patient’s pathophysiological conditions, underlying disease and advanced age</td>
<td>Cefalotin 1 g + amicacycin 1 g</td>
<td>81 years old/erysipela, arterial hypertension and diabetes mellitus type II</td>
</tr>
<tr>
<td>Elevated serum creatinine</td>
<td>Incorrect dose of amicacycin due to patient’s pathophysiological conditions, underlying disease and advanced age</td>
<td>Ceftriaxone 1 g + amicacycin 1 g + clindamycin 600 mg</td>
<td>88 years old/community pneumonia, arterial hypertension, diabetes mellitus type II and respiratory failure</td>
</tr>
<tr>
<td>Elevated serum creatinine and BUN, required hemodialysis</td>
<td>Incorrect dose of gentamicyn due to patient’s pathophysiological conditions, underlying disease and advanced age</td>
<td>Ceftriaxone 1 g + gentamicyn 180 mg</td>
<td>77 years old/erysipela, pyogenic arthritis, arterial hypertension, diabetes mellitus type II and chronic renal failure</td>
</tr>
<tr>
<td>Elevated serum creatinine</td>
<td>Incorrect dose of amicacycin due to patient’s pathophysiological conditions and advanced age</td>
<td>Ceftriaxone 1 g + clindamycin 600 mg + amicacycin 1 g</td>
<td>79 years old/community pneumonia, urinary tract infection and diabetes mellitus type II</td>
</tr>
<tr>
<td>Elevated serum creatinine</td>
<td>Drug interaction</td>
<td>Cefalotin 1 g + gentamicin 160 mg</td>
<td>69 years old/arterial disease complication due to diabetes mellitus type II</td>
</tr>
<tr>
<td>Elevated serum creatinine</td>
<td>Drug interaction</td>
<td>Cefalotin 1 g + gentamicin 60 mg</td>
<td>88 years old/community pneumonia</td>
</tr>
<tr>
<td>Elevated serum creatinine</td>
<td>Drug interaction</td>
<td>Ceftriaxone 1 g + amicacycin 500 mg</td>
<td>68 years old/community pneumonia, chronic obstructive pulmonary disease and anemia</td>
</tr>
</tbody>
</table>

patients. Twenty-five (28.7%) patients received two or more antibiotics (mean 1.6 antibiotics per patient). Nine patients (10.3%) were treated with four or more antibiotics.

The most frequently prescribed antibiotics were the following: ceftriaxone (20.0%); cefalotin (13.3%); ciprofloxacin (12.5%); and an association of ampicillin + sulbactam (12.5%). Cephalosporins (34.1%) were the most prescribed group of antibiotics, followed by penicillins (20.0%), quinolones (17.8%), aminoglycosides (9.6%), lincosamides (3.7%), and macrolides (2.9%).

Of 43 cases diagnosed with respiratory diseases, 37 (86.0%) were treated following the hospital’s protocol for pneumonia treatment.

During the monitoring period, there were identified 91 drug events, of which 3 (3.3%) were classified as adverse reactions. The other 88 events (96.7%) were related to the process of drug use: seven (7.7%) were medication errors and 81 (89.0%) were near misses.

The three adverse reactions due to quinolone use are described in Table 1. All adverse reactions were classified as probable according to Naranjo algorithm and type A by Rawlins & Thompson criteria.

Table 2 shows all medication errors: four incorrect dose prescription and three drug interactions due to the association between betalactams and aminoglycosides.

With respect to 81 near-misses, two (2.5%) were inappropriate indications when there was no need for antibiotics. One was prophylactic therapy with no indication described in the literature. The second one was a therapeutic indication in a patient without any clinical or laboratory signs suggestive of infection requiring antibiotic therapy. In 23 cases (28.4%), treatment duration was inappropriate since it was shorter than that recommended in the literature. It was also found a case of an antibiotic given through the wrong route of administration (1.2%). Fifty-five (67.9%) possible drug interactions were also detected.

**DISCUSSION**

For most patients only one antibiotic was prescribed, which was also reported by Mazzeo et al. in a study carried out in an Italian university hospital. In both studies, it was also found that more than 25% of the patients were treated with two or more antibiotics. The concomitant use of two or more antibiotics is somewhat supported and recommended in specific circumstances. However, the selection of an appropriate combination requires knowledge on potential interactions between antibiotics. These interactions can affect both the microorganism and its host. The most remarkable consequences include: toxicity risk arising from the combination of two or more agents; selection of microorganisms that are resistant to potentially unnecessary antibiotics; and increased costs to patients.

The majority of cases of pulmonary tract complications were treated following the study hospital’s protocol, which is suggestive of prescribers’ high adherence. This adherence can provide many benefits, for example, reducing resistant pathogens and most likely providing more effective and safe treatment to patients. According to Brown, a combination of strategies can increase adherence to protocols, such as incorporation of practice by decision makers or their dissemination among department heads. In the present study, the fact that it was conducted in a university hospital can explain providers’ high adherence to the protocol because it is a setting where the focus is on prescribers’ training. The same was reported by Ali et al., who showed that the most important influence for prescription choice in medical schools was teachers and senior doctors’ guidance.

There were classified as adverse drug reactions the events proven to be unavoidable, although the likelihood of their occurrence was known. In all cases, drugs were appropriately used and indicated. The three cases of adverse reactions seen in the present study included gastrointestinal conditions associated with quinolone use, which are also described in the literature. They were classified as type A because they were originated from normal though increased pharmacological action of a drug prescribed at usual therapeutic doses. These three cases were prescribed dose-related, which is consistent with similar studies.

Based on Naranjo algorithm, adverse reactions were considered probable concerning their causality. For pharmacovigilance centers, the main goal for determining a causal relationship is to assure that every reporting follows a regulated analysis process and provides feedback to the reporting agent and to the scientific community. This is no formula for an absolute and safe outcome since this analysis always involves personal evaluation and allows for different interpretations. Algorithms are ultimately an attempt to unify criteria from different evaluators and different national and international organizations.

Adverse drug reactions occurred in young patients, which contrasts with other studies where the elderly were more prone to these reactions because of changes in the intrinsic pharmacodynamics and pharmacokinetics caused by advanced age and loss of functional body reserve requiring prescription adjustments.
Medication errors were seen in elderly patients. The same was reported by Gallelli et al., who believed these errors would be more related to concurrent use of different drugs than to age-related factors.

Of the seven errors found, four were related to inappropriate prescriptions due to patients’ pathophysiological conditions, underlying disease and age requiring antibiotic dose reduction. Lesar et al. reported in a tertiary university hospital in the United States that a major factor associated to medication errors was declining renal and hepatic functioning, which require adjustments in drug therapy.

The three cases of drug interactions between betalactams and aminoglycosides seen in this study are well-known and described in the literature and regarded as preventable. They could have resulted from inadequate knowledge on drug interactions as reported by Leape et al., who noted that lack of knowledge on drug interactions was the major cause associated to medication errors in 6% of the events studied.

Near-misses found in this study were always associated to treatment duration shorter than that recommended in the literature. Reduction of antibiotic therapy duration can lead to increased microorganism resistance.

Medication errors and near-misses occurred at prescription time, possibly due inadequate knowledge on antibiotics or patient information. Many authors claim these are the most common reasons for errors in a hospital setting, especially at prescription time. Prescription errors included incorrect dose (the most common one), followed by inappropriate drug choice, known patient’s allergy, incorrect dose frequency, and drug interactions.

The present study did not assess all steps of the drug use process including prescription transcription, pharmacy dispensation and administration by nursing staff. The observed rate of errors and near-misses may be underestimated.

Antibiotic protocol availability and high adherence in certain instances at the hospital studied did not prove to be enough to prevent all adverse drug events. Nevertheless, this is a good tool for limiting antibiotic use and can result in cost reduction and prevention of the emergence of resistant microorganisms in hospitals, as reported in a university hospital in Croacia. These authors state that for improving antibiotic prescription, in addition to protocols, other approaches are required such as prescribers’ education.

There are several strategies proposed for the prevention of adverse drug events such as electronic prescriptions. It has the advantage of much shorter preparation time as previous prescriptions can be recovered and are legible and transcription by nursing staff is eliminated. Although this process contributed for patient risk reduction, most Brazilian hospitals have only basic computerized services implemented or lack effective computer systems as remarked by Góes. The cost of information systems is an obstacle to their full implementation in Brazil.

Another useful tool for the prevention of drug events is the use of single doses: drugs are provided in individual packages following the medical prescription and dispensed by the pharmacy ready to the administered to the patient. This tool provides more drug safety, traceability and identification, reduces side storage, promotes job integration of several different providers, and allows for double checking and checking by the different providers involved in this process.

The implementation of adverse event monitoring and notification programs in hospital settings is an important action for the prevention of these events. These programs promote event surveillance and encourage their documentation and notification. Thus, they support mechanisms for safe use of drugs in risk patients and promote education of health providers enabling them to identify potential events. In a similar study, Mazzeo et al. monitored antibiotic-induced adverse events in an university hospital in Italy and noted this was a good strategy for detecting associations between drug exposure and the occurrence of adverse events in both children and adults.

In conclusion, all events seen in the present study were also described in the literature and therefore could have been avoided, stressing the importance of preventive actions. Inadequate knowledge on drugs or lack of patient information at prescription time seem to have been the major factors involved in the occurrence of adverse events in the present study. This is a health concern with several implications, including increasing costs.

The study results can be generalized and its methods can be applied in similar studies in other hospital settings for estimating the magnitude of adverse drug events in Brazil as well as for the development of preventive actions consistent with the Brazilian situation.
REFERENCES


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