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Inadequate and Chaotic Antibiotic and Antipyretic Prescription in a Sample of Brazilian Children

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ABSTRACT

Aim: Pharmacotherapy for inpatient children should be restricted in order to avoid serious adverse drug reactions. The objective of this work was to evaluate the antibiotic prescriptions for children. *Methods:* during 2007 to 2011, we collected hospital records of 195 children from 2 to 10 years old in a public Brazilian hospital. *Results:* Dipyrone was the most used drug for those children, followed by the broad-spectrum antibiotics cephalotin and gentamicin. *Conclusion*: There was massive use of dipyrone, an antipyretic drug forbidden in many countries. Lacking of performing antibiotic sensibility testing and widely use of broad-spectrum antibiotics increase the risk of antibiotic-resistant strains.
KEY-WORDS: antibiotics; dipyrone; children

INTRODUCTION

In Brazil there is no specific regulatory public policy regarding registry and prescription of pharmaceuticals for children. As a tragic consequence inappropriate prescription of drugs for children into the hospitals is too much frequent. Many therapeutic drugs have no information regarding pediatric dosages which increase the risk of pharmaceutical intoxications for this specific age group [1].

Current recommendations regarding drug prescription for hospitalized children asserts that they should be minimized and restricted used and those administrations should follow an adequate diagnostic and management of the clinical condition of the pediatric patient [2, 3]. As a consequence of adequate prescription the incidence of both drug interactions and drug intoxication are reduced as well as the drug administration therapeutic regimens are also improved for pediatric patients [4]. In this regard, many strategies such as electronic registry and better hospital information systems have been proposed to improve drug prescription (especially antibiotic prescriptions) for pediatric patients [5, 6]. However, lack of knowledge by prescribers can result in inadequate drug treatment of children [7, 8]. The most common prescribing errors are associated with incorrect doses, illegible details or unsafely drug interactions. It is important to emphasize that lack of information on pediatric drug prescription also occurs in developed countries such as reported in Canada [9]. Lacking on information regarding secure therapeutic dosages of non-steroidal anti-inflammatory drugs for children has been associated to serious consequences such as severe hemorrhagic acute kidney damage [10].

Drug-drug interactions are classified in three groups as follows: pharmacokinetic interactions, pharmacodynamic interactions, and mixed interactions [11]. Drug-nutrient interactions are also found in pediatric patients. These interactions of clinical significance comprise change of kinetic and/or dynamic profile of a drug or a nutrient [12].

Beyond the toxicological problems of inadequate drug use for children, antibiotic prescription poses another risk for children's health: the precocious antibiotic resistance which is a world-wide public health problem [13].

For the first time, we report here the inadequate pattern of drug prescription for inpatient children in a countryside region from Central-Western Brazil.

METHODS

This was a pharmacoepidemiologic study covering records of inpatient children from 2 to 10 years old hospitalized in the "Hospital Getulio Vargas" from Aragarças municipality, Goias State, Central-Western Brazil. Aragarças has a children population of 3183 citizens. Any subject and physician identification data from the records were previously hidden and then they were photographed. The selection of records covered the period from august 2008 to February 2011, resulting in 195 inpatient children (51.3% male and 48.7% female). Because of lacking of data, we did not include children less than 2 years old. Records from patients with incomplete data or filling out errors were excluded. Essential collected data cover information such as the prescribed drugs

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included in the National List of Essential Medications ("RENAME") [14], drug therapeutic classes, and solicitation of clinical laboratory clinical examinations.

All patients signed the free and informed consent form and the study received approval by the Ethics Committee on Research of the Julio Müller University Hospital (protocol 987/CEP-HUJM/2011). Epiinfo® 3.5.3. was used for statistical analysis. The chi-square test was used to verify possible differences among the results, with a significance level of $p<0.05$ for the adherence with the Bonferroni's correction. Evaluation of medicinal drug interactions was done using the Micromedex® program.

RESULTS

No samples for microbiologic isolation or antibiotic susceptibility tests were taken from patients.

From a total of 1193 drug prescriptions dipyrone was the most frequently used (30.8%; n=368), followed by a cefalothin (14.0%; n=168) and gentamicin (11.3%; n=136). Other frequently prescribed drugs were ipratropium bromide (8.0%, n=95), ranitidine (7.1%, n=86), chloramphenicol (5.0%, n=57), steroidal anti-inflammatory drugs (6.1%, n=73), metoclopromide (3.0%, n=35), and other classes (14.7%, n=175).

Since dipyrone use was banned in many European countries and in the United States none of dipyrone interactions with other drugs were found in the Micromedex® database.

Table 1 lists the most prescribed antibiotics. Cefalothin lidered the antibiotic prescriptions 33.7% (n=168), followed by gentamicin (27.2%; n=136), and chloramphenicol (11.42%; n=57). 76.4% of the inpatient children (n=149) had received at least one antibiotic prescription during hospitalization. Although cefalothin prescription was significantly different compared to chloramphenicol ($p<0,005$), gentamicin did not.

The majority of prescribed antibiotics were the broad-spectrum drugs (Table 2), representing 99.4% (n=496); and those antibiotic with bactericidal activities were most frequently utilized (88.6%; n=442).

Micromedex® identified eighteen cases of drug interactions. Antibiotics were involved in fifteen interactions such as ampicillin and gentamicin (n=13); amoxicillin and gentamicin (n=1); and furosemide and gentamicin (n=1).

DISCUSSION

Proscribed in many countries dipyrone has been associated with very serious adverse reactions such as agranulocytosis, pancytopenia, serious hypotension, anaphylaxis, asthma, serum sickness, hypersensitivity vasculitis, alveolitis, pneumonitis, hepatitis, transient renal insufficiency in children and adults, aplastic anemia in children, bone marrow aplasia in Chron's disease patient, and haemolytic-uraemic syndrome [15-21]. Agranulocytosis is a rare and serious disease often caused by drugs with a 10% mortality rate. The most common manifestations are infections such as tonsillitis, pharyngitis, stomatitis or pneumonia [22]. Although rare and especially associated with long-term drug use, the considerable number of literature reports regarding dipyrone-induced agranulocytosis is of great concern and poses awareness for hospital pharmacists and physicians [15-17, 23-26]. Long time ago, it was reported a near-fatal case of sepsis and agranulocytosis in the USA [27]. Dipyrone-induced agranulocytosis was also associated with severe enterocolitis [28]. Beyond agranulocytic reactions, dipyrone have also been implicated in allergic rhinoconjuntivitis, anaphylatic shock, exanthematous dermatitis, and the Sweet syndrome dermatosis [29-31].

Cephalotin was the second most used drug in this study. It belongs to the first generation of the semi-synthetic antibiotic cephalosporins with broad-spectrum of action since it inhibits the bacterial cell wall. Gentamicin is also a broad-spectrum antibiotic which belongs to the aminoglycoside class capable of inducing errors into the mRNA genomic codification. It has been observed toxic effects of gentamicin on kidney, cochlea and vestibular organs, and on testis [33-36]. Chloramphenicol was the unique bacteriostatic antibiotic frequently used into that hospital. Adverse chloramphenicol reactions include acute hepatitis, reduced spermatozoa production, aplastic anemia and Grey baby syndrome [37-39].

Ampicillin and gentamicin interactions were the most common found in this study. This antibiotic interaction has been associated with serious toxic adverse reactions causing systemic lupus erythematosus, Stevens-Johnson's syndrome, and toxic epidermolysis [40]. Bashir et al. [41] reported that ampicillin and gentamicin interaction was only the 5th most common interaction.

In this study we report one furosemide-gentamicin interaction. This is in accordance with a previous study in hospitals from two Pakistani populations [41]. This drug interaction has been associated with nephrotoxicity and ototoxicity [41,42].

Beyond the bacterial isolation from the patient, the antibiotic susceptibility testing is mandatory for the rational therapeutic choice of the adequate antibiotic to be used in. We discovered that by lacking of financial resources the laboratory hospital did not perform those tests. The percent of patients in whom susceptibility testing was performed was minor than 2%. Aragarças as well dozens of Brazilian country cities have very limited health resources and no diagnostic laboratory. Then, physicians are used to give their diagnosis based

only on physical examination of the patients without soliciting complimentary laboratory exams. In case of infectious diseases they usually prescribe broad-spectrum antibiotics. This hospital and a large number of other hospitals in country cities have no commission for controlling of hospital infections. This problem associated to using broad-spectrum antibiotics creates a very harmful situation for the inpatient children; that is, it destroys the natural children's intestinal microbiota contributing also for selection of antibiotic-resistant microorganisms.

CONCLUSION

In conclusion, since antibiotic susceptibility tests were not performed we report lacking of an adequate use of anti-inflammatory and antibiotic drugs expositing hospitalized children to potential harmful effects.

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Table 1 – Major antibiotics prescribed for hospitalized children at “Getulio Vargas hospital”, Brazil.

Antibiotic	**Frequency (*f*)**	**(%)**
Cefalothin	168	33.7 ***
Gentamicin	136	27.3
Chloramphenicol	57	11,4
Ampicillin	41	8.2
Ceftriaxone	35	7.0
Sulfamethoxazole + Trimethoprim	30	6.0
Metronidazole	17	3.4
Amoxycillin	3	0.6
Benzoilmetronidazole	3	0.6
Benzilpenicillin	3	0.6
Cephalexin	3	0.6
Oxacillin	3	0.6
Total	**499**	**100**

*** statistical difference between cefalothin and chloramphenicol (p<0,05)

Table 2 – Mechanism of action and spectrum of the antimicrobial agents prescribed to children in “Getulio Vargas Hospital”, Brazil.

Spectrum of action	**Frequency (*f*)**	**(%)**	**Mechanism**	**Frequency(*f*)**	**(%)**
Broad	496	99.4 ***	Bactericidal	442	88.6 ###
Narrow	3	0.6	Bacteriostatic	57	11.4
Total	**499**	**100**		**499**	**100**

*** indicates statistical difference between groups (p<0,05).