

The incidence and clinical relevance of drug interactions in pediatrics

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ABSTRACT

Objective: To investigate the prevalence of the major drug interactions in children and verify the rate and profile of drug interactions in hospitalized pediatric patients. **Materials and Methods:** A retrospective study was designed and data collected from the files of hospitalized children in Pulmonology, Nephrology, and Gastroenterology wards of a Pediatric Clinic, from July 1999 to 2004. **Results:** From the analyzed material, we detected 34 cases of interactions, of which 1 was pharmacodynamics interaction, 13 were pharmacokinetic interactions, and 20 of unknown mechanisms. According to the rate of significance, 4 cases were categorized in the first significance rate of interaction, 18 cases in the second significance rate, 1 case of the third significance rate, 4 cases of the fourth significance rate, and 7 cases of the fifth significance rate. According to onset of cases, 33 cases were of delayed onset, and according to severity of interactions, in 7 cases we noticed major severity interaction, in 19 cases moderate severity and in 8 cases minor severity. **Conclusions:** The presence of drug interactions is a permanent risk in the pediatric clinic. Then, we can conclude that continued education, computer system for prescriptions, pharmacotherapy monitoring of patients, and the pharmacist participation in the multidisciplinary team are some manners of improving the treatment to hospitalized patients.

Key words: Children, drug interactions, therapy

INTRODUCTION

A drug–drug interaction may be the pharmacologic or clinical response to the administration of a drug combination, different from that anticipated from the known effects of the two agents when given alone. Clinically significant drug interactions, which pose potential harm to the patients, may result from changes in pharmaceutical, pharmacokinetic, or pharmacodynamic properties.

Patient factors that increase the risk for drug interactions include being critically-ill, polypharmacy, having impaired hepatic or renal function, hypoxemia, or metabolic disturbances, and being elderly. Given the paucity of data on drug interactions in pediatric patients, children should also be considered at a special risk.^[1]

The clinical result of a drug–drug interaction may manifest as antagonism ($1 + 1 < 2$), synergism ($1 + 1 > 2$), or idiosyncratic reaction (a response unexpected from the known effects of either agent).

Adverse drug interactions pose a significant threat to hospitalized patients. Most patients receiving potentially interacting drugs do not experience adverse drug events; however, serious adverse events are known to occur.^[2–4] Evidence from epidemiologic studies suggest that drug

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interactions contribute to a small, but significant number of adverse events in hospitalized patients.^[5-8] With multiple drugs often prescribed, the potential for adverse drug interactions is an important concern. No associated adverse drug events were identified, but the retrospective design of the study probably limited our ability to detect them. The purpose of the study is to verify the rate and profile of drug interactions in medical prescriptions to hospitalized pediatric patients.

MATERIALS AND METHODS

The data have been collected in a retrospective design from the files and drug list of children hospitalized in Pulmonology Nephrology and Gastroenterology wards in the Pediatric Clinic, from July 1999 to 2004.

Drug interactions have been analyzed by types of interactions. They are as follows:

- (a) Pharmacodynamic interactions
- (b) Pharmacodynamic–pharmacokinetic interactions
- (c) Pharmacokinetic interactions

To evaluate the clinical significance of drug interactions we analyzed the data of 148 patients according to the significance rate of interaction, onset of interactions, severity of interaction, and documentation of clinical manifestation of interaction, in an aim to evaluate the significance rate of interaction the data were divided in to five categories (category 1 through 5), according to severity of interaction and documentation.

The methodology to assess the significance rate of interaction was based on Editorial Group's Assessment of the Interaction's Severity and Documentation.^[9]

RESULTS

Initially, we collected data from 148 cases from which 34 cases had drug interactions. We analyzed the cases with drug interaction by the type of interactions, significance of interaction, rate of onset and severity.

Table 1 presents the structure of drug interaction by type. Of 34 cases of interaction, 1 (2.94%) was pharmacodynamic, 20 (58.82%) cases were unknown, and pharmacokinetic (38.24%) were 13 cases.

According to the rate of significance, 4 cases were of the first significance rate of interaction, 18 cases of the second significance rate, 1 case of the third significance rate, 4 cases of the fourth significance rate, and 7 cases of the fifth significance rate. According to onset of cases that were of delayed onset, and

according to severity of interactions in 7 cases we have noticed major severity interaction, in 19 cases moderate severity, and in 8 cases minor severity.

The case of pharmacodynamic interaction (1/34) is an interaction of the moderate significance, delayed onset, minor severity, and suspect documentation.

Pharmacokinetic interactions have shown greater variability according to the significance rating, severity, and their documentation.

More frequent interactions were those of the second significance rating, delayed onset, moderate severity, and established documentation (5/34 or 14.71%), while 3 cases of interactions were of the first significance rate and other 3 cases of the fifth significance rate (8.87%). The first significance rate pharmacokinetic interactions were of delayed onset, major severity of interaction, and probable documentation, while the fifth significance rate were of delayed onset, minor severity of interaction, and probable documentation. As the fourth significance rate interactions were 5.88% of cases. In these cases, the interaction was of delayed onset and major severity of interaction [Table 2].

Unknown type of interactions have shown greater variability according to the significance rate, onset, severity of interaction and their documentation, as well. More frequently, these interactions belonged to the second significance rate (13 or 38.23%) of whom 9 cases (26.47%) are of suspect documentation, while 4 cases (11.76%) are of probable documentation [Table 3].

Table 1: Drug interactions

	No.	(%)
Types of interactions		
Pharmacodynamic	1	2.94
Unknown	20	58.82
Pharmacokinetic	13	38.24
Interactions according to rate significance		
1	4	11.76
2	18	52.94
3	1	2.94
4	4	11.76
5	7	20.59
Interactions according to rate of onset		
Rapid interaction	1	2.94
Delayed interaction	33	97.06
Interactions according to severity		
Major	7	20.59
Moderate	19	55.88
Minor	8	23.53

Structure of cases by types of interactions, significance of interaction, rate of onset, and severity

Table 2: Drug interactions according to categories (no. 34)

Types of interact	Significance	Rate of onset	Severity	Documentation	No.	(%)
Pharmacokinetic	1	Delayed	Major	Possible	3	8.82
	2	Delayed	Moderate	Established	5	14.71
	4	Delayed	Major	Possible	2	5.88
	5	Delayed	Minor	Possible	3	8.82
Pharmacodynamics	3	Delayed	Minor	Suspect	1	2.94
Unknown	1	Rapid	Major	Suspect	1	2.94
	2	Delayed	Moderate	Suspect	9	26.47
	2	Delayed	Moderate	Possible	4	11.76
	4	Delayed	Major	Possible	1	2.94
	4	Delayed	Moderate	Possible	1	2.94
	5	Delayed	Minor	Possible	4	11.76

Variables: Types of interactions, significance of the interactions, rate of onset of interaction, severity of interaction, and documentation of interaction

Table 3: Drug interactions according to categories and drug's name (no. 34)

Types of interaction	Sign	Onset of interact	Severity	Document	No.	Drug 1	Drug 2
Pharmaco kinetics	1	Delayed	Major	Possible	1	Digoxin	Furosemide
					2	Erythromycin	Terphenadine
					5	Erythromycin	Metilprednizolon
	4	Delayed	Major	Possible	2	Rifampicin	Paracetamol
	5	Delayed	Major	Possible	1	Isoniazid	Prednisone
Pharmaco dynamics	3	Delayed	Minor	Suspect	2	Isoniazid	Diazepam
					1	Captopril	Furosemide
	1	Rapid	Major	Suspect	1	Amikacin	Furosemide
					3	Amikacin	Ceftriaxone
	2	Delayed	Moderate	Suspect	3	Gentamicin	Ceftriaxone
					1	Gentamicin	Cefaclor
					1	Gentamicin	Cephalexin
					1	Streptomycin	Ceftriaxone
					3	Amikacin	Penicillin
Unknown	4	Delayed	Major	Possible	1	Rifampicin	Nifedipine
					1	Captopril	Digoxin
	5	Delayed	Moderate	Possible	1	Chloramphenicol	Penicillin
					2	Erythromycin	Cloxacillin
					1	Erythromycin	Penicillin
					1	Chloramphenicol	Paracetamol

Variables: Types of interactions, significance of the interactions, rate of onset of interaction, severity of interaction, documentation of interaction, and names of that drug interactions

DISCUSSION

In our study, we encountered a variety of drug interactions at the pediatrics clinic, but what needs more attention are the cases of first significance rate interaction, rapid onset, and major severity of interaction. Below we elaborate the most important drug interactions seen during the study in detail.

Digoxin interacts with furosemide and other loop diuretics because of changes in the electrolyte concentration induced by diuretics. Although loop diuretic drugs themselves do not alter the kinetics of digoxin excretion, they induce a dose-dependent loss of potassium from the body, resulting in a decreased serum potassium concentration. It is well known that hypokalemia is associated with sensitivity to digitalis and, thus, increases its toxicity but it is not well appreciated that when the serum

potassium is as low as 2 to 3 mEq/l, the tubular secretion of digoxin is nearly blocked. This reduced tubular secretion of digoxin results in a diminished plasma clearance of digoxin and thereby a prolonged elimination half-life of digoxin. Thus, hypokalemia itself can result in an increase in the serum digoxin level as well as enhancing toxicity. Such an electrolyte imbalance can precipitate or give contribution to arrhythmias, especially among patients with previous cardiac arrhythmias.

The ability of macrolide antibiotics to interact with the biotransformation of some other drugs has been widely recognized, mostly with erythromycin and troleandomycin. Both drugs bind strongly to and inhibit markedly CYP 3A4.

The non-sedating antihistamine terfenadine is used widely in the treatment of patients with allergies. Terfenadine undergoes

rapid first-pass metabolism in the liver, where cytochrome P450III_A enzyme converts it to the active form, terfenadine carboxylate. If metabolism is inhibited, then the unmetabolized terfenadine accumulates and cardiotoxicity may ensue. This includes the development of torsade de pointes, a potentially fatal cardiac arrhythmia. Thus, co-administration of macrolides and terfenadine causes an increase in the serum level of terfenadine to cardiotoxicity levels.

Co-administration of methylprednisolone and erythromycin can also increase the pharmacologic and toxic effect of methylprednisone. These interactions occur because of increased serum levels of methylprednisone.

Therapeutic efficacy of paracetamol (analgesic/antipyretic) may be diminished by rifampicin which can even increase the toxicity of paracetamol. Rifampicin can induce hepatic microsomal enzymes, which metabolizes paracetamol more quickly to metabolites, which are potentially hepatotoxic.^[10]

The isoniazid serum level can be decreased by corticosteroids, by increasing the rate of hepatic acetylating in slow accelerations and by increasing renal clearance in slow as well as rapid accelerations.

By decreasing renal clearance, isoniazid can potentiate benzodiazepine action, through inhibition of oxidative metabolism of benzodiazepines in liver.

Administration of amino-glycosides or of loop diuretics, even alone, can cause ototoxicity.^[11] Experimental data show that the synergistic effect appears when amino-glycosides are parenterally combined with these diuretics. Manifested ototoxicity depends on doses and serum levels of respective drugs.

Administration of amino-glycosides in combination with cephalosporin can increase nephrotoxicity through an unknown yet mechanism.

Parenteral penicillins inactivate certain amino-glycosides. Synergism of these antimicrobials is well documented. Nevertheless, some amino-glycosides are more inactivated by some penicillin's. These problems are even bigger when this happens *in vitro* or in a syringe where physicochemical incompatibility occurs. *In vivo* inactivation of amino-glycosides by penicillin depends on diminished renal function and that is why the patient should be carefully monitored. The dose of antimicrobials should be lowered, if the patient has moderate or high renal insufficiency.

Rifampicin can reduce therapeutic effects of nifedipine, potentially through increased metabolism of nifedipine

on the bowel wall (cytochrome P 450 3A4) induced by rifampicin.

Combination of penicillin and chloramphenicol may show synergism against certain microorganisms, but on animal studies it has been reported even for cases of antagonism.

The mechanism of this antagonism is not clear and still not entirely determined. The same reaction happened when combining with erythromycin.^[12]

CONCLUSION

The presence of drug interactions is a permanent risk in hospitals especially in pediatric hospitals. Then, we can conclude that continued education, serum drug concentration monitoring in children, and participation of clinical pharmacologist in the multidisciplinary team during the application of drug therapy, computer system prescriptions (a computer software that provides a program that does not let entering two or more drugs that interfere with each other, and also that informs the doctor of the adverse effects and interactions of each drug prescribed) are necessary for the prevention of drug interactions, for improvement of treatment of hospitalized children.

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