Assessment of Interactions of Drugs Prescribed for Pediatric Patients in Bangladesh

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Abstract

Drug-drug interactions (DDIs) represent an important clinical problem. During inpatient admissions, infants, children, and adolescents are typically exposed to different medications, increasing their risk of potential drug-drug interactions (pDDIs). While drug interactions are reported to be common, there are only few publications of the prevalence of such interactions among pediatric patients in Bangladesh. The present study tries to estimates the prevalence and characteristics of pDDI exposure of pediatric patients treated in children's hospitals. This observational retrospective study was carried out on 155 patients admitted to a children's hospital located at Dhaka during January 2019 to August 2019. The medications of the patients were analyzed for pDDIs by using Medscape drug interaction checker. The prescriptions were analyzed for demographic characteristics, medical and detailed drug history. Drug-drug interactions (DDIs) were evaluated for total numbers, types and severity of DDIs. Total 155 prescriptions with mean age 2.12 ± 2.08 years were analyzed and a total of 25 pDDIs were recorded. The prevalence of pDDI was 17%, of which 12 (48%) were pharmacodynamic interactions, 10 (40%) were pharmacokinetic interactions and 3 (12%) of unknown mechanism. According to the severity of interaction, 4 (18%) cases were categorized as serious, 15 (55%) cases as moderate and 6 (27%) cases as minor. The occurrence of DDIs were significantly associated ($r=0.912$, $p<0.05$) with the number of drugs prescribed. The present study has identified pDDIs and also documented interactions in pediatrics patients. It has highlighted the need for screening prescriptions of pediatric patients for pDDIs and proactive monitoring of patients who have identified risk factors in order to promote detection and prevention of possible adverse drug interactions.

Key words: Drug-Drug Interactions, Pediatric, Pharmacokinetic, Pharmacodynamic, Prescriptions.

Introduction

The concomitant and extended utilization of two or more drugs in a treatment, either due to the patient's pathological condition or the need for action or effect complementation, is known as polypharmacy. Polypharmacy may bring numerous benefits but not always produce desirable effects. They can sometimes lead to unfavorable therapeutic effects. Polypharmacy has been implicated as a significant risk factor in the pediatric population for developing medication-related adverse drug events (ADEs), likely as a consequence of exposure to potential drug–drug interactions which can be identified when the administration of a drug combination lead to an unexpected change in the clinical condition of the patient (Bista *et al.*, 2007). The concept of potential Drug-Drug interaction (pDDI) based on the possibility a drug to alter the effects of another when both are simultaneously administered, and produce different pharmacological or clinical effects than expected known effects when individually prescribed (Alvim *et al.*, 2015). It is the

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qualitative or quantitative change in the effect of a drug either pharmacokinetic or pharmacodynamic. Potential drug–drugs interactions (pDDIs) are observed to be one of the most frequently appearing challenge that may alter the pharmacokinetic and pharmacodynamics of the drugs thus alter the overall therapeutic response (Baxter and Preston, 2010). Many adverse events can be prevented by identifying pDDIs. For the general population, many studies found that DDIs responsible for 23% of hospital admission and higher health care costs (Lubinga and Uwiduhaye, 2011; McDonnell and Jacobs, 2002).

Drug interactions may produce beneficial and desirable effects or harmful and undesirable effects. Potential drug-drug interactions do not necessarily occur in all patients (Sehn *et al.,* 2003; Magro *et al.,* 2012a). Vast majority of the drug-drug interaction studies involved adult patients. By contrast, studies of the occurrence of pDDIs in children are almost entirely lacking. Children can be more vulnerable to the occurrence of potential DDIs than adults because: a) Hospitalized children are typically seriously ill and need combination of therapy. As a result, they are often exposed to multiple drugs that could interact with each other in potentially harmful ways; b) They can react differently to drug than adults, which is explained by changes in absorption, distribution, metabolism and excretion; c) limited physiologic reserve and incapability to properly communicate with healthcare professionals and d) calculation errors in medications dosing (Kearns *et al.,* 2003; Wang *et al.,* 2007; Langerova *et al.,* 2013).

Drug-drug interactions may increase the risk of developing medication-related adverse drug events, leading to serious clinical morbidity and mortality. Research on DDIs in infants is of particular urgency and importance but most of studies are limited to adult patients. Some information such as the estimates of the prevalence of pediatric DDIs, reliable knowledge regarding the risk posed by specific DDIs, an adequate understanding about pathways by which DDIs may lead to harmful ADEs in pediatric patients, moreover the epidemiology of pediatric DDI is largely unknown. This information's

are integral to developing and studying strategies to alleviate clinically important ADEs associated with specific DDIs (Feinstein *et al.,* 2014, Dechanont *et al*., 2014). There are scarce data on DDIs in pediatric population in our country. Therefore, there is an utmost need to gather data regarding drug-drug interactions in pediatrics population. For this reason, this study was initiated to assess the prevalence and characteristics of pDDI exposure of pediatric patients treated in children's hospitals.

Materials and Methods

Study design: This was an observational retrospective study on conducted on prescription collected for the period of 8 months from January 2019 to August 2019 at a children's hospital in Dhaka.

Study population and setting: The study population included 100 indoor patients and100 outdoor patients, out of which only 155 patients were selected for this analysis because they were treated with two or more drugs. The patients whose prescriptions contain only one drug were excluded. (Food-drug interaction and herbal drug interactions are not checked). Confidentiality about patients' identification was maintained. Socio-demographic data was obtained from the patients after obtaining their verbal informed consent.

Procedure for potential drug-drug interactions identification: Total 155 prescriptions were selected by simple randomization. Demographic data (age, gender and body weight), medical history, co morbidities and drug related data (name of drug, dose, duration, frequency, route and concomitant medication) were recorded in a specially designed form. All collected prescriptions were evaluated for DDIs by the online Medscape drug interaction checker, which is freely accessible software (Multi-Drug Interaction Checker, Medscape). DDI were also checked by referring standard text books of pharmacology (Goodman and Gilman's The Pharmacological Basis of Therapeutics, 13[th]ed.). The prescriptions were analyzed for different variables of DDIs like total numbers of interactions, types and severity. All the significant DDIs were classified

based on mechanism like pharmacodynamic, pharmacokinetic and unknown. The severity of DDIs was classified as minor, moderate and serious. All identified potential DDIs were recorded and graded according to their level of severity and a description was given on their mechanism of action and adverse consequences, as well as recommendations. By definition, a potential DDI categorized as serious indicates that there is potential for serious interaction, which can affect the clinical evolution or promote permanent damages to the patient and regular monitoring by the treating physician is required or alternate medication may be needed. The moderate category refers to the possibility of significant interaction, which can produce aggravations or clinical alterations, requiring changes in the therapy and monitoring by treating physician is likely required. A minor categorization means that interaction is unlikely, minor or non-significant.

Data analyses: The prevalence of potential DDIs was defined as the number of patients with any potential DDI divided by the total number of patients that received two or more drugs in the study period and multiplied by 100. Potential DDIs total number was defined as the number of potential DDIs detected by means of Medscape drug interaction checker (Multi-Drug Interaction Checker, Medscape). The percentage of patients with at least one contraindicated, serious, significant and minor potential DDIs was defined as the number with at least one of these potential DDIs divided by the total number of patients who had potential DDIs and then multiplied by 100. For descriptive purposes, patients were classified in 6 categories according to age. The number of medications was defined as the total number of drugs administered to the patients.

Descriptive statistics, mean, frequency distribution was applied for analyzing the data. The statistical software namely SPSS 20.0 was used for the analysis of the data and Microsoft word and Excel had been used to generate graphs, tables etc.

Results and Discussion

Initially data were collected and analyzed from 155 prescriptions. Average 3 drugs were prescribed per prescription. Total numbers of therapeutic classes of drugs prescribed were 34. Most frequently prescribed therapeutic class was: Antimicrobial antibiotics (60%), among them most often prescribed drug was 3rd generation cephalosporin (25%), followed by 2nd generation cephalosporin (13%) andaminoglycoside (9%). Other classes of drugs commonly given to the patients on the infectious disease were 4-qunolone (8%), anthelminthic (5%) and 1st generation cephalosporin (5%).

Out of 155 prescriptions, 23 (15%) prescriptions had drug-drug interactions and 132 (85%) prescriptions had no drug-drug interactions. Maximum number of prescriptions 21 (13.54%) had one drug-drug interaction, followed by 2 (1.3%) prescriptions had two interactions.

Total 25 interactions were identified, which were analyzed by the mechanism and the significance of interaction. Based on mechanism, 10 (40%) interactions were pharmacokinetic interaction, 12 (48%) pharmacodynamic interaction and 3 (8%) were of unknown mechanism. (Table 1)

According to the severity of interaction 4 (18%) interactions were serious, 15 (55%) were of moderate and 6 (27 %) were of minor. (Table 1). The combination of sulbutamol and ketotifen shown most drug-drug interaction.

Of all 10 pharmacokinetic interactions observed, 4 interactions could affect absorption; all of this causes the decrease of the level or effect on other drug by decreasing gastric absorption. 3 (30%) interactions could effect on distribution and 3(30%) interactions on metabolism. Out of these 2 (67%) drug combinations could decrease the level of other drug by increasing metabolism and 1 (33%) could increase the level of another drug by decreasing metabolism. (Figure 1). Most common CYP450 enzymes involved in these interactions were CYP2C9 phenobarbitone + (sulfamethaxozole + timethoprime), CYP3A4 phenobarbitone + prednisolone and CYP2E1 metronidazole + paracetamole. No interactions were found that could effect on excretion of the drugs. (Table 1).

Table 1. Most frequent specific pDDIs stratified according to pDDI seriousness.

Co-administered drugs	Therapeutic classes	Potential ADE	Types of interaction	No. of patient exposed
		Severe		
Ciprofloxacin + Ondansetron	4-Qunoloe + antiemetic	QTc interval increases, electrolyte abnormalities, CHF or brady arrhythmias	Pharmacodynamic	3(14%)
Iron hydroxide poltmaltose + Moxifloxacin	Oral iron preparation + 4-Qunolone	Iron decreases the level of moxifloxacin by inhibiting GI absorption	Pharmacokinetic	1(5%)
		Moderate		
Phenobarbitone + Amikacin	Barbiturate + Amioglycoside	Decreased effect of amikacin	Pharmacokinetic	3(14%)
Promethazine + Azithromycin	Antiemetic + Macrolide	Prolonged QTc interval	Pharmacodynamic	1(5%)
Ciprofloxacin + Ketorolac	4-Qunolone + Analgesic	Risk of CNS stimulation and seizures.	Unknown	1(5%)
Phenobarbitone + Prednisolone	Barbiturate + Glucocorticoid	Phenobaebital decrease the level or effect of prednisolone by affecting 1) Hepatic /intestinal enzyme CYP3A4 metabolism.or by 2)P-glycoprotein (MDR1) efflux transporter	Pharmacokinetic	1(5%)
Ciprofloxin + Zinc sulfate monohydrate	4-Quolone + Mineral preparation	Decreased effect of ciprofloxacin.	Unknown	1(5%)
Sulfamethaxozole + timethoprime	Antibiotic	Prolonged QT interval.	Pharmacodynamic	1(5%)
Levofloxacin + Betamethasone	4-Qunolone + Glucocorticoid	Synergistically increase the risk of tendon rupture.	Pharmacodynamic	1(5%)
Cefuroxime + omeprazole	2nd generation cephalosporin + PPI	Esomeprazole decrease the level or effect of cefuroxime by increasing gastric pH	Pharmacokinetic	1(5%)
		Minor		
Calcium gluconate + Amikacin	Mineral preparation + Aminoglycoside	Amikacin decreases the levels of Calcium gluconate by inhibition of GI absorption	Pharmacokinetic	2(9%)
(Vitamin-B+Zinc) + Ranitidine	Vitamin-mineral + H-2 blocker	Ranitidine decrease the level of vitamin B complex	Unknown	1(5%)
Phenobarbitone + (Sulfamethaxozole +timethoprime)	Barbiturate + Antibiotic	Phenobarbital decrease the level or effect of sulfamethoxazole by affecting hepatic enzyme CYP2C9/10 metabolism	Pharmacokinetic	1(5%)
Metronidazole + Paracetamole	Antiprptozoal drug + Analgesic	Metronidazole increase the level of acetaminophen by affecting enzyme CYP2E1 metabolism	Pharmacokinetic	1(5%)

Of all pharmacokinetic interactions pheno-barbitone + amikacin, (n=3) were most commonly observed interactions. Most of the interactions 5 (50%), are moderate, followed by 4 (40%) minor and 1 (10%) serious. (Table 1)

Out of all 12pharmacodynamic interactions, 6 showed pharmacodynamic synergism i.e. increase prolong QTc interval in 5 prescriptions, increase the risk of tendon rupture by both drug in 1 prescription. A total of 6 interactions showed pharmacodynamic

antagonism. i.e. showed an alteration in sedative effect. (Figure 1)

Of all 12 pharmacodynamic interactions, salbutamol+ketotifen (n=5) were most commonly observed interactions. Maximum interactions 9 (48%) were of moderate severity followed by 3 (12%) were of severe severity. (Table 1)
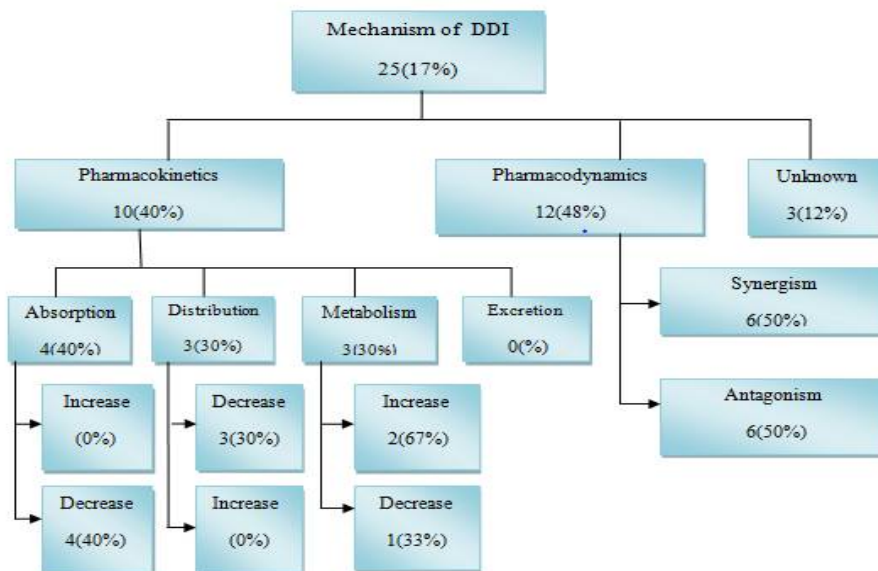

Figure 1. Drug-drug interaction based on their mechanism.

The study population was classified in 6 different age groups, <1 month 26 (17%), 1-5 months 34 (22%), 6-11 months17 (11%), 1-6 years 61 (40%), 7-12years 4 (3%) & 13-17 years (2%). Mean age of patient was 2.12±2.08 years. Among 23 interactions, 9 (35%) were found in the age group: <1 month, 3(12%) in 1-5 month, 2(8%) in 6-11 month, 8(35 %) in 1-6 years, 1(4%) in 7-12 years and 2 (13%) in 13-17 years.

No direct correlation was observed between the age of the patient and the number of drugs prescribed, the age of the patient and the number of DDIs. However, the number of drugs prescribed and the occurrence of DDIs were significantly associated (r = 0.912, p < 0.05). A positive correlation was observed as the number of DDIs increases as the number of prescribed drug increases.

The present study was conducted with aim and objective to identify and evaluate the drug-drug interactions in pediatric patients. There is reason to believe that hospitalized children may be a population at increased risk for drug interaction. Children admitted to hospital have critical medical conditions that make them more susceptible to the administration of multiple drugs, to complex treatment regimens, to long hospital stays, to take consultations from different specialist physicians and to take multiple medications.Maximum number of patients prescribed three to four drugs per prescription. So the probability of drug–drug interaction is high in pediatric population. In this study we found 17% prevalence of potential DDI which is within the range of values reported by different authors (from 3.8% to 75%) (Langerova *et al.*, 2014; Yeh *et al.*, 2014; Oshikoya *et al.*, 2013; Fernandez de Palencia Espinosa *et al.*, 2014, Lebowitz *et al.*, 2016; Dai *et al.*, 2016). There is wide variability in the potential DDIs prevalence values reported in the literature, which can be explained by **a)** the included population, **b)** the study design and **c)** the software used for the identification of DDI. (Morales-Rios *et al.*, 2018)

Table 2. Demographic characteristics of patients included in the study

Age range	No. of prescription (n=155)	Frequency of administered drugs	Prevalence of PDDI (%)			
			Total(25)	Sever(4)	Moderate(15)	Minor(6)
< 1 month	26(17 %)	1-6	9(35%)	1(11%)	5(67%)	3(33%)
1-5 months	34(22%)	2-4	3(12%)	0(0%)	2(67%)	1(33%)
6-11 months	17(11%)	1-4	2(8%)	0(0%)	1(50%)	1(50%)
1-6 years	61(40%)	1-6	8(35%)	3(33%)	5(67%)	0(0%)
7-12 years	4(3%)	2-3	1(4%)	0(0%)	0(0%)	1(100%)
13-17 years	2(2%)	3	2(13%)	0(0%)	2(100%)	0(0%)

Classification of drug interaction based on severity criteria enhances decision making ability by assessing risk versus benefit alternatives. Minor drug interactions do not result in any troublesome outcomes and management usually not required. Moderate drug interactions could result worsening in clinical condition of patient. Treatment to manage such type of interactions could be considered. Major drug interactions could lead to life threatening condition; therefore it should be considered essential to counter such problems as soon as they are identified (Ahmad *et al.,* 2015). In present study maximum interactions were moderate in nature followed by mild and serious interactions. In these cases, vigorous monitoring of prescriptions and awareness of interactions is needed to prevent the side effects which indirectly reduce the cost of the therapy.

In present study, most of the interactions were pharmacodynamic 12 (48%) followed by pharmacokinetic 10 (40%) interactions. There were few interactions which were having unknown mechanism.

Drug interactions can alter the absorptions in terms of either increased or decreased absorption, altered gastric emptying and altered gut flora. Altered absorption due to DDIs can reduce the concentrations of another drug. The most common interactions which leads to alteration of the absorption of the other drug were detected with Iron hydroxide poltmaltose+moxifloxacin, cefuroxime+omeprazole, calcium gluconate+amikacin,

The rate and extent of absorption may be important, in the case of drugs given in single doses where a threshold concentration for drug effect exists (e.g. analgesics, antibiotics). A delay in absorption in these circumstances, especially if the rate of elimination of the drug is high, may result in failure of therapeutic efficacy or drug resistance (Magro *et al.,* 2012 b). In drug displacement interaction, there is a reduction in extent of plasma protein binding of one drug by the presence of another which competes for the same binding sites. In this study, potential alterations of the distribution of one drug by another drug by plasma protein binding competition were detected with phenobarbitone + amikacin, phenobarbitone + prednisolone.

The clinical significance of increased drug metabolism is decreased plasma level of the co-administered drug. Similarly decrease metabolism of other drug resultant increase in level of slowly metabolized drug and prolongation of its effect. In both the cases alteration in dosing and close monitoring is required to avoid unnecessary ADRs. A potential chance of metabolism was observed in the group of drugs like phenobarbitone + (sulfamethaxozole + timethoprime), metronidazole + paracetamole, phenobarbitone + prednisolone. DDIs can lead to change in metabolism of other drugs, own metabolism or particular drug by either enzyme induction or inhibition. The Cytochrome P450 (CYP450) enzymes play an important role in the biotransformation of a wide number of drugs. Many drugs that undergo CYP mediated oxidative biotransformation is responsible for the large number of clinically significant DDIs during multiple drug

therapy (Palleria *et al.*, 2013). Genetic polymorphism of CYP plays an important role in therapeutic effect of drug treatment (Gallelli *et al.*, 2010; Gallelli *et al.*, 2012). In present study the most common CYP450 enzyme involved in the interactions were CYP3A4, CYP2C9 and CYP2E1.DDIs due to altered excretion process, can lead to toxicity or sub therapeutic effect. In this study no interaction was found which affecting excretion.

The pharmacodynamic interaction of a drug can be altered by competition at receptors, and non-receptor. Pharmacodynamic interactions can occur when two drugs have similar actions through different cellular mechanisms. In present study almost 12 (48%) of interactions from total, observed due to pharmacodynamic changes either by synergism or antagonism. Evidence of electrolyte disturbance causes electrolyte abnormalities, CHF or brady arrhythmias was observed in present study by group of drugs like ciprofloxacin + ondansetron. In present study the drugs causing prolongation of QTc interval were (sulfamethaxozole + timethoprime), promethazine + azithromycin, and ciprofloxacin + ondansetron.

This study provides the baseline data for future studies of potential DDIs in pediatric patients. This study was done only by using freely available DDI checker software on internet which provides only a 'potential' estimate of DDI occurrence. These results may thus underestimate the true rate in this patient population. However, despite these limitations, the study approach is currently widely used to assess the clinical relevance and risk of exposure to potential DDIs.

Conclusion

Although the prevalence rates of DDIs are low, it is a permanent risk in hospitals, especially in pediatric hospitals and life-threatening interactions may develop. So physicians must be reminded of the potential DDIs when prescribing medications for newborns and infants in order to minimize the risk of their consequences. Continued medical education, computerized prescriptions, monitoring of patients drug therapy and the participation of pharmacists in the multidisciplinary team are some ways of averting drug interaction of hospitalized children.

Conflict of Interest

Authors do not have any conflict of interest.

Abbreviation Used

DDIs: Drug-drug interactions; **CYP450:** Cytochrome P 450; **PPIs:** Proton pump inhibitors; **ADRs:** Adverse drug reactions;

References

Ahmad, A., Khanm, M.U., Haque, I., Ivan, R., Dasari, R., Ravankar, A., Pravin, A. and Kuraikose, S. 2015. Evaluation of potential drug-drug interactions in general medicine ward of teaching hospital in southern India. *J. Clin. Diagn. Res.***9**, 10-13.

Alvim, M.M., Silva, L.A., Leite, I.C. and Silverio, M.S. 2015. Adverse events caused by potential drug-drug interactions in an intensive care unit of a teaching hospital. *Rev. Bras. Ter. Intensiva*. **27**, 353-359.

Baxter, K. and Preston, C.L. 2010. *Stockley's Drug Interactions*. 8th ed, Pharmaceutical Press, London, UK, pp 3-9.

Bista, D., Palaian, S., Shankar, P.R., Prabhu, M.M., Paudel, R. and Mishra, P. 2007. Understanding the essentials of drug interactions: a potential need for safe and effective use of drugs. *Kathmandu Univ. Med. J. (KUMJ)*. **5**, 421-30.

Brunton, L.L., Hilal-Dadan, R. and Knollmann, B.C. 2018. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 13th ed.McGraw Hill, New York, USA.

Dai, D., Feinstein, J.A., Morrison, W., Zuppa, A.F. and Feudtner, C. 2016. Epidemiology of polypharmacy and potential drug-drug interactions among pediatric patients in ICUs of U.S. children's hospitals. *Pediatr. Crit. Care Med.* **17**, 218-228.

Dechanont, S., Maphanta, S., Butthum, B. and Kongkaew, C. 2014. Hospital admissions/visits associated with drug-drug interactions: a systematic review and meta-analysis. *Pharmacoepidemiol Drug Saf.* **23**, 489-497.

Feinstein, J., Dai, D., Zhong, W., Freedman, J. and Feudtner, C. 2015. Potential drug-drug interactions in infant, child, and adolescent patients in children's hospitals. *Pediatrics*. **135**, 99-108.

Fernandez de Palencia Espinosa, M.A., Diaz Carrasco, M.S., Fuster Soler, J.L., Ruiz Merino, G., De la Rubia Nieto, M.A. and Espuny Miro, A. 2014. Pharmacoepidemiological study of drug-drug interactions in onco-hematological pediatric patients. *Int. J. Clin. Pharm.***36**, 1160-1169.

Gallelli, L., Colosimo, M., Tolotta, G.A., Falcone, D., Luberto, L. and Curto, L.S. 2010. Prospective randomized double-blind trial of racecadotril compared with loperamide in elderly people with gastroenteritis living in nursing homes. *Eur. J. Clin. Pharmacol*. **66**, 137-44.

Gallelli, L., Galasso, O., Urzino, A., Saccà, S., Falcone, D. and Palleria, C. 2012. Characteristics and clinical implications of the pharmacokinetic profile of ibuprofen in patients with knee osteoarthritis. *Clin. Drug Inv.***32**, 827-833.

Kearns, G.L., Abdel-Rahman, S.M., Alander, S.W., Blowey, D.L., Leeder, J.S. and Kauffman, R.E. 2003. Developmental pharmacology - drug disposition, action, and therapy in infants and children. *N. Engl. J. Med.* **349**, 1157-1167.

Langerova, P., Prokes, M., Konvalinka, M., Furstova, J. and Urbanek, K. 2013. Incidence of potential drug interactions in medication prescriptions for children and adolescents in the University Hospital Olomouc, Czech Republic. *Eur. J. Pediatr.* **172**, 631-638.

Langerova, P., Vrtal, J. and Urbánek, K. 2014. Incidence of unlicensed and off-label prescription in children. *Italian J. Pediatr*. **40**, 12-16.

Lebowitz, M.B., Olson, K.L., Burns, M., Harper, M.B. and Bourgeois, F. 2016. Drug-Drug interactions among hospitalized children receiving chronic antiepileptic drug therapy. *Hosp. Pediatr*. **6**, 282-289.

Lubinga, S.J. and Uwiduhaye, E. 2011. Potential drug-drug interactions on in-patient medication prescriptions at Mbarara Regional Referral Hospital (MRRH) in western Uganda: prevalence, clinical importance and associated factors. *Afr. Health Sci*. **11**, 499-507.

Magro, L., Moretti, U. and Leone, R. 2012 a b. Epidemiology and characteristics of adverse drug reactions caused by drug–drug interactions. *Expert Opin Drug Saf.* **11**, 83-94.

Medscape. Available from:http://reference.medscape.com/drug-interactionchecker.

McDonnell, P.J. and Jacobs, M.R. 2002. Hospital admissions resulting from preventable adverse drug reactions. *The Annals of Pharmacotherapy*, **36**, 1331-1336.

Mino-Leon, D., Galvan-Plata, M.E., Doubova, S.V., Flores-Hernandez, S. and Reyes-Morales, H.A. 2011. Pharmacoepidemiological study of potential drug interactions and their determinant factors in hospitalized patients. *Rev. Invest. Clin.* **63**, 170-178.

Morales-Rios, O., Jasso-Gutierrez, L., Reyes-Lopez, A., Garduño-Espinosa, J. and Muñoz-Hernandez, O. 2018. Potential drug-drug interactions and their risk factors in pediatric patients admitted to the emergency department of a tertiary care hospital in Mexico. *PLoS ONE*. **13**, e0190882.

Oshikoya, K.A., Oreagba, I.A., Godman, B., Oguntayo, F.S. and Fadare, J. 2016. Potential drug-drug interactions in pediatric outpatient prescriptions in Nigeria and implications for the future. *Expert Rev. of Clin. Pharmacol.* **9**, 1505-1515.

Oshikoya, K.A., Oreagba, I.A., Ogunleye, O.O., Lawal, S. and Senbanjo, I.O. 2013. Clinically significant interactions between antiretroviral and co-prescribed drugs for HIV-infected children: profiling and comparison of two drug databases. *Ther. Clin. Risk Manag.* **9**, 215-221.

Palleria, C., Di Paolo, A., Giofrè, C., Caglioti, C. and Leuzzi, G. 2013. Pharmacokinetic drug-drug interaction and their implication in clinical management. *J. Res. Med. Sci.* **18**,601.

Sehn, R., Camargo, A.L., Heineck, I. and Ferreira, M.B.C. 2003. Interações medicamentosas potenciais emprescrições de pacientes hospitalizados. *Infarma.* **15**, 77-81.

Wang, J.K., Herzog, N.S., Kaushal, R., Park, C., Mochizuki, C. and Weingarten, S.R. 2007. Prevention of pediatric medication errors by hospital pharmacists and the potential benefit of computerized physician order entry. *Pediatrics*. **119**, 77-85.

Yeh, M.L., Chang, Y.J., Yeh, S.J., Huang, L.J., Yen, Y.T., Wang, P.Y., Li, Y.C. and Hsu, Y.C. 2014. Potential drug-drug interactions in pediatric outpatient prescriptions for newborns and infants. *Comput. Methods Programs Biomed*. **113**, 15-22.