PATTERNS OF DRUG PRESCRIBING AND PRESCRIBING ERRORS AT IN-PATIENT PEDIATRIC DEPARTMENTS OF GOVERNMENT HOSPITALS, KARACHI, PAKISTAN

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Abstract. Trend of drug prescribing and prescribing errors including adverse drug-drug interaction in prescriptions at in-patient pediatric departments of two government hospitals in Karachi, Pakistan was evaluated in a prospective observational study from 1 December 2017 to 28 February 2018 using the World Health Organization core indicators. Drug prescriptions contained 4 ± 2 (mean ± SD) drugs per prescription, with ceftriaxone and paracetamol being the most common. Prescriptions of more than five drugs were 5 times more prone to have drug-drug interactions compared to those of fewer drugs. Children were prescribed a higher number of drugs than the WHO recommended 1.6-1.8 drugs per prescription. Brand name drugs were the choice of the majority of pediatricians. There was a noticeable absence of the latest national essential list of medicines at pediatric wards. Further nationwide studies should be conducted to ascertain the complete status of pediatric prescriptions in Pakistan so that improvements to the system can be recommended.

Keywords: drug-drug interaction, in-patient, Karachi, pediatric department, prospective study

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INTRODUCTION

Rational prescribing of drugs and correctly written prescriptions have substantial impacts on public health, with incorrectly prescribed drugs being a foremost concern (Lund *et al*, 2010).

The World Health Organization (WHO) has developed indicators to improve health care services, especially to children (WHO, 1993; Vooss and Diefenthaeler, 2011), one core indicator being an essential drugs list (EDL): "Essential drugs are those that satisfy the health care needs of the majority of the population; they should therefore be available at all times, in adequate amounts and in the appropriate dosage forms" (WHO, 1993). By increasing access to essential drugs and their balanced usage, a country's health situation should improve and augment gains in economic development (WHO, 2000).

Prescribing drugs, in particular to children, should be of great concern as an unnecessary drugs usage leads to waste of financial resources, potential exposure to adverse drug reactions (ADRs), lengthy hospital stays and development of drug resistance (Ghaleb *et al*, 2010; Martinez-Mir *et al*, 1999). Prescribing drugs to children should take into account physiological differences, changes in pharmacokinetic/ pharmacodynamics responses and regulatory (United States Food and Drug Administration (US FDA) and/or WHO) guidelines. Prescription errors occur more often in pediatric compared to medical practices (Di Paolo *et al*, 2012). Antibiotics constitute the major class of drugs prescribed to pediatric patients. A study in Italy and Denmark has revealed the probable overuse and misuse of antibiotics in the Italian pediatric population, more so than in the Danish population (Lusini *et al*, 2009).

Over-prescribing of pediatric population occur in both developed (Shankar *et al*, 2006, Sturkenboom *et al*, 2008, Clavenna *et al*, 2009) and developing countries alike (Javed, 2007; Palikhe, 2004; Dimri *et al*, 2009; Siddiqi *et al*, 2002). Middle Eastern countries are in a better situation as they follow international guidelines, including those from US FDA, European Agency for the Evaluation of Medicinal Products and WHO (Al Balushi *et al*, 2013).

In Pakistan, the problem is compounded by frequent issuance of incorrect and/or unsuitable combinations of drugs (Nizami *et al*, 1996). However, there is limited available evidence regarding the country's overall drug prescribing trends among pediatric in-patients. The study investigated the trend of drug prescribing and prescribing errors including adverse drug-drug interactions at in-patient pediatric departments of two government hospitals in Karachi. Assessing prescribing practices should assist to rationalize prescriptions in the pediatric population while improving the health care system and reducing the family financial burden.

MATERIALS AND METHODS

Study area, design and duration

A prospective observational study was carried out from 1 December 2017 to 28 February 2018 in pediatrics in-patient departments (IPD) of two state-owned hospitals (total of 120 beds) in Karachi, Pakistan. The study protocol was approved by the Ethical Review Committee, Hamdard University, Karachi (approval no. ERB-17-02). Prior verbal consent was obtained from parents or legal guardian of each participating child.

Data collection, inclusion/exclusion criteria and analysis procedure

Sample size (n = 377) was calculated using a Raosoft® software (Raosoft Inc, Seattle, WA), with power, response distribution, margin of error, and confidence interval of 80, 50, 5, and 95%, respectively. In-patients ≤12 years of age were enrolled using a convenient sampling technique (Zavaleta-Bustos *et al*, 2008). Prescription data of patients were recorded in a predesigned proforma developed by an expert team of ten pharmacists and ten physicians and routinely used in clinical ward rounds by undergraduate pharmacy students. Only registered (Pakistan Medical and Dental Council) pediatricians' prescriptions were included in the study. A copy of the prescriptions was also made. Illegible prescriptions were excluded from the study. Prescriptions containing only fluid replacement therapy, medical supplies and vaccines therapy were excluded as were prescriptions for patients in intensive care unit, with intellectual disability or in comatose state.

Prescribing indicators are average number of drugs per prescription, percent generic drugs prescribed, percent prescriptions of antibiotics, percent prescriptions for injections, and percent prescribed drugs from EDL (WHO, 1993). Prescriptions were also assessed for prescribing practices, omission errors in writing prescriptions and drug-drug interactions (DDIs). Prescribing errors included failure to record patient's name, age, gender, weight, diagnosis, attending physician's name and signature; drug dosage and form, recommended dose, directions for use, and route of administration. Each prescription was checked twice to determine any error. Probability of a prescription containing combination of drugs with DDI was evaluated as previously described (Lacy *et al*, 2002; Joint Formulary Committee, 2013) and using a Micromedex 2.0 (https://www.micromedexsolutions.com/home/dispatch/ssl/true).

Statistical analysis

Data were analyzed by the Statistical Package for the Social Sciences (SPSS) version 20.0 software package (IBM Corp, Armonk, NY). Pearson correlation was used to observe association between dependent and independent variables with a p-value <0.05 considered statistically significant. Association between number of drugs and patient's age and gender was also analyzed.

RESULTS

Age (mean ± SD) of pediatric patients (n = 392) was 5.0 ± 2.1 years, 52% males and 48% females, with (mean ± SD) weight of 13 ± 9 kg. Of the valid prescriptions (n = 440/500) obtained from IPDs of two state-owned hospitals in Karachi, Pakistan during 1 December 2017 to 28 February 2018, number (mean ± SD) of drugs per prescription was 4 ± 2 (Table 1), with 30% of prescriptions recording four drugs and 6.5% indicating ≥8 drugs, a total of 1,916 drugs. Parenteral route of administration was described in 77% of the prescriptions. Noticeably, all recommended values of the five WHO core prescribing indicators (average

number of drugs per prescription, percent generic drugs prescribed, percent prescriptions of antibiotics, percent prescriptions for injections, and percent prescribed drugs from EDL) employed in the study were not met (Table 1).

The most commonly prescribed antibiotic was ceftriaxone (53.6%) followed by vancomycin (15.0%) and amikacin (12.3%) (Table 2). Among non-antibiotics, paracetamol was prescribed in 62.7% of the drugs for use through oral and parenteral routes, albuterol alone and in combination with other respiratory drugs in 12.9%, and among antiallergics chlorpheniramine in 7.8%. It is worth noting the antiemetic drug domperidone prescribed in 10% of non-antibiotics category is not among WHO EDL for pediatric patients (WHO, 1995) and is not recommended by Medscape to be used in pediatric patients (Medscape, 2018). Among other drugs that should be prescribed with caution were amlodipine (1%) and diazepam (2.7%) (Table 2).

DDIs were found in 30 (6.8%) of prescriptions (Table 3). None of the drug combinations constituted a major contraindication, but 7/15 (47%) drug combinations were considered of moderate DDI. Prescriptions with >5 drugs were 5 times more prone to have drugs with DDI compared to prescriptions with a lower number of drugs (p-value = 0.0001, Pearson's correlation analysis).

As expected, no major errors (<20%) in writing prescriptions were observed as the study was conducted in hospital pediatric IPDs. The most common error was not recording the patient weight, followed by a missing signature of the attending physician (Fig 1).

Table 1

WHO core prescribing indicators among pediatric in-patients at two state-owned hospitals, Karachi, Pakistan (1 December 2017 - 28 February 2018)

WHO core prescribing indicator[a]	Value[b]	Maximum recommended value of prescribing indicator[c]
Average number of drugs per prescription (SD)	4 (2)	1.6-1.8
Percent generic drugs prescribed	3	100.0
Percent prescriptions of antibiotics	83	20.0-26.8
Percent prescriptions of injections	77	13.4-24.1
Percent prescribed drugs from essential drugs list	73	100.0

[a]WHO (1993); [b]Values observed in the current study; [c]Vooss and Diefenthaeler (2011)
WHO: World Health Organization

DISCUSSION

The investigation into the trend of drug prescribing and prescribing errors including adverse drug-drug interactions at in-patient pediatric departments of two government hospitals in Karachi revealed children were receiving four times the number of drugs than the WHO recommended range of 1.6–1.8 drugs per visit (WHO, 1993). Nevertheless, this observation was similar to other earlier studies (Nizami *et al*, 1997; Siddiqi *et al*, 2002) and higher than the number of drugs per prescription reported in a more recent

Table 2

Antibiotics and other drugs prescribed to pediatric in-patients at two state-owned hospitals, Karachi, Pakistan (1 December 2017 - 28 February 2018)

Class of drug	Name of drug	Percent prescribed*
Antibiotics		
Penicillin	Amoxicillin	5.5
	Amoxicillin/clavulanic acid	4.1
	Ampicillin	4.5
	Cloxacillin	3.2
	Imipenem	1.8
Cephalosporin	Cefixime	2.7
	Cefotaxime	5.1
	Ceftriaxone	53.6
	Cephradine	0.9
	Ceftazidine	3.6
Macrolide	Azithromycin	0.5
	Clarithromycin	1.4
Glycopeptide	Vancomycin	15.0
Aminoglycoside	Amikacin	12.3
	Gentamycin	0.9
	Tobramycin	0.5
Fluoroquinolone	Ciprofloxacin	4.1
	Ofloxacin	2.7
	Total	100.0

Table 2 (cont)

Class of drug	Name of drug	Percent prescribed*
Other class of drug		
	Diclofenac	1.8
	Ibuprofen	6.5
	Mafenamic acid	0.9
	Paracetamol	62.7
	Tramadol	3.2
	Tramadol/dicofenac	0.9
	Acephylline	2.8
	Chlorpheniramine	7.8
	Diphenhydramine	4.6
	Ketotifen	3.3
	Dimenhydrinate	3.6
	Domperidone	10.0
	Albuterol/salbutamol	12.9
	Atropine	6.8
	Montelukast	2.9
	Dexamethasone	14.1
	Hydrocortisone	6.8
	Prednisolone	1.8
	Artemether/lumefantrine	4.2
	Amlodipine	0.9
	Diazepam	2.7
	Furosemide	1.8
	Sodium valproate	0.5
	Total	100.0

*>100 as the same drug could appear in more than 1 prescription

Table 3

Drug combinations having potential adverse drug-drug interaction (DDI) prescribed to pediatric in-patients at two state-owned hospitals, Karachi, Pakistan (1 December 2017 - 28 February 2018)

Adverse DDI	Drug combination	Number of prescriptions (%) (n = 440)
Major	None	0 (0)
Moderate	Albuterol + Ibuprofen	14 (3.2)
	Albuterol + Pseudoephedrine	
	Albuterol + Tramadol	
	Albuterol + Tripolidine	
	Ciprofloxacin + Ibuprofen	
	Dexamethasone + Diazepam	
	Omeprazole + Rifampicin	
Minor	Acetaminophen + Valproate	28 (6.4)
	Acyclovir + Vancomycin	
	Atropine + Dimenhydrinate	
	Clonazepam + Paracetamol	
	Dexamethasone + Omeprazole	
	Diclofenac + Vancomycin	
	Hydrocortisone + Montelukast	
	Ibuprofen + Ofloxacin	

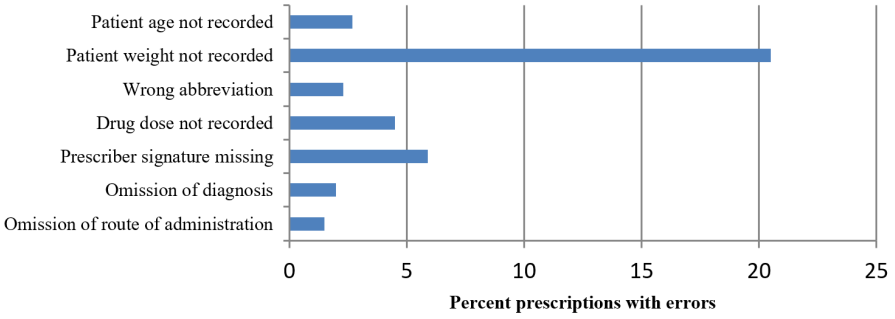

Fig 1 - Prescribing errors for pediatric in-patients at two state-owned hospitals, Karachi, Pakistan (1 December 2017 - 28 February 2018)

survey (Al Balushi *et al*, 2013). Pediatric in-patients in Nepal also were prescribed a similar number of drugs observed in the present study (Palikhe, 2004). Excessive number of drugs prescribed in pediatrics might be due to a lack of good clinical practice guidelines at the institution, insufficient continuous medical education and incentives offered to physicians by pharmaceutical companies. Over-medication poses a risk of DDIs and places unnecessary financial burden on patients' families (Atif *et al*, 2016b).

While parenteral route of drug was the common practice in the pediatric IPDs studied, this practice is less common in other parts of the world. For example, pediatricians in Nepal prescribe 38% of drugs to be administered intravenously (Palikhe, 2004); in Oman 5% of drugs in pediatric departments are administered parenterally (Al Balushi *et al*, 2013); and in Switzerland the oral route was the most common route of drug administration for pediatric patients (Di Paolo *et al*, 2012). Use of intravenously administered drugs may increase risk of blood infection and raises treatment cost. However, in Pakistan patients' families often demand physicians to prescribe parenteral administration (*eg* injection) with the belief that this leads to rapid and more complete cure (Atif *et al*, 2016a).

The majority of drugs prescribed were from WHO EDL for pediatrics (WHO, 1995), similar to a report from India (Chatterjee *et al*, 2007), while in Nepal the proportion is lower (Palikhe, 2004).

In developing countries, a large fraction of the annual budget goes to financing health costs (Gupta *et al*, 2002). WHO (2000) strongly recommends using generic medicines to reduce a country's health cost burden. The present study reveals only 5% of pediatric medication employed generic drugs while Das *et al* (2001) reported 12% of consultants prescribe generic drugs. On the other hand, in Nigeria and the United Arab Emirates the majority of drugs prescribed are generic in origin (Sharif *et al*, 2015, Nduka *et al*, 2017).

More than 75% of the prescriptions in pediatric IPDs were for antibiotics compared to an earlier report of only 9.4% in a pediatric ward (Riaz *et al*, 2011). A study from India revealed 25% of prescriptions for pediatrics contain at least one antibiotic (Chatterjee *et al*, 2007), while in Oman 16% included antibiotics (Al Balushi *et al*, 2013). In Pakistan, inadequate laboratory facilities to conduct microbial identification and antibiogram profiling may encourage attending physicians to prescribe broad-spectrum antibiotics as presumptive treatment. Another contributing factor is an absence of microbial disease stewardship program at tertiary-care hospitals. It is well recognized that excessive use of antibiotics is a common phenomenon in developing countries leading to rapid development of antimicrobial resistance and resulting in prolonged illnesses and costly hospitalization, thereby further contributing to the country's health cost burden (Moorthi *et al*, 2011; Chishti, 2015).

It is noticeable that third-generation cephalosporin ceftriaxone represented over half of antimicrobials prescribed in pediatric IPDs. In an earlier report, antimicrobials account for 49% of drugs prescribed by general physicians and pediatricians, with amoxicillin and co-trimoxazole being the most common (Nizami *et al*, 1997). In Pakistan, antibiotics are prescribed depending upon clinical conditions rather than concerning the patients' culture sensitivity laboratory findings (Ali *et al*, 2013). In Iran, ceftriaxone and vancomycin are the two most prescribed antibiotics for pediatric in-patients (Fahimzad *et al*, 2016) and in Oman azithromycin and co-amoxiclav are the most common prescribed antibiotics (Al Balushi *et al*, 2013). Frequent medication with broad-spectrum antibiotics, especially in children, should be of concern.

The present study shows a high frequency of prescribed paracetamol compared to other countries: in India, Oman and Switzerland, paracetamol is the most frequently prescribed drug but at a lower rate (~20%) (Dimri *et al*, 2009; Di Paolo *et al*, 2012; Al Balushi *et al*, 2013). This pattern of drug prescribing as well as of drugs not recommended in pediatric practice should be investigated further.

In the present study <10% of prescriptions contain drugs with mild or moderate DDI, a lower frequency than reported in other studies conducted in pediatric (25.8%) (Ismail *et al*, 2013) and geriatric cardiology (77.5 %) (Ismail *et al*, 2012) wards in the country. The high rate of DDIs among drugs prescribed to the elderly is probably due to greater prevalence of co-morbidities in this population (Murtuza *et al*, 2016). The most common combinations of drugs with DDIs prescribed to pediatric patients were antibiotics, bronchodilators, corticosteroids, and NSAIDs, similar to a previous report (Ahmad *et al*, 2015). Although the number of drugs >5 is significantly associated with DDI, this appears to be apply only to pediatric patients (Nesar *et al*, 2018).

The most common error in a pediatric patient proforma was omission of weight. A study in two hospitals in Boston, MA, noted that frequency of medication errors for pediatric in-patients is 5.7%, the most common being dosing error (28%) and failure to record patient weight (3.7%) (Kaushal *et al*, 2001). This latter type of recording error, including missing weight unit, also occurs at a relatively high frequency in USA (Shah and Manzi, 2018).

Folli *et al* (1987) recommended that if a pharmacist notices a discrepancy in a prescription, the order should not be dispensed until the error is corrected, and that for prescriptions from pediatric IPD, the resident pharmacist should be trained to recognize possible mistakes or omissions in a prescription and be updated on the latest information regarding DDIs among pediatric drugs. Thus, awareness programs should be launched by government and other stakeholders to inform health caregivers of the danger of DDIs when combination of pain, fever and respiratory medications are prescribed to children.

Limitations of the present study were (i) the short duration of data collection, (ii) involvement of pediatric

wards in only two hospitals, (iii) lack of information on the patients' illnesses limiting assessment of the need for the drugs, and (iv) absence of input from dispensing pharmacists.

In summary, the survey of drug prescribing patterns at pediatric in-patient departments of two government hospitals in Karachi revealed that the number of prescribed drugs was four times higher than WHO recommendation, generic drugs constituted a very small proportion (5%), highly frequent prescription (54% of all antibiotics) of third generation cephalosporin ceftriaxone and among non-antibiotics, a significant proportion being antiemetic domperidone (10%), diazepam (2.7%) and amlodipine (1%), drugs not recommended for medication of children, and low (<10%) prescribing of drug combinations with mild to moderate adverse drug-drug interactions. Prescribing errors were of non-major types and at low frequency (<20%), mostly omission of patient weight. An absence of posting of the latest national essential drugs list at the pediatric wards was noted. These findings indicate a need for establishment of microbial disease stewardship programs at tertiary care hospitals to improve prescribing patterns of antibiotics in pediatric wards, and a nationwide survey is recommended to ascertain the status of prescribing patterns and prescribing errors in pediatric wards of government hospitals.

CONFLICTS OF INTEREST DISCLOSURE

The authors declare no conflicts of interest.

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