



A Study of Prescribed Dose of Drugs in Patients Visiting Out Patient Department of Pediatric Department of a Tertiary Care Teaching Hospital.

KEYWORDS

dose calculation, pediatric patients, medication error

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INTRODUCTION:

Children are unique population with distinct development and physiological differences from adults, clinical trials in children are essential to develop age-specific, empirically – verified therapies and interventions to determine and improve the best medical treatment available.¹ Even widely used pediatric medications may have the potential for serious adverse effects. Indeed, many of the medications that are being used currently for children have never been tested rigorously for pediatric safety and efficacy, a problem that federal regulators have been attempting to resolve over the past decades.² Calculation of dose of drugs prescribed for pediatric population remains the major challenge for pediatricians. Iatrogenic injuries occur frequently in hospitalized patients and often remains the serious sequelae.³ As the pharmacokinetics in infants and children are different, simple proportionate reduction in the adult dose may not be adequate to determine a safe and effective pediatric dose.^{4,5} A large number of children's drug dosage rules have been described, almost all using percentage of an adult dose to calculate an appropriate child's dose. An advantage of these rules is that modifications to adult doses to allow for sickness in adults are appropriately incorporated in to calculations for children.⁶⁻⁸ Reports in the literature quote many examples of prescription errors in children, of 2-10 times the recommended dose.¹⁰⁻¹⁴ This study was designed to analyze the appropriateness of dose of drugs prescribed in pediatric age group of patients visiting outpatient department (OPD).

METHODOLOGY:

This was an open label cross-sectional study spreaded over a period of one year and three months May 2012 to August 2013, conducted in Shree Krishna Hospital and Medical Research Centre, a 550 bed tertiary care teaching rural hospital. Patients coming to outpatient department (OPD) of Pediatric department of either sex falling into different age groups according to ICH guidelines were included in the study. Patients coming for only vaccination were excluded from the study. Total 400 patients were included in the study. Parents or guardians of the eligible patients were explained about the research study and written informed consent was obtained in the native language of the patient. Analysis of demographic data and medication details was done separately. Prescribed total daily dose and its mean standard deviation was calculated according to frequency of administration for each drug. Standard dose was calculated according to

Clark's formula: $\frac{\text{Child's weight in kg}}{70 \text{ kg}} \times \text{adult dose in mg} = \text{Paediatric dose in mg}$

Standard total daily dose and its mean standard deviation was calculated and was compared to that of with prescribed. Data were entered in to the Microsoft Excel 2007 and separate master charts was prepared and analysed using SPSS version 16.0. Mean \pm standard deviation for prescribed total daily dose and standard total daily dose of all the drugs was calculated and was compared using independent Student's t-test. Standard error of mean was calculated and Degrees of freedom was calculated for each drug. Prescribed total daily dose was considered statistically significantly different than standard total daily dose if t-value was greater for that degrees of freedom according to the probability table for t-test at 95% confidence interval. Before starting this study, necessary permission was taken from the Human Research Ethics Committee (HREC). Confidentiality of all participants was maintained at all levels.

RESULTS:

Total 400 prescriptions were collected from outpatient department (OPD) of pediatric department.

Table 1 shows the demographic details of the patients enrolled. Out of 400, 244 (61%). patients were in the age group of 2-11 years. Out of 400 patients, 227(56.75%) patients were male and 173(43.25%) were female. As weight is one of the parameter for calculating the standard dose according to Clark's formula it was one of the most important detail to be recorded. Majority of the patients weighed between 1-10kg (169, 42.25%), followed by 11-20kg (146, 36.5%), 21-30 kg (61, 15.35%), 31-40 kg (18, 4.5%) and 41-50 kg (6, 1.5%).

Table 1. Demographic details

PARAMETERS	NO. OF PATIENTS (n =400)	% OF PATIENTS
SEX		
MALE	227(56.75%)	56.75%
FEMALE	173(43.25%)	43.25%
AGE		
0-27 DAYS (NEW-BORNS)	0(0%)	0%
28DAY-1YEAR(INFANTS)	89(22.25%)	22.25%
1-2 YEARS(TODDLERS)	50(12.5)	12.5
2-11 YEARS(CHILDREN)	244(61%)	61%
12-18YEARS (ADOLESCENTS)	17(4.25%)	4.25%

WEIGHT (KG)		
1-10KG	169(42.25%)	42.25%
11-20KG	146(36.5%)	36.5%
21-30KG	61(15.25%)	15.25%
31-40KG	18(4.5%)	4.5%
41-50KG	6(1.5%)	1.5%
HEIGHT (cms)		
35-55cms	39(9.75%)	9.75%
56-75cms	105(26.25%)	26.25%
76-95cms	107(26.75%)	26.75%
96-115cms	55(13.75%)	13.75%
116-135cms	73(18.75%)	18.75%
136-155cms	21(5.25%)	5.25%
BMI		
1-10	61(15.25%)	15.25%
11-20	243(60.75%)	60.75%
21-30	96(24%)	24%

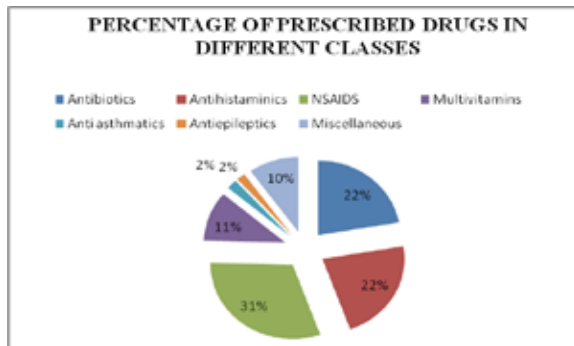
Total 1042(100%) drugs were prescribed. Out of these 616(59.12%) drugs were prescribed by brand name and 425(40.87%) were prescribed by generic name, 593(56.94%) oral liquid (syrup, suspensions) formulations and 441(42.93%) oral solid (tablet, capsule) formulations were prescribed. 19(1.83%) inhalational (metred dose inhaler, rotahaler) formulations were prescribed (Table 2).

Table 2 Drug details

PARAMETRES	NO. OF DRUGS (%)
BRAND NAME	626(59.12%)
GENERIC NAME	425(40.87%)
TOTAL	1042(100%)
DOSAGE FORMS	
ORAL SOLID	441(42.93%)
ORAL LIQUID	593(56.94%)
INHALATIONAL	19(1.83%)
TOTAL	1042(100%)

Out of 1042 maximum number of drugs were prescribed from the group of Non-Steroidal Anti-inflammatory Drugs (NSAIDs) 322(22%) followed by antibiotics and antihistaminics 232(22%) each. 22(2%) and 18(2%) drugs were prescribed from antiasthmatics and antiepileptic group respectively. 103(10%) miscellaneous drugs (Domperidone, Ranitidine, Dicyclomine) were prescribed (Figure 1).

Figure 1 Distribution of drugs according to pharmacological classes



NSAIDs were maximum times prescribed. Among NSAIDs Paracetamol and Ibuprofen were prescribed most frequently. Out of 322(31%) NSAIDs paracetamol was 270(83.8%) and ibuprofen was 52(16.14%) times prescribed. Next groups of drugs with second highest frequency of prescription were antibiotics (232,22%) and antihistaminics (232,22%). Amoxicillin(65, 28.01%), azithromycin(56, 24.13%), cotrimoxazole(35, 15.08%) were most common antibiotics prescribed. Other antibiotics like cefixime, metronidazole, ciprofloxacin, cefpodoxime and linezolid were also prescribed. Chlorpheniramine maleate (95, 40.94%) and pheniramine maleate (81, 34.91%) were most common antihistaminics prescribed, followed by diphenhydramine (32, 13.79%) and cetirizine (24, 10.34%). Antiepileptic(18, 2%) and antiasthmatic (22, 2%) group of drugs were also prescribed in fairly good frequency. Out of 18(2%) antiepileptics, phenytoin and sodium valproate were 12(66%) and 6(33.33%) times prescribed respectively. Salbutamol(16, 72.7%) and budesonide(6, 27.2%) were prescribed as antiasthmatics. Some miscellaneous(103, 10%) drugs, dicyclomine(47, 45.63%), domperidone(33, 32.03%) and ranitidine(23, 22.3%) were also prescribed (Table 3).

Table 3. Individual drugs prescribed according to class

Sr. No.	Drugs and categories	Frequency of prescription(%)	Percentage of drugs of total drugs(1042) prescribed
I	Antibiotics	232(100)	22
Ia	Amoxicillin	65(28.01)	6.23
Ib	Azithromycin	56(24.13)	5.37
Ic	Cotrimoxazole	35(15.08)	3.3
Id	Cefixime	29(12.5%)	8.5
Ie	Metronidazole	20(8.62)	1.91
If	Ciprofloxacin	18(7.75)	1.72
Ig	Linezolid	6(2.58)	0.57
Ih	Cefpodoxime	3(1.29)	0.28
II	Antihistaminics	232(100)	22
IIa	Chlorpheniramine maleate	95(40.94)	9.21
IIb	Pheniramine maleate	81(34.91)	7.78
IIc	Diphenhydramine	32(13.79)	3.07

	IId	Cetirizine	24(10.34)	2.30
III		NSAIDS	322(100)	31
	IIIa	Paracetamol	270(83.85)	25.91
	IIIb	Ibuprofen	52(16.14)	4.99
IV		Antiepileptics	18(100)	2
	IVa	Phenytoin	12(66.66)	1.15
	IVb	Sodium valproate	6(33.33)	0.58
V		Antiasthmatics	22(100)	2
	Va	Salbutamol	16(72.7)	1.54
	Vb	Budesonide	6(27.2)	0.57
VI		Multivitamins	113(100)	11
VII		Others	103(100)	10
	VIIa	Dicyclomine	47(45.63)	4.51
	VIIb	Domperidone	33(32.03)	3.16
	VIIc	Ranitidine	23(22.34)	2.20

Comparison of prescribed and standard total daily doses of antibiotics, antihistaminics and NSAIDs.

Table 4. Comparison of doses of Antibiotics

Sr. No.	Drug	No. of times prescribed	Prescribed dose (mean±standard deviation)	Standard Dose (mean±Standard deviation)	t- value (independent t-test)
1	Amoxicillin	65	939.538±598.727	787.477±868.131	0.0068
2	Azithromycin	56	265.892±168.316	165.535±102.288	5.27
3	Co-trimoxazole	35	534.857±206.851	507.43±205.025	0.22
4	Cefixime	29	410.345±30.132	264±65.791	28.61
5	Metronidazole	20	975±974.999	495.231±407.329	2.03
6	Ciprofloxacin	18	491.667±361.67	530±736.884	0.3
7	Linezolid	6	733.333±37.91	800±326.597	0.4
8	Cefpodoxime	3	666.667±690.667	300±141.417	0.9

Table 5. Comparison of doses of Antihistaminics

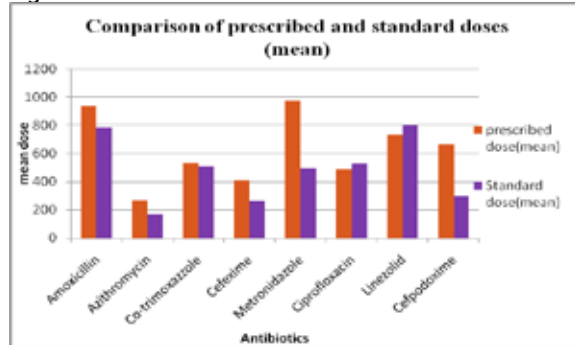
Sr. No.	Drug	No. of times prescribed	Prescribed total daily dose (mean± standard deviation)	Standard total daily dose (mean± standard deviation)	t-value (independent t-test)
1	Chlorpheniramine maleate	95	17.72±16.79	9.8±5.63	0.5
2	Pheniramine maleate	81	42.25±21.85	26.48±13.39	7.1
3	Diphenhydramine	32	39.06±22.45	21.87±10.43	3.9
4	Cetirizine	24	9.12±5.37	6.25±1.91	2.4

Table 6. Comparison of doses of NSAIDs.

Sr. No.	Drug	No. of times prescribed	Prescribed total daily dose (mean± standard deviation)	Standard total daily dose (mean± standard deviation)	t-value (independent t-test)
1	Paracetamol	270	878.212±415.657	521.090±323.04	11.14
2	Ibuprofen	52	692.307±395.086	626.923±372.162	0.5

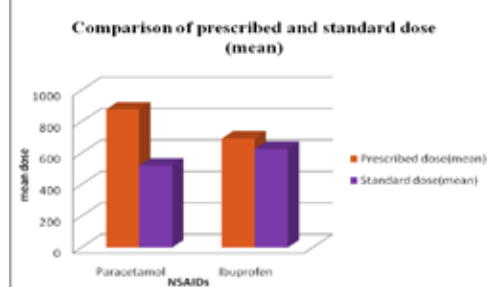
t-value for azithromycin was 5.27, which was higher than 1.96 for 95% confidence interval suggested that prescribed total daily dose was statistically significantly higher than the standard total daily dose. Similarly, prescribed total daily dose was statistically significantly different than the standard total daily dose of cefixime as t-value 28.61>1.96 for 95% confidence interval. Statistical significant difference between prescribed total daily dose and standard total daily was also found with metronidazole [t-value 2.03>1.96 for 95% confidence interval]. Prescribed total daily doses were not statistically significantly different from the standard total daily doses for other antibiotics like, cotrimoxazole, ciprofloxacin, linezolid, cefpodoxime and amoxicillin. (Table 4) (Figure 2).

Figure 2.



t-value for pheniramine maleate was 7.1 which was higher than 1.96 for 95% confidence interval suggested that prescribed total daily dose was statistically significantly different than the standard total daily dose. Prescribed total daily dose was statistically significantly different from the standard total daily dose of diphenhydramine and cetirizine also, as t-value for diphenhydramine was 3.9 which was higher than 2.00 for 95% confidence interval and t-value for cetirizine was 2.4 which was higher than 2.02 for 95% confidence interval (Table 5). Prescribed total daily dose was statistically significantly different from the standard total daily dose of paracetamol [t-value 11.14>1.96 for 95% confidence interval] (Table 6) (Figure 3).

Figure 3.



DISCUSSION:

Infancy and childhood is the period of rapid growth and development. Compared to adult medicine, drug use in

paediatric patients is not extensively researched, specially the dose of the prescribed drugs. Weight based dosing is needed for drugs prescribed in paediatric patients and involves extensive calculations than for adults. Thus children are particularly more vulnerable to medication dosing errors. All 400 patients were classified in to different age groups according to ICH classification of children by age⁹ in newborns, infants, toddlers, children and adolescents. Out of 400 patients 244(61%) patients were in the age group of 2-11 years (children). In this study there were more male children (227, 56.75%) than females (173, 43.25%). In a similar study by Kaushal R et al, 2001³, in 1120 admissions and 3932 patient-days during which 10778 orders were written. The patients included 183(16%) neonates, 326(29%) infants, 223(20%) preschoolers, 161(14%) school-aged children, 191(17%) teenagers and 36(3%) adults. In same study 525(49%) were female patients. In a study by Domecq C et al, 1980¹⁰ in Santiago, Chile, it was shown that 83% of ADR in males and 93% of ADR in females were dose related effects. It shows that may be females are more prone to dose related errors, but association of dosing errors with sex is not carried out in our study so it can not be confirmed. Out of 400 patients 169(42.25%) patients had weight between 1-10 kg. One prospective cohort study carried out by Kaushal R et al, 2001³ in 1120 patients in two academic institutions showed that 3.7% of institutions' medication errors were due to missing or wrong weights. This depicts the importance of recording of weight accurately. Out of total drugs 1042 drugs 616(59.12%) were prescribed by brand name and 593(56.94%) were prescribed by oral liquid dosage form. In a study by Mirza NY et al, 2008¹¹, showed that of total 1483 medicine formulations prescribed 1027(69.3%) were prescribed by brand names, which shows inclination of prescriber to prescribe a drug by brand names. In a similar type of study by Pramit T et al, 2012¹², showed that out of total drugs prescribed 90% were administered by oral route and out of that 75% of the prescribed dosage forms were syrups followed by tablets (7.2%), capsules (0.4%) and inhalation (1.6%). These similar findings suggests more common use of oral liquid dosage form in paediatric patients in outpatient setting. The possible reasons for less prescribing by generic name could be prescribers' doubt about bioavailability and efficacy of generic formulations, prescriber's ignorance about the price variations between generic and branded and lack of information on the availability of various generic formulations. Another possible reason could be the easy availability, easy recall of branded. Most commonly used dosage form was oral liquid. Children are more comfortable with the dosage forms like syrup and drops than tablets or capsules and this finding is well taken. The administration of liquids can be a major contributing error in dosing in children. The use of different size of spoons may lead to under dosing and over dosing of medication. Of total 1042 drugs 322(22%) drugs were prescribed from NSAIDs group followed by 232(22%) antibiotics and antihistaminics. Pramit T et al, 2012¹¹, found that only 79(6%) drugs of 1331 were antibiotics. Where as in a study by S Dimri et al, 2008¹³, showed that percentage encounter with an antibiotic prescribed was found to be 29.1% and NSAIDs (paracetamol) contributed to the majority (76%) of drugs prescribed. These findings corresponds with our study. In our study we observed out of total 1042 drugs 322(31%) were NSAIDs and out of these 270(83.8%) were paracetamol and 52(16.14%) were ibuprofen. Dimri S et al, 2009¹³ found out that out of 254 prescriptions paracetamol was most commonly prescribed drug, 83 cases. This was similar to our study. A study carried out by Shamshy

K et al, 2011¹⁴, observed significant use of antimicrobials. Among those cephalosporins (38,83%) contributed highest, followed by aminoglycoside (22.78%) and penicillin derivatives(18,87%). Cephalosporins like cefotaxim and ceftriaxone were antimicrobial agents of choice for pediatric patients which accounts for 20.03%. In contrast to these findings in our study among antimicrobial agents penicillin derivative like amoxicillin (28.01%) and aminoglycoside like azithromycin (24.13%) were major contributors. In our study out of all prescribed antibiotics statistical significant difference between prescribed and standard total daily doses was observed in azithromycin (t-value 5.21>1.96 for 95% confidence interval), cefexime (t-value 28.61>1.96 for 95% confidence interval) and metronidazole (t-value 2.03>1.96 for 95% confidence interval). A study carried out by Elias GP et al. 2005¹⁵, showed that standard doses calculated by Clark's formula for amoxicillin and erythromycin was not statistically significant(p>0.05) in three groups of children, group 1: age 1-3years, group 2: age 3-5 years and group 3: age 6-12 years. This finding is similar to our study. In a study by Lesar TS et al, 1998¹⁶ showed that errors most commonly involved children(69.5%) and that too because of antibiotics(53.5%). Our study, we observed the statistically significant difference in the prescribed and total daily doses in pheniramine maleate, dphenhydramine and cetirizine. Kaushal R et al, 2013³, observed that 6% dosing errors with antihistaminics. But they have not mentioned the individual drugs of this group. Authors compared their findings with a similar adult study, the rate of dosing errors was 12 times higher in children than adults in prescribed antihistaminics. The many calculations required in paediatrics to do weight based dosing may be an important factor contributing to the high rates of prescribing errors. There was lack of published studies on dose calculation of different antihistaminic drugs in paediatric patients. In our study there was statistical significant difference in prescribed and standard doses of paracetamol which was similar to the study carried out by Elias GP et al, 2005¹⁵. They calculated standard dose of paracetamol with the formula based on body surface area and found out it was statistically significantly different than the prescribed dose. It was much closer to the hepatotoxic dose of paracetamol for children. This was observed in the children of age group of 1-5years. A study carried out in 213 children aged 6 weeks to 16 years by Obu HA et al, 2012¹⁷, observed that dose and frequency of administration of drug was much higher than the standard dosing guideline given in pediatric reference text book. In contrast to our study they did not use any formula to calculate the standard dose according to weight, age or body surface area, it was compared with the standard dosing guideline of the reference text books.

LIMITATION:

It was a cross sectional study, no follow-up was done to identify the adverse drug reactions in patients who had been prescribed over doses of drugs. Moreover, it was conducted at only one tertiary care teaching hospital. Comparison with government and private hospitals will strengthen our findings.

CONCLUSION:

There was significant difference in the prescribed and standard doses of antibiotics, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and antihistaminic drugs in OPD based patients. This study illustrates the area where children are vulnerable to medication error, where violations in practice are most likely so increasing the risk and where risk reduction strategies can be introduced. Perhaps reduction in dosing error will reduce drug induced adverse drug

reactions in children, which can be done by careful monitoring and employing strategies like e-prescriptions.

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