An observational study to analyse the dose appropriateness of drugs prescribed in intensive care units of pediatric department

Sumit Patel[1,*], Akanksha Prajapati[2]

[1,2]Assistant Professor, Dept. of Pharmacology, GCS Medical College, Hospital and Research Centre, Ahmedabad, Gujarat, India

***Corresponding Author:**
Email: dr.sumitpatel@gmail.com

Abstract

Introduction: Pediatric age group comprises about 40% of total population of India. Many medications are available to children and the safety of paediatric medications is an important public health issue. The challenge all the paediatricians are facing is the calculation of appropriate dose of drugs prescribed. A patient's weight is often used to calculate the appropriate medication dose. When medication errors arise due to inaccurate or unknown patients' weights, the dose of a prescribed medication could be significantly different from what is appropriate. Therefore the study was undertaken to compare the prescribed dose with standard dose of the drugs by using Clark's formula.

Materials and Methods: Study was an open label cross-sectional. Children admitted to ICUs were included. Data of total 400 patients were collected, 200 from PICU and NICU each. Analysis of NICU and PICU was done separately. Comparison of prescribed total daily dose of each drug with the standard total daily dose was done.

Results: Total 712 and 437 drugs were prescribed in PICU and NICU. Antibiotics were the major group of drugs prescribed in both PICU and NICU. In comparison of prescribed and standard total daily dose of drugs, statistically significant difference was observed with antimicrobials, Antiepileptic, NSAIDs and antihistaminic.

Conclusions: There was significant difference in means of prescribed and standard doses of drugs in various groups, which was higher in PICU as compared to NICU. E-prescriptions can reduce Perhaps dosing error and will reduce drug induced adverse drug reactions in children.

Keywords: Clark's formula, Dose calculation, Pediatric patients, PICU and NICU.

Introduction

Pediatric age group comprises a major part of whole of the Indian population which constitute about 40% of total population of India.[1] Children have distinct development and physiological differences from adults. The pharmacokinetic and pharmacodynamics of the administered drugs are greatly altered in the pediatric age group due to the changing physiology.[1] More rigorous studies required in children to develop age-specific, empirically–verified therapies and interventions to determine and improve the best medical treatment available.[2] Most diseases encountered in pediatric age group are self-limiting however, they are often treated not only inappropriately but, also over enthusiastically.[3] Many different medications both over the counter and prescription are available to children and the safety of pediatric medications is an important public health issue. Indeed, many of the medications that are being used currently for children have never been tested rigorously for pediatric safety and efficacy, a hurdle that federal regulators try to resolve over the past decades.[4] The challenge all the pediatricians are facing is the calculation of appropriate dose of drugs prescribed for pediatric population. Iatrogenic injuries can occur frequently in hospitalized patients and often remains the serious sequelae.[5] A prescribed medication dose can differ significantly from the appropriate dose as a result of missing or inaccurate patient weights.[6]

All dosage rules based on a single physical dimension only hold good while that dimension is associated with other normal dimensions. Thus one could use an age-based rule if associated height and weight for that age were typical; however, there is substantial normal variation in height and weight with age and so weight is used more usually as the dimension for calculation of dose.[7]When medication errors arise due to inaccurate or unknown patients' weights, the dose of a prescribed medication could be significantly different from what is appropriate. There is little information in the literature that specifically mentions medication errors that result from missing or inaccurate patients weights.[5-7] The most common method for dose adjustment in children in clinical practice is to normalize the adult dose by bodyweight, assuming linear relationship between weight and dose.[8] There are numerous studies observing the medication errors in pediatric patients of outpatient and inpatient setting. However, there are no known studies in my knowledge that compare the prescribed dose with standard dose by using weight based formula, especially in pediatric and neonatal intensive care units (PICU and NICU). Therefore the study was undertaken to compare the prescribed dose with standard dose of the drugs by using Clark's formula.

Materials and Methods

Study was an open label cross-sectional study, conducted in tertiary care teaching rural hospital of central Gujarat. Patients of both the sexes and falling different age groups according to ICH guidelines for age

in children admitted to ICUs were included in the study. Data of total 400 patients were collected, 200 from PICU and NICU each. Before starting this study, necessary permission was taken from the Human Research Ethics Committee. 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. The important information regarding patients' details and medication details was recorded in the case record forms. Case sheets (patients' files) were used to complete the case record forms. Analysis of NICU and PICU was done separately. The prescribed total daily dose of each drug was compared with the standard total daily dose which was calculated by Clark's Formula.

$$\text{Clark's formula: } \frac{\text{Child's Weight in Kg}}{70\text{ kg}} \times \text{Adult dose in mg} = \text{Pediatric dose in mg}$$

Data were entered in to the Microsoft Excel 2007 and separate master charts were prepared for NICU and PICU and analysed using SPSS version 16.0. Mean ± standard deviation for prescribed total daily dose and standard total daily dose of all the drugs were calculated and compared using independent Student's t-test.

Results

In PICU total 712 drugs were prescribed in 200 patients. Out of these 516 (72.47%) were prescribed by brand name and 196 (27.53%) were prescribed by generic name (Table 1). Out of 712, 75 (10.53%) oral solid dosage forms were prescribed, 266 (37.336%) were prescribed by oral liquid dosage form, 26 (3.65%) inhalational dosage forms were prescribed and 345 (48.45%) parenteral dosage forms were prescribed. In NICU total 437 drugs were prescribed in 200 patients. Out of 437, 225 (51.48%) were prescribed by brand name and 212 (48.51%) drugs were prescribed by generic name (Table 1). 69 (15.78%) drugs were prescribed by oral dosage form and 368 (84.21%) drugs were prescribed by parenteral dosage form (Table 1).

Table 1: Drugs prescribed

Parameter	PICU n (%)	NICU n (%)
Total drugs prescribed	712(100)	437(100)
Brand name	516(72.47)	225(51.4)
Generic name	196(27.53)	212(48.6)
Dosage form		
Oral solid	75(10.53)	----------
Oral liquid	266(37.36)	69(15.78)
Inhalational	26(3.65)	----------
Parenteral	345(48.45)	368(84.21)

Table 2: Comparison of prescribed drugs according to different pharmacological classes

Drug Class	PICU n(%)	NICU n(%)
Antibiotics	141(19.80)	152(34.78)
Nsaids	149(20.93)	
Antihistaminics	40(5.62)	
Antiasthmatics	47(6.60)	
Multivitamins		
Antiepileptics	38(5.34)	59(13.50)
Iv- fluids	147(20.65)	
Others	150(21.07)	225(51.48)
Total medications	712 (100)	437(100)

Out of 712 drugs prescribe in PICU 149 (22.40%) were NSAIDs group, followed by IV-fluids (147, 22.10%), antibiotics (141, 21.20%), antiasthmatics (47, 7.06%), antihistaminics (40, 6.01%), antiepileptics (38, 5.7%) and others (150, 22.55%) (Table 2).

In NICU total 437 drugs were prescribed. Out of 437, 152 (43.78%) were antibiotics 59 (13.50%) antiepileptics and 225 (51.48) were other drugs (vitamin k, heparin, calcium and fluconazole) (Table 2).

In comparasion of prescibed and standard total daily dose of drugs in PICU, statistically significant difference was obsereved in dose of ibuprofen ($p<0.0001$), whereas there was no statistical significant difference in dose of paracetamol (Table 3). In antimicrobials, statistically significant difference between prescribed and standard total daily dose was observed in ceftriaxone and ampicillin (Table 3).

Among antiasthmatics and antihistaminics statistically significant difference in prescribed and standard total daily was observed in budesonide and phenirimine maleate (Table 3).

Statistically significant difference in prescribed and standard total daily dose was observed only with lorazepam in antiepileptics group. In NICU statistically significant difference in prescribed and standard total daily dose was observed with piperacillin + tazobactum combination in antimicrobials group. There was no statistical significant difference found between prescribed and standard total daily doses of antiepileptics (Table 4).

Also no statistical significant difference found in prescribed and standard total daily doses of in miscellaneous (vitamin k, heparin, calcium and fluconazole) group.

Table 3: Comparison of prescribed and standard daily dose of drugs in PICU

S. No.	Drug	No. of times prescribed	Prescribed dose (mean±standard deviation)	Standard Dose (mean±Standard deviation)	p- value* (independent t-test)
NSAIDs					
1	Paracetamol	84	669.411±446.08	611.647±366.37	0.3604
2	Ibuprofen	65	390.76±269.59	227.69±41.30	**<0.0001**
Antimicrobials					
3	Cefotaxim	58	1165.51±673.07	961.20±587.88	0.0844
4	Ceftriaxone	51	1158.82±523.98	705.58±457.77	**<0.0001**
5	Ampicillin	20	700±261.00	550±246.97	**0.0696**
6	Cefexime	8	300±99.99	275±96.81	0.6193
7	Amikacin	5	410±79.99	430±256.12	0.8718
8	Azithromycin	4	312.5±113.87	250±35.34	0.3348
Atiasthmatic and Antihistaminics					
9	Salbutamol	26	354.61±236.64	315.38±158.57	0.4858
10	Budesonide	21	214.28±99.86	157.14±49.47	**0.023**
11	Chlorpheniramine maleate	20	13.6±7.71	16±4.79	0.2444
12	Pheniramine maleate	20	34.21±18.02	25±1.0	**0.0282**
Antiepileptics					
13	Phenobarbital	13	38.07±17.68	33.84±13.71	0.5020
14	Lorazepam	13	3.41±0.1	2.15±0.74	**<0.0001**
15	Phenytoin	8	32.5±13.65	23.15±9.54	0.1346
16	Sodium Valproate	4	235±40.91	240±101.97	0.9304

*p<0.05 considered as significant

Table 4: Comparison of prescribed and standard daily dose of drugs in NICU

S. No.	Drug	No. of times prescribed	Prescribed dose (mean±standard deviation)	Standard Dose (mean±Standard deviation)	p- value * (independent t-test)
Antimicrobials					
1	Piperacillin + Tazobactum	80	833.65±380.67	684±208.18	**0.0024**
2	Amikacin	37	41.32±16.74	38.25±19.06	0.4640
3	Meropenem	18	54.72±33.13	53.88±34.80	0.9413
4	Vancomycin	17	75.88±60.96	72.35±51.84	0.8568
Antiepileptics					
1	Phenobarbital	40	26.5±13.66	24.75±9.56	0.5088
2	Phenytoin	19	23.68±6.96	22.10±7.59	0.5079

*p<0.05 considered as significant.

Discussion

Children are often considered as little adults in terms of dosage while the drugs are prescribed. With more than three decades ago the term therapeutic orphans was created to highlight the fact that children were not included in clinical trials for a new drug development.[9] They have the period of rapid growth and development. Medications used in pediatric patients as compared to adult are not extensively researched, especially the dose of the prescribed drugs. Weight based dosing is needed for drugs prescribed in pediatric patients and involves extensive calculations than for adults. Thus children are particularly more vulnerable to medication dosing errors. Dosing errors are among the most common type of medication errors. More is known about medication errors in hospitalized patients than in outpatient setting.[10] On the basis of the research regulations such as the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) the research studies involving the individuals of less than 18 years of age

were encouraged for improved safety in drug use, creation of various formulations and for pharmacokinetic assays.[11-12] In PICU out of 712 drugs, 516 (72.47%) drugs were prescribed by brand name and highest contribution by parenteral dosage forms (345, 48.45%). A similar study carried out by Shankar PR et al, showed that a parenteral dosage form accounted for 52.8% of total drugs prescribed in ICU.[13] A study carried out in intensive care units in 2010 observed that 77% of drugs were prescribed by brand names.[14] This is similar to our study suggesting more inclination towards using brand names while prescribing. Surprisingly we observed that in NICU, 48.6% of drugs were prescribed by generic name. In this study NSAIDs (20.93%) and antibiotics (19.80%) were the major groups prescribed in PICU while Antibiotics (34.78%) and antiepileptics (13.50%) in NICU. Shankar PR et al, showed that antibiotics were prescribed in 57.5% of patients.[13] The significant difference in prescribed and standard doses was observed with ibuprofen in PICU. In a study carried out by Ghaleb MA et al, observed that dosing errors was third most common error, was observed with diclofenac sodium from NSAID group of drugs.[15] In PICU, statistically significant difference in the prescribed and standard doses of ceftriaxone and ampicillin while in NICU it was observed with Piperacillin + Tazobactum. In one of the study carried out in 2010, observed that Ampicillin(24.7%) was the major contributor of dose errors, followed by cloxacillin (16.1%), ceftriaxone (3.2%).[16] This was similar to our study findings suggesting, that antibiotics are most frequently prescribed group of drugs and most frequently prescribed by parenteral route of administration in inpatients setting. In PICU we observed the statistically significant difference in the prescribed and standard doses of budesonide and pheniramine maleate.

We could not find any similar study to compare this group of drugs.

Dosing error was found with lorazepam in antiepileptic group. In a study by Andrea DC et al, shows that lorazepam (25.7%) was second most common drug causing dose error.[17] In a study carried out by Vazim A et al, observed dosing errors with phenytoin which was because of overdose and it is not significant but similar to our study findings.[18] Studies found that most of the medication errors occurs with multiple drugs used by parenteral routes and these are common practice in ICUs.[19-20] Studies showed that paper based prescribing and drug dose calculations using a local formulary are major factors for dosing errors. The use of a pre-programmed computerized physician order entry system would be of assistance. Accuracy and appropriateness of dosing could be improved by the use of electronic prescribing systems in pediatrics. These systems eliminate illegible prescriptions, incorporate dose calculators and dose range checking can alert prescribers when doses are outside predetermined ranges.[21]

Conclusion

There was significant difference in means of prescribed and standard doses of drugs when they were prescribed in PICU as compared to NICU. Significant difference was observed in antimicrobial, NSAIDs and antiepileptic group of drugs. E-prescriptions can reduce perhaps dosing error and will reduce drug induced adverse drug reactions in children.

Limitations

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.

References

1. Park K. Park's Textbook of Preventive and Social Medicine. 20th ed. Jabalpur (India): Banarsidas Bhanot; 2009;Ch. 40:P. 159.
2. Frankking FNJ, Van Der Lee JH, Klassen TP, Offringa M. "Survey of current guidance for child health clinical trials." The Star Child Health Project: Standards for research with children. Pg; 5-7.
3. Ghai OP, Paul VK. Rational drug therapy in pediatric practice. *Indian Pediatrics.* 2006;25:1095-1109.
4. Vernacchio L, Kelly JP, Kaufman DW, Mitchell AA. "Medication use among<12 years of age in the United States: Results from the Slone Survey." *Pediatrics*. 2009;124(2):446-54.
5. Kaushal R, Bates DW, Landrigan C, McKenna KJ, Clapp MD, Frank F, Goldmann D. "Medication errors and adverse drug events in pediatric inpatients." *JAMA*. 2001;285:2114-20.
6. Committee on drugs and committee on health care. American Academy of Pediatrics. Prevention of medication error in the pediatric inpatient setting. *Pediatrics* 1998; 102:428-30.
7. Pennsylvania Patient Safety Advisory. "Medication Errors: Significance of Accurate Patient Weights." Pediatric Patient Safety Advisory. 2009Mar;6(1):10-5.
8. Lack AJ, Stuart ME. "Calculation of drug dosage and body surface area of children."*British Journal of Anaesthesia* 1997;78(5):601-5.
9. Shirkey H. Therapeutic orphans. Pediatrics 1999;104:583-4.
10. Shahrokhi A, Ebrahimpour F, Arash G. "Factors effective on medication errors: A nursing view." Journal of Research in Pharmacy Practice. 2013; 2(1):18-23.
11. Meadows M. Drug Research and Children. FDA Consumer Magazine. 2003. Available from: URL:http://www.fda.gov/cder/pediatric. Last accessed Oct 2013
12. Hawcutt DB, Smyth RL. The New European Regulation on Pediatric Medicines - Regulatory Perspective. Ped Drug. 2008;10:143--6.
13. Shankar PR, Partha P, Dubey AK, Mishra P, Deshpande VY. "Intensive care unit drug utilization in a teaching hospital in Nepal." *Kathmandu University Medical Journal.* 2005;3(10):130-37.
14. Farooq JA, Mustafa A, Pandita KK, Rehana K, Mufti S, Yattoo GH et al. "Drug utilization at SKIMS – A tertiary care hospital*." International Journal of Current Medical Science and Practice*. 2013:18(1-2):35-40.

15. Ghaleb MA, Barber N, Franklin BD, Wong IC. "The incidence and nature of prescribing and medication administration errors in paediatric inpatients." Archives of Diseases of Childhood. 2010; 95:113-118.
16. Feleke Y and Girma B. "Medication administration errors involving paediatric in-patients in a hospital in Ethopia." *Tropical Journal of Pharmaceutical Research*. 2010;9(4):401-7.
17. Andrea DC, Brian LE, Katherine B, Jeffrey FB, Sandra LK, Deb SS. "Medication administration errors in adult patients in the ICU." *Intensive Care Medicine*. 2001;27:1592-98.
18. Vazim A and Delfani S. "Medication errors in an internal care unit of a large teaching hospital: A direct observation study." *Acta Medica Iranica*. 2012; 50(6):425-31.
19. Wilson DG, McArteny RG, Newcombe RG, McArteny RJ, Gracie CR, Stuart AG. "Medication errors in pediatric practice: insights from a continuous quality improvement approach." *European Journal of Pediatrics*. 1998;157:769-774.
20. Taxis K, Barber N. "Ethnographic study of incidence and severity of intravenous drug errors." *British Medical Journal.* 2003; 326;1-4.
21. Gerstle RS. "Electronic prescribing systems in pediatrics: the rationale and functionality requirements." *Pediatrics*. 2007;119:1229-1231.