Original Article

Off-Label Drug Use in a Pediatric Intensive Care Unit

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ABSTRACT

Objective. To determine the extent and nature of off-label drug use in children admitted to a Pediatric Intensive Care Unit (PICU)

Methods. This prospective exploratory study was conducted in a tertiary care hospital in a metropolitan city in India after obtaining clearance from the institutional ethics committee. Subjects admitted in PICU from February-August 2006 were enrolled in the study. In addition to the demographic data and diagnosis, details of drugs prescribed (name, dose and route and frequency of administration) were obtained from hospital records. British National Formulary 2005 was used to determine if the prescriptions were off-label and if so, they were categorized as off-label for age, indication, dosage or frequency and route of administration. Descriptive statistics was used to determine the proportion of off-label drug use. Fischer's exact test was used to determine if there was significant difference ($P<0.05$) in off-label use between patients with multiple system affection and those with single system affection and between those requiring artificial ventilatory support and those not requiring it.

Results. Three hundred subjects received 2237 analyzable prescriptions. Of these 1579 (70.58%) prescriptions were off-label in nature. Off-label drug use was prevalent in all age-groups and in all systemic afflictions. The proportion of off-label drug use was not influenced by severity of illness, as judged by involvement of multiple systems or need for ventilatory support. The list of off-label drugs used included old as well as new molecules. Most commonly used drugs in PICU were also the most common off-label drugs.

Conclusion. Off-label drug use is highly prevalent in PICU settings. **[Indian J Pediatr 2009; 76 (11) : 1113-1118]** *E-mail: drsbavdekar@vsnl.com.*

Key words: *Drugs prescription; Drug utilization; Drug labeling; Drug therapy*

The drug licensing process was introduced in the 1960s to ensure that only quality drugs with proven safety and efficacy enter the market.[1]

Several studies have reported the proportion of off-label drug use in hospitalized children to be in the range of 25%-90%.[2-11] It has been indicated that the proportion of off-label drug use depends on many factors including type of healthcare setting (community/ hospital; primary, secondary or tertiary; general or specialty) and disease profile.[12] However, there are very few published reports focusing exclusively on off-label drug use in children in intensive care setting.[13-15] Hence, a study was carried out amongst children admitted to Pediatric Intensive Care Unit (PICU) to determine the prevalence and category of off-label drug use and to explore relationship, if any, between off-label use and severity of illness.

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MATERIAL AND METHODS

The study was conducted after obtaining permission from the Institutional Ethics Committee. As the study procedure consisted of collecting data from the hospital case records, the institutional ethics committee provided a waiver from obtaining written informed consent from parents and assent from children provided confidentiality of participants was maintained.

The study was carried out in the Pediatric Intensive Care Unit (PICU) of one of the tertiary care centers in the city of Mumbai attached to a medical college. The patient management in the nine-bedded PICU is carried out by 12 resident doctors (six registrars and six house officers) under the guidance of six senior consultants

(Two professors, one associate professor and three lecturers). Seven nurses provide nursing care round the clock. The PICU is equipped with seven ventilators, nine cardioscope monitors, 12 SpO_2 monitors and four end-tidal CO_2 monitors. In the PICU, the prescriptions are written by resident doctors *as per* the protocols followed in the PICU and under the guidance of consultants.

The study enrolled patients aged 28 day-12 yr admitted to the PICU from February- August 2006. In this prospective observational exploratory study that surveyed the prescriptions of drugs issued to children admitted to the PICU, patients' demographic data [age, sex and weight], diagnosis, details of drugs used (name, dose, frequency, route of administration, indication) were obtained. The following drugs were excluded from analysis: standard intravenous infusions, 0.9% heparin used to maintain patency of intravenous lines, intravenous sodium bicarbonate, intravenous potassium chloride, blood products, oxygen therapy, drugs given by nebulisations, drugs used for local applications (ear-drops, eye-drops, ointments, rectal suppositories), nutritional supplements (*e.g.*, : multivitamin preparations, iron and Calcium supplements) and multiple drug combinations.

Being an exploratory study, no sample size calculations were required. All patients admitted in the PICU during the study period of six months were enrolled and constituted the sample for the study. The *British National Formulary [BNF] version 2005*[16] was used as the reference for determining whether a drug's use was off-label or not. The percentage of therapeutic courses with off-label drugs, the contribution of off-label drugs in the total number of drugs prescribed, number of inpatients receiving off-label drugs and the types of drugs used in off-label fashion were determined.

Demographic data were presented as summary statistics (Mean± SD). Frequency of off-label prescribing was expressed as percent of the total. Fischer's exact test was used to determine if there was a significant difference in the number of off-label prescriptions received by ventilated patients (*vs*. non-ventilated subjects) and by children with multiple-system involvement (*vs*. single-system involvement).

RESULTS

This study spanning over 6-month period beginning February 2007 enrolled 300 consecutive subjects (Mean age: 3.57+/-3.70 years; boys 182; 60.6%) admitted to the PICU. Infants aged 1month- 1 year accounted for the largest age-group (122; 40.7%). One hundred and thirty three (44.33%) patients were ventilated and subjects had multi-system involvement. As shown in table 1, of the 2237 prescriptions analyzed, 1579 (70.58%) were off-label. An overwhelming 96% of enrolled subjects received at least one off-label prescription. Off-label drug use accounted for 65-75% of all prescriptions, in all age groups (Table 2). In infants the off-label drug use

Table 1. Data Regarding Prescriptions Studied

Parameter	Frequency
Total number of prescriptions	2837
Number of prescriptions analyzed	2237 (78.85)
Number of off-label prescriptions	1579 (70.58)
Average number of prescriptions per patient	9.45
Average number of prescriptions analyzed per patient	7.45
Number of off-label prescriptions per patient	5.26
Number of patients receiving at least one off-label Drug	290 (96.67)

Figures in parentheses indicate percentage

Table 2. Off-label Drug Use in Different Age Groups and Category of off-label use

Age Groups	No. of Patients (n=300)	No. of Pres. (n=2237)	OL	Category of Off-label Use (Number of Prescriptions)				
				Age	Dose	Frequency	Indication	route
All Age-Groups	300	2237	1579 (70.58)	547 (28.06)	866 (44.43)	404 (20.72)	132 (6.77)	22 (1.13)
1-12mo	122	927	683 (73.67)	265 (31.36)	349 (41.30)	177 (20.94)	54 (6.39)	11 (1.30)
>1-2yr	115	171	112 (65.49)	38 (18.90)	63 (31.34)	27 (13.43)	7 (3.48)	3 (1.49)
>2yr-6yr	54	408	280 (68.62)	85 (23.16)	169 (46.05)	83 (22.62)	25 (6.81)	5 (1.36)
>6yr	97	731	504 (68.94)	159 (26.06)	285 (46.72)	117 (19.18)	46 (7.54)	3 (0.49)

OL: Off-label; Pres: Prescription; Figures in parentheses indicate percentages

Note: The total number of off-label uses exceeds that of off-label prescriptions because a prescription may be off-label for more than one category.

Table 3. Most Common Off-label Drugs Used

Rank for OL Use	Rank for Overall Use in PICU	Drug	No. of prescriptions	No. of OL/UL prescriptions	Percentage of OL/ UL Prescriptions for each drug	Category of OL Use
1	3	Dopamine-iv	114	114 (5.18)	100	Age
2	4	Ranitidine-iv	100	100 (4.47)	100	Age
3	1	Cefotaxime-iv	143	92 (4.11)	64.33	Dose
4	7	Ceftriaxone-iv	68	68 (3.04)	100	Dose, Fr
5	6	Amikacin-iv	79	59 (2.64)	74.68	Dose, Fr
6	8	Terbutaline-sc	58	58 (2.59)	100	Age, Dose
7	10	Calcium gluconate-iv	51	51 (2.27)	100	Dose, Fr
7	2	Cloxacillin-iv	121	51 (2.27)	42.15	Dose, Fr
9	15	Metronidazole-iv	45	45 (2.01)	100	Age, Dose, Fr, Indication
10	10	Piperacillin-Tazobactum-iv	42	42 (1.87)	100	Age
11	17	Dobutamine-iv	40	40 (1.78)	100	Age
12	10	Hydrocortisone-iv	52	38 (1.69)	73.10	Dose, Fr
13	19	Dexamethasone-iv	36	36 (1.60)	100	Dose, Fr, Indication
13	10	Adrenaline-iv	52	36 (1.60)	69.23	Indication
13	19	Diazepam-iv	36	36 (1.60)	100	Dose
16	24	Captopril-tab	32	32 (1.43)	100	Age
17	9	Midazolam-iv	55	29 (1.29)	52.73	Dose
18	5	Furosemide-iv	97	28 (1.25)	28.86	Indication, Dose, Fr
19	25	Sucralphate-syp	27	27 (1.21)	100	Dose
20	28	Aminophylline iv	26	26 (1.16)	100	Age
20	10	Kesol-syp	52	26 (1.16)	50	Dose, Fr

Figures in parentheses indicate contribution of the concerned drug to overall off-label drug use in terms of percentage; Fr: Frequency; iv: intra-venous; OL: Off-label; sc: subcutaneous; syp: syrup; tab: tablet;

rate was the highest (74%). Across all age groups, the commonest reason for off-label drug use was variation in dose. "Age" as a category for off-label drug use was most common in infants (31%).

Table 3 lists the drugs in the order of decreasing frequency of off-label drug use and also enlists the category of off-label drug use. Amongst the top 20 off-label drugs, all except captopril, sucralphate and aminophylline were amongst the top-20 prescribed drugs in PICU. In addition, except for phenobarbitone, digoxin-elixir, mannitol and paracetamol-syrup all other top-20 drugs used in PICU made it to the top-20 off-label drugs. The list included older molecules such as dopamine, dobutamine, amikacin and cefotaxime as well as newer molecules such as piperacillin-tazobactam. Table 4 lists the commonly used off-label drugs in various age-groups. In this list, Dopamine (intra-venous), Ranitidine (intra-venous), Piperacillin Tazobactum (intra-venous), Dobutamine (intra-venous), Captopril (tablet) and Sucralphate (syrup) were off-label for use in children. In addition, age is a factor for off-label drug use in case of the following drugs: terbutaline (subcutaneous, off-label below 2 yr of age), Metronidazole (intra-venous, off-label during infancy), and Aminophylline (intra-venous; off-label below 6 mo of age). Frusemide-intravenous used for the management of hypertension in children and

Table 4. Common Off-label Drugs in Different Age Groups

Age	Common Off-label Drugs Used
1-12 mo	Dopamine-iv; Cefotaxime-iv; Terbutaline-sc; Amikacin-iv; Calcium gluconate-iv; Ranitidine-iv
>1yr-2yr	Ranitidine-iv; Cefotaxime-iv; Dopamine-iv; Diazepam-iv; Cloxacillin-inj; Ceftriaoxone-iv
>2yr-6yr	Ranitidine-iv; Dopamine-iv; Cefotaxime-iv; Metronidazole-iv; Amikacin-iv; Calcium gluconate-iv ; Terbutaline-sc
>6yr	Dopamine-iv; Ranitidine-iv; Cefotaxime-iv; Ceftriaoxone-iv; Dobutamine-iv

iv: intra-venous ; sc: subcutaneous ; yr: year

Metronidazole used in the management of hepatic encephalopathy constitute off-label drug use in the category of "indication". Thirty-six (70%) prescriptions of the Adrenaline-intravenous preparation for ventilated patients were off-label for indication as they were prescribed as intravenous infusion after a cardiopulmonary resuscitation for increasing the heart rate. All dexamethasone-intravenous prescriptions given to ventilated patients were "off-label for indication", as they were prescribed prior to extubation to decrease the laryngeal inflammation. Table 5 that lists the off-label drug use according to the primary systemic affection depicts that off-label drug use pervades all systemic affections with off-label drug use ranging from 65-85% in various systemic affections. The proportion of off-

Table 5. Off-label Drug Use in Various Systems

System	Pres	OL	Parameter for off-label use				
			Age	Dose	Frequency	Indication	Route
Central nervous system	357	237 (66.38)	70 (24.30)	141 (48.95)	56 (19.44)	20 (6.94)	1 (0.34)
Cardiovascular system	668	440 (65.86)	180 (35.02)	213 (41.43)	86 (16.73)	32 (6.23)	3 (0.58)
Dermatological	5	3 (60)	1 (25)	2 (50)	1 (25)	0 (0)	0 (0)
Endocrine system	26	20 (76.92)	7 (35)	7 (35)	4 (20)	1 (5)	1 (5)
Gastrointestinal	4	3 (75)	3 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Hematological	125	78 (62.41)	29 (29.59)	43 (43.87)	19 (19.38)	4 (4.08)	3 (3.06)
Hepato-biliary	82	56 (68.29)	16 (20.51)	32 (41.02)	18 (23.07)	12 (15.38)	0 (0)
Infectious Disease	405	312 (77.03)	109 (27.31)	174 (43.60)	85 (21.30)	28 (7.02)	3 (0.75)
Metabolic	41	30 (73.17)	13 (32.50)	17 (42.50)	5 (12.5)	4 (10)	1 (2.5)
Neuro-muscular	9	6 (66.67)	3 (25)	3 (25)	2 (16.67)	1 (8.33)	0 (0)
Renal system	81	70 (86.41)	21 (22.10)	38 (40)	27 (28.42)	6 (6.31)	3 (3.15)
Respiratory system	419	311 (74.22)	92 (22.33)	190 (46.11)	100 (24.27)	23 (5.58)	7 (1.69)
Toxins	15	11 (73.33)	3 (27.27)	6 (54.54)	1 (9.09)	1 (9.09)	0 (0)

Pres: Prescriptions; Figures in parentheses indicate percentages

Table 6. Relationship between Off-label Prescriptions with Number of Systems Involved and Requirement of Artificial Ventilation

	Prescriptions		Significance*
	All	Off- label	
Artificially Ventilated (n= 133)	1241	896 (72.19)	P=0.0621
Non-ventilated artificially (n=167)	996	683 (68.57)	
Involvement of one system (n=191)	1350	959 (71.03)	P=0.5376
Multi-system involvement (n=109)	887	620 (69.90)	

Figures in parentheses indicate percentages
*Fischer's exact test

label drug use was highest in disorders of the renal system (86.4%), wherein apart from commonly used off-label drugs in PICU, Calcitriol-tablet and Nifedipine-tablet/capsule were off-label for age.

Considering the subjects with multi-system involvement or those requiring artificial ventilation as more critically ill, off-label rates in them were compared with those who had single system involvement or those who did not require artificial ventilation, respectively (Table 6). However, no significant difference was demonstrated.

DISCUSSION

This study, probably the first from India, demonstrates that like elsewhere in the world, Indian PICUs are characterized by a high rate of off-label prescribing. The off-label drugs included new molecules as well as those that have been used for several years. The proportion of off-label drug use in the PICU was higher than that in the general pediatric wards at our institution, itself[10] as

Table 7. Studies Related to Off-label Drug use in Pediatric Intensive Care Unit

Authors	Setting	Methodology and study duration	Number of Prescriptions (Patients)	Prevalence of off-label drug Prescriptions (%)
Carvalho *et al*[13]	Brazil	Prospective, 6wk	747 (51)	49.5%
Turner *et al*[14]	Dutch	Prospective, 4mo	862 (166)	31%*
t'Jong[15]	Dutch	Prospective, 5wk	308 (27)	16%
Present Study	India	Prospective, 6mo	2237 (300)	70.58%

*Off-label and unlicensed drug use

well as that reported in other PICU settings (Table 7).[13-15] As drug trials are carried out less frequently in infants than in older children, the highest rate of off-label drug use was noted in infants. . Similar to other studies in children,[3,4,5,13,17,18] "change in dose" was the commonest category of off-label drug use. This could be related to doctors preferring to prescribe doses *as per* textbooks and guidelines in preference to dosages stated in license.

The study had its limitations: Similar to some other studies,[13-15] standard intravenous fluids, blood products, oxygen, total parenteral nutrition solutions and locally applied medications (eye- and ear-drops, ointments and rectal suppositories) were excluded from analysis, as the focus was on systemic "off-label" drugs. Although the study sample size could be considered to be 'small' to make generalizations; both study-population and study-duration were higher than those reported in earlier publications related to PICU settings.[13-15] Extending the study to one-year period, however, would have helped us determine "off-label" use in all seasons of the year. It may also be clarified that as the drugs were prescribed for indications and at dosages provided in various guidelines, textbooks and scientific literature under the guidance of consultants; the off-label use was not due to prescription errors. As licensing information is not easily available in India, British National Formulary was used for classifying drugs. We thought that logistical issues should not be allowed to thwart a study on such an important topic. The fact that others have used similar strategies, also influenced our decision.[13,19]

Off-label drug use is not illegal, unethical or inappropriate, provided it is based on sound scientific evidence, expert medical judgment or published literature and is carried out with good intent and in the best interest of the patient. However, in such situations, the prescriber takes up greater responsibility. This responsibility could become arduous in PICU settings where children are already in a critical state and when some reports have indicated that off-label use is associated with higher rates of adverse events.[20-23] On the other hand, using such drugs is a necessity, given the fact that over 70% of all Physicians' Desk Reference (PDR) entries do not have adequate pediatric labeling,[24] three-fourths of prescription drugs currently marketed in the US lack pediatric use information with disclaimers for pediatric use in labels[25] and approximately 28% of drugs mentioned in various guidelines do not have adequate pediatric prescribing information.[26] High off-label drug use indicates that the licensing system is ineffective in safeguarding the children's right of access to safe medicines.

It is noteworthy that several steps have been initiated with variable success.[1,4,12,27-32] The WHO through its "Make medicines child size" initiative is also focusing on making safe, appropriately formulated medicines accessible to children.[33] The steps required would vary depending on the situation in a given country. Making licensing information available in public domain, ensuring that drugs likely to be used in children have pediatric labeling information, providing incentives for conducting clinical trials for generating pediatric data, allowing professional bodies to suggest additional indications to be included in the license for marketed drugs and educating public regarding need to undertake trials in children are examples of initiatives that would help children receive safe drugs. This study has determined the extent and nature of off-label drug use in critically ill children. It hopefully would motivate the stakeholders to take appropriate collaborative steps to ensure that children have access to safe and effective medicines.

Key Messages

- The off-label drug use in PICU subjects accounted for 70% of prescriptions. This is higher than that reported in studies carried out in other countries. It was prevalent in patients of all age-groups, with "alteration in dose" as the commonest category of off-label drug use.
- Drugs commonly used in an off-label manner were Dopamine- intravenous, Ranitidine-intravenous, Cefotaxime-intra-venous, Ceftriaxone- intravenous, Amikacin-intravenous, Terbutaline-subcutaneous and Piperacillin Tazobactum-intravenous.
- Most common off-label drugs used were the drugs those that have been used in pediatric practice over several years

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