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Research

A Prospective Study of on-Label and off-Label Drug use in Paediatrics at Tertiary Care Hospital

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Abstract

The study to be undertaken with an aim of investigation of incidence and pattern of off-label drug use, to identify drugs most commonly used as off-label, and to identify factors associated with off-label drug use in Indian paediatrics population at tertiary care hospital.This study was conducted in Inpatient Paediatrics Department of S.N.Medical College and H.S.K Hospital and Research Centre, Bagalkot. According to age group, use of licensed and unlicensed medication out of 1205 medications, 851 are licensed medications of which 415 (34.43%) were used for neonates, 308(25.56%) infants, 100 (8.29%) young child, 28 (2.32%) child. 16 are unlicensed medications of which 4 (0.33%) were used for neonates, 5 (0.41%) infants, 6 (0.49%) young child & 1 (0.08%) child. 338 are off-labelled medications out of this 124 (10.29%) were neonates, 173 (14.35%) were infants, 30 (2.48%) were young child, and 11 (0.91%) are child.The beneficial effects of studying off-label drugs that are being prescribed to children include important dose changes, frequency, as well as improved safety information on how to more appropriately prescribe these drugs for the paediatric population.

Keywords: A Prospective Study, On-Label & Off-Label Drug, Paediatrics, Tertiary Care Hospital.

INTRODUCTION

Many drugs used to treat children in hospital are either not licensed for use in children (unlicensed) or are being prescribed outside the terms of the product license (off label prescribing)[1,2]. Most of prescription drugs are approved with no or very limited testing in children or teens under age 18. As a result, the vast majority of

drugs that are approved to treat diseases and conditions that primarily strike adults are prescribed off-label, when a doctor chooses to use them to treat a child or teen[3]. These off–label drugs received by children were of no scientific evidence and more of by clinical experiences. This is a concern because adverse drug reactions in children may be more common with unlicensed and off-label treatment than with drugs licensed for pediatric use and the practice may result in either over-or under dosing of drugs in different age groups.

World Health Organization (WHO), defines that any medicines outside the specifications described in the license constitutes Off-label use [4].The off-label drugs use includes the following categories as per the WHO[5].(a) The administration of a higher dose or more frequent administration (dose), (b) The administration for indications not described in the license (indication), (c) The administration to paediatric patients outside the range for which it has been licensed (age), (d) Use of alternative routes of administration (route) and (e) the administration of different formulation other than those indicated in the license (formulation)[6].In US when a Doctor writes a prescription to treat your ailment you probably assume that the drug has been approved for that use by the Food and Drug Administration (FDA).When a Doctor prescribes a drug for an unapproved use, it is called an "off-label" prescription. The term refers to the fact that all drugs have "labeling" detailed written descriptions of their interned use based on studies submitted to the FDA. According to American Academy of Paediatrics only fraction of medicines marketed has been studied in paediatrics patients and majorities (70-80%) of marketed medicines are not labeled. Only 20-30% of drugs approved by FDA are labelled for paediatric use[7.] Several prospective and retrospective studies that have been conducted in various health care setting in the USA, Europe, Australia have shown high proportion of unlicensed and off -label use to the extent of 72% of all prescription and 3% of all paediatrics patients[8,9]. Unlicensed or label drugs use should expose paediatric patients to the risk of drug related problems such as adverse drug reactions, drug selection problems, dosing problems, drug use and drug interactions. These types of problems should be avoided, if the medications prescribed as per the licensed indications in paediatrics. There is no much study done in an extensive way which can provide information on the use of off-label drugs in paediatrics.

A review of literature of study was to determine the extent and nature of off-label drug use in children admitted to a paediatric general ward in a tertiary health care centre. Consecutive patients aged 1 month to 12 years admitted to the general wards in a tertiary care centre in Mumbai over a two-month period were prospectively enrolled in the study. British National Formulary [BNF] 2005 was used to ascertain, if the drug use was "off-label". The off-label use was categorized as: administration of a greater/lesser dose, administration at a higher/lower frequency than indicated, administration for indications not described, administration of a drug not licensed for use in that age group and/ or use of alternative routes of administration. Descriptive statistics was used for calculating the off-label drug use. Two thousand prescriptions received by 600 subjects (M:F= 1.47:1) were analyzed. One thousand and forty-five (50.62%) prescriptions were off-label. The off-label drug use rate was 1.74+/-1.56 per patient. The maximum rate of off-label drugs was in infants (2.33/patient).

'Alteration in dosage' was by far the commonest reason for off-label use; followed by 'age' and 'indication'. furosemide (i. v.), diazepam (i.v), cefotaxime (i.v), ethambutol (tab) and prednisolone (tab) were the five commonest off-label drugs used in the study population. Off-label drug use was highly prevalent in general paediatric ward of a tertiary care hospital in India[10].Off-label prescribing of medicines is prevalent worldwide because it gives freedom to physicians to apply new therapeutic options based on the latest evidence. Although physicians may lawfully prescribe approved drugs for any use consistent with available scientific data and proper medical practice, but unfortunately, usually this is done without adequate scientific data. Often, when the best available therapeutic option fails, patients demand new approach or new treatment which ultimately leads to off-label uses. Major concerns about efficacy and safety have been raised by inappropriate use of off-label drugs because it leads to drug being used without risk-benefit analysis by the regulatory agency. Although the regulatory approval process requires ample proof of efficacy and safety for granting approval for specific indications of prescription drugs but unfortunately, more clarity is required about regulations governing off-label use of medicine. Above all because of the financial aspects involved it is highly impractical to expect that pharmaceutical companies will restrict or stop off-label promotion. Off-label use might be compared to double-edged sword which might be very useful for some patients while it can also expose them to unrestricted experimentation, unknown health risks, or ineffective medicine. Hence, there is an urgent need for guidance to encourage proper off-label use of medicine by the distribution of scientifically valid and authentic information from the pharmaceutical companies. In fact, few countries such as the USA and France have taken an initiative and have come up with the regulations about off-label use of medicine[11].

Therefore, there is a need for the study to be undertaken with an aim of investigation of incidence and pattern of off-label drug use, to identify drugs most commonly used as off-label, and to identify factors associated with off-label drug use in Indian pediatrics population at tertiary care hospital.The Objectives of the study are to study the labeled and off-label medicines in pediatric population. Specific objectives are to assess the pattern of labeled and off-label drugs in pediatric population, toassess the incidence of labeled and off-labeled drugs in pediatric population

METHODOLOGY

Study site: This study was conducted in inpatient paediatrics department of S.N. Medical College and H.S.K Hospital and Research Centre, Bagalkot.
Study design: This was a prospective and observational study to determine the incidence and pattern of labelled and off-label of drugs use and the relationship between ADRs and off-label drugs in paediatric in patients treated at H S K hospital and research centre, Bagalkot.
Study period: The study was conducted over a period of seven months from November 2013 to May 2014.

Study criteria
a) **Inclusion criteria**

1. Pediatric patient who was admitted.
2. Patient only <18 years of age were included
3. Patient should receive at one medicine

b) Exclusion criteria

1. Patients received standard intravenous replacements solutions, parenteral Nutrition, heparin used to maintain the potency of intravenous lines and Intravenous 0.9% sodium chloride.
2. Patients receives blood products and immunization

c) Age criteria: the study considered the following age groups
Neonate: 0-30 days of age
Infant: 1month-2years
Young Child: 2-6years
Child: 6-12years

Source of data
All the relevant and necessary data were collected from
a) Patient case profile,
b) Treatment chats,
c) Interviewing health care professionals
d) Interacting with patient or care taker at bed side (family relatives)
e) Any other relevant sources.

Personal interviews with patient/patient's attendant Personal interviews with reporting persons/clinicians Past history of medication use, which are generally obtained from-Past prescriptions, Reports of Medical and surgical interventions, Referral letters, discharge cards/Advice on discharge.

METHODOLOGY

Study procedure

The all the patient admitted during the study period form inpatient basis were reviewed prospectively on daily basis by the study clinical pharmacist [Pharm D student]. The patient who met the study criteria was included into the study. Data were of those patients collected and documented. All the enrolled patient was monitored intensively from day-to-day basis till the day of discharge and change to drug therapy, if any was noted on a daily basis and documented. Reported forms were collected and the necessary details are documented. Finally, the data obtained is analysed and results are formulated.

Design and forms used in the study

A suitable data collection form was prepared for the collection and documentation of patient data includes demographics, past medication details, allergic status, reason of admission, current medication including name of the medication, dose, route and frequency of admission, reason for use, duration of use, licensed (approved drugs status) or un-licensed or off-label medication.

Details regarding the total number of drugs used with respect to labelled and off-labelled, licensed and un-licensed medication and conditions of the patient at the time of patient discharge were also incorporated in data collection form. The inpatient data collected and created in separately in computer-based formats and stored, and retrieved when they required in MS office accesses format.

RESULTS

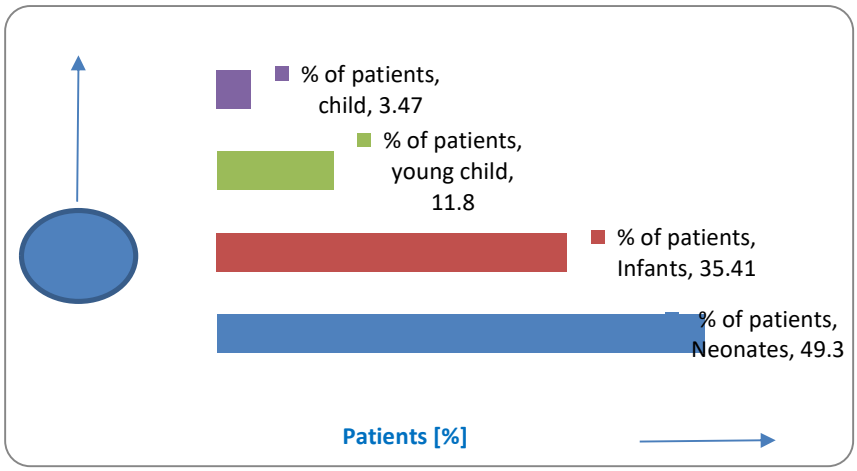

Fig 1: Patient characteristics of in-patient paediatrics at tertiary care hospital.

Table 1: Patient characteristics of in-patient paediatrics at tertiary care hospital

Sl. No.	Gender	No. of inpatients	No. Inpatients [%]
01	Male	89	61.80
02	Female	55	38.19

Table 2: Percentage of Co-morbidities in paediatrics in-patients at tertiary care hospital

Sl No.	No. of co morbidities	No. of in patients	No. of inpatients [%]
01	Nil	83	57.63
02	One	41	28.47
03	Two	15	10.41
04	Three	2	1.38
05	Death	3	2.08

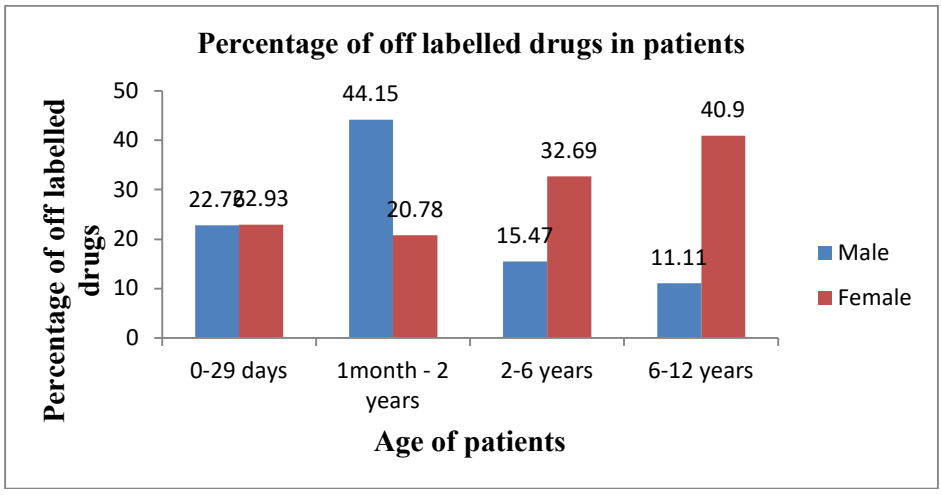

Fig 2: Percentage of Off-Labelled medication use on different groups of paediatric patients

Table 3: Different combination of medication in each prescription of paediatric patient

Sl No.	Number of medications	No .of inpatients	% No. of inpatients
01	01	2	1.38
02	02	3	2.08
03	03	5	3.47
04	04	4	2.77
05	More than 4 drugs	130	90.27

Table 4a: Frequency of medication used on a label and off-label of different class of drugs usedpatient paediatrics

S.No	Class of drug	Frequency of medication use	Frequency of Labelled use	Frequency of Off labelled drug
1	Ionotropic agents	39	05	34
2	Cephalosporins	144	144	00
3	Flouroquinolones	94	09	85
4	Anti epileptic agents	144	49	95
5	Bronchodilators	35	35	0
6	Aminoglycosides	57	57	0
7	Expectorants	24	13	11
8	Azoles	8	8	0
9	Corticosteroids	16	14	2
10	H2 Antagonist	100	100	0
11	Diuretics	7	06	1
12	Pencillins	66	65	0
13	Analgesics	50	47	03
14	Vitamins	73	73	0
15	5HT3 receptor antagonist	16	16	0
16	LMW Heparin	1	1	0
17	Hepato protective	2	02	0

Table 4b: Frequency of medication used on a label and off-label of different class of drugs used in in-patient paediatrics

S.No.	Class of drug	Frequency of medication use	Frequency of Labelled use	Frequency of Off labelled drug
1	CNS stimulant	6	0	06
2	β-agonist	27	24	3
3	Antiviral agents	03	03	0
4	Antianxiety agents	07	02	05
5	Nitroimidazoles	11	11	0
6	Phosphodiesterase inhibitors	4	0	4
7	GABA agonist	5	02	03
8	Dopamine antagonist	4	02	02
9	Probiotics	12	12	00
10	Macrolide antibiotics	12	12	00
11	Antiemetic agents	21	21	00
12	Butyrylphenones	2	00	02
13	Mucolytics	25	15	10
14	Anticholinergics	6	2	4
15	Others	184	117	67
	Total [6a+6b]	**1205**	**867**	**338**

Table 5a: Percentage of different formulations used in in-patients paediatrics

Route of administration	Medication	Frequency of labelled(%)	Frequency of off-labelled(%)
Injectable	Dopamine	-	2.32
	Cefotaxime	5.22	-
	Ofloxacin	-	4.73
	Levofloxacin	0.41	2.15
	Amikacin	4.56	-
	Ranitidine	8.38	-
	Phenobarbital	2.07	-
	Fosphenytoin	1.57	-
	Ceftriaxone	2.32	-
	Calcium gluconate	3.90	-
	Lorazepam	-	2.15
	Levitiracetam	-	0.91
	Midazolam	-	0.49
	Metronidazole	0.82	-
	Fluconazole	0.66	-
	Vancomycin	0.25	-
	Azithromycin	0.083	-
	Sodium valproate	-	1.26
	Ceftazidime	3.86	-
	Aminophylline	0.84	-
	Caffeine	-	0.42
	Dexamethasone	0.67	-
	Hydrocortisone	0.16	-
	Acyclovir	0.25	-
	Optineuron	0.34	-
	Dobutamine	-	0.75

Table 5b: Percentage of different formulations used in in-patients paediatrics

Route of administration	Medication	Frequency of labelled(%)	Frequency of off-labelled(%)
Injectable	Meropenem	0.58	-
	Piperacillin +Tazobactam	3.53	-
	Artesunate	0.25	-
	Amoxicillin +Clavulanic acid	1.42	-
	Methyl Prednisolone	0.16	-
	Ondansetron	1.34	-
	Pantoprazole	0.083	0.16
	Paracetamol	0.42	-
	Linezolid	0.16	0.083
	Propolol	0.083	-
	Thiopentene	0.083	-
	Enoxaparin	0.083	-
	Adrenaline	0.083	-
	Vit.k	2.60	-
	Dicyclomine	-	0.083
	Ciprofloxacin	-	0.083
	Ampicilline + cloxacilline	0.083	-
	Ceftriaxone + tazobactam	0.33	-
	Furosemide	0.50	-
	Pheniramine maleate	0.16	-
	Cefpodoxime	0.083	-
	Chlormphenicol	0.083	-
	Cefoperazone	0.083	-

	NTG	-	0.083
	Clindamycin	0.083	
	Morphine	-	0.083
	Ketamine	-	0.083
	Ceftriaxone + sulbactam	0.083	-
	MgSO4	0.58	-
	Sulbactam+cefaperazone	0.083	-
	Gentamycin	0.083	-

Table 5c: Percentage of different formulations used in in-patients paediatrics

Route of administration	Medication	Frequency of labelled(%)	Frequency of off-labelled(%)
Injectable	Atropine	0.083	-
	T.T	0.083	-
	Dopa+dobutamine	-	0.083
	Ornidazole+Ofloxacin	-	0.083
Syrups	Calcium supplement	1.93	-
	Phenobarbital	0.33	-
	Paracetamol+phenylephrine+ chlorpheneramine	1.07	0.45
	Ambroxol+guaniphensin	0.50	-
	Chlorphenaraminemaelate+paracetamol	0.16	-
	Sucralfate	0.41	-
	Paracetamol	2.35	-
	Elemental zinc	1.51	-
	Lactulose	0.16	-
	Terbutalinesulphate+Ambroxol	0.25	-
	Ambroxal+Terbutalinesulphate+ Guaphensin	0.50	0.8
	Sodium valproate	-	1.76
	Azithromycin	0.834	-
	Piracetam	-	0.58
	Levitiracetam	-	0.42
	Digoxinpaedia	0.083	-
	Ferroussulphate	0.25	-
	Mefanemicacid	0.84	-
	Hydroxyzinehcl	0.24	-
	Phenytoin	0.083	-
	Silymarin	0.083	-
	Levofloxacin	-	0.083
	Bevon	0.24	-
	Dicyclomine	-	0.16
	Albendazole	0.083	-

Table 5d: Percentage of different formulations used in in-patients' paediatrics

Route of administration	Medication	Frequency of labelled(%)	Frequency of off-labelled(%)
Syrups	Prednisolone	0.083	-
	Pseudoephinephrine+ Chlorpheniramine	0.083	-
	Phenylephrine +Chlorpheneramine	0.16	0.16
	Disodium hydrogen citrate	0.083	-
	Reserprine	-	0.083
	Ofloxacin	-	0.16
	Orofer XT	0.16	-
	A TO Z	0.75	-

	Monteleukast	0.083	-
	Ibuprofen + Paracetamol	0.16	-
	Phenylephrin+Chlorpheniramine	0.083	-
	Erythromycin	-	0.083
	Cyproheptadinhcl+Tricholine citrate	0.083	-
Tablets	Clobazam	-	1.09
	Spirnolacteone	0.083	-
	Acetazolamide	0.083	-
	Diazepam	-	0.16
	Clonazepam	-	0.42
	Sildenafil	-	0.33
	Tolperisone	-	0.083
	Prednisolone	0.25	-
	Baclofen	0.25	0.25
	Folic acid	0.50	-
	Lasanoprazole	0.083	-
	Pantoprazole	-	0.083
	Lactic acid	0.25	-
	Pyridoxin	0.083	-
	Levocetirizine	0.083	-

Table 5e: Percentage of different formulations used in in-patients paediatrics

Route of administration	Medication	Frequency of labelled(%)	Frequency of off-labelled(%)
Tablets	Naproxen	-	0.083
	Vit C	0.083	-
	Hydroxyl chloroquine	0.083	-
	Calcium	0.42	-
	Haloperidol	-	0.16
	Propranolol	-	0.083
	Amlodipine	-	0.083
	Tramadol + Acetoaminophen	-	0.083
	Desirox	0.16	-
	Ursodecholyic acid	0.083	-
Capsules	klumin	0.083	-
Nebulisers	Ipratropium Bromide	0.33	-
	Adrenaline	-	0.16
	Salbutamol	1.99	-
	Duolin	0.41	-
	Budesonide	0.25	-
Ophthalmic	Ofloxacin	0.25	-
	Ciprofloxacin	0.083	-
	Levofloxacin	0.083	-
	Phenylephrine + Naphazoline	0.083	-
Drops	Paracetamol	0.58	-
	A -Z	0.25	-
	Salbutamol+ Ambroxal +Guaphenisine	0.58	0.16
	Otrivin saline nasal drops	0.74	-
	Phenylephrine+ Chlorpheniramine + Paracetamol	-	0.083
	Silmethicone + Dill oil + Fennil oil	0.083	-

Table 5f: Percentage of different formulations used in in-patients' paediatrics

Route of administration	Medication	Frequency of labelled(%)	Frequency of off-labelled(%)
Drops	Ambroxalhcl	0.16	-
	Domperidone	0.16	-
	Arbivit	0.16	-
Sprays	Xylometazoline	0.083	-
Suppositories	Paracetamol	0.16	-
Suspensions	Domperidone	0.25	-
Powders	ORS	1.07	-
	Saccharomyces boulariddi	0.74	-
	D-cet	0.083	-
	Potassium bind sachets	0.083	-
	Kids protein powder	0.49	-
Creams	Ezinapi	0.16	-
	Fusidic acid	0.083	-
Gels	Zytec	0.083	-
Granules	L-glutamine	0.083	-
	Calcitrol	0.083	-
Lotions	Calamine lotion	0.083	-

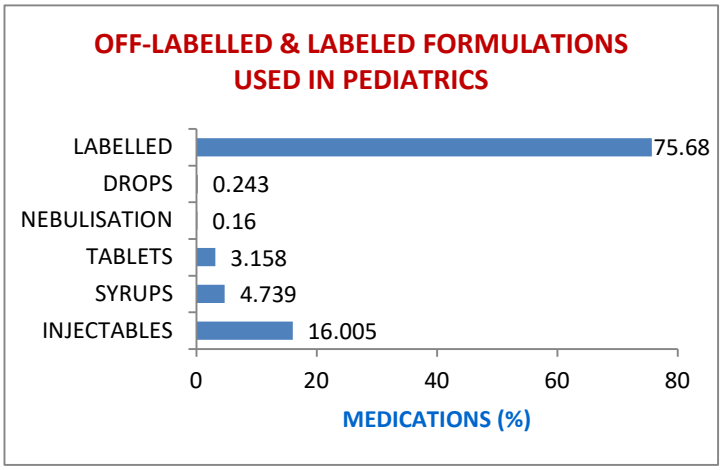

Fig 3: Percentage of different formulations used in in-patients paediatric population

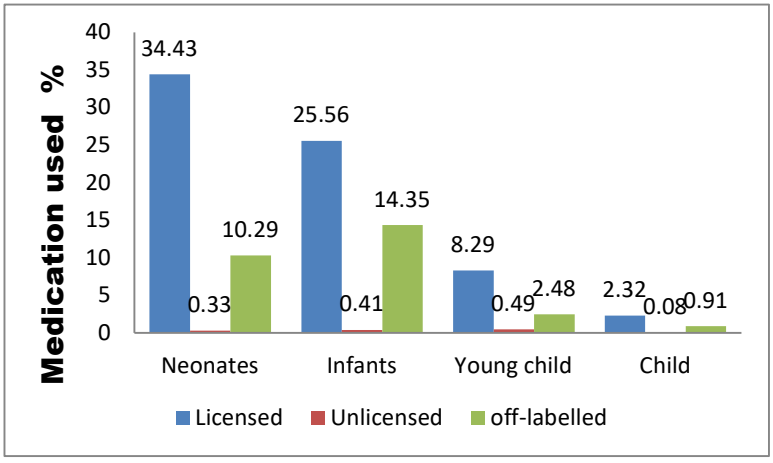

Fig 4: Percentage of Licensed, Unlicensed &Off- labelled medication used

paediatrics at tertiary care hospital.

Table 6: Incidence ofin-patient's paediatrics at tertiary care hospital

Sl.No.	Gender	No. of patients	Incidence of patients [%]
1	Male	89	61.80
2	Female	55	38.19

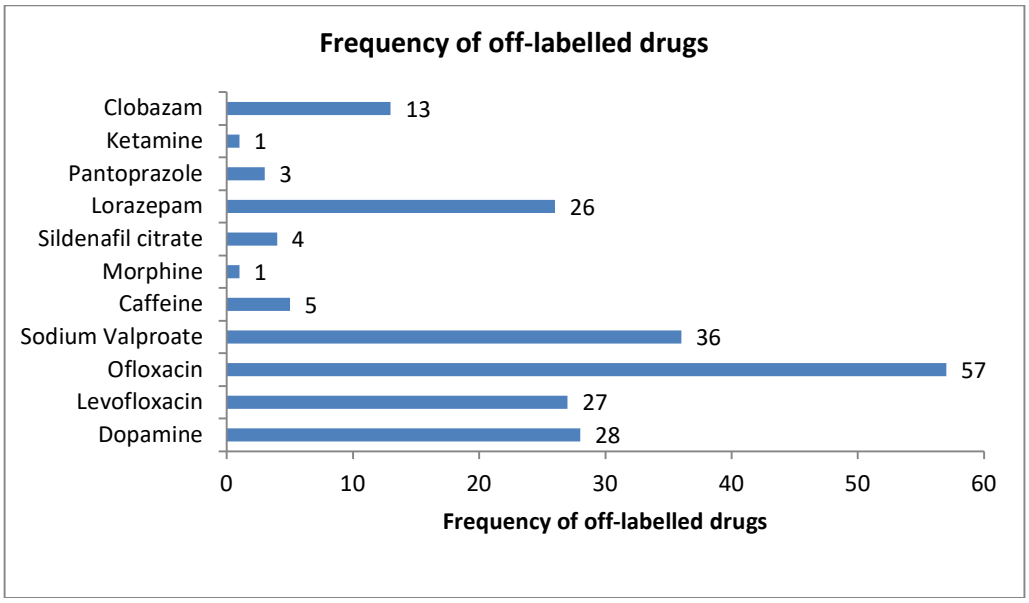

Fig 5: Most commonly used off-labelled medications in- patients paediatrics at tertiary care hospital.

DISCUSSION

Licensed medicines represent the gold standard for treatment quality, safety, and efficacy. In comparison to adults, children are commonly treated with medicines that are not studied in the paediatric population and are thus unknown safety and efficacy profile of drug used inadequate paediatric labelling of drugs was often attributed to the lack of scientific documentation in children due to lack of clinical trials.

However, in some cases, the available evidence outside the drug labelling might be sufficient to extend the indications to children without further clinical studies. For example, five proton pump inhibitors (PPI) marketed in EU only omeprazole has a paediatric indication. furthermore, it would appear that regardless of the number of studies, the dosing recommendations and safety data are still not readily available to physicians, for example different dosing recommendation for gentamycin are given in various guidance documents (eg. BNFC, Textbooks) for neonates, which may also confuse the prescribes.

In present study patients were grouped gender wise into male and female and their respective percentage proportion is calculated. A total of 144 patients were treated at the paediatric department during the period of six months from Nov 2013 to May 2014. Among 144 enrolled in-patients, 89 (61.80%) were male and 55 (38.19%) were female patients. Majority 71 (49.30%) were neonates, followed by infants 51 (43.75%) and young child 17 (11.80%) and then 5 (3.47%) were child patients.

In this study use of off- labelled drugs in 89 male patients, 44 (22.76%) were found neonates, 34 (44.15%) were infants, 9 (15.47%) were young child, and 2 (11.11%) are child population. Similarly, 55 female paediatric patients, 27 (22.93%) were neonates, 17 (20.78%) were infants, 8 (32.69%) of young child, and 3 (40.90%) of child population.

Among the study population 144 in-patients presented with 83 (57.63%) were nil co-morbidity, 41 (28.47%) were single co-morbidity, 15 (10.41%) were two co-morbidity, 2 (1.38%) of presented with three co-morbidities respectively. The average co-morbidity observed in the study patient population.

According to number of medications used in 144 in-patients, 2 (1.38%) patients had received 1 medication, 3 (2.08%) patient received 2 medication, 5 (3.47%) patient received 3 medications, 4 (2.77%) patients received 4 medications and 130 (90.27%) more than 4 medications were used.

According to the formulation associated with labelled and off labelled medication. Out of 24.04% of off labelled medications, further in which 16% are injectables,5% syrups, 3% tablets, 0.04% nebulisation, 0.04% drops and 76% labelled medications were used.

In the off-labelled category, dopamine, ofloxacin, levofloxacin, sodium valproate, pantoprazole, morphine, ketamine, & sildenafil citratewere the most commonly prescribed medications. Results summarized in table 10and fig.10.

The data pertaining to off-label medication use with respect to pharmacological class observer in our study was similar to the study carried out by Samir shah etal1, where in central and autonomic nervous system drugs used were most frequently prescribed in an off-label manner followed by GI tract drugs and antibacterial agents.[19]

In present study admitted in-patient unit off-label medication use was observed with drugs acting on CNS system (11.61%), Gastro Intestinal (1.32%), general anti-infectious drugs (7.05%), & cardiovascular system (2.82%). These above data are similar to the Benjamin et al study.[20]

According to age group, use of licensed and unlicensed medication out of 1205 medications, 851 are licensed medications of which 415 (34.43%) were used for neonates, 308(25.56%) infants, 100 (8.29%) young child, 28 (2.32%) child. 16 are unlicensed medications of which 4 (0.33%) were used for neonates, 5 (0.41%) infants, 6 (0.49%) young child & 1 (0.08%) child. 338 are off-labelled medications out of this 124 (10.29%) were neonates, 173 (14.35%) were infants, 30 (2.48%) were young child, and 11 (0.91%) are child. Results are summarized in table 6.

According to gender incidence of patients, out of 144 in-patients' paediatrics 89 (61.80%) were males and 55 (38.19%) are female population. Results are summarized in fig 5.

WHO provided guidelines for prioritisation of paediatric medicines used. There are two recently published list of paediatric priority medicines having different aims and also content. Global model list of essential medicines for children intended for use for children up to 12 years of age by the WHO (http. whqlibdoc. who.int/hq/2011/1195054.eng.pdf) comprises of data from 59 unique country priority lists. It represents a list of minimum medicines needs for a basic health care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. The medicines were selected on the basis of global burden of diseases and the evidence of efficacy and safety for preventing or treating maternal, neonatal & child mortality and morbidity. The list includes medicines for treating pneumonia, diarrhoea, malaria, vitamin A deficiency, medicines for paediatric palliative care, HIV/TB prophylaxis and medicines for neonatal care (Hilled etal.2012).[21] There kinds of adherence to guidelines will helps to provide safety use of medicines in neonates.

Though off-label drug use occurs in adults, the problem is substantially greater in children became many of routinely used drugs have not been tested in paediatric populations. With greater co-operation between pharmaceutical industry, clinical researchers, health care professionals, regulatory authorities the necessary studies need to be carried out to ensure improver prescribing in children.

With these studies, the structure documentation of off-label use & the use of non approver drugs, including the clinical out-comes of such treatment, could greatly improve knowledge in this area.

CONCLUSION

In conclusion, the beneficial effects of studying off-label drugs that are being prescribed to children include important dose changes, frequency, as well as improved safety information on how to more appropriately prescribe these drugs for the paediatric population.

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