

Off-label drug use among hospitalized paediatric patients at tertiary care teaching hospital

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Abstract

Objective: To determine the extent and nature of use of off-label drugs in hospitalized paediatric patients at tertiary care teaching hospital.

Methods: The prospective observational study was conducted among the patients admitted in neonatal intensive care units & Paediatrics inpatient wards. The study was carried out over a period of 12 months. Patients’ demographic details, clinical examinations, diagnosis and details of the drug treatment were obtained from hospital records. All prescribed drug were analysed to identify its off-label use by using national formulary of India. Descriptive statistics was used for calculating the off-label drug use.

Results: A total of 1164 patients were included in the study receiving 5362 drugs during their hospital stay. Out of 5362 drugs, 1480 (27.6%) were prescribed in off-label manner. The most common type of off-label use was related to dose (35.3%), followed by frequency (30.4%) and indication (27.1%) of particular drug use. Anti-infective for systemic use (51.3%) was the most common drug group found for off-label prescribing.

Ceftriaxone (344 times) was the most frequently prescribed drug for off label use followed by paracetamol (160 times) and ondansetron (143 times).

Conclusion: Off-label use of drug is common practice in hospitalized paediatric patients. We recommend further large-scale study with special emphasize on prescription of off-label drugs and its consequences in terms of efficacy and safety, like occurrence of ADRs, failure of therapy, increase in morbidity or mortality.

Keywords: off-label, national formulary of India, paediatric patients.

Introduction

Children constitute a large proportion of the population in developing countries. Paediatric population, with age of 0 to 14 years, constitutes almost 30% of the total population of India. Pediatrics is among the most vulnerable population groups. Significant changes in the pharmacokinetics (PK) and pharmacodynamics (PD) occur as preterm infants mature toward term, as infants mature during the first few years of life, and as children reach puberty and adolescence.^[1] As children have traditionally been excluded from clinical trials, many

drugs are marketed and used in children even when only limited, if any, information is available about their safety and efficacy in children. Many medicines administered to children are used outside the terms of the product license (includes changing the licensed dose or route of administration, use for a different indication or age group) or in an unlicensed manner (modified formulation, extemporaneous preparations). The off-label use of a medicine does not reflect inappropriate prescribing, but may occur because there is a lack of a suitable licensed medicine for children. This kind of use is not contraindicated and has to be considered necessary when there is no other option. However this practice may expose children to unwanted side-effects or under/over-dosing without the expected efficacy/safety.^[2] Off-label use among children represents an important health issue as the effects and health risks may be unexpected.^[3] Various studies have been published about the amount of and problems associated with off-label drug use in children. The magnitude of off-label prescribing is accounted to be 18% to 60% in children; it may be up to 90 to 93% in neonates.^[4] Extent of off-label drug use is not exactly known because of variations in concept of off-label terms, different methods or subject populations. Data on the extent of off-label prescribing in children are limited in India. A study that investigated the use of off-label drugs in a pediatric patient at Mumbai reported its prevalence as 41.25%.^[5] A prospective observational study on the use of off-label drugs in pediatric inpatients reported that 70% of medicines were used off-label.^[3] Although it is well known that many children receive drugs that have not been tested in pediatric patients, very few studies are done in India to determine extent and nature of these drug use in India.

Aim

To determine the extent and nature of use of off-label drugs in hospitalized paediatric patients at tertiary care teaching hospital.

Materials & Methods

The study was conducted at a tertiary care teaching hospital, situated in an urban setting in western India. It was conducted among the patients admitted in neonatal intensive care units (NICU) & paediatric inpatient wards over a period of 12 months. All patients of either gender and up to 12 years of age admitted in the paediatric wards and neonatal intensive care units were included while patients receiving only standard intravenous replacement solutions, blood products, oxygen therapy and drugs under clinical trial were excluded from study. Prior approval from the Institutional Ethics Committee (IEC) was obtained. During the study period, the investigator daily visited the pediatric inpatient wards and neonatal intensive care units and enrolled the patients based on inclusion and exclusion criteria as described above. Data like patients' demographic details, clinical examinations, diagnosis and details of the drug treatment were obtained. For each prescribed drug, dosage form with its strength, dose, frequency, route, duration of treatment were recorded. All prescribed drug were analysed to identify its off-label use by using national formulary of India (NFI) as a reference source. In the current study, off-label drug use was defined as the administration of a drug in a different manner from those approved by the national drug regulatory authority. Extent and pattern of off-label prescribing was assessed in the study population. The reasons for off label use of drug includes, use of a drug in indications not approved, as a greater/ lesser dose or at a higher/lower frequency than approved, in age group in which it is

contraindicated, use of drugs by alternative routes other than approved by regulatory authority. Study population was further divided into three different pediatric age groups (1) Neonates - 0 day to 1 month, (2) Infants - 1 month to 1 year, (3) Other pediatric patients – 1 year to 12 years. Comparison of off-label prescribing amongst the different pediatric age groups was also done. Descriptive statistics were used to define total number of off-label drugs used, reasons for off-label use in different age groups, off-label prescribing according to WHO-ATC class, most common drugs used in off-label manner.

Results

A total of 1164 patients were enrolled, out of which, 711 patients were from pediatric ward and 453 patients were from neonatal intensive care unit. The mean age of the patients from pediatric ward was 3.78±3.39 years with a range of 1 month to 12 years. Out of total 711 patients, 420 (59%) were boys while 291 (41%) were girls. The mean age of the patients from NICU was 2.49±4.57 days with a range of 0 day to 25 days. Out of total 453 patients, 219 (48%) were boys while 234 (52%) were girls. Respiratory disorders (47.2%) (Including pneumonia, bronchiolitis, bronchitis, to nsilo pharyngitis & diphtheria) and gastrointestinal diseases (12.5%) (including acute gastroenteritis (AGE) & dysentery) were the two most common diseases observed in patients of pediatric ward. Majority of patients in NICU were suffered from respiratory distress syndrome (RDS) (41%), septicemia (11.4%) and severe birth asphyxia (SBA) (9.9%). A total 1164 patients were included in the study receiving 5362 drugs during their hospital stay. Out of 5362 drugs, 1480 (27.6%) were prescribed in off-label manner. Number of drugs used in off-label manner was found significantly higher in pediatric patients (age

between 1-12 year) other than neonates and infants when compared by chi square test ($p < 0.0001$). (Table 1)

Table 1: Off-label drug use in different pediatric age groups (Values are expressed as absolute number and percentage in parentheses)

Age groups	Neonates (n=2106)	Infants (n=905)	Other pediatric patients (Age between 1-12 year) (n=2351)
No. of off – label drugs	267 (12.6)	280 (30.9)	933 (39.6) *

* Significantly high in other pediatric patients group as compared to neonates & infants $p < 0.0001$ (Chi square test)

The most common reason for off-label prescribing was use of higher/lower dose than stated for particular pediatric patients (35.3%, n=1643). Other common reasons for off-label prescribing were due to higher/lower frequency (30.4%, n=1643) and indication for drug use (27.1%, n=1643). Off-label medicines use for age group in which it is contraindicated and alternative route was found to be 2.9% (n=1643) and 4.0% (n=1643), respectively. (Table 2)

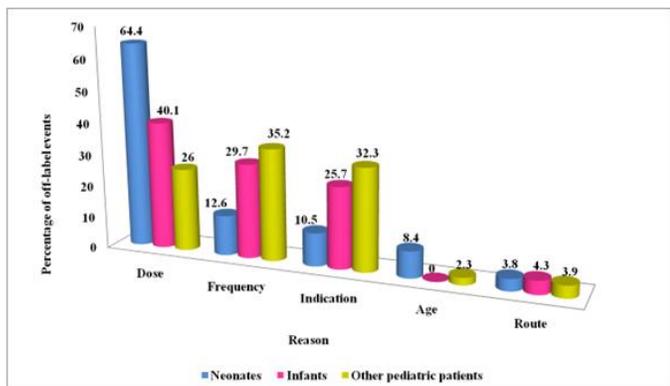
Table 2: Reasons for off-label drug use (Value are expressed as absolute number and percentage in parentheses)

Reason No. of drugs	Indication	Dose	Frequency	Route	Age
(n=1643)	446 (27.1)	581 (35.3)	501 (30.4)	66 (4.0)	49 (2.9)

Dose was most common reason for off-label prescribing in neonates (64.4%, n=284) and infants (40.1%, n=299). Frequency (35.2%, n=1066) was the most common reason for off-label prescribing in other pediatric patients followed by indication (32.3%, n=1066) and dose

(26.0%, n=1066). The use of drugs in patients for restricted age limits was highest in neonates followed by other pediatric patients. No drug was used off-label according to age criteria in infants. Route of drug administration was consistent among the patients of all three age groups. (Figure 1)

Figure 1: Reasons of off-label prescribing in different age groups (Value are expressed as percentage)



Out of total 1480 off-label drugs, anti-infective for systemic use (760 drugs, 51.3%) was found most common class contributed highest proportion for off-label prescribing. While nervous system (323 drugs, 21.8%) and alimentary tract & metabolism system (164 drugs, 11.0%) were the other most common classes for off-label prescribing. Off-label prescribing was also found for cardiovascular system (74 drugs, 5.0%), respiratory system (72 drugs, 4.8%), systemic hormonal preparation (48 drugs, 3.2%), musculoskeletal system (13 drugs, 0.8%) and anti-parasitic products (6 drugs, 0.4%). Ceftriaxone (344 times) was the most frequently prescribed drug for off label use followed by paracetamol (160 times) and ondansetron (143 times). Other commonly prescribed off-label drugs were amikacin (107 times) and amoxicillin-clavulanic acid (100 times). (Table 3)

Table 3: Most common off-label drugs used in study population (Value are expressed as absolute number)

Drug	No. of times off-label use	Reason for off-label use
Ceftriaxone	344	Frequency, indication
Paracetamol	160	Dose
Ondansetron	143	Indication
Amikacin	107	Frequency, dose, indication
Amoxicillin-Clavulanic acid	100	Frequency, dose, indication

Discussion

Over the past few years, studies performed in different settings have reported that off-label drug use is common in the pediatric population. It is because as there is no alternative to such drugs in the market or no standard treatment plan is available due to the scarcity of pediatric clinical data.^[6] Due to absence of data regarding efficacy and safety, doctors use their medical judgment to decide on a particular drug and dose for children. A common approach by doctors is to use data from adults and adjust the dose according to a child's weight. Experimenting over the years has taught doctors to use many drugs in children safely and effectively. But this trial-and-error approach has also resulted in many tragedies. For example, in the 1950s, the antibiotic chloramphenicol was widely used in adults to treat infections resistant to penicillin. But many newborn babies developed gray baby syndrome and died after receiving the drug because their immature livers couldn't break down the antibiotic. These tragedies indicate that adult experiences with a drug are not always a reliable predictor of how children will react.^[7] The study done to examine the impact of off-label and unlicensed prescribing on adverse drug reactions reported that off-label and unlicensed medicines were more likely to be implicated in an ADR than authorized medicines (relative risk 1.67).^[8] A prospective study in an Indian tertiary care hospital

reported that number of off-label medicines given to patient significantly increased the hazard of an ADR (hazard ratio 1.28) (Saiyed MM et al, 2015).^[9]

The proportion of off-label prescribing in present study (27.6%) was lower than reported in previous studies conducted in India by Saiyed et al in which 70 % drugs were used in off label manner and Joban Putra et al in which 41.25% drugs were used in off-label manner.^[3&5]

However, our finding was almost similar to a recent study conducted in pediatric teaching hospital in Western Australia which reported 25.7% of off-label drug use.^[10] Other studies done in Brazil in 2012 by Ferreira Lde A et al (23.4%) and in Comenius University in Bratislava by Slazneva J et al (22%) also found similar results.^[11&12] Study done at northwestern Ethiopia found 75.8% off-label use of medicine.^[13]

Finding of our study was also similar to a previous study conducted in Germany that found 30% of the medicines have been used off-label.^[14] Higher rate of off-label use of drugs in study done by Joban Putra et al might be due to study populations which included patients admitted in pediatric intensive care unit (PICU) only. Patients in PICU are severe and critically ill, prescriber must have to consider all kinds of therapeutic options to save life of patients.

In present study, most common reason for off-label prescribing was due to variation in dose as observed in other studies conducted in India.^[3,15-17] Similar result was also found in different studies conducted in Australia, Germany, Brazil and Pakistan.^[10,11,14,18] However, indication was observed as most common reason for off-label prescribing in a recent study conducted in Maharashtra.^[5] Off-label medicine use such as under- and over-dosing could bear the risk of potential health hazards. Under dosing may results into

therapeutic failure and over dosing leads to drug toxicity. Inappropriate dosing is of particular concern for antibiotic use with respect to the development of resistances.^[19&20]

In present study, off-label use was found higher after the age of 1 year possibly due to lack of pediatric dosing guidelines in these patients in spite of having licensed drugs. Another study by Saiyed et al observed highest off-label prescribing in age group of 1 to 2 years. This is contradictory to the findings of previously published study where a highest rate for off-label drug use was noted in infants.^[15] The main reason for differences in most common age groups for off-label drug use may be related to differences in the study population. For examples, Czarniak et al included patients from the emergency department, inpatient wards and also of outpatient clinics that is different from present study which included hospitalized patients only.

In our study highest proportion of off-label drugs was prescribed in anti-infective for systemic use class which was also the most frequently prescribed WHO-ATC class in overall. This finding of our study was similar to two other Indian studies.^[3&21] However, in a study from Chicago, off-label use was lowest for antibiotics and maximum for gastrointestinal medications.^[22] In a study from Spain, highest proportion of off-label drugs was prescribed in respiratory system which was also the most frequently prescribed WHO-ATC group.^[23] The highest percentage of off-label prescribing was for drugs of the cardiovascular system and respiratory system in study from Western Australia.^[10]

The reason for these variations in most common WHO-ATC class with off-label drug use may be related to prevalence of specific diseases in a particular region which influences the drug usage pattern. In developed

countries infectious disease are less prevalent than disease affecting other systems like cardiovascular, alimentary tract and metabolism, while in developing countries like India, infectious disease are still more prevalent contributing highest proportion of not only off-label use but also overall drug usage.

In our study, Ceftriaxone was the most frequently prescribed drug for off label use followed by paracetamol and ondansetron. In other study from India, dextromethorphan was the most frequently prescribed drug for off label use followed by azithromycin and ondansetron.^[17] In a Brazilian pediatric hospital fenoterol, ceftriaxone and metamizole were the most commonly prescribed off-label drugs.^[24] In multicentric study from various European nations, most common off-label drugs were paracetamol and ibuprofen.^[25]

These wide variations in the most common drug for off-label use between different studies can be explained by different type of morbidities observed in different study population. Type of drug prescribed varies according to the disease pattern of patient's indifferent settings, and disease pattern varies according to geographical area. So, geographical variation exists in class of the drug being used in off-label manner. It is also influenced by choice of individual prescribers and availability of drugs in that particular region.

So from above discussion, it can be concluded that extent and nature of off-label drug use depends upon classification methods, study populations, pediatrician's prescribing habits, treatment protocols, diseases characteristics and most importantly pediatric drug regulation. The association of the prescription of off-label drugs and its consequences in terms of efficacy and safety, like ADRs, failure of therapy, increase in

morbidity or mortality, was not assessed in our study due to practical difficulties in the field.

Conclusion

Off-label use of drug is common practice in hospitalized paediatric patients. However, non-availability of licensed drugs and lack of information regarding use of drug in pediatric population might be the reasons. Though association between ADRs and off-label drug use is yet to be confirmed, it should be discouraged as it may increase risk to the patients. Efforts should be put to make more number of licensed drugs available for pediatric population by promoting clinical research in this age group. There is a need to create awareness about off-label drug use and its consequences by educating prescriber.

Furthermore a rule should be established regarding off-label use of drug which can obligate the prescriber legally to keep clear, accurate and legible records of the drug used in this manner. Auditing and monitoring of these records should be done regularly. It is first attempt to find out extent and nature of off-label use of drugs in our hospital which may prove to be foundation for future research in this area. We recommend further large-scale study with special emphasize on prescription of off-label drugs and its consequences in terms of efficacy and safety, like occurrence of ADRs, failure of therapy, increase in morbidity or mortality.

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