USAGE OF OFF-LABEL DRUGS AMONG PRETERM BABIES ADMITTED IN A LEVEL III NEONATAL INTENSIVE CARE UNIT ATTACHED TO A MEDICAL COLLEGE IN SOUTHERN KARNATAKA

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ABSTRACT

BACKGROUND

Drug therapy in the neonatal age group is not always supported by systematic clinical testing. Organ immaturity and consequently difficulties adapting to extra-maternal life are reasons for preterm neonates being often multi-morbid and in need of intensive care. Consequently, they are exposed to high number of drugs, putting them at a higher risk of adverse drug reactions. This study gives an insight to the extent of usage and nature of off-label drug use among preterm infants admitted in Neonatal Intensive Care Unit (NICU) attached to a tertiary care hospital.

MATERIALS AND METHODS

This cross-sectional study was conducted over a six-month period (Aug. 2015 - Jan. 2016) in a Level III NICU attached to a Medical College in Southern India. All inborn and outborn Preterm infants admitted in NICU, during the study period were included in the study. Drugs prescribed were categorised based on World Health Organization Anatomical Therapeutic Chemical (WHO-ATC) Classification System.[9] Data collected was evaluated for off-label category of drugs using the National Formulary of India (NFI, 4th edition, 2011)

RESULTS

The study included a total of 154 Preterm infants, with majority of the study population in the late Preterm (>34 weeks gestational age) group accounting for 66.2% (n=102). A total of 1426 medications were administered to Preterm infants during the hospitalisation of which 1083 (75.9%) medicines were prescribed in off-label manner. The most common cause of off-label prescribing was for age (55%). The extent of off-label prescribing was highest (78%) in very Preterm 28- 34 weeks gestational age group, followed by 76.2% in late Preterm >34 weeks gestational age group. Of the 154 Preterm infants included in the study, 150 (97.4%) received at least one off-label medication and 100% of the Extreme Preterm group infants received one or more off-label medicines. Among the total off-label medicines (n= 1083) prescribed, 58% was accounted by Anti-infectives for Systemic use group of drug.

CONCLUSION

Off-label prescribing is a reality and will not end soon. Implementing evidence-based approach can significantly improve rationality of neonatal pharmacotherapy.

KEYWORDS

Preterm, Neonatal Intensive Care Unit, Drug Therapy, Off-label.

BACKGROUND

Global policies for prescribing medicines have been changing based on the need of therapeutic measures adapted to the particular stage of life. There are two different entities for non-labelled prescriptions, which are off-label and unlicensed usage of drugs. Off-label drugs are medicines which are used beyond the conditions of the registered product as specified by summary of product characteristics (SPC) with reference to age, dosage, frequency, route of administration and indications for its use. Unlicensed drugs are those that do not have marketing authorisation, not licensed to be used in a country or does not have an appropriate formulation for its use.[1]

Drug therapy in the neonatal age group is not always supported by systematic clinical testing. Often evidence of safety and efficacy in adults is extrapolated to neonates, making their efficacy and safety in neonates questionable, in particular preterm babies.[2] Organ immaturity and consequently difficulties adapting to extra-maternal life are reasons for preterm neonates being often multi-morbid and in need of intensive care. Consequently, they are exposed to high number of drugs, putting them at a higher risk of adverse drug reactions.[3] Various national and international studies have been published on the amount of and problems associated with Off-label medicines use in Children. The magnitude of Off-label prescribing is accounted to be between 18% and 60% in infants but it may be up to 90% in Neonates.[2-8] This study gives an insight to the extent of usage

and nature of off-label drug use among preterm infants admitted in Neonatal Intensive Care Unit (NICU) attached to a tertiary care hospital.

The aim of this study was to determine the extent and nature of off-label drug use among Preterm infants in NICU.

MATERIALS AND METHODS

Study cohort: This cross-sectional study was conducted over a six-month period (Aug 2015-Jan 2016) in a Level III NICU attached to a Medical College in Southern India. All inborn and outborn Preterm infants admitted in NICU, during the study period were included in the study. Once babies were discharged or shifted to other centres, no further data were collected. Case sheet, investigation reports and treatment chart of all the Preterm infants was reviewed, after approval from the ethics committee. Data extraction sheet was used to collect the data regarding demographic details, indication for admission, final diagnosis and medications administered. Medicines given prior to NICU admission, E.g. in the delivery room, were taken from the patient record (inborn) or from referral letter (outborn). Data regarding the following were not recorded: intravenous fluids, total parenteral nutrition, routine oral nutritional supplements, vaccines, Vitamin K, topical anaesthetic cream, oxygen and blood products.

Drugs prescribed were categorised based on World Health Organization Anatomical Therapeutic Chemical (WHO-ATC) Classification System.[9] Data collected was evaluated for off-label category of drugs using the National Formulary of India (NFI, 4th edition, 2011).[10] There were five off-label categories as depicted in Table 1. Categories of off-label use were allocated for each medicine prescribed according to the reason(s) why their use was deemed off-label.

	Categories	Reasons
1	Age	Drug not recommended in patients below certain age
2	Dose	Dose higher than recommended
3	Indication	Drug prescribed for indication outside of those listed in the NFI
4	Route of administration	Drug administered by a route not described in the NFI
5	Absence of Paediatric information (PI)	Not mentioned at all in the NFI regarding Paediatrics use
Table 1. Reasons for Use of Off-Label Medicine in Different Categories		

Statistical analysis: Variables such as Preterm category, Birth weight, were regarded as continuous and expressed as mean with Standard deviation (SD). Preterm infants were subgrouped as extreme Preterm (with gestational age <28 wks.), very Preterm (28- 34 wks.) and late Preterm (>34 wks. gestational age). Categorical variables are presented as numbers with percentages (%). The collected data was analysed using Statistical Package for the Social Sciences (SPSS version 11.0).

RESULTS

Demographic Characteristics

The study included a total of 154 Preterm infants, comprising 83 (53.9%) male and 71 (46.1%) female. The median Birth Weight and Gestational Age was 1712 grams (SD ± 914) and 34 wks. (SD ± 2.75) respectively. The majority of the study population were in the late Preterm (>34 wks. gestational age) group accounting for 66.2% (n=102); 27.3% (n= 42) very Preterm and 6.5% (n=10) extreme Preterm infants. About 17% of the Preterm infants were outborn, transferred in from another hospital for NICU care. With the study population including Preterm babies, the spectrum of morbidity pattern included respiratory distress syndrome, sepsis, asphyxia, hypotension, hyperbilirubinaemia, apnoea of prematurity, patent ductus arteriosus, necrotising enterocolitis, intraventricular bleed, etc. On average babies stayed in NICU for 17 days (median= 10, SD ± 18.5 days) before discharge or shift back to the referral unit. Not surprisingly, extreme Preterm stayed longest, with 70% of babies in this group treated for more than 40 days in NICU. In total, 21 babies died during the NICU stay, of which 3(14.2%) were extreme Preterm, 6 (28.5%) very Preterm and 16 (57.1%) late Preterm infants. A summary of patient demographics is given in Table 2.

	All Preterm	<28 wks.	28-34 wks.	>34 wks.
Number of patients	154	10	42	102
Birth weight (g) median (SD)	1712 grams (SD ± 914)	910 grams (SD ± 221)	1360 grams (SD ± 340)	1920 grams (SD ± 546)
Length of hospital stay (days) median (SD)	17 days (SD ± 18.5 days)	39.5 days (SD ± 33.1 days)	23.6 days (SD ± 21.2 days)	16.7 days (SD ± 19.4 days)
Survival (%)	86.3%	70%	85.7%	88.2%
Table 2. Demographics of the Study Population				

A total of 1426 medications were prescribed for 154 Preterm infants during hospitalisation. The mean number of drugs administered to the patient was 8.4 (median =7, SD± 7.66, minimum= 0, maximum=17).

According to the WHO-ATC classification system, Anti-infectives for Systemic use (n= 815) and drugs for the Respiratory System (n= 206) have been prescribed most often, followed by drugs for the Central Nervous System (n=157). Medications were mostly administered by intravenous route followed by oral route. Among Anti-infectives Ampicillin and Gentamycin were prescribed most often. Cardiovascular drugs comprising predominantly Dopamine and Frusemide were mainly given to late preterm and very preterm infants. Central nervous system drugs comprising analgesics and anti-epileptics drugs, phenobarbitone and midazolam showed a high number of prescriptions. Of the Respiratory drugs administered, Aminophylline and Caffeine citrate were most frequently given, followed by Surfactant.

Nature of Off-Label Prescribing

A total of 1426 medications were administered to Preterm infants during the hospitalisation; 1083 (75.9%) medicines were prescribed in off-label manner when its usage was validated with National Formulary of India (2011). The most common cause of off-label prescribing (978, 55%) was due to age (category 1), as depicted in Table 3. Off-label medicines use for dose and absence of Paediatric information was found to be 730 (41.2%) and 44 (2.5%), respectively.

Off-Label Prescribing in Different Neonatal Groups

In the study, we attempted to distribute the receipt of off-label medicines in different neonatal age groups as shown in Table 3. The extent of off-label prescribing was highest (78%) in very preterm 28-34 weeks gestational age group, followed by 76.2% in late preterm >34 weeks gestational age group. Of the 154 patients included in the study, 150 (97.4%) patients received at least one off-label medication and 100% of the extreme preterm group infants received one or more off-label medicines.

Age Group	Total Medicine	Off- label Medicine (%)	Off- Label Categories				
			Age (%)	Dose (%)	Indication (%)	Route (%)	Absence of Paediatric Information (%)
All Preterms (n= 154)	1426	1083 (75.9)	978 (55)	730 (41.2)	16 (0.9)	07 (0.4)	44 (2.5)
< 28 weeks (n= 10)	160	110 (68.7)	94 (54)	72 (41.3)	02 (1.1)	01 (0.7)	05 (2.9)
28-34 weeks (n= 42)	450	351 (78)	282 (55.4)	210 (41.3)	04 (0.8)	02 (0.4)	111 (2.1)
> 34 weeks (n= 102)	816	622 (76.2)	602 (55.1)	448 (41)	10 (0.9)	04 (0.4)	28 (2.5)
Table 3. Off-label Medicine use in Different Gestational Age Groups							

*Note: The total number of off-label uses exceeds that of off-label drugs because a drug may be off-label for more than one category. Figures in parentheses indicate percentage.

Off-Label Prescribing by WHO-ATC Class and Drugs

Among the total off-label medicines (n= 1083) prescribed, 58% was accounted by Anti-infectives for Systemic use group of drugs (Table 4). Of the total medicines prescribed in different ATC group of drugs, the rate of Off-label prescription was highest among the Anti-infectives for Systemic use (648, 79.5%) and drugs for the Respiratory System (159, 77.2%) as shown in Table 5. Majority of off-label medicines prescribed were Ampicillin, Amikacin, Cefotaxime, Linezolid, Vancomycin, Fluconazole, Meropenem, Metrogyl, Netilmicin, Piperacillin-Tazobactam in Anti-infectives for Systemic use; Aminophylline in drugs for the respiratory system; Phenobarbitone and Midazolam in drugs acting on the nervous system; and domperidone and ranitidine in alimentary tract and metabolism group of drugs.

Total Medicine	Total off-label Medicines	WHO- ATC Group with Off-label Medicine Use					
		Anti-infective for systemic use (%)	Respiratory system	Nervous system	Alimentary tract	Cardiovascular system	Other system
1426	1083	648 (59.8)	159 (14.7)	121 (11.2)	71 (6.6)	78 (7.2)	6 (0.5)
Table 4. Off-label Medicine use According to WHO-ATC Class							

*Note: The total number of off-label uses exceed that of off-label drugs because a drug may be off-label for more than one category. Figures in parentheses indicate percentage.

WHO ATC System	Total Medicine	Off-label Medicine (%)	0ff-label categories				
			Age (%)	Dose (%)	Indications (%)	Route (%)	Absence of paediatrics information (%)
Anti-infective for systemic use	815	648 (79.5)	571 (57.1)	389 (38.9)	05 (0.5)	04 (0.4)	30 (3.1)
Respiratory system	206	159 (77.2)	123 (46.2)	138 (51.9)	-	-	05 (1.9)
Nervous system	157	121 (77.1)	146 (57.9)	103 (40.9)	-	-	03 (1.2)
Alimentary tract and metabolism	108	71 (65.7)	39 (44.8)	41 (47.2)	05 (5.7)	-	02 (2.3)
Cardiovascular system	132	78 (59)	81 (57)	51 (35.9)	04 (2.9)	03 (2.1)	03 (2.1)
others	8	06 (75)	08 (27.7)	18 (62)	02 (6.9)	-	01 (3.4)
Table 5. Off- Label Medicine use According to WHO-ATC and Off-label Category							

*Note: the total number of off-label uses exceed that of off-label drugs because a drug may be off-label for more than one category. Figures in parentheses indicate percentage.

DISCUSSION

In our study, we observed that 75.9% of the prescriptions to Preterm infants were off-label. Previous studies from developed countries have reported 36-93% prevalence of off-label or unlicensed use of drugs in neonates.[11-14] An Indian study based on the National Formulary of India reported a prevalence of 70% off-label prescription.[2] Various reasons for wide range reported are off-label classification methods, different licensing policies, sample size, unit treatment protocols, disease characteristics and difference in drugs included in audit. We found that 97.4% of Preterm infants and 100% of Extreme Preterm infants received at least one off-label prescription. Similar values are reported in the literature: O'Donnell et al reported that 80% of all patients had received at least one unlicensed or off-label medicine, whereas Conroy et al indicated 90% of patients in NICU had done so.[13-14]

Of the medicines prescribed during the study period, it was observed that Antibiotics, respiratory medicines and nervous system medicines were frequently prescribed in off-label manner, similar to another study from India in NICU by Suksham Jain in NICU.[2] In a study from Chicago, off-label use was lowest for antibiotics and maximum for gastrointestinal medications.[11] In a German study by Neubert, analgesics and cardiovascular drugs were prescribed frequently without having information for use in Neonates.[3] These differences in off-label drug use in different units can be explained by type of morbidities observed in a setting. Neonatal prematurity, sepsis and perinatal asphyxia are the most common causes of neonatal morbidity and mortality in India.[15] Thereby high prevalence of off-label use of antibiotics, respiratory medicines and anticonvulsants is expected.

A strict drug approval procedure is the way to ensure quality data on safety and efficacy of drugs for different paediatric age groups. This might ensure paediatric labelling for new medicines yet to be introduced in the market, but it is unlikely to happen so for drugs already being used in infants in an off-label manner. The situation can be improved when prescribers report their experiences with different off-label medicines in the form of research articles or discussion in scientific programmes.

CONCLUSION

Understanding various risk factors and spectrum of off-label medicine use can assist developing prevention strategies. Off-label prescribing is a reality and will not end soon. Implementing evidence-based approach can significantly improve rationality of neonatal pharmacotherapy.

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