RESEARCH BRIEF

Off-label Use of Drugs in Neonatal Intensive Care Units

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Objective: To estimate proportion of off-label medication use in neonates and to evaluate evidence of efficacy and safety of these medications. **Methods**: Chart audit in neonatal intensive care units of two institutions in Chandigarh, India. **Results**: Among 568 prescriptions in 156 neonates, 286 (50%) were off-label. Of these, 56% drugs were not approved for use in neonatal age group and 26% prescriptions were off-label for frequency, dose, indication, route or rate. Most common off-label drugs were anti-infective and antiepileptic. Despite lack of regulatory approval, one-third off-label drugs had level I-II evidence of safety and efficacy for use in neonates. **Conclusion**: Use of off-label drugs is common in sick neonates.

Keywords: *Audit, Neonate, Prescription, Treatment.*

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 [1], making their efficacy and safety in neonates questionable. Such drugs, when used in neonates, may either be not licensed (unlicensed), or may be prescribed outside the terms of the product license (off-label) [2].

Unlicensed drug refers to extemporaneous dispensing, purchase of unlicensed formulations, purchasing of drugs licensed in other countries, use of chemicals etc. Off-label use is neither experimentation nor research on that drug, but should be based on sound scientific knowledge. Off-label drug refers to use of drug with lower (or higher) than recommended dose, drugs not licensed in neonates, used for indication for which the drug is not licensed, or given by alternative routes of administration [2].

Off-label drug practice can vary as per unit policy. There is some information available on off-label use of medicines in pediatric age group in India [3], but data on neonates are lacking. The aim of this study was to study the incidence of off-label or unlicensed medication use in two neonatal intensive care units (NICU), and to study the available evidence for safety and efficacy for these drugs.

METHODS

This audit exercise was conducted simultaneously in a Level II and a Level III NICU in Northern India over a three-month period (June-August 2009). Prescription writing at both centers was done by physicians who had passed postgraduate medical education in Pediatrics. Nursing staff was trained for neonatal intensive care services.

All intramural neonates admitted in NICU were eligible for inclusion in the study. Inborn neonates staying for more than 6 hours in the NICU, and receiving any drug therapy were enrolled. Prescription writing was done manually by senior residents and all drugs given to the neonates were recorded; except routine nutritional supplements, intravenous fluids, inotropes, vaccines, vitamin K, topical anesthetic cream, fluid or heparin for flushing the intravenous lines, oxygen and blood products. Demographic details, diagnosis, and drug prescription details (route of administration, indication for use, formulation, frequency, and time to administer etc.) were recorded. The data were recorded prospectively as a chart audit by the study investigators who were not part of the treating team. The treating physicians, resident doctors and staff nurses were not aware of findings of the chart audit.

Accuracy of dose was checked from standard neonatal drug formularies. British National Formulary of drugs, 2005 version and Neofax 2008 were referred for dosage [4,5]. The entire data were verified for validity by a co-investigator who was not part of data entry. A drug was labelled as off-label if: not approved or licensed for use in neonates, different dose, alternative route, using adult preparation for neonates after dose modification, using drug approved for term neonates in preterms and vice-versa, or formulation modified.

Parenteral medications, safety and efficacy and Food and Drug Administration (FDA) approval in neonates were searched in Cochrane Central Register of Controlled Trials (CENTRAL), The Cochrane Library 2009 (Issue1), MEDLINE (1966 to July 2009), and Ovid database. Levels of evidence in support of the use in neonates were defined [6] as: Level I, based on at least one randomized clinical trial regardless of its size or heterogeneity of group; Level II, based on a well-designed clinical trial without randomization; Level III, based on a non-experimental descriptive study; and Level IV, based on case reports and expert opinion.

The study was approved by the Institutional Research and 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.

As it was a pilot study, we took a sample of convenience over a three-month period, where all consecutive admissions to NICU were eligible for enrolment if they met the inclusion criteria. Data were analyzed using SPSS Version 11.0. Confidentiality regarding patient's identity and records was maintained. Descriptive statistics were used to define total number of off-label drugs used (expressed as a percentage of the total), number of drugs, broad indications for off-label use, and levels of evidence available for safety and efficacy of these drugs.

RESULTS

During the study period, 568 prescriptions of 156 neonates were analyzed. The median (IQR) birth weight, gestation age and duration of NICU stay were, 1348 (1076, 1800) grams, 32 (30, 35) weeks, 8 (5,18) days, respectively. The median (IQR) number of medications per patient was 3 (1,6). Survival rate for all gestation ages was 78% during this time period.

Table* I** enlists various drugs used off-label for age, dose, duration, indication, frequency and rate. The proportion of off-label prescriptions was 50.3% (286/568). Among the entire off-label drugs, 75% prescriptions (56% medicines) were not approved by FDA for use in neonatal age group; 26% prescriptions were off label for frequency, dose, duration, indication, route and rate. Twelve percent of prescriptions had avoidable medication error. Most common off-label medicines were anti-infective and antiepileptic drugs (Table* II)**. In spite of lack of FDA approval, one third of such medicines had level I-II evidence of safety and efficacy for use in neonates (Level I evidence for safety and efficacy in 2 and 5 drugs and level II in 6 and 3 drugs, respectively).

DISCUSSION

In this prospective audit we observed that nearly half of the prescriptions in NICU were off-label. Our study also had 12% avoidable off-label prescriptions of dose, frequency and duration. Previous literature from developed countries has reported 36-93% prevalence of off-label or unlicensed use of drugs in neonates [2,6-9].

In a study from Chicago, off-label use was lowest for antibiotics and maximum for gastrointestinal medications [6]. In Dutch Intensive care units, most common drug used off-label was caffeine [7]. In another study from various European nations, most common off-label drugs were paracetamol and ibuprofen [8]. In an Australian study, morphine was among commonest off-label drugs used in NICU [9]. In our study, most common off-label medications were antibiotics and anti-epileptics, similar to another study from India in pediatric age group [3].

Differences in definition of off-label use, different licensing policies or practices and difference in drugs included in audit may account for the wide range reported

TABLE I *OFF-LABEL DRUGS PRESCRIBED IN NICU

Off -label for age	Ciprofloxacin, Piperacillin-tazobactum, Meropenem, Cefaparazone, Phenobarbitonc, Phenytoin, Lorazepam, Paracetamol, Ranitidine, Domperidone, Metaclopromide, Sildenafil, Hydrocortisone, Filgastrium, Pancuronium, Mercurochrome ,Ciprofloxcin and Gatifloxacin eye drops
Off-label for dose	Ciprofloxacin, Piperacillin-tazobactum, Amikacin, Vancomycin, Meropenem, Paracetamol, Ranitidine, Domperidone
Off-label for duration	Vancomycin, Topical eye drops, Theophylline
Off-label for frequency	Ciprofloxacin, Piperacillin-tazobactum, Amikacin, Vancomycin, Meropenem, Cefotaxime, Fluconazole Kloxacillin, Phenobarbitone, Ranitidine
Off-label for rate	Vancoycin, Domperidone
Off-label for route	Frusemide, Varicella Zoster Immunoglobulin
Off-label for indication	Paracetamol, Budesunide nebulization, Ranitidine, Vitamin A

** All these medicines are licensed for pediatric use.*

TABLE II CATEGORIES OF VARIOUS MEDICINES USED OFF-LABEL

Drug category	*Dose*	*Duration*	*Frequency*	*Indication*	*Route*	*Rate*	*Age (hr)*	*No. of Off-label drugs*	*Total number of medications*
Anti-infective	55	6	46	2	1	1	125	188	295
Anticonvulsant	-	-	1	-	-	-	42	42	59
Circulatory	-	-	-	1	1	-	17	18	42
Pulmonology	-	3	-	-	-	-	3	7	121
Gastrointestinal	4	-	1	1	-	-	7	9	13
Immune-modulator	-	-	-	1	-	-	2	3	3
Sedative and Paralytic	-	-	-	-	-	-	2	2	11
Pain	2	-	-	4	-	-	4	4	4
Topical	-	3	1	-	-	-	10	11	15
Endocrinal	-	-	-	-	-	-	-	-	2
Others	-	-	-	1	-	-	1	2	3
*Total	61(10.4)	12(2)	48(8.20)	10(1.7)	2(0.34)	1(0.17)	213(36.3)	286(50.3)	568

**Figures in brackets represent percentage.*

previously. Geographical variation also exists in class of the drug being use off-label. Differences in off-label drug use in different units can be explained by type of morbidities observed in a setting. Neonatal prematurity, sepsis and birth asphyxia are most common causes of neonatal morbidity and mortality in India [10]. Therefore, high prevalence of off-label use of antibiotics and anti-epileptics is expected.

Errors in drug dose, duration and frequency are frequently avoidable if prescriptions are double-checked and revised daily with reference to body weight, postnatal age and renal functions.

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