



## EXTENT AND PATTERN OF OFF-LABEL AND UNLICENSED DRUG UTILIZATION IN NEONATAL INTENSIVE CARE UNIT IN THE TERTIARY CARE TEACHING HOSPITAL

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**ABSTRACT** **Background & Objectives:** Many drugs that are used to treat children have not undergone evaluation to assure acceptable standards for optimal dose, safety and efficacy. As a result, drugs that are used to treat children are either not licensed for use in pediatric patients (unlicensed) or prescribed outside the terms of the product license (off-label). The extent of off-label and unlicensed drug use in neonates is unknown. Hence the purpose of the study is to determine the extent and pattern of off-label and unlicensed use of drugs amongst neonates in neonatal intensive care unit of a tertiary care hospital. **Materials and Methods:** A prospective study was carried out on 69 patients admitted in a tertiary care hospital for the period of five months. Demographic data and complete prescriptions were noted in predesigned case record form. The off-label drugs were categorized by using National Formulary of India. Off-label drugs were classified in regards to their indications by using Anatomical Therapeutic Chemical Classification. The frequency was measured in terms of percentage and multiple binary logistic regressions were used for selecting confounding factors. **Results:** A total of 329 drugs were prescribed out of which 183 (55.6%) were off-label and 65 (19.8%) were unlicensed remaining 81 (24.6%) labelled drugs. Most off-label drugs were prescribed for indication of alimentary tract (93.6%) and anti-infective (38.6%). Significant confounding factors for prescription of unlicensed drugs were single diagnosis (OR 0.20, P<0.05) and hospital stay (OR 1.30, P<0.05) Common reasons for off-label prescribing were dosage 52.4% and age 23.2%. **Conclusion:** There was a high extent of utilization of off-label and unlicensed drugs. Hence, national drug regulatory authorities need to review and revise existing guidelines for safe administration of such drugs.

**KEYWORDS :** Prescription, Off-label, Unlicensed, Neonatal Intensive Care Unit

### INTRODUCTION

Newborns represent a patient population with special concerns regarding drug therapy, because prematurity and low birth weight may have a significant effect on the pharmacokinetics and pharmacodynamics of many drugs, making the administration of medicines rather delicate.<sup>1,2</sup>

Newborns can be admitted to a neonatal intensive care unit (NICU) for several reasons, including extreme prematurity or complications from delivery,<sup>3</sup> where they receive multi-professional care and are often administered medicines that do not have proof of safety and efficacy obtained from randomized clinical trials in this patient population.<sup>4</sup>

Off-label prescription is not illegal. It is not necessarily incorrect and is present in several pediatric protocols. The quality of drug therapy is not necessarily related to the licensing status of the drug. However, there are several clinical, ethical and safety factors that should be considered and there are no guidelines to assist off-label prescriptions. The decision on this type of prescription should be assessed according to clinical indication, treatment options, and risk-benefit analysis.<sup>5</sup>

Several national and international studies have been published on off-label and unlicensed drug used in different setup of pediatric patient. The result shows high magnitude of off-label and unlicensed, prescribing accounting about 17-90%.<sup>6-16</sup> There are few studies conducted on pediatric outpatient and inpatient in Indian context, however there is no data pertaining to the study conducted among the pediatric patients admitted in NICU. Hence this prospective study was conducted to assess the extent of utilization of off-label and unlicensed drugs in pediatric department of NICU at a tertiary care teaching hospital.

### MATERIAL AND METHODS

The prospective, cross section study was carried out among the pediatric patients admitted in the pediatric department of NICU at a tertiary care hospital of Gujarat Medical Education and Research Society (GMERS) medical college, Dharpur, Patan, Gujarat, India for five months.

### Inclusion And Exclusion Criteria

Neonates (age 0-28 days) who were receiving at least one drug, admission period of more than 24 hours in NICU department and those legal guardians of patients who gave written consent were included in this study. While the pediatric patients on Nutritional supplements,

intravenous fluids, vaccines, vitamin K, fluid or heparin for flushing the intravenous lines, oxygen and blood products were excluded from this study.

Demographic details (like age, gender, and weight), diagnosis, and drug prescription details (dose, route of administration, indication, frequency etc.) were entered into the database using the World Health Organization Anatomical Therapeutic Chemical (WHO-ATC) classification system. The National Formulary of India version 2016 was used as the reference for determining whether a drug's use was off-label or not.<sup>17-18</sup>

### Statistical Analysis

The categorical data were presented as proportions while the continuous variables such as age, number of drugs, number of diagnoses and stay in hospital were expressed as mean with standard deviation (SD). Risk factors for off-label prescribing were analyzed with multivariate binary logistic regression. The odds ratio (OR) with 95% confidence interval (CI) was used to determine the predictor for off-label prescribing. A probability value of less than 0.05 was considered statistically significant for all analysis. The data were analyzed using Statistical package for Social Science (SPSS) version 23 was used for statistical analysis.

### RESULTS

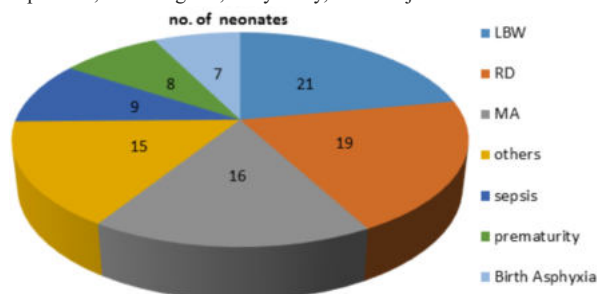
Based on the eligibility criteria a total 69 patients were enrolled in this study for period of five months. Of them, 47 (68.10%) were male and 22 (31.90%) female. In context to the age of the patients, the age ranged from 1 to 25 days with mean age of 2.43± 4.85 days. The weight of the patients ranged between 1.5 to 4 kg with mean weight of 2.27± 0.60 kg and the number of hospital stay ranged between 1 to 22 days with mean stay of 5.90± 4.43 days.

**Figure-1-** shows, the majority of patients suffering from low birth weight 21(30.4%) followed by respiratory distress 19(27.5%), MA-meconium aspiration 16(23.2%).

The most ten common off-label and unlicensed drugs were calcium gluconate 59 (32%), followed by Amikacin 35(19%), linezolid 21(11.50%), Meropenam 14 (7.70%), caffeine 12 (6.60%), cefotaxime 9 (5%), Ranitidine 9 (5%), Phenobarbitone 9 (5%), Netilmycin 6 (3.30%) and Ceftazidime 6 (3.30%)

LBW-low birth weight, RD-respiratory distress, MA- meconium

aspiration, other-oliguria, delayed cry, neonatal jaundice etc.



**Figure-1** Indications for Admission to Neonatal Intensive Care Unit

A total of 329 medications were prescribed during hospitalization, out of 329 medications, 183 (55.6%) medicine were classified as off label. The common indication of prescribing the off-label drugs was dose (52.4%) followed by age (23.2%) and frequency (22%) (Table 1).

**Table-1** Indication Of Prescribing The Off-label Drug

| Indication of prescribing off label drug | n (%)       |
|--|-------------|
| Dose                                     | 174 (52.4%) |
| Age                                      | 77 (23.2%)  |
| Frequency                                | 73 (22%)    |
| Indication                               | 04 (1.2%)   |
| Absence of pediatric information         | 04 (1.2%)   |
| Not in NFI (unlicensed drug)             | 65 (19.8%)  |

**Table -2** shows classification of drugs according Anatomical Therapeutic Classification (ATC). Of 329 drugs prescribed, 189 (57.4%) were indicated for systemic anti-infective drugs followed by alimentary tract and metabolism 78(23.7%). Off label drugs prescribed mainly for respiratory system and alimentary tract and metabolism.

A total 329 drugs prescribed were classified into their specific ATC Classification categories, highest drugs prescribed Anti-infective for systemic use, so antibiotics are more prescribe.

**Table-2** Off-label Drug Use According To ATC And Drugs

| WHO-ATC system                  | Total drug  | licensed   | Off-label drug | Unlicensed drug |
|---------------------------------|-------------|------------|----------------|-----------------|
| Anti-infective for systemic use | 189 (57.4%) | 74 (39.2%) | 73 (38.6%)     | 42 (22.2%)      |
| Nervous system                  | 28 (8.5%)   | 03 (11%)   | 13 (46%)       | 12 (43%)        |
| Alimentary tract and metabolism | 78 (23.7%)  | 04 (5.1%)  | 73 (93.6%)     | 01 (1.2%)       |
| Respiratory system              | 8 (2.4%)    | 00         | 08 (100%)      | 00              |
| Cardiovascular system           | 12 (3.6%)   | 00         | 12 (100%)      | 00              |
| Hormonal preparation            | 02 (0.6%)   | 00         | 02 (100%)      | 00              |
| Blood and blood forming agents  | 10 (3.0%)   | 00         | 00             | 10 (100%)       |
| Dermatology system              | 02 (0.6%)   | 00         | 02 (100%)      | 00              |

**Table 3** shows, Significant confounding factors for prescription of unlicensed drugs were single diagnosis (OR 0.19,  $P < 0.05$ ) and hospital stay (OR 1.30,  $P < 0.05$ ) and was not significant for off-label drugs ( $P > 0.05$ ).

**Table –3** Multivariate Binary Logistic Regression Model

| Parameter        | Predictor for off-label drug use |         | Predictor for unlicensed drug use |         |
|------------------|----------------------------------|---------|-----------------------------------|---------|
|                  | OR (95% CI)                      | P value | OR (95% CI)                       | P value |
| Age              | 791(0)                           | 1       | 1(0.89-1.13)                      | 0.87    |
| Male             | 0(0)                             | 1       | 2.39 (0.64-8.96)                  | 0.19    |
| Female           |                                  |         |                                   |         |
| Weight           | 1.9 (0.03-128)                   | 0.75    | 0.51 (0.18-1.43)                  | 0.20    |
| No. of Diagnosis | 0(0)                             | 1       | 0.19 (0.05-0.87)                  | 0.03*   |
| Single           |                                  |         |                                   |         |
| Double           |                                  |         |                                   |         |

|          |              |   |                  |       |
|----------|--------------|---|------------------|-------|
| Stay     | 1(0.66-1.53) | 1 | 1.30 (1.08-1.57) | 0.05* |
| Constant | E12          | 1 | 2.7              | 0.47  |

OR: Odd ratio, CI: Confidence interval

$p < 0.05$  = significant,  $p < 0.001$  = highly significant

**DISCUSSION**

In this prospective study, we observed that one third of the prescriptions in NICU were off-label and unlicensed. Our study has reported prevalence of off-label and unlicensed use of drugs in neonates were 55.6% and 19.8% respectively, which is in accordance with previous literature from developed countries which reported 36-93%<sup>10-16</sup> Previous studies in NICU in different countries reported almost similar findings, Africa reported by Thomas<sup>19</sup>, Dell'Aera et al<sup>20</sup> reported 12.0% and 50.5% in an Italian NICU, O'Donnell et al<sup>21</sup> reported 11% and 47% and Conroy et al<sup>22</sup> reported 9.9% and 54.7%. proportion of unlicensed and off label drugs were 12% and 51% respectively and higher finding reported by de limba costa et al<sup>23</sup> 96.4% (off-label drugs) and 66.8% (unlicensed drugs). Brazil study shows higher NICU stay 18.3± 19.4 days as compare to our study 5.90± 4.43 days. This might be due to difference in prevalence of disease across different countries.

In our study, common diagnosis observed in NICU was low birth weight, and respiratory distress. Most common drugs prescribed were antibiotics which is opposite finding of Kumar P. et al<sup>24</sup> who reported off-label use was lowest for antibiotics and maximum for gastrointestinal medication. In Dutch ICU, most common drug used off-label was caffeine.<sup>25</sup> In another study from various European nations, most common off-label drugs were paracetamol and ibuprofen.<sup>26</sup> In an Australian study, morphine was among common off-label medications.<sup>13</sup> In our study, NICU patients, amikacin, netilmycin phenobarbitone, ranitidine, cefuroxime and meropenam were the most frequently prescribed off-label drugs out of 10 most common prescribed drugs. Whereas, linezolid, caffeine & cefpodoxime were prescribed as unlicensed because of absence of pediatric information in NFI. Findings of our study differ from other study. In NICU Caffeine was prescribed 100% as unlicensed drugs in previous study. Reports of recurrent apnoea are a common problem among the preterm babies and a Cochrane review in 2010 by Hendersen-Smart et al,<sup>26</sup> demonstrated that methylxanthine was effective in reducing apnoea in premature infants. Caffeine is unlicensed in South Africa, as well as in Europe, and yet it is considered the safest of the methylxanthines for the treatment of apnoea of prematurity.<sup>27</sup> In an Australian study, morphine was among the commonest off-label drug used in NICU.

Variations in results reported worldwide may be because of difference in definition of off-label use, differences in licensing policies or practices and difference in drugs used. Even, geographical variable also exist in class of one drug being use off-label. Common category of off-label prescribing was dosage; the reason for off-label drug use was lack of pharmacokinetic data and clinical trial in children which resulted in to larger discrepancies in terms of which dose estimation, lead pediatricians to use doses based on extrapolation from adult parameter.<sup>23</sup>

The limitation of this study include that the present study was conducted only in one tertiary care teaching hospital. To generalize the result the further a multi-centric study needs to be conducted enrolling larger sample size. We did not assess the outcomes of medication use, so we cannot argue about the real risk versus benefits of their use.

**CONCLUSION**

The results shows there was a high extent of utilization of off-label and unlicensed drugs. Hence, national drug regulatory authorities need to review and revise existing guidelines for safe administration of such drugs. Greater awareness among pediatrician regarding the pattern of off-label drugs is required to be generated. More quality of data on safety and efficacy of off-label drugs to rationalize pediatric pharmacotherapy.

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