

Multi-medication in an Italian Neonatal Intensive Care Unit: focus on drugs with nephrotoxic potential

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Background. Off-label administration is common in pediatrics, especially among preterm neonates [1]. In this population, clinicians must often treat life-threatening conditions without complete knowledge of the risk-benefit profile of available treatments. The kidney is a major target of toxicity with a contribution of prematurity, diet, pharmacological treatments and many typical conditions affecting preterm newborns [2]. The aim of the study was to describe the most common patterns of drug use in an Italian Neonatal Intensive Care Unit (NICU), with specific focus on drugs with known renal side effects.

Methods. The study involved preterm neonates admitted to NICU of Sant'Orsola-Malpighi Hospital (Bologna, Northern Italy), born between 01/01/2009 and 31/12/2011. Medical records of each neonate weighing <1,500 g were collected and analyzed to describe drug use and patterns. The analysis focused on protein intake and therapeutics with potential renal side effects, either because of their well-known nephrotoxicity (i.e. amikacin) and their interaction with renal developmental factors (e.g. furosemide) [3]. The study was approved by relevant Ethical Committee.

Results. Data on 159 neonates were recorded. Antibacterial (95%) and antifungal (68%) agents are among the most frequently prescribed drugs for prevention and treatment of recurrent infections. Among antibacterials, ampicillin was the preferred antibacterial agent (95%) as monotherapy, whereas ampicillin+amikacin as combination (85%). These drugs were especially administered for the first postnatal period and on average for less than five days. Fluconazole was used in all patients receiving at least one antifungal agents (68%), whereas amphotericin B in less than 10% of cases. The majority of preterms were exposed to diuretics (54%) and 84% of them were treated with furosemide, especially for one-day therapy (52%).

Babies weighing less than 1,000 g at birth had a higher exposure rate to antibacterial agents comparing to those with birth weight between 1,000 and 1,500 g (100% vs. 91%) and also a longer duration of therapy (48 days on average vs. 14 days on average). The difference between these patients was even greater for antifungal drug exposure (93% vs. 49%) and diuretics (84% vs. 32%). Concerning the amount of daily protein intake administered with the parenteral nutrition the average daily dose was similar between groups (2.4 g/kg vs. 2.1 g/kg) but patients weighing less than 1,000 g at birth received proteins for a period twofold longer than patients weighing more than 1,000 g at birth (35 days vs. 17 days).

Conclusion. Antibacterials and antifungals were widely used in NICU especially for the prevention of infections. Despite the high exposure rate of drugs with nephrotoxic potential, their use was mainly for short-term periods, which mitigates the risk of renal failure occurrence. Extremely low birth weight infants (< 1,000 g at birth) had a higher prevalence of exposure to the selected drugs and also a greater duration of therapy compared to other neonates. Results of this study warrant a prospective investigation on actual drug-induced renal injury in NICUs, in order to improve clinical knowledge and safe use of drugs in this population.

1. Guideline on the investigation of medicinal products in the term and preterm neonate. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) and Paediatric Committee (PDCO), 2009.
2. The interplay between drugs and the kidney in premature neonates. Schreuder MF, Bueters RR, Allegaert K. *Pediatr Nephrol.* 2014;29:2083–91.
3. Drug-Induced Renal Damage in Preterm Neonates: State of the Art and Methods for Early Detection. Girardi A, Raschi E, Galletti S, Poluzzi E, Faldella G, Allegaert K, De Ponti F. *Drug Saf.* 2015 Apr 12, doi 10.1007/s40264-015-0288-6.