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Review

Off-label drug in the newborn

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Proceedings

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Abstract

The lack of specific drugs and labelling recommendations for the neonatal population is a long-standing problem throughout the world. With the introduction of the Paediatric Regulation in 2007, in Europe tangible steps have been made to increase clinical research in children, but only a limited number of clinical trials included neonates that remain therapeutic orphans. This leads to a widespread use of medicines outside the terms indicated in the product license (off-label as regards dose, route of administration, indication, age group) or in an unlicensed manner (formulations modified, extemporaneous preparations, imported medicines, chemicals used as drugs). This use, often made on the basis of a consolidated clinical experience in absence of other authorized options, does not imply that a drug is contraindicated or disapproved, but simply means that insufficient data are available to grant approval status and the risks and benefits of using a drug in a particular situation have not been examined. Given the importance that neonatal population not be denied of drugs that are clearly beneficial, an updated overview of the worldwide situation of off-label and unlicensed drug use in the newborn will be presented, by analyzing also the impact of recent legislative initiatives and the well recognized problems (increased risk of ineffective or toxic treatments, adverse drug reactions and medication errors).

Keywords

Newborn, medicines, off-label use.

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Introduction

Despite the history of catastrophic adverse events derived from inadequate study of drugs prior to their widespread use [1-3] and the need for clinical studies in the neonatal population has been identified as a high priority [4, 5], drug therapy in neonates remains characterized by a lack of systematic clinical testing and limited prescribing information [6]. This leads to a widespread use of medicines outside the terms indicated in the product license (off-label) or without a marketing authorization (unlicensed), as demonstrated by different studies performed in Neonatal Intensive Care Units (NICUs) [7-13]. This kind of use is not contraindicated and has to be considered necessary when there is no other option, but could expose the neonate to adjunctive risks in absence of adequate information about safety [14, 15].

In this article an updated overview of the worldwide situation of off-label and unlicensed drug use in the neonatal population will be presented, by analyzing also the impact of recent initiatives by FDA and EMA on neonatal studies and labelling.

What is known about off-label/unlicensed drug use in the newborn

In the last years, some encouraging initiatives have been adopted with the aim to reduce the off-label use of medicines in the paediatric population. However, while as regards children an increase in registered clinical trials and drugs approved has been observed [16, 17], little has changed as regards to the labelling of drugs prescribed to neonates, that continue to be considered therapeutic orphans. This condition is understandable because few therapeutic indications are unique for this patient population and the number of drugs required is relatively small. So, there is very little incentive for pharmaceutical companies to develop drugs and dosing guidelines for neonatal population, since the necessary studies would be expensive to carry out. Difficulties in developing formulations appropriate for neonates are also of concern to drug companies. In addition, the reluctance of parents to give permission to allow their children to be research subjects, practical difficulties in carrying out clinical trials and the lack of adequate research funding could explain why medicines have not been adequately studied in neonates [18].

The lack of approval for neonatal use does not imply a medicine is contraindicated or disapproved: it simply means that insufficient data are available to grant approval status and the risks or benefits of using a drug in a particular situation have not been examined. This creates an ethical dilemma for the clinician that has the option of either depriving the neonate of potential therapeutic benefits or using a drug despite disclaimers and paediatric inexperience. However, understanding the distinction between the lack of approval for a particular use or dosing regimen versus explicit warnings or contraindications is essential: who administer drugs to neonates often prescribe outside the terms indicated in the product license (off-label use as regards dose, age group, route of administration, different indication) or in an unlicensed manner (formulations modified, extemporaneous preparations, imported medicines, chemicals used as drugs) because there is no other option, often on the basis of a consolidated clinical experience [7].

In the USA, policy changes resulted in an increased number of drug studies involving children [19], following the creation of an extensive Paediatric Pharmacology Research Unit Network and the promulgation of new FDA regulations comprising financial incentives and legal obligations to evaluate new and older paediatric medicines [20-22]. Paediatric research grew as a result of financial incentives for the pharmaceutical industry and more than 500 paediatric labelling changes occurred [16, 23]. However, off-label use of drugs remained a large and complex issue in preterm and full-term neonates and in 2012 the FDA Safety and Innovation Act was approved to advance neonatal drug studies [24].

In Europe, a Network for Drug Investigation in Children has been established and a guidance has been issued in 1999 to encourage a common and scientifically advanced methodology for paediatric research [25], but no significant difference in the situation was initially observed [26-28]. Afterwards, there have been tangible steps to increase and expand therapeutic research in children. In June 2006, the European Commission introduced the Paediatric Regulation n. 1901, came into force on 26 January 2007, aimed to reduce the need for off-label use in paediatric patients and to improve the information available: this regulation enforces companies to study medicines in the paediatric

population, to report experimental research results and to develop age-appropriate formulations [29]. The central instrument of this Regulation is the Paediatric Investigation Plan (PIP) or a waiver, approved by the Paediatric Committee established within the European Medicines Agency (EMA): since July 2008, a PIP or a waiver is necessary to validate a marketing application for medicines not authorized in the EU and since January 2009 this also applies to submissions of new indications, routes or formulations for authorized products. The aim of a PIP is to obtain relevant data through clinical trials without subjecting paediatric population to unnecessary trials to support marketing authorization, while a waiver is granted if a product results potentially unsafe or uneffective. Some positive signs have been reported three years after the introduction of the Paediatric Regulation with an increase in the number of registered clinical trials, but only 26% included the neonatal population [5]. Most of the paediatric developments regards areas important for adults such as cardiovascular and infectious diseases, oncology, endocrinology [17]. 26 drug substances obtained an agreed PIP already approved (for example furosemide, midazolam, voriconazole, esomeprazole) or to be completed within some years (for example paracetamol, budesonide, meropenem, sildenafil), but only one-quarter of PIPs address neonates [5]. In addition, a priority list of drugs requiring data in the different paediatric age group, updated every year, was established by EMA [30]. Finally, some collaborative projects were funded by the EU in the co-operative programme of FP7: TINN and TINN2 (Treat Infections in Neonates) projects to evaluate anti-infective agents included in the EMA priority list (ciprofloxacin, fluconazole and azithromycin); GRIP (Global Research in Paediatrics), a consortium of paediatric research and training in paediatric pharmacology [31].

In Italy, following the European Paediatric Regulation two new laws have been published in the Gazzetta Ufficiale [32, 33] to favour authorization of medicines for paediatric population subsets, but in the first three years of application neonatal trials were only 1% among all therapeutic areas of application [34]. Recently, on May 2014, a communication campaign entitled "Drugs and paediatrics" was issued by AIFA [35]. Moreover, since 2010 the Working Group Paediatrics of AIFA prepared a list of medicines used in an off-label manner, but considered consolidated and with a scientific evidence [36].

Despite these encouraging initiatives and the sixfold increase observed in the number of neonatal drug trials in the last years [37], the study of products specific for the neonatal population resulted in very few labelling changes, therefore most of the exposure to drugs remains off-label for neonates.

In an interesting paper published at the beginning of 2014 [38] the authors tried to quantify progress made in neonatal studies and neonatal information in product labelling as a result of recent legislation. By reviewing FDA databases between 1997 and 2010, 28 drugs examined in 41 different studies included also neonates and lead to 24 related labelling changes (6% on a total of 406 paediatric labelling changes made during the study period), while 4 of the products studied in neonates did not obtain a labelling change (bivalirudin and ophthalmic ciprofloxacin, ofloxacin and gatifloxacin). Among these 24 labelling changes, only 11 (46%) implied an approval for use in neonates and comprised 4 medicines for human immunodeficiency virus (didanosine, stavudine, lopinavir/ritonavir, nevirapine), 3 for anesthesia (sevoflurane, remifentanil hydrochloride, rocuronium bromide) and 4 for other conditions (famotidine, fenoldopam, linezolid, plasma volume substitute). The remaining 13 labelling changes (54%), comprising drugs such as acetaminophen IV, linezolid for CNS infections, caspofungin, nitric oxide and gastroesophageal reflux drugs, reported the statement "safety and effectiveness have not been established". With the exception of nitric oxide and some gastroesophageal reflux drugs, the number of neonates enrolled in the studies was relatively small. From 2005 to 2010, the authors assembled a cohort of neonates obtained from an administrative database (all infants cared by the Pediatrix Medical Group) to determine the exposure to the 28 drugs studied in neonates. Interestingly, of the 11 drugs with a neonatal indication 7 were never used in the neonatal population and the other 4 drugs were used infrequently.

After the introduction of the European Paediatric Regulation, some authors [39] hypothesized a reduction in paediatric off-label prescriptions and evaluated the impact of the EU legislation in force for 4 years on the prevalence and frequence of such prescribing in three paediatric wards, comprised a NICU, in Finland: for this purpose, the prescriptions collected in 2001 were reviewed in 2011 in each of the three wards during the same 2-week period. Surprisingly, in 2011 the proportion of patients receiving at least one off-label/unlicensed

prescription resulted significantly higher (79% vs 58%, $p < 0.001$): this could not have been explained by differences in the diagnoses and conditions, similar and typical for patients usually treated in the three wards studied. As regards newborns, in 2011 all treated patients received at least an off-label/unlicensed medicine and significantly more prescriptions were off-label in 2011 than in 2001 (51% vs 22%, $p < 0.001$), probably related to an increase in drug use within NICUs (in 2001 the median number of prescriptions for each newborn was 2 compared to 9 in 2011). The medicines most commonly used in an off-label manner in 2011 were 2 analgesics, paracetamol and fentanyl, whose rate of prescription increased in the 10-year period. Finally, the authors compared the medicines prescribed within the three studied wards to the WHO List of essential medicines for children: half the 20 most commonly prescribed medicines resulted in the WHO List, 2 unlicensed (caffeine, thiopental) and 8 off-label. These data seem to indicate that the recent European legislation had only a minor impact on the authorizing status of medicines commonly used in paediatric patients, particularly neonates, even if the reasons for an off-label prescription sometimes changed during the 10-year period (for example, some new formulations were feasible in the last years).

Other authors [40] investigated the impact of the European Paediatric Regulation on medicines used off-label in the paediatric population by extracting information from the national Danish database throughout a whole year (November 2011-October 2012). Moreover, it has been evaluated whether drug substances had a PIP. Thirteen percent of the 100 most prescribed medicines were used off-label: it has been confirmed the frequent off-label use of carbapenems, proton pump inhibitors, some corticosteroids (triamcinolone, dexamethasone) and paracetamol in preterm newborns. Only 5 drugs had a PIP (cyclosporin, posaconazole, melatonin, testosterone and golimumab) and neonates were included in one-third of PIPs.

Garazzino et al. [41] analyzed new antibiotics for paediatric use by reviewing a decade of regulatory trials submitted to EMA from 2000, before and after the introduction of the European Paediatric Regulation. For the 11 newly approved antibiotics, 31 clinical trials enrolling also children were identified in Europe, but many of these trials did not provide a neonatal subset analysis. Among paediatric-specific studies, only 2 focused on neonates.

This minor impact of the European Paediatric Regulation on the authorizing status of medicines for newborns also emerges by the analysis of the literature, as reported in **Tab. 1**. In fact, if we compare articles published before [42-48] and after the new legislation [8-13, 39, 49-54], no significant differences either in the number of off-label prescriptions or in the percentage of neonates receiving an off-label prescription have been observed: up to 80% of patients admitted to NICUs continue to receive at least one off-label or unlicensed drug prescription and the percentage of these kind of prescriptions ranges between 34 and 87%.

Consequences

Off-label and unlicensed drug use in the newborn leads to well-recognized problems, such as lack of adequate prescribing information and suitable formulations, increased risk of adverse drug reactions (ADRs) and medication errors [14]. A document focusing on adverse events and off-label use in children has been released by EMEA in 2004 [55] and more recently a European survey concluded that adverse events are more serious and frequent when off-label/unlicensed medicines are used [56].

Firstly, the off-label and unlicensed use of medicines has been associated with an increased risk of ADRs [15, 57] in a vulnerable patient population where the incidence of ADRs is high [58, 59]: this association derives from pharmacokinetic data insufficient to support any claim about safety and the risk/benefit balance of a pharmacological treatment in a neonate to be considered continuously changeable and periodically re-evaluated. Moreover, polypharmacy (often involving drugs not adequately tested in newborns) is a common practice in NICUs and this situation obviously increases the risk of developing ADRs [60]. In addition, the presence of preservatives and other excipients could constitute problems for neonates: some authors [6] reported that in the Netherlands about half of the oral liquid preparations and 7% of the parenteral formulations contain potentially harmful excipients. The existence of an association between an off-label/unlicensed drug use and a higher risk of developing serious ADRs in the neonatal population has been reported by some authors [43, 61, 62] and underlined in a literature analysis, where the percentage of such prescriptions involved in the occurrence of ADRs in paediatric patients, comprised neonates, ranged between 23 and 60% [7].

Table 1. Summary of European studies reporting off-label/unlicensed (OL/UL) drug use in newborns.

Country	Year	Study period	Number of patients	Total number of prescriptions	Number of OL/UL prescriptions (%)	Patients receiving an OL/UL prescription (%)
UK [42]	1999	13 weeks	70	455	298 (65%)	90%
UK [43]	1999	13 weeks	100	323	178 (55%)	n.i.
France [44]	2000	2 months	40	257	187 (73%)	n.i.
Netherlands [45]	2001	5 weeks	66	621	468 (76%)	n.i.
Spain [46]	2005	3 months	48	236	148 (63%)	n.i.
Switzerland [47]	2006	6 months	11	94	44 (47%)	100%
Italy [48]	2007	2 months	34	176	110 (63%)	n.i.
Germany [49]	2009	3 months	81	748	384 (52%)	n.i.
Finland [50]	2009	2 weeks	37	155	94 (60%)	79%
Germany [9]	2010	11 months	183	1,978	1,226 (62%)	70%
Italy [8]	2010	1 month	38	88	47 (53%)	n.i.
Italy, Greece, UK [52]	2010	2 weeks	110	290	218 (75%)	97%
France [51]	2011	4 months	65	265	122 (46%)	71%
Estonia [10]	2011	6 months	490	1,981	1,719 (87%)	98%
Turkey [11]	2012	1 day	464	1,315	288 (62%)	n.i.
Sweden [53]	2012	4 days	476	1,875	868 (64%)	n.i.
Croatia [54]	2012	12 days	68	187	63 (34%)	40%
Italy [12]	2014	1 month	126	483	254 (53%)	n.i.
Ireland [13]	2014	2 months	110	900	n.i.	75%
Finland [39]	2014	2 weeks	27	308	234 (76%)	100%

n.i.: not indicated.

Secondly, this kind of use has been associated with an increased risk of medication errors [14]. Neonates are highly vulnerable to medication errors, resulting up to 8 times greater in NICUs than in other departments [63]. The major potential for medication errors in the neonatal population derives from polypharmacy, the absence of evidence on pharmacotherapy and the lack of neonate-specific formulations [64]. Formulations commonly used are not initially developed for this patient population and risks related to the need in adjusting doses, manipulating the original formulation and using extemporaneous preparations should be taken into account [14, 65]. As a result of the limited range of licensed medicines in appropriate dosage forms and the need for weight-based dose prescribing in neonates, more calculations and dilutions are necessary compared with those required in adults, leading to an increased number of opportunities for errors [66]. In a prospective study performed in two different medical centers, Kaushal et al. [67] reported 616 medication errors, with a rate significantly higher in the NICU setting. This trend has been further confirmed in a systematic review on medication errors in neonates, where dose errors resulted the most common type of error [66].

Finally, inadequate dosage information may result into toxic effects (over-dosing) but also ineffective treatments (due to under-dosages) [68]. During the 1980s-1990s dexamethasone was widely used to prevent chronic lung disease and to facilitate weaning from ventilator support at doses extrapolated from older patients, leading to impaired neurological development [69]. Similarly, the "gray baby syndrome" derived from dosages of chloramphenicol causing an accumulation of the drug [70]. Instead, fluconazole doses resulted therapeutically inadequate for neonates of less than

30 weeks' gestational age affected by systemic candidiasis [71].

Conclusions

Drug therapy in neonates is complicated by limited clinical testing and prescribing information for this patient population and the lack of specific drugs and labelling recommendations for the neonatal population is a long-standing problem throughout the world.

The introduction of the European Paediatric Regulation increased clinical research in children, but only a limited number of clinical trials included neonates, despite the need for clinical trials in preterm and tern newborns has been identified by EMA as a high priority [4, 5]. Undoubtedly, some encouraging steps have been made, as demonstrated by the availability of some new formulations for neonates in the last years. However, the limitations of this legislation have been underlined in relation to neonatal trials [72] because the potential profit for the pharmaceutical industry from studying medicines in neonates remains minimal. As reported by some authors [39-41] and also from the analysis of the literature, little progress has been observed on the authorizing status of medicines for newborns since the first study was published in 1999: this means that the EU Paediatric Regulation entered into force in January 2007 had only minor impact on the off-label prescriptions of medicines commonly used in neonates and infants. Perhaps, the 6-year period may be too short for significant changes particularly as regards preterm newborns, a patient population where the rate of survival dramatically increased in the last years and polypharmacy is frequent. Otherwise, the Paediatric regulation may be too weak to meet the clinical needs.

Therefore neonates, who represent the most vulnerable the paediatric subpopulation, remain a group of patients with a limited access to evidence-based therapy. This leads to an increased risk of ADRs and medication errors [14] and to the great variability in drug use observed both within and between different countries in absence of guidelines [73]. Instead, medicines prescribed for neonates should be used according to licensed indications whenever possible, to ensure on one hand that this patient population should not be exposed to unnecessary risks and on the other hand not be denied of drugs that are clearly beneficial. Only a strong collaboration among all those dealing with drug use in neonates as well as a harmonization of interventions will ensure that neonates do not remain therapeutic orphans.

Declaration of interest

The Author declares that there is no conflict of interest.

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