

Unlicensed and Off-Label Drug Use in an Australian Neonatal Intensive Care Unit

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ABSTRACT. *Objectives.* To determine the extent of unlicensed and off-label drugs prescribed in the level 3 neonatal intensive care unit (NICU) at the Royal Women's Hospital, Melbourne, Australia.

Methods. A prospective cohort study was conducted of all infants who were admitted to the NICU during a 10-week period. Each drug prescribed was evaluated in relation to the licensed approved uses to determine whether the drug was administered in a licensed manner or was unlicensed or used in an off-label manner.

Results. There were a total of 101 admissions involving 97 infants. A total of 1442 prescriptions were administered; 42% were licensed, 11% were unlicensed, and 47% were off-label. Twenty-one percent were off-label for 2 or more reasons. Eighty percent of infants received either an unlicensed or an off-label prescription or both; this proportion rose to 93% of extremely low birth weight infants.

Conclusions. This is the largest study performed of unlicensed and off-label drug use in the NICU. This practice remains widespread despite clear recommendations to improve this undesirable situation. The attendant risks to infants and prescribers remain. It is time for legislation to be introduced to govern this area. *Pediatrics* 2002;110(5). URL: <http://www.pediatrics.org/cgi/content/full/110/5/e52>; neonates, unlicensed drugs, off-label drugs.

ABBREVIATION. NICU, neonatal intensive care unit.

In Australia it is a requirement that drugs be licensed by the Therapeutic Goods Administration. This is to ensure that they are safe, efficacious, and of good quality. Most drugs that are administered to adults have licensed approval outlining the indications for which they may be used and the doses at and the routes by which they should be administered. However, many drugs that are given to children are unlicensed. Furthermore, many licensed drugs are prescribed to children outside of their approved terms of use (ie, off-label).

Several categories of unlicensed drugs have previously been described.^{1,2} Some are made in local pharmacies (referred to as homemade products) and not by pharmaceutical companies. An example in

our neonatal intensive care unit (NICU) is 6% sodium chloride, an oral sodium supplement made at the Royal Children's Hospital, Melbourne. The modification of a licensed product renders it unlicensed. An example is spironolactone, used for the treatment of chronic lung disease of prematurity. No registered pediatric preparation of spironolactone is available in Australia. The adult tablet is crushed and reconstituted in a solution, a portion of which is then used. Occasionally, chemicals are administered to children for therapeutic reasons. Examples are chloral hydrate, used for sedation, and copper and zinc sulfate as dietary supplements. There are also novel agents available as "specials," which are used for therapeutic purposes in infants. An example is inhaled nitric oxide for the treatment of pulmonary hypertension.

Prescribing licensed drugs outside of the specified terms of approval for their use renders that use off-label. A common reason is that the indication for the drug is not approved, eg, methylxanthines for the treatment of apnea of prematurity. Neither aminophylline nor theophylline, the only commercially available methylxanthines in Australia, is approved for use in this condition (caffeine is available only as an unlicensed product in Australia).

Many frequently used drugs are not approved for use in neonates. Examples include morphine, dopamine, and dobutamine. Some registered drugs that are specifically contraindicated in neonates are used. The use of phenobarbitone, for example, is contraindicated in neonates because of concerns raised in the 1980s regarding the association between a potentially fatal metabolic acidosis and "gaspings syndrome" and benzyl alcohol,³ a preservative used in the only commercially available preparation of phenobarbitone in Australia.

Administering a drug at a dose or a frequency or by a route other than those approved renders its use off-label. An example of this type of drug use is administration of 1 mmol/mL potassium chloride solution, intended for intravenous use, given as an oral supplement. The objective of this study was to assess the extent and nature of unregistered and off-label drug use in a large NICU.

METHODS

We conducted a prospective, observational study of all prescriptions for the dynamic cohort of infants who were admitted to the NICU of the Royal Women's Hospital, Melbourne, during a 10-week period (December 3, 2001, to February 10, 2002, inclusive). This is one of the largest NICUs in Australia, admitting >450

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Received for publication Apr 29, 2002; accepted Jul 29, 2002.

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PEDIATRICS (ISSN 0031 4005). Copyright © 2002 by the American Academy of Pediatrics.

infants per year. Data collected included the gender, gestational age, birth weight, and age and weight at administration of prescription. In keeping with most (but not all) published work on this subject, prescriptions for parenteral nutrition, standard crystalloid intravenous fluids, oxygen, and drugs used in research studies were not included. All other prescriptions were compared with the *Australian Prescription Products Guide 2002* and classified as licensed, unlicensed, or off-label in keeping with previously described methods.^{1,2}

RESULTS

During the 10 weeks, there were 101 admissions of 97 infants (2 were admitted twice, and 1 was admitted 3 times). The median gestational age was 31 weeks (range: 22.7–41.4), and the median birth weight was 1560 g (range: 414–4790 g). Twenty-seven (28%) were term infants; the most common reason for admission was respiratory distress.

The total number of prescriptions was 1442, and the median number that each infant received was 7 (range: 0–132). Sixty-nine different drugs were prescribed. A total of 609 prescriptions (42%) met the approved terms of use. A total of 152 prescriptions (11%) were for unlicensed medications; the most common reason was that they were made in a local pharmacy. A total of 681 prescriptions (47%) were off-label; the most common reason was that the indication for which they were prescribed was not approved. A total of 305 prescriptions (21%) were off-label for 2 or more reasons. Seventy-eight infants (80%) received an unlicensed or off-label drug or both. This rose to 93% (23 of 25) of infants who weighed <1000 g.

Table 1 illustrates the 10 most frequently used drugs during the 10-week study period. Four appear in italics, as their use was either unlicensed or off-label. Table 2 illustrates the most frequently used unlicensed or off-label drugs.

DISCUSSION

Prompted by tragedies that affected developing fetuses (thalidomide) and newborns (chloramphenicol), drug licensing was introduced to ensure the safety and efficacy of drugs used in clinical practice. Drug trials, however, have been conducted almost exclusively in adult volunteers. The use of these drugs in children is often based on the modification of adult formulations and extrapolation of doses used in adults. This neglects important differences in pharmacokinetics between adults and children in development. A review of the 1994 Australian Monthly Index of Medical Specialties showed that >70% of

the products that it contained had no information about the use of the product in children or had a partial or general disclaimer regarding their use in children.⁴ This proportion is similar to that found on review of the Physician's Desk Reference in the United States.⁵ This illustrates that children do not have equity of access to safe, regulated drugs. Thus, drug legislation that originally was designed to protect patients and physicians against unsafe drug use has become an obstacle to making proper drugs available for a vulnerable minority of patients.

The use of unlicensed and off-label drugs in pediatrics was first raised as a matter for concern in the late 1960s in the United States.⁶ More recently, attention has been focused on the extent of unlicensed and off-label drug use in Europe. These studies have described the extent of such prescribing among inpatients on general pediatric medical and surgical wards.^{7–12} Only 1 study has described the extent of this in Australia.² Unlicensed and off-label prescribing practices also have been described in European office-based pediatric practice,¹³ primary care,^{14–17} and pediatric intensive care.¹⁸ Five European studies have described such prescribing in neonates.^{7,8,19–21} One study showed an increased incidence of adverse drug reactions associated with the use of unlicensed and off-label medications compared with licensed medications in children on pediatric wards, including a NICU.²¹ One other study showed an increased number of adverse drug reactions associated with drugs used outside of the terms of their product license in pediatric intensive care.²²

The proportion of unlicensed and off-label drugs used in our study (11% and 47%) is similar to that described in France by Avenel et al¹⁹ (10% and 62%) and in the United Kingdom by Conroy et al²⁰ (10% and 54.7%) and Turner et al²¹ (55% combined). The proportions are different to those found by 't Jong et al^{7,8} in the Netherlands (62% and 14%); this is explained by the extensive use of medications modified by and formulations manufactured by hospital pharmacies in that country. We found that in Australia, as in the United Kingdom, the incidence of unlicensed and off-label prescribing in NICUs is greater than among patients on general medical and surgical pediatric wards² (16% combined). In our study, this is largely accounted for by the frequent use of drugs (eg, morphine, methylxanthines, inotropics), which are not approved for use in newborns. The frequency of use of these drugs underlines their fundamental importance in the care of the sick newborn; the lack of licensed alternatives suggests that these are the drugs that most urgently require labeling.

The reasons traditionally given for the lack of proper testing of drugs in children has been that such trials are not economically viable for the small number of prescriptions that will be used and that consent for such trials is difficult to obtain.²³ Concerns have also been raised about whether pharmaceutical trials are ethical in infants. The current situation—that drugs that have not been formally evaluated in children are in widespread use—is more unethical than undertaking proper studies to clarify whether these agents are safe and efficacious.

TABLE 1. The 10 Most Frequently Used Drugs in the NICU

Medication*	Number	Percentage
Gentamicin	204	14.1
<i>Morphine</i>	119	8.3
Vancomycin	110	7.6
Benzylopenicillin	98	6.8
<i>Theophylline</i>	81	5.6
<i>Aminophylline</i>	79	5.5
Frusamide	69	4.8
Vitamin K	45	3.1
<i>6% Sodium chloride</i>	41	2.8
Phosphate	38	2.6

* Italics indicate unlicensed or off-label use.

TABLE 2. The 10 Most Frequently Used Unlicensed or Off-Label Drugs

Drug	No. (%) of Total Prescriptions	Reason(s) for Unlicensed/ Off-Label Status
Morphine	119 (8.3)	Off-label: "safety and effect in neonates have not been established"
Theophylline	81 (5.6)	Off-label: not indicated for prevention or treatment of apnea of prematurity
Aminophylline	79 (5.5)	Off-label: not indicated for prevention or treatment of apnea of prematurity
6% Sodium chloride Phosphate	41 (2.8)	Unlicensed: "homemade" product
	41 (2.8)	Off-label: not indicated for prevention or treatment of osteopenia of prematurity
Dobutamine	34 (2.4)	Off-label: not indicated for treatment of hypotension in neonates
Paracetamol	30 (2.1)	Off-label: "administration to infants under 1 mo is not recommended"
Spironolactone	21 (1.5)	Unlicensed: modified licensed product
Dopamine	21 (1.5)	Off-label: not indicated for treatment of hypotension in neonates
Phenobarbitone	21 (1.5)	Off-label: "use of this preparation . . . is not recommended in neonates"

Concerns have been raised regarding prescriber liability in the event of adverse outcomes associated with unlicensed or off-label drug prescription.^{2,7,20,24} A recent statement from the American Academy of Pediatrics²⁵ said that off-label prescribing does not necessarily constitute negligent practice; on the contrary, the practice of medicine may require the off-label use of drugs to provide the most appropriate treatment for a patient. Although this is the case, uncertainty still clouds the issue.

In 1997, the US Food and Drug Administration Modernization and Accountability Act introduced legislation to ensure that new drugs submitted for approval contained information and recommendations regarding their use in children unless the drug is specifically not intended for use in the pediatric age group. The "rewards" for conducting research in children include extension of the traditional period of patent and intellectual property rights to the formulation to increase financial return on the drug.^{23,24} Since the institution of such legislation, approximately 400 trials have been undertaken.⁴

The European Commission invited submissions from clinicians, pharmacists, the pharmaceutical industry, and other interested parties for draft legislation regarding the proper licensing/registration of drugs used in children in the European Union.²³

In 1997, the report of the Working Party for Medicines in Children of the Australian Drug Evaluation Committee was issued.³ This report made a number of suggestions as to how the use of such drugs in children could be improved. Nearly 5 years later, few, if any, of these recommendations have been implemented.

CONCLUSION

This is the largest study that has specifically investigated unlicensed and off-label drug use in infants who require neonatal intensive care. It shows that, as in Europe and the United States, unlicensed and off-label drug prescribing is common in Australian NICUs and is more prevalent than in general pediatric practice. The extent of this prescribing illustrates that sick neonates do not benefit from the same

safeguards as adults. Infants of extremely low birth weight are at greatest risk because of the high number of unlicensed and off-label drugs that they receive. Prescribing unlicensed and off-label drugs puts the neonatal pediatrician at risk of liability. Unfortunately, if they are to give their patients the best care they know, they have no choice. This is most unsatisfactory for the doctors and the children.

The Department of Health, pediatricians, pharmacists, and the pharmaceutical industry have a responsibility to ensure that the children are not discriminated against and are given treatment that has been appropriately tried and tested. This is going to be expensive and difficult, but if we do not start soon, we will be in the same position in another 5 years.

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DOI: 10.1542/peds.110.5.e52

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