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Unlicensed and Off-Label Drug Use in Children

Implications for Safety

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Abstract

A significant number of children receive either an unlicensed or an off-label drug during their stay in hospital. Studies throughout Europe have shown that at least one-third of children in hospital and up to 90% of neonates in a neonatal intensive care unit receive such drug prescriptions. The medicines that are most frequently used off-label include analgesics, antibiotics and bronchodilators. The purpose of licensing a drug is to ensure safety, efficacy and quality. If a drug is used in a different manner, one would expect a greater risk of toxicity. Only three studies have commented on the risk of toxicity in relation to unlicensed or off-label drug use. Only one of these three studies prospectively tried to evaluate the risk associated with off-label and unlicensed drug prescription. This study suggested that the percentage of unlicensed and off-label drug use was significantly associated with the risk of an adverse drug reaction. Two studies looking at adverse drug reactions suggest that there is a greater risk of a severe adverse drug reaction occurring in association with the off-label or unlicensed use of drugs. One study found that five out of eight severe adverse drug reactions were associated with the off-label use of a medicine. The other study found that 14 of 19 drug prescriptions associated with 17 severe adverse drug reactions were either unlicensed or off-label. The risk of prescribing off-label and unlicensed drugs in children is not clear from the limited data available.

1. Therapeutic Orphans

The term 'therapeutic orphan' was first used by Shirkey in 1968, when he described how many medicines were not recommended for use in children on the basis that there was insufficient clinical evidence.[1] In the US, the 1962 Kefauver-Harris Amendment had been passed which meant that new drugs had to be shown to be both safe and effective in patients of all ages. This legislation was passed in response to two tragedies affecting newborn infants.

Several neonates receiving the antibiotic chloramphenicol developed the grey baby syndrome. This consisted of vomiting, abdominal distension, irregular respiration, cyanosis, cardiovascular collapse and subsequent death.[2] This was later shown to be due to impaired metabolism of chloramphenicol by neonates.[3] Reduction in the dose of chloramphenicol administered prevented the occurrence of such a syndrome.

The other drug tragedy involved neonates exposed *in utero* to thalidomide.[4] Pregnant women took the tranquillising agent, which at the time was thought to be exceptionally safe in healthy adults. Unfortunately, if taken between 27 and 32 days

gestation it resulted in phocomelia (a shortening or complete absence of the limbs) in the neonate.

In the UK the Medicines Act was passed in 1968. This requires that all medicines manufactured and marketed in the UK have been authorised by the Licensing Authority, the Medicines Control Agency. The aim of the licensing system is to ensure that medicines are examined for safety, efficacy and quality.[5] The legislation was introduced to protect children in particular.

2. The Nature of Unlicensed and Off-Label Drug Use in Children

A classification system for both unlicensed and off-label drug use was first described by Turner et al. in 1997.[6] The term 'off label' was used to describe the use of a medicine in a manner different from that recommended by the manufacturers in their product licence. This may be for one of several reasons: use in a different indication, dose, age, route or contraindication.

Examples of off-label drug use in the UK are shown in table I.

Unlicensed drug use can be classified as follows: modifications to a licensed medicine; particular formulations (usually a suspension) manufactured under a 'specials' manufacturing licence (such a medicine, although produced under the standards of good manufacturing practice, has not formally been tested in clinical trials); use of chemicals as medicines; medicines used prior to the granting of a licence and imported medicines.

Examples of unlicensed drug use in the UK are illustrated in table II.

3. The Extent of Unlicensed and Off-Label Prescribing in Children

The first study documenting the extent of unlicensed and off-label drug prescriptions was carried out in the UK in children in intensive care.[7] This study showed that 70% of children received either an unlicensed or off-label drug prescription, and almost one-third of drug prescriptions were either unlicensed or off-label. Subsequently, other studies have been carried out in the accident and emergency department setting[8] and in paediatric inpatients, all showing a significant degree of off-label

Table I. Examples of off-label drug use in the UK (reprinted from Turner et al.,[6] with permission)

Off-label for:	Examples
Indication	Dinoprostone is licensed as an oxytocic agent but is used in paediatric cardiac patients to maintain a patent ductus arteriosus
	Immunoglobulin is licensed for the treatment of idiopathic thrombocytopenic purpura and hypogammaglobulinaemia but is also used in the treatment of Kawasaki disease and epilepsy
Dose	Dalivit®[a] multivitamin drops are licensed for infants aged <1 year in a dose of 0.3ml daily. In cystic fibrosis patients 1ml daily is given
	Salbutamol (albuterol) nebules for nebulisers are licensed in adults for doses of up to 40mg daily. In practice older children may receive up to 60mg daily
Age	Diazepam rectal solution is not licensed for children aged <1 year[b]
	Fluticasone inhalers are not recommended under the age of 4 years[b]
	Amiloride tablets are not recommended for use in children[b]
Route	Epinephrine injection is nebulised to treat croup
	Potassium chloride 15% injection is given orally as a potassium supplement
	Lorazepam injection is used rectally to treat status epilepticus
Contraindicated	Ciprofloxacin is not recommended in children because it has been linked to arthropathy in weight-bearing joints of immature animals
	Tetracycline is not recommended in children because it is selectively taken up in developing bones and teeth and may lead to dental staining and enamel hypoplasia

a Use of tradenames is for product identification purposes only and does not imply endorsement.

b All these drugs are used outside the licensed age range.

Table II. Examples of unlicensed drug use in the UK (reprinted from Turner et al.,[6] with permission)

Reason unlicensed	Examples
Modification to licensed medicine (e.g. extemporaneous preparation, cytotoxic reconstitution or preparation by a Central Intravenous Additive Service)	Amiodarone suspension; cyclosporin eyedrops; quinalbarbitone powders
Medicines which are licensed but the particular formulation is manufactured under a 'specials' licence	Furosemide 10 mg/ml suspension; hydralazine 12.5mg tablets; propranolol solution 5 mg/5ml
Chemicals used as medicines	Betaine powder; sodium phenylbutyrate; tobramycin powder
Novel medicines available as 'specials'	Caffeine injection; nitric oxide gas; tolazoline injection
Imported medicines	Chlorothiazide suspension (US); phenazopyridine tablets (US); taurolidine irrigation (Switzerland)

and unlicensed drug prescribing.[9-12] These studies have been carried out in several different countries (table III). Bronchodilators and analgesics were the medicines most frequently prescribed off-label in paediatric inpatients in the UK, Sweden, Germany and Italy.[9,12]

The paediatric patient group with the highest incidence of unlicensed and off-label drug prescriptions are neonates, with 90% of babies in neonatal intensive care receiving an unlicensed or off-label drug prescription and two-thirds of drug prescriptions being unlicensed or off-label.[13] Antibiotics and vitamins were the most frequently prescribed off-label medicines in neonates. There have been three studies showing that this is also a problem in the community;[14-16] the issue is not confined to children in hospital. A study in primary care in the UK showed that 11% of GP prescriptions were for unlicensed or off-label drugs.[15]

Studies involving different groups of patients in different European countries have shown that off-label drug prescribing is more common than unlicensed drug prescribing (table IV).

4. Why Prescribe Off-Label?

It is important to understand that health professionals working with children are forced into a situation whereby they have to use either unlicensed or off-label medicines to ensure that children receive appropriate treatment. Studies have shown that even new medicines which are likely to be of significant benefit to paediatric patients (for example, drugs for the treatment of HIV and diabetes mellitus) are often not licensed for use in children.[18] The medicines extensively used off-label include analgesics, antibiotics and bronchodilators. These are all essential drugs for the treatment of ill children. The purpose of licensing is to ensure that medicines are evaluated for safety, and therefore one would expect that the use of off-label or unlicensed medicines would be associated with a greater risk. Decisions regarding doses for children and the provision of formulations suitable for administration are difficult because of a lack of information and commercially available preparations.

5. Risk of Toxicity in Children

A recent systematic review and meta-analysis[19] shows that the overall incidence of adverse drug reactions (ADRs) in children in hospital is 9.5% [95% confidence interval (CI) 6.8 to 12.2%]. For paediatric outpatients the overall incidence of ADRs is significantly lower (1.7%; 95% CI 0.4 to 4.9%). Only three studies have assessed ADRs in hospitalised children in relation to medicines that are used either in an unlicensed or off-label manner.[10,20,21]

A prospective study of ADRs in a paediatric intensive care unit detected 76 ADRs in 63 patients out of a total study group of 899 patients.[20] The most frequent ADRs were skin rashes, cardiovascular changes and gastrointestinal disturbances. One-third of the ADRs reported involved the use of an off-label drug.

This study detected eight severe ADRs [hypotension (3), respiratory arrest (2), respiratory depression (2), prolonged sedation (1)] involving six different drugs (morphine, midazolam, diazepam,

Table III. Extent of unlicensed and off-label drug prescriptions in children in various countries and settings

Study	Country	Setting	Unlicensed and off-label drug prescriptions (%)	Patients receiving unlicensed and off-label drug prescriptions (%)
Turner et al. 1996[7]	UK	PICU	31	70
McKenzie et al. 1997[8]	US	A & E		34
Turner et al. 1998[9]	UK	Inpatients	25	36
Turner et al. 1999[10]	UK	Inpatients	35	48
Turner 1999[11]	Australia	Inpatients	16	36
Conroy et al. 1999[13]	UK	NICU	65	90
Wilton et al. 1999[14]	UK	Community		22
Conroy et al. 2000[12]	Europe	Inpatients	46	67
McIntyre et al. 2000[15]	UK	Community	11	
Chalumeau et al. 2000[16]	France	Community	33	56
Jong et al. 2000[17]	The Netherlands	PICU	48	92

A & E = accident and emergency; **NICU** = neonatal intensive care unit; **PICU** = paediatric intensive care unit.

labetalol, dopamine, epoprostenol). Analysis of the original data presented shows that five of these severe ADRs occurred in association with the off-label use of a medicine.

Many case reports describing ADRs in children relate to the off-label use of medicines.[22] It is, however, the relative risk (RR) associated with the unlicensed or off-label use of a medicine that is of interest to health professionals working with children. Only one study has tried to evaluate this risk objectively.[10] This study involved over 4000 drug prescriptions and more than 1000 patient admissions. A total of 157 ADRs were detected in association with 112 (3.9%) of the 2881 licensed drug prescriptions and 95 (6%) of the 1574 unlicensed or off-label drug prescriptions. Statistical analysis in this study showed different findings in association with different statistical techniques. The main statistical finding in the study was that the number of medications administered was significantly associated with the risk of an ADR (Mann-Whitney test, $p < 0.0001$; multivariate analysis RR 1.27, 95% CI 1.21 to 1.34, $p < 0.0001$).

Subsequent multivariate analysis did not show a significant relationship between the use of unlicensed and off-label drugs and the risk of an ADR (RR 1.74, 95% CI 0.89 to 3.41, $p < 0.106$). The percentage of unlicensed and off-label drug use, however, was significantly associated with the risk of an ADR (Mann-Whitney test $p < 0.0001$). This study detected 17 severe ADRs [respiratory depression (8), hypotension (4), liver failure (2), seizures (1), bleeding (1), bradycardia (1)] involving 19 drugs. 14 of the 19 drug prescriptions were either unlicensed or off-label, suggesting that there is a greater risk of a severe ADR occurring in association with the off-label or unlicensed use of drugs.

A recent study involving a novel scheme for the reporting of adverse drug reactions in children described 171 suspected ADRs involving 105 drugs in a total of 95 separate reports.[21] 24 of the 95 reports included at least one suspected drug that

Table IV. Drug prescriptions in paediatric and neonatal inpatients in different European settings

Study	Country	Patients	Unlicensed (%)	Off-label (%)
Conroy et al. 2000[12]	UK	Paediatrics	7	23
Conroy et al. 2000[12]	Sweden	Paediatrics	4	26
Conroy et al. 2000[12]	Germany	Paediatrics	4	37
Conroy et al. 2000[12]	Italy	Paediatrics	0.3	66
Conroy et al. 2000[12]	The Netherlands	Paediatrics	14	45
Conroy et al. 1999[13]	UK	Neonates	10	55

was used in an off-label manner. Unfortunately, this is likely to be an underestimate of the extent of unlicensed and off-label drug use, as the information received did not enable full evaluation of the extent of off-label drug prescriptions.

6. Conclusion

The risk of prescribing off-label and unlicensed drugs in children is not clear. Several studies have suggested that there may be a greater risk in relation to such usage. One purpose of licensing is to ensure the safety of medicines, and one would expect that the use of medicines in a non-approved way would increase the potential for drug toxicity. It is clear, however, that further research is required in this area to provide more detailed information about the relative risks of unlicensed and off-label drug prescribing to paediatric patients.

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