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Unlicensed and off-label drug use in a Swiss paediatric university hospital

A pilot study

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Summary

Background: Many medicines used in newborns, infants, children and adolescents are not licensed ("unlicensed") or are prescribed outside the terms of the marketing authorization ("off-label"). Several studies have shown that this is a common practice in various healthcare settings in the USA, Europe and Australia, but data are scarce in Switzerland.

Objectives: The aim of our prospective study was to determine the proportion of unlicensed or off-label prescriptions in paediatric patients.

Methods: This pilot study was conducted prospectively over a six month period in the department of paediatrics of a university hospital.

Results: Sixty patients aged from three days to 14 years were included in the study. A total of 483 prescriptions were written for the patients. More than half of all prescriptions (247; 51%) followed the terms of the marketing authorization. 114 (24%) were unlicensed and 122 (25%) off-label. All patients received at least one unlicensed or off-label medicine.

Conclusion: The use of unlicensed or off-label medicines to treat children was found to be common. Co-operation between the pharmaceutical industry, national regulatory authorities, clinical researchers, healthcare professionals and parents is required in order to ensure that children do not remain "therapeutic orphans".

Key words: drug; unlicensed; off-label; paediatrics, inpatients

Introduction

The licensing process of medicines aims at ensuring their safety, effectiveness and high quality. Most medicines used in adults fulfil these criteria. In contrast, a serious dilemma in paediatric drug labelling was identified more than thirty-five years ago, the so-called "therapeutic orphans" [1, 2]. As a matter of fact, many medicines used to treat children are either not licensed (frequently referred to as "unlicensed") or are prescribed outside the terms of their product license ("off-label"). A common case of unlicensed use in our country is the preparation of a hydrochlorothiazide suspension from tablets, since this suspension is not available on the market. Examples of off-label use include salbutamol metered-dose inhaler under 4 years (off-label for age), or midazolam intravenous solution administered by nasal route for acute seizure (off-label for indication and route of administration).

So far, several prospective and retrospective studies have been conducted in various healthcare contexts (general medical and surgical wards, neonatal and paediatric intensive care units) in the USA, Europe and Australia [3–10]. These studies have brought to light a high proportion of unlicensed and off-label use, reaching up to 72% of all prescriptions and 93% of all paediatric patients. Furthermore, an English study has shown that adverse drug reactions in hospitalised children were more frequently associated with unlicensed and off-label drug prescriptions than with the licensed ones (6% vs. 3.9%) [5].

Few comparable data are available in our country, with only one preliminary report of a study carried out in the neonatal and paediatric intensive care units of the Basel University Hospital [10]. Our study was therefore designed to assess the extent and nature of unlicensed and off-label drug use in the different paediatric wards of our university hospital.

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Patients and methods

This pilot study was prospectively conducted over a 6-month period (from October 2001 to March 2002) at the University Hospital CHUV and the Children's Hospital of Lausanne (HEL) (total: 100 beds). The protocol was accepted by the local Ethics Committee of the Faculty of Biology and Medicine of the University of Lausanne.

Data were collected from physicians' drug prescription sheets during 24 hours of hospitalisation for 60 randomly chosen paediatric inpatients in six different wards: 50 patients from the CHUV (neonatal, paediatric intensive care, intermediate care, medical, and surgical wards), and 10 patients from the HEL ward. The details recorded included the patient's initials, date of prescription, ward, date of birth, weight, diagnosis, and medicines (with dosage form, dose and frequency of administration, route of administration and special instructions). The patients' age was classified according to the International Conference on Harmonisation [11]: a) preterm and term newborn infants (0 to 27 days); b) infants and toddlers (28 days to 23 months); c) children (2 to 11 years); and d) adolescents (12 to 18 years). Standard intravenous replacement solutions, sodium chloride 0.9% infusions, blood products (except albumin) and oxygen were not recorded. For the different wards, the indication for use of the drugs was discussed with the responsible physician.

All prescriptions were similarly analysed to determine whether the medicines were used in a licensed or unlicensed manner. Unlicensed medicines were subdivided into three classes: 1) medicines prepared or modified by the hospital pharmacy (batch or extemporaneous preparations); 2) medicines prepared by authorized manufacturers especially for Swiss hospitals; and 3) medicines imported from a foreign country.

Licensed medicines were further classified into three classes: 1) medicines following the terms of the marketing authorization; 2) medicines used in an off-label manner as they contained no information for paediatric use; and 3) medicines licensed for paediatric use, but off-label for: a) age; b) indication and contra-indication; c) dose and frequency of administration; or d) route of administration.

The primary reference source was the Swiss Drug Compendium [12], edited by Documed Inc. and approved by Swissmedic, the Swiss Agency for Therapeutic Products. Alternative sources of information included the package insert. All parts of the medicine's monograph or package insert were screened for information regarding paediatric use.

Data were collected on a database and summarised using standard descriptive methods.

Results

Sixty patients were included in our study (31 male, 29 female). Their median age was 1.6 years (range 0.0–13.7). Eleven aged less than a month (18.3%), 20 (33.3%) aged 1–23 months, 24 (40.0%) aged 2–11 years and 5 (8.3%) were adolescents.

A total of 483 prescriptions were written for the paediatric patients corresponding to 204 different medicines. The number of prescriptions per patient ranged from 2 to 20, the median being 7.5. The 10 most frequently administered drugs were paracetamol (7%), morphine (5%), cholecalciferol (4%), amoxicillin/clavulanic acid (3%), sodium chloride (3%), mefenamic acid (3%), multivitamins (3%), heparin (3%), potassium chloride (3%), and spironolactone (2%).

Of the 483 prescriptions, 369 (76%) were licensed and 114 (24%) were unlicensed. Of the 369 licensed prescriptions, 247 (51%) followed the terms of the marketing authorisation and 122 (25%) were off-label. All patients received at least one unlicensed or off-label medicine.

The incidence of unlicensed and off-label prescriptions was higher in the paediatric intensive care unit (58%) than in any other, especially the neonatal (36%) and surgical wards (37%) (table 1).

The proportion of unlicensed and off-label prescriptions was quite similar between the different age groups (range 47–52%) (table 2). Infants and toddlers (1–23 months) received more unlicensed medicines (33%) than the other groups.

The most common reason of unlicensed pre-

Table 1

Unlicensed and off-label prescriptions in the six different paediatric wards.

	Neonatology *	Intensive Care *	Intermediate Care *	Medicine *	Surgery *	HEL **	Total
No of patients, n	10	10	10	10	10	10	60
No of prescriptions, median (range)	6.0 (3–12)	8.5 (3–20)	6.5 (4–10)	8.5 (6–13)	8.0 (5–12)	6.5 (2–12)	7.5 (2–20)
No of prescriptions, n (%)	67 (100)	106 (100)	71 (100)	91 (100)	75 (100)	73 (100)	483 (100)
Following the terms of the marketing authorisation, n (%)	43 (64)	44 (42)	36 (51)	41 (45)	47 (63)	36 (49)	247 (51)
Total Unlicensed and off-label, n (%)	24 (36)	62 (58)	35 (49)	50 (55)	28 (37)	37 (51)	236 (49)
Unlicensed, n (%)	14 (21)	28 (26)	16 (23)	15 (16)	17 (23)	24 (33)	114 (24)
Off-label, n (%)	10 (15)	34 (32)	19 (27)	35 (38)	11 (15)	13 (18)	122 (25)

* Wards from the University Hospital CHUV; ** Ward from the Children's Hospital of Lausanne (HEL)

Table 2

Unlicensed and off-label prescriptions according to age.

	0–28 days	1–23 months	2–11 years	12–18 years	Total
No of patients, n	11	20	24	5	60
No of prescriptions, median (range)	6.0 (3–20)	8.0 (2–18)	7.5 (3–13)	9 (4–12)	7.5 (2–20)
No of prescriptions, n (%)	94 (100)	166 (100)	182 (100)	41 (100)	483 (100)
Following the terms of the marketing authorisation, n (%)	50 (53)	80 (48)	97 (53)	20 (49)	247 (51)
Total Unlicensed and off-label, n (%)	44 (47)	86 (52)	85 (47)	21 (51)	236 (49)
Unlicensed, n (%)	18 (19)	55 (33)	36 (20)	5 (12)	114 (24)
Pharmacy preparations, n (%)	9 (10)	42 (25)	27 (15)	4 (10)	82 (17)
Medicines prepared for Swiss hospitals*, n (%)	4 (4)	6 (4)	9 (5)	1 (2)	20 (4)
Foreign medicines, n (%)	5 (5)	7 (4)	0 (0)	0 (0)	12 (2)
Off-label, n (%)	26 (28)	31 (19)	49 (27)	16 (39)	122 (25)
No paediatric information, n (%)	13 (14)	14 (8)	26 (14)	13 (32)	66 (14)
Age, n (%)	6 (6)	10 (6)	6 (3)	0 (0)	22 (5)
Indication & contra-indication, n (%)	0 (0)	1 (1)	4 (2)	1 (2)	6 (1)
Dose & frequency, n (%)	6 (6)	3 (2)	11 (6)	2 (5)	22 (5)
Route of administration, n (%)	1 (1)	3 (2)	2 (1)	0 (0)	6 (1)

* by authorized manufacturers

Table 3

The 10 drugs most frequently used in an unlicensed and off-label manner in the study.

Medicines	No (%)	Licence category
Morphine injection 10 mg/ml	20 (4)	Off-label (no paediatric information)
Sodium chloride injection 100 mg/ml	15 (3)	Unlicensed (medicines prepared for Swiss hospitals)
Heparin injection 50 UI/ml	13 (3)	Unlicensed (pharmacy preparation)
Spironolactone oral suspension 5 mg/ml	9 (2)	Unlicensed (pharmacy preparation)
Hydrochlorothiazide oral suspension 5 mg/ml	8 (2)	Unlicensed (pharmacy preparation)
Ondansetron injection 2 mg/ml	8 (2)	Off-label for indication, or for dose & frequency, when administered differently from the label
Captopril oral capsules for paediatric use	5 (1)	Unlicensed (pharmacy preparation)
Dopamine injection 25 mg/ml	5 (1)	Off-label (no paediatric information)
Mefenamic acid suppositories 250 mg	5 (1)	Unlicensed (pharmacy preparation)
Potassium chloride injection 7,45%	5 (1)	Off-label for route of administration, when administered through an enteral tube

scription was the administration of preparations manufactured by the pharmacy (17% of the total of prescriptions), followed by medicines sold especially to hospitals (4%) and foreign medicines (2%). The most common category of off-label use was the lack of specific paediatric information (14%). The other off-label uses were related to age (5%), dose and frequency of administration (5%), indication & contra-indication (1%), and route of administration (1%).

The ten most frequently prescribed unlicensed and off-label drugs are shown in table 3.

Discussion

This study has shown that, as in other countries, the unlicensed and off-label use of medicines in paediatric patients was frequent in our university hospital where only about half of the prescriptions followed the terms of the marketing authorisation.

After tragedies such as the sulfanilamide-related deaths in the 1930s and the birth defects associated with thalidomide in the 1960s, changes in laws and regulations were introduced for the testing of new drugs to ensure their effectiveness and safety in humans [13]. The testing of medicines has mainly benefited adults. With the exception of some therapeutic classes, such as antibiotics and vaccines, many medicines have not been tested in children for ethical and economic reasons. This problem is encountered in all countries, and Switzerland is no exception to this situation. Contrary to the understanding of some physicians, it is not illegal to prescribe unlicensed or off-label medicines, but their use should be based on scientific evidence, expert medical judgment, or the literature [14, 15]. Physicians must be aware of their responsibilities and have sufficient knowledge or experience to show that they are acting reasonably and in the best interest of their patient [14, 15].

In our study the drug use in the six wards differed. This is not astonishing as each of the wards had different subspecialties and prescribing habits. Several most commonly prescribed drugs were unlicensed (oral morphine, sodium chloride additive, diluted heparin, spironolactone suspension) or off-label (morphine injection). Unlicensed or off-label prescriptions were more frequent in the paediatric intensive care unit, which had the highest number of patients with complex therapy. In contrast, the proportion was lowest in the neonatal ward. This may imply that neonatologists are inherently conservative before administering drugs to premature and term neonates.

Among the unlicensed medicines, an important proportion consisted of in-house preparations as a result of the lack of suitable commercialised paediatric formulations. Some were batch preparations such as choral hydrate, caffeine citrate and morphine solutions. Others were extemporaneous preparations obtained by crushing the licensed tablets or opening the capsules and using the contents to prepare oral small strength capsules, solutions or suspensions. This applied particularly to cardiovascular drugs (captopril, furosemide, hydrochlorothiazide, and spironolactone). The production of paediatric preparations in hospital pharmacies is common to all European countries [16, 17]. The second category of unlicensed medicines consisted of those specially produced for hospitals by pharmaceutical companies. The third category was foreign medicines imported from European countries. For instance, oral digoxine solutions or metronidazole suspensions were imported from France, since no pharmaceutical company currently markets them in our country. The import of medicines may resolve the problem of extemporaneous preparations. However, three concerns occur with foreign medicines: 1) the different language of the package insert; 2) their availability in a public pharmacy once the patient is discharged; and 3) their reimbursement by the health insurance company.

Many licensed medicines were used in an off-label manner because information regarding paediatric use was not available. Most, such as morphine and dopamine, have been prescribed for a long time worldwide. Consequently, other sources of information from the USA, United Kingdom and Australia are used in our hospital by physicians for paediatric patients. These references sometimes recommend varying dose ranges and pose a dilemma for paediatricians when deciding on the proper treatment. Regarding the other medicines used in an off-label manner, age limitations or doses decided by the manufacturers were in contrast with the clinical reality. Thus, metered-dose inhaler of salbutamol contained dose information for children over 4 years, but there is a large experience of use in infants and toddlers. In another example, gentamicin doses in neonates were adapted from results of therapeutic drug monitoring of plasma levels and, in such a case, off-label use is an alternative to the doses described in the label [18].

The frequency of unlicensed and off-label drug prescriptions reported in the literature varies according to methods and clinical settings [3–10]. For example, Conroy et al. [6] have found 7% unlicensed and 39% off-label medicines in the paediatric medical wards of five European hospitals, and 't Jong et al. [8] have identified 28% unlicensed and 44% off-label medicines in a paediatric ward of a general hospital in the Netherlands. Finally, Lampert et al. [10] have found 10% unlicensed and 46% off-label prescriptions in the neonatal and paediatric intensive care units of the Basel University Hospital (Switzerland).

Our results should be interpreted in the light of the study's limitations. This being a pilot study, 60 patients were included and were representative of the commonest categories of hospitalised paediatric patients during the review period. Moreover, the 204 various medicines represented 75% of those most commonly ordered from the pharmacy by the six wards during the study period. We also chose to consider only 24 hours of hospitalisation in order to allow comparisons between the paediatric wards and between the age categories. Finally, we did not analyse the proportion of commercial medicines handled and modified by nurses before intravenous administration. We considered that many intravenous medicines were marketed for adults and that their dilution was a common practice. We therefore recorded only their licence category. It is important to add that, even though dilution of intravenous formulations may be commonplace in a paediatric setting, it is not without its risks to paediatric patients [19].

Being aware of the above problems and parallel to the European Agency for the Evaluation of Medicinal Products [20], the Swiss Agency for Therapeutic Products has decided on measures to improve the situation for paediatric patients [21]. Firstly, during the license revision of each medicine, information regarding paediatric use in the leaflet will be checked and a complement requested if necessary. Secondly, manufacturers who voluntary conduct a new drug development for children will obtain an additional 5-year data protection. It will be interesting to observe the consequences of these two decisions in the coming years in university hospitals and in other settings (non teaching hospitals, ambulatory practice).

In conclusion, the use of unlicensed or off-label medicines to treat children was found to be common in paediatric inpatients in a Swiss university hospital. Cooperation between the pharmaceutical industry, regulatory authorities, clinical researchers, healthcare professionals and parents is required in order to ensure that children do not remain "therapeutic orphans".

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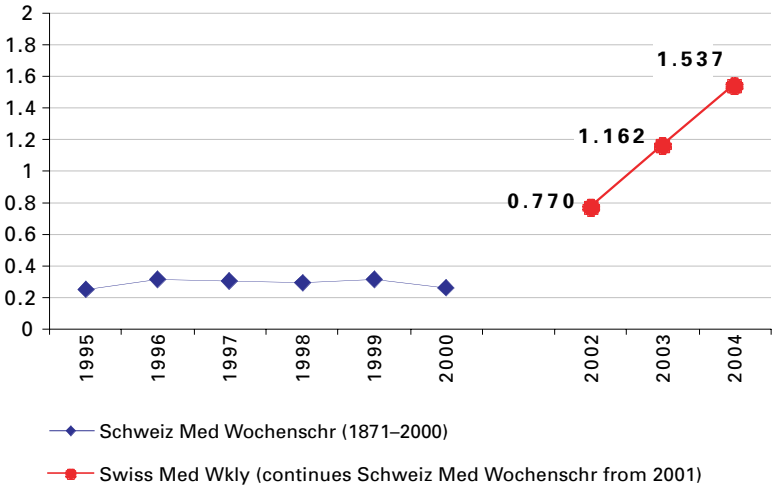

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