Unlicensed and Off-Label Medication Use in a General Pediatrics Ambulatory Hospital Unit in Israel

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Abstract

Background: Many medications used for children have not undergone evaluation to assure acceptable standards for optimal dose, safety and efficacy. As a result, the majority of children admitted to hospital wards receive medications outside the terms of their license (off-label) or medications that are not specifically licensed for use in children (unlicensed). The extent of unlicensed and off-label medication use in ambulatory children is unknown.

Objective: To determine the extent of unlicensed and off-label medication use in a general pediatrics ambulatory hospital unit in Israel.

Patients and Methods: We conducted a retrospective analysis of the medical records of 132 outpatient children treated in the General Pediatrics Ambulatory Unit of the Soroka Medical Center, Beer Sheva, in November–December 1998.

Results: The children's ages ranged from 1 month to 18 years (mean ± SD 50±58 months). Of the 222 prescriptions given to these children, one-third were unlicensed (8%) or unlabeled (26%). Different dose and age were the most common categories of off-label medication use. All 18 cases of unlicensed use were due to modification of licensed drugs (tablets were crushed to prepare suspensions). Altogether, 42% of children received medicines that were off-label and/or unlicensed.

Conclusions: More off-label than unlicensed medications were used. Further investigations are required to establish the extent of unproved drug use in both hospitalized and ambulatory pediatric patients in Israel. Recommendations recently issued by the Ministry of Health's National Council for Child Health and Pediatrics constitute a first step in the Israeli contribution to the international effort demanding testing of medications for children.

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A recent collaborative study from five European countries [1] confirmed previous reports from the United Kingdom [2–4], France [5] and Israel [6], indicating that the majority of children admitted to hospital wards receive medications outside the terms of the their license (off-label), or medications that are not specifically licensed for use in children (unlicensed). This phenomenon was born out of necessity – the absence of such prescribing would deny many children of effective treatment. While medicines prescribed for adults undergo formal evaluation of efficacy, safety and optimal dose, over the years children have remained "therapeutic orphans" [7]. This term was coined in 1968 by the American pediatrician Dr. Harry Shirkey; it referred to the potential or actual negation of drug treatment in sick children, for the reason that those medicines were not properly evaluated in children. It does not mean that those medications are contraindicated in children, but that there are insufficient data to obtain official approval for their use in children.

Recent legislation passed in the Unites States [8] encourages the pharmaceutical industry to study medications in children, and more recently a bill was introduced in the British parliament [9] aimed at strengthening the testing and licensing of medicines for children. An ad hoc committee of the National Council for Pediatrics and Child Health of the Ministry of Health in Israel has recently presented a series of recommendations relating to this issue in this country [10].

Adverse drug reactions may be a significant problem associated with the unlicensed or off-label use of medications in children [11]. Studies on unlicensed and off-label use of medicines in children have been carried out in hospital general medical and surgical pediatric wards, in pediatric intensive care units and in a neonatal intensive care unit [1–6]. On the other hand, the extent and type of unlicensed and off-label medicine use in ambulatory pediatric patients is unknown. The present study examines the unlicensed and off-label use of medicines in a pediatrics ambulatory unit in Israel.

Patients and Methods

The medical records of outpatient children treated in the General Pediatrics Ambulatory Unit of the Soroka Medical Center, Beer Sheva, during November and December 1998 were reviewed. This hospital unit is a 10 bed pediatric ambulatory service that operates 5 days a week from 8 a.m. to 3 p.m. Children with a variety of acute illnesses (such as pneumonia, soft tissue and skeletal infections, etc.) and sub-acute or chronic conditions (failure to thrive,

abdominal pain, anemia, etc.) are diagnosed and treated in the Unit.

We recorded the patients' age, weight and indications for drug therapy, as well as drug dosage, frequency, form, and route of administration. All prescribed drugs were assessed for unlicensed and off-label use. The category of unlicensed use included only modification of a licensed drug form (for instance, crushing tablets for preparing a suspension). The category of off-label use was based on published criteria [2], namely: a) prescribing a drug at a dose and frequency that differed from that described in the drug label (different dose); b) administration of a drug for an indication that was not covered by the product license (different indication); c) prescribing a drug for a patient whose age was outside the range for which the medicine is licensed (inappropriate age); and d) use of a different route of administration. As a primary reference source we used the Physician's Drug Reference [12] and the Israel Drug Compendium [13]. When a drug was not included in these sources the package insert was used as a secondary reference source.

Results

A total of 132 patients were admitted to the General Pediatrics Ambulatory Unit during the study period and they received 222 medicine prescriptions. The patients' ages ranged from 1 month to 18 years (mean ± SD 50±58 months), and 74 of the children were male (56%) and 58 female (44%). The minimal and maximal number of therapeutic courses was 1 and 6 respectively (mean ± SD 1.7±1).

A total of 63 different drugs were administered to the 132 patients. The 10 most commonly prescribed medicines are shown in Table 1. Table 2 indicates the 10 most commonly prescribed unlicensed or off-label medicines.

A total of 93 prescriptions were given for 16 different antibiotics. Six of those antibiotic prescriptions (37.5%) were off-label. Fifteen prescriptions were off-label for different dose, two (clindamycin) for inappropriate age, and two (co-trimoxasole) for different indication.

Table 1. The 10 most commonly used medications in the Pediatric Day-Hospital Unit

Drug	No. of prescriptions
Ceftriaxone	26
Ferrous carbonate	17
Amoxycillin trihydrate + clavulanic acid (Augmentin)	13
Amoxycillin trihydrate	13
Human normal immunoglobulin	12
Hydrocortisone	11
Clindamycin	9
Cephalexin monohydrate	7
Levothyroxine sodium	7
Salbutamol	7

Table 2. The 10 most commonly used unlicensed and off-label drugs in the Pediatric Day-Hospital Unit

Medication	Total no. of drug prescriptions	No. (%) of unlicensed or off-label prescriptions
Ferrous carbonate	17	14 (82.4)
Levothyroxine sodium	7	7 (100)
Cisapride	6	6 (100)
Salbutamol	7	6 (85.7)
Clindamycin	9	5 (55.6)
Amoxycillin trihydrate	13	5 (38.5)
Budesonide	4	4 (100)
Aluminium hydroxide + magnesium hydroxide	3	3 (100)
Amoxycillin trihydrate + clavulanic acid (Augmentin)	13	2 (15.4)
Captopril	2	2 (100)

Table 3. Unlicensed and off-label prescriptions out of 222 prescriptions given in the Pediatric Day-Hospital Unit

	No. of prescriptions	% of the total no. of prescriptions
Unlicensed	18	8
Off-label	58	26
Total	76	34

Table 4. Categories and frequency (%) of off-label medication use in the Pediatric Day-Hospital Unit

Category of off-label drug use	No. (%)
Different dose	40 (50)
Inappropriate age	28 (35)
Different indication	11 (13.8)
Different route of administration	1 (1.2)
Total number of off-label use	80 (100)

One-third of all prescriptions were unlicensed (8%) or off-label (26%) [Table 3]. Different dose and age were the most common categories of off-label medication use. Data on categories and extent of drugs used off-label are shown in Table 4. All 18 cases of unlicensed use in our patients were due to modification of licensed drugs (dispensing a drug in a different form, i.e., tablets crushed to prepare suspensions). Forty-two percent of the patients (56 of 132) received one or more off-label or/and unlicensed medicines.

Discussion

A previous study indicated that the extent of unlicensed and off-label medication use in a general hospital pediatric ward in Israel [6] is similar to that of five European countries [1] (about half of all prescriptions). The results of the present study revealed that many pediatric patients received medications that were not available in liquid form for oral administration, and that the pharmacy department crushed tablets to make them suitable for children. Bioavailability and stability data are often not available for

those preparations. As found also in the European survey [1], the children in our study received off-label anti-asthmatic medications. Salbutamol inhalations were prescribed for asthmatic children under the age of 2 (off-label for age); and budesonide, an inhaled steroid, was prescribed off-label for age and dose. Another example of inappropriate age is the prescription of cisapride for children with gastro-esophageal reflux, since the safety and effectiveness of this medicine in pediatric patients are not established [12,14]. Due to the emergence of penicillin-resistant pneumococcal strains, amoxycillin was prescribed at higher than approved doses (off-label for dose) [15].

The exposure of children to unlicensed and off-label medications is considerable, particularly in neonatal intensive care units (90% of babies) [4] and in pediatric general intensive care units (70%) [3]. In the present study over 42% of children treated in a general pediatric day-hospital unit received unlicensed or off-label prescriptions. Since the vast majority of sick children are treated in primary and secondary ambulatory clinics, the magnitude of the problem involving ambulatory patients is probably quite significant. The study by Lifshitz et al. [6] and the present investigation provide data on the use of unlicensed and off-label medication in a general pediatric ward and in a general pediatrics ambulatory unit in a single hospital in Israel. The pediatric population served by this hospital (approximately 50% Jews of diverse of ethnic origin, and 50% Moslem Bedouins) is different from the population in other areas of the country. Thus, the data may not accurately reflect the situation in Israel. Similar studies in a representative sample of different types of pediatric units, in hospitals and in community clinics in different geographic locations could provide data reflecting the type and extent of unlicensed and off-label medication use in the country as a whole.

There is a growing awareness that children cannot be denied the rights that adults have with regard to properly tested medications. Certainly, legislative changes in the United States [8] and the recent European guidance on the clinical investigation of medicinal products in children [16] encourage the pharmaceutical industry to conduct clinical trials in children with new medications relevant to the pediatric age group. In addition, research networks have been established in the United States and Europe to address the issue of unlicensed and off-label medications already in common use in children [17].

In this regard Israel is far behind American and European accomplishments. Nevertheless, the Israel Ministry of Health has taken the first step with a set of recommendations issued by its National Council for Pediatrics and Child Health. These recommendations aim at getting medications tested in children, which involves funding for research as well as ethical issues of clinical trials in children, and making available in Israel those pediatric formulations that are marketed abroad [10]. It remains to be seen to what extent those recommendations will be put into effect. If children in this country are not to be left behind, the Israeli regulatory agency (the Ministry of Health) and the pediatric and clinical pharmacology communities must take an active role in the international effort to promote the study of medications in children.

References

1. Conroy S, Choonara I, Impicciatore P, Mohn A, Arnell H, Rane A, Knoeppel C, Seyberth H, Pandolfini C, Raffaelli MP, Rocchi F, Bonati M, Jong G, de Hoog M, van den Anker J. Survey of unlicensed and off label drug use in paediatric wards in European countries. *Br Med J* 2000;320:79–82.
2. Turner S, Longworth A, Nunn AJ, Choonara I. Unlicensed and off label drug use in paediatric wards: prospective study. *Br Med J* 1998;316:343–5.
3. Turner S, Gill A, Nunn T, Hewitt B, Choonara I. Use "off-label" and unlicensed drugs in paediatric intensive care unit. *Lancet* 1996;347:549–50.
4. Conroy S, McIntyre J, Choonara I. Unlicensed and off-label drug use in the neonate. *Arch Dis Child Fetal Neonatal Ed* 1999;80:F142– 5.
5. Avenel S, Bomkratz A, Dassieu G, Janaud JC, Danan C. (No title available). *Arch Pediatr* 2000;7:143– 7 (Medline).
6. Lifshitz M, Gavrilov V, Gorodischer R. Unlicensed and off-label drug use in hospitalized children. *Harefuah* 1999;137:532–4 (Hebrew).
7. Shirkey H. Therapeutic orphans. *J Pediatr* 1968;72:119–20.
8. DePalma A. Regulatory and legislative issues. FDA seeks pediatric information on common drugs. http://pharmaceuticalonline.com/regulatory-articles/19980417–177.
9. Yamey G. MP introduces bill to protect children from unlicensed medicines. *Br Med J* 2000;320:208.
10. Committee for licensing medications in children. National Council for Child Health and Pediatrics, Ministry of Health, Israel. Recommendations. January 2000.
11. Turner S, Nunn AJ, Fielding K, Choonara I. Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study. *Acta Paediatr* 1999;88:965– 8.
12. Sifton DW, ed. Physicians' Desk Reference. 53rd edition. Montvale: Medical Economics Company, 1999.
13. York V, Azulay R, eds. Israel Drug Compendium. Tel Aviv: Medcom, 1995.
14. Cohen RC, O'Loughlin EV, Davidson CP, Moore DJ, Lawrence DM. Cisapride in the control of symptoms in infants with gastroesophageal reflux: a randomized, double-blind, placebo-controlled trial. *J Pediatr* 1999;134:287– 92.
15. Klein JO. Clinical implications of antibiotic resistance for management of acute otitis media. *Pediatr Infect Dis J* 1998;17:1084–9.
16. European Medicines Evaluation Agency. Note for guidance in clinical investigation of medicinal products in children. London: EMEA, 1997.
17. Bonati M, Choonara I, Hoppu K, Pons G, Seyberth H. Closing the gap in drug therapy. *Lancet* 1999;353:1625.

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