Unapproved Prescriptions in Two Pediatric Intensive Care Units in Israel

Vladimir Gavrilov, MD, PhD,¹ Matityahu Berkovitch, MD,²
Galina Ling, MD,¹ Galit Brenner-Zadda, MD,² Matityahu Lifshitz, MD,¹ and
Rafael Gorodischer, MD¹

¹Department of Pediatrics, Soroka University Medical Center, Ben-Gurion University of the Negev, Beer-Sheva, Israel, and ²Department of Pediatrics, Assaf Harofe Medical Center, Tel Aviv University, Zrifin, Israel

ABSTRACT

Background: Many medications prescribed to children worldwide have not been approved for pediatric use because the necessary clinical trials have not yet been performed. Children given these drugs have been shown to be at increased risk for adverse drug reactions.

Objective: The aim of this study was to assess the extent of unapproved (off label and/or unlicensed) use of medications in pediatric intensive care units (PICUs) in Israel.

Methods: Medications administered to patients treated in the PICUs of Soroka University Medical Center (SMC) and Assaf Harofe Medical Center (AHMC) were reviewed. Analyses were retrospective at SMC and prospective at AHMC.

Results: The records of 158 patients were included in the study—116 patients at SMC (73.4%; 62 boys, 54 girls; mean [SD] age, 38.9 [50.4] months) and 42 at AHMC (26.6%; 26 boys, 16 girls; mean [SD] age, 63.3 [69.3] months). They received a total of 123 different medications. Sedatives and antibiotics were the most frequently prescribed drug classes at SMC (15.2% and 6.5%, respectively), and antibiotics, acetaminophen, and antiasthmatic drugs were most frequently prescribed at AHMC (14.4%, 13.6%, and 6.8%, respectively). Sympathomimetic drugs, sedatives, and antibiotics were the drugs most commonly prescribed in an unlicensed or off-label manner at SMC (11.4%, 11.4%, and 6.5%, respectively); at AHMC, they were antiinfectives, sympathomimetics, antiasthmatic drugs, and acetaminophen (18.7%, 16.9%, 12.7%, 6.8%, respectively). The percentage of patients receiving unapproved medications (SMC, 93 [80.2%]; AHMC, 38 [90.5%]) and the percentage of unlicensed and off-label prescriptions (SMC, 243 [41.5%]; AHMC, 118 [41.0%], respectively) were similar between the 2 PICUs. Inappropriate age was the most common off-label category, followed by different dose, different indication, and different route.

Conclusion: The results of this study of unapproved prescriptions in 2 PICUs in Israel show a high number of such prescriptions and indicate an urgent need to investigate the use of those medications in children. (*Curr Ther Res Clin Exp.* 2003;64:734–742) Copyright © 2003 Excerpta Medica, Inc.

Key words: off-label medications, unlicensed medications, pediatric intensive care, pediatric drugs.

INTRODUCTION

Medications used in adults are approved after their efficacy, safety, and optimal dose are assessed in controlled clinical trials. In contrast, many medications prescribed to children worldwide have not been approved for pediatric use because the necessary clinical trials have not been performed. This has been shown in studies in Europe, Israel, and Australia in hospital general pediatric and surgical wards,^{1–4} ambulatory settings,^{5–7} neonatal units,^{8,9} and 2 pediatric intensive care units (PICUs), 1 in the United Kingdom¹⁰ and 1 in the Netherlands.¹¹ Children who receive unapproved medications (off label and/or unlicensed) are at increased risk for adverse drug reactions (ADRs).¹² Documentation of the types of medications prescribed outside the terms of their license is helpful not only in raising medical and public awareness of this therapeutic anomaly but also in establishing a list of priorities for medications to be studied in the pediatric population.

The extent of exposure to unapproved medications reported in PICUs in the United Kingdom¹⁰ and the Netherlands¹¹ was considerably greater than in ambulatory settings and in general pediatric hospital wards. The magnitude of this anomaly in PICUs in other countries is unknown.

The aim of this study was to assess the extent of unlicensed and off-label use of medications (unapproved medications) in PICUs in Israel.

PATIENTS AND METHODS

This report summarizes data from 2 separate studies of patients treated in the PICUs of 2 hospitals in Israel: Soroka University Medical Center (SMC) located in Beer-Sheva, and the Assaf Harofe Medical Center (AHMC) in Zrifin. Each study used a different design. Information from SMC was reviewed retrospectively, whereas data from AHMC were recorded prospectively. All medical records were reviewed for February, May, August, and November 2000 in the SMC PICU and February and May 2000 and February 2001 in the AHMC PICU.

During review of the medical records, each patient's age and body weight, and the drug indication, route of administration, dose, and formulation prescribed were recorded. All medications were reviewed in both hospitals.

Prescribed medications were assessed for unlicensed and off-label use according to published criteria.¹ Off-label use included prescription of a medication

at a dose, indication, age, or route that differed from that described on the drug label. Unlicensed use included modification of a licensed drug formulation (ie, crushing tablets for preparing a suspension) and use of medications licensed abroad but not in Israel. Primary reference sources used were the *Physicians' Desk Reference*¹³ and the *Israel Drug Compendium*.¹⁴ When a drug was not included in those sources, the package insert was consulted.

Statistical Analysis

Descriptive statistics and the Student *t* test were used for analysis of results. $P \leq 0.05$ was considered statistically significant.

RESULTS

A total of 403 patients were admitted to the PICU in the 12 months of the year 2000 at SMC, and 454 patients were admitted in the 24 months of the years 2000 and 2001 at AHMC. In both units, most patients were admitted due to trauma, infectious illness, seizure, or asthma. The records of 158 patients were included in the study—116 patients at SMC (73.4%; 62 boys, 54 girls; mean [SD] age, 38.9 [50.4] months) and 42 at AHMC (26.6%; 26 boys, 16 girls; mean [SD] age, 63.3 [69.3] months) (Table I).

In total, 874 prescriptions for 123 drugs were analyzed (SMC, 586 [67.0%]; AHMC, 288 [33.0%]). The mean (SD) number of prescriptions per patient was significantly greater at AHMC (6.9 [5.2]) than at SMC (5.0 [3.4]) ($P < 0.05$).

Table I. Characteristics and prescribing information of study patients (N = 158) at each center.

Characteristic	Soroka University Medical Center (n = 116)	Assaf Harofe Medical Center (n = 42)
Sex, no. (%)		
Boys	62 (53.4)	26 (61.9)
Girls	54 (46.6)	16 (38.1)
Age, mo		
Mean (SD)	38.9 (50.4)	63.3 (69.3)
Range	0.2–198	0.5–216
No. (%) of medications (N = 123)	100 (81.3)	82 (66.7)
No. (%) of prescriptions per patient		
Mean (SD)	5.0 (3.4)	6.9 (5.2)*
Range	1–15	1–23
No. (%) of patients receiving unapproved prescriptions (N = 131)	93 (80.2)	38 (90.5)

* $t = 2.15$; $P < 0.05$ versus Soroka University Medical Center.

Results were similar in the PICUs at SMC and AHMC with regard to the percentage of patients who received unapproved medications (93 [80.2%] vs 38 [90.5%], respectively), the percentage of prescriptions given in an unapproved manner (243 [41.5%] vs 118 [41.0%], respectively), and the percentage of off-label prescriptions (234 [39.9%] vs 118 [41.0%], respectively). Sedatives (midazolam hydrochloride and triclofos sodium) and antibiotics (cefuroxime sodium and ceftriaxone) were the most commonly used drug classes at SMC (15.2% and 6.5%, respectively), whereas antibiotics (amoxicillin/clavulanic acid and cefuroxime), acetaminophen, and antiasthmatic drugs (albuterol and ipratropium bromide) were the most frequently prescribed drug classes at AHMC (14.4%, 13.6%, and 6.8%, respectively) (Table II).

The principal clinical conditions that caused physicians to prescribe unapproved medications were restlessness and anxiety, infection, asthma, and fluid overload. The 10 medications most commonly prescribed in an off-label or unlicensed manner are shown in Table III. Sympathomimetic drugs (epinephrine hydrochloride and albuterol), sedatives (midazolam and triclofos), and an antibiotic (cefuroxime) were the classes most commonly prescribed in an unapproved fashion at SMC (11.4%, 11.4%, and 6.5%, respectively), whereas anti-infectives (amoxicillin/clavulanic acid, cefuroxime, ceftriaxone, and metronidazole hydrochloride), sympathomimetic drugs (albuterol and epinephrine), antiasthmatic drugs (ipratropium bromide and budesonide), and acetaminophen were most commonly prescribed in unapproved fashion at AHMC (18.7%, 16.9%, 12.7%, and 6.8%, respectively).

Table II. The 10 most commonly prescribed medications at each center.

Rank	Soroka University Medical Center		Assaf Harofe Medical Center	
	Medication	No. (%) of Prescriptions (n = 586)	Medication	No. (%) of Prescriptions (n = 288)
1	Midazolam	35 (6.0)	Acetaminophen	26 (9.0)
2	Furosemide	29 (4.9)	Amoxicillin/clavulanic acid	14 (4.9)
3	Triclofos*	28 (4.8)	Albuterol	11 (3.8)
4	Cefuroxime sodium	27 (4.6)	Cefuroxime sodium	10 (3.5)
5	Acetaminophen	26 (4.4)	Epinephrine hydrochloride	9 (3.1)
6	Dexamethasone		Midazolam hydrochloride	9 (3.1)
	sodium phosphate	26 (4.4)	Ipratropium bromide	9 (3.1)
7	Fentanyl	24 (4.1)	Ranitidine hydrochloride	9 (3.1)
8	Epinephrine hydrochloride	20 (3.4)	Furosemide	9 (3.1)
9	Ceftriaxone	19 (3.2)	Dexamethasone	
10	Ibuprofen	14 (2.4)	sodium phosphate	8 (2.8)

*Triclofos, a sedative-hypnotic compound, is rapidly metabolized to trichloroethanol, the active metabolite of the related medication chloral hydrate.

Table III. The 10 medications (no. [%]) most commonly prescribed off label or unlicensed at each medical center.

Rank	Soroka University Medical Center			Assaf Harofe Medical Center		
	Medication	No. (%) of Prescriptions (n = 586)	No. (%) of Unapproved Prescriptions (n = 243)	Medication	No. (%) of Prescriptions (n = 288)	No. (%) of Unapproved Prescriptions (n = 118)
1	Epinephrine hydrochloride	20 (3.4)	18 (7.4)	Albuterol	11 (3.8)	7 (5.9)
2	Midazolam hydrochloride	35 (6.0)	18 (7.4)	Epinephrine hydrochloride	9 (3.1)	9 (7.6)
3	Triclofos	28 (4.8)	18 (7.4)	Ipratropium bromide	9 (3.1)	8 (6.8)
4	Cefuroxime sodium	27 (4.6)	16 (6.6)	Acetaminophen	26 (9.0)	8 (6.8)
5	Ibuprofen	14 (2.4)	12 (4.9)	Amoxicillin/		
6	Ranitidine	12 (2.0)	12 (4.9)	clavulanic acid	14 (4.9)	8 (6.8)
7	Dexamethasone sodium phosphate	26 (4.4)	11 (4.5)	Ranitidine	9 (3.1)	7 (5.9)
8	Morphine hydrochloride	11 (1.9)	11 (4.5)	Budesonide	8 (2.8)	6 (5.1)
9	Albuterol	11 (1.9)	10 (4.1)	Metronidazole		
10	Vecuronium bromide	14 (2.4)	6 (2.5)	hydrochloride	6 (2.1)	6 (5.1)
				Ceftriaxone	7 (2.4)	4 (3.4)
				Cefuroxime sodium	10 (3.5)	4 (3.4)

In both hospitals, the most common category of off-label prescribing was inappropriate age (SMC, 98 prescriptions [41.9%]; AHMC, 51 [43.2%]). Different dose (SMC, 67 [28.6%]; AHMC, 39 [33.1%]) and different indication (SMC, 60 [25.6%]; AHMC, 44 [37.3%]) were less prevalent, and different route of administration (19 [8.1%] vs 9 [7.6%]) was the least common (Table IV).

Instances of inappropriate age were the use of morphine hydrochloride in children of all ages and the use of albuterol in children aged <2 years, as the safety and efficacy of these drugs in children of these ages have not yet been established. Examples of different dose were prescribing greater than approved doses of midazolam, triclofos, and acetaminophen. An example of different indication was the prophylactic use of antibiotics in children who had fever, but no diagnosis covered by the product license. The use of ranitidine hydrochloride for gastroduodenal ulcer prophylaxis in children with head trauma also was a case of different indication. Different route of administration was represented by the use of epinephrine by inhalation in infants with bronchiolitis or croup.

As expected, the largest number of medications prescribed off label for age-related reasons were for infants and the smallest number for adolescents. The most frequently prescribed age-related off-label medications for infants aged up to 2 years at SMC were albuterol, cefuroxime, midazolam, azithromycin, and morphine (10 [4.3%], 7 [3.0%], 7 [3.0%], 5 [2.1%], and 4 [1.7%] of all off-label prescriptions, respectively), whereas these drugs comprised ipratropium bromide, albuterol, budesonide, and metronidazole (5 [4.2%], 5 [4.2%], 3 [2.5%], and 3 [2.5%], respectively) at AHMC. Morphine was the most frequently prescribed age-related off-label medication for children aged >2 to 12 years (7 [3.0%] of all off-label prescriptions) at SMC, and captopril, budesonide, and metronidazole fell into this category (3 [2.5%], 3 [2.5%], and 1 [0.8%], respectively) at AHMC. Metronidazole was prescribed off label for age only once in this age group for an adolescent at AHMC.

Table IV. Categories and frequency of off-label prescriptions.*

Category	Soroka University Medical Center (n = 234)	Assaf Harofe Medical Center (n = 118)	Total (N = 352)
Inappropriate age, no. (%)	98 (41.9)	51 (43.2)	149 (42.3)
Different dose, no. (%)	67 (28.6)	39 (33.1)	106 (30.1)
Different indication, no. (%)	60 (25.6)	44 (37.3)	104 (29.5)
Different route of administration, no. (%)	19 (8.1)	9 (7.6)	28 (8.0)

*Some prescriptions were off label in >1 category.

There were 14 prescriptions (2.4%) for unlicensed drugs at SMC, 12 (2.4%) for use of a liquid form of ibuprofen* that is not licensed in Israel and 2 (0.3%) for modification of a licensed pharmaceutical form (tablet of propranolol dispensed as a suspension). There were no cases of unlicensed drug use at AHMC.

Although data from the hospitals are not entirely comparable due to different study designs, the combined information from both hospitals showed that 82.9% of PICU patients (131/158 children) received unapproved medications and 41.9% of prescriptions given to them (366/874) were for off-label or unlicensed use.

DISCUSSION

Variability in results between the 2 PICUs studied was expected because (1) the 2 hospitals are located in different parts of Israel and provide care to populations that differ culturally and ethnically, (2) physicians may have different prescribing habits in the 2 PICUs, and (3) data at SMC were collected retrospectively at representative months of the year whereas data at AHMC were collected prospectively and only in the winter and spring months. However, despite the different designs, results were similar in the PICUs at SMC and AHMC with regard to the percentage of patients who received unapproved medications, the percentage of medications used in an unapproved manner, the percentage of off-label prescriptions, and the frequency of off-label prescriptions by category. Those results are consistent with reports from PICUs in the United Kingdom¹⁰ and the Netherlands,¹¹ where 70% to 92% of patients were treated with at least 1 unlicensed or off-label drug. All of these data together indicate the international nature of the large magnitude of unapproved use of medications in PICUs.

Because most medications used in children have been tested only in adults, their efficacy, safety, and optimal dose in pediatric patients remains doubtful. If untoward events develop after their use, pediatricians may be liable to judiciary actions. The common practice of unapproved prescribing is based on recommendations in pediatric textbooks^{15,16} and current pediatric literature. In the conflict between prescribing medications strictly according to their product license or according to recommendations in pediatric textbooks, and the use of sound clinical judgment, pediatricians take actions that they believe are in the best interest of the patient. Still, they must keep in mind that unapproved prescribing is not supported by sufficient scientific evidence.

The clinical consequences of prescribing off-label and unlicensed medications are unclear at present. Two studies, 1 performed in a regional hospital in the United Kingdom¹² and the other in physicians' offices in France,¹⁷ suggest that ADRs are a significant problem following the use of unlicensed and off-label medications.

*Trademark: Motrin® (McNeil-PPC, Inc., Fort Washington, Pennsylvania).

A sense of urgency in studies of medications used in PICUs exists, both because of the extent of the problem and because PICUs treat the sickest children who often have life-threatening conditions.

CONCLUSION

The results of this study of unapproved prescriptions in 2 PICUs in Israel show a high number of such prescriptions, and indicate an urgent need to investigate those medications in children.

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Address correspondence to:

Rafael Gorodischer, MD
Department of Pediatrics
Soroka University Medical Center
PO Box 151
Beer-Sheva 84101
Israel
E-mail: rafaelg@bgumail.bgu.ac.il