ARTICLE

Risk of Drug Interactions among Children Accessing Drugs through Health Canada's Special Access Programme

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ABSTRACT

Objective: To evaluate if children treated with unlicensed medications obtained through Health Canada's Special Access Programme (SAP) are at risk of undetected drug interactions.

Methods: This case series reports on all ambulatory patients between 0 and 18 years of age who were treated at a mother-and-child tertiary care teaching hospital, who received an unlicensed medication through the SAP for at least 4 months, and for whom the authors had access to the community pharmacist. All potential level I, II, and III drug interactions, as determined by 2 frequently used references, were identified from the patients' files.

Results: From January 7 to June 25, 2003, 65 (90%) of the 72 eligible patients agreed to take part in the study. The subjects were receiving the following medications: cisapride (n = 25), nitisinone (n = 10), hydroxocobalamin (n = 8), cysteamine (n = 5), melatonin (n = 4), divalproex sodium (n = 4), interferon-gamma (n = 4), stiripentol (n = 2), phenylbutyrate (n = 2), or methylcobalamin (n = 1). In total, 474 (35%) of 1351 months of treatment (for 39 patients) involved an unlicensed medication known to be associated with potential drug interactions. Three of the 39 patients (8%) actually experienced an interaction: these exposures, all involving cisapride, occurred during a total of 4 months (0.8%). Only 11 (17%) of the 66 community pharmacists noted use of an unlicensed medication in the patient's file.

Conclusion: Three of the 39 patients exposed to unlicensed medications known to have potential drug interactions did in fact have an interaction (in 4 different months). Measures should be taken to decrease the risk associated with the use of unlicensed medications available through Health Canada's SAP.

Key words: pediatric population, drug interactions, Health Canada Special Access Programme, cisapride, unlicensed drugs

RÉSUMÉ

Objectif : Évaluer le risque d'interactions médicamenteuses non décelées chez les enfants qui reçoivent des médicaments non homologués obtenus par le truchement du Programme d'accès spécial (PAS) de Santé Canada.

Méthodes : On a répertorié les cas de tous les patients ambulatoires âgés de 0 à 18 ans qui ont reçu à un hôpital universitaire de soins tertiaires mère-enfant un médicament non homologué par le truchement du PAS, pendant une période d'au moins quatre mois, et pour lesquels les auteurs de cet article avaient accès à un pharmacien communautaire. Toutes les interactions médicamenteuses potentielles de grades I, II et III, telles que définies dans deux ouvrages de référence couramment utilisés, ont été déterminées à partir des dossiers médicaux des patients.

Résultats : Entre le 7 janvier et le 25 juin 2003, 65 (90 %) des 72 patients admissibles ont consenti à participer à l'étude. Les sujets recevaient les médicaments suivants : cisapride (n = 25), nitisinone (n = 10), hydroxocobalamine (n = 8), cystéamine (n = 5), mélatonine (n = 4), divalproex sodique (n = 4), interféron-gamma (n = 4), stiripentol (n = 2), phénylbutyrate (n = 2) ou méthylcobalamine (n = 1). Un médicament non homologué et associé à des interactions médicamenteuses potentielles connues a été administré pendant 474 (35 %) des 1351 mois de traitement (chez 39 patients). Une interaction médicamenteuse a été observée chez trois de ces patients (8 %), chacune impliquant le cisapride, et est survenue sur une période totale de quatre mois (0,8 %). Seulement 11 (17 %) des 66 pharmaciens communautaires ont consigné l'utilisation d'un médicament non homologué dans le dossier du patient.

Conclusion : Une interaction médicamenteuse a été observée (au cours de quatre mois différents) chez 3 des 39 patients qui ont pris un médicament non homologué associé à des interactions médicamenteuses potentielles connues. Des mesures devraient être adoptées afin de réduire le risque associé à l'emploi de médicaments non homologués qu'on peut obtenir par le truchement du PAS.

Mots clés : population pédiatrique, interactions médicamenteuses, Programme d'accès spécial de Santé Canada, cisapride, médicaments non homologués

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INTRODUCTION

Health Canada's Special Access Programme (SAP) allows Canadian physicians to prescribe medications that are not available on the Canadian market when standard therapies are ineffective, inconvenient, or not available,[1] for example, medications that have been withdrawn from the market because of their toxicity (e.g., cisapride), drugs that are not marketed in Canada (e.g., nitisinone), and those available in specific formulations in other countries but not in Canada (e.g., efavirenz in oral suspension).[2,3]

Unlicensed medications obtained through the SAP can be requested only by physicians and pharmacists practising in a hospital; community pharmacists are not allowed to request these drugs.[4] There are many reasons why physicians and pharmacists might not be aware of the use of an unlicensed medication by their patients. Patients are often followed by specialists other than the one prescribing the unlicensed medications, as well as by primary care physicians. Medications other than the unlicensed medications must be obtained at a community pharmacy, where the pharmacist may or may not be aware of unlicensed medications distributed by a hospital.[5] Such fragmentation of the patient's drug files and the number of health care professionals involved can increase the risks of drug interactions.[6-8] This makes medication reconciliation especially difficult.

Among adults, drug interaction rates of 0.4% to 6% have been reported.[6-8] However, no studies have documented the rates of drug interactions in a general pediatric population. The use of unlicensed medications has been studied in other countries, but none of these investigations has considered interactions.[2,3,9-22] The objective of the current study was to assess whether children treated with unlicensed medications obtained through Health Canada's SAP were at risk of drug interactions. In addition, there was an attempt to determine if physicians and pharmacists not involved in the prescription of or medical services associated with the unlicensed medication were aware of their patients' use of such medications.

METHODS

Ambulatory patients up to 18 years of age who were treated in a 450-bed mother-and-child tertiary care teaching hospital and who received an unlicensed medication through the SAP for at least 4 months were eligible for this case series study. Those who had stopped taking their unlicensed medication less than 6 months before recruitment but had taken it for a total of at least 4 months were also eligible. The 4-month period was set to maximize SAP drug exposure while resources were available to collect the data. Subjects were identified from a list of all ambulatory patients who had received their unlicensed medications from the hospital pharmacy department. The pharmacy department does not provide any medications to ambulatory patients other than SAP medications. Patients who did not speak English or French were excluded. Patients who received antiretroviral drugs were also excluded because of confidentiality issues. This project was approved by the institution's ethics committee.

Recruitment and data collection took place from January 7 to June 25, 2003. Parents were asked to provide consent for the researchers to contact their children's physicians and pharmacists for a telephone interview. The children's family doctors and pediatricians from outside the hospital, as well as community pharmacists, were contacted to evaluate the quality and amount of information they received with respect to the use of unlicensed medications. Specifically, the pharmacists and physicians were asked if the unlicensed medications were recorded in their patients' files.

The analysis was conducted for all periods during which the patients had used an unlicensed medication and for which the community pharmacist provided data. All level I, II, and III drug interactions listed in *Hansten and Horn's Drug Interactions Analysis and Management*[23] and *Drug Interaction Facts*[24] were considered. These ratings refer to severity, clinical risks, and quality of documentation. The 3 levels selected refer to interactions that need clinical follow-up, that may lead to severe consequences, and that are well documented. *Micromedex MD*[25] was used as a supplementary resource when no information was available about a potential interaction or when the other references had conflicting information. Interactions involving anticonvulsants were excluded because such drugs were prescribed by hospital neurologists (who prescribe interacting anticonvulsants regularly and are familiar with the management of such interactions), they are commonly used, and drug interactions are taken into account in drug treatment. For these drugs, it would have been too difficult to determine if the interaction was intentional or not.

The number of months during which a potential medication interaction took place was computed using the method of Jones and others,[26] summarized briefly here. The first day of treatment with an unlicensed medication was considered day 1. The number of consecutive 30-day periods during which the patient received the unlicensed medication was determined, and the number of those 30-day periods during which

the patient was exposed for at least 1 day to a combination of medications with known interactions with the unlicensed medication was counted.

RESULTS

During the study period, a total of 72 patients met the inclusion criteria from the list of patients receiving drugs through the SAP; the parents of 65 patients (90%) consented to participation in the study. For the other 7 patients, the parents agreed to participate by telephone but did not return the written consent form by mail, despite two reminders. The files of 63 of the patients were obtained from the pharmacists after at most 2 follow-up contacts.

The patients were receiving a variety of drugs, the most common being cisapride (n = 25) and nitisinone (n = 10) (Table 1). The patients were divided about equally between the sexes (34 [52%] boys and 31 [48%] girls). Half of the patients were no more than 20 months of age when they started to take the unlicensed medication. Twenty-four (37%) of the patients were followed only by the physician who had prescribed the unlicensed drug, and 41 (63%) were followed by at least one other physician. Most of the patients (60 [92%]) had only one community pharmacist.

Data concerning the types of physicians who prescribed the unlicensed medications and how these drugs were obtained are presented in Table 1. From the moment each patient started taking the unlicensed medication until the end of his or her participation in the study, the total duration of therapy was the equivalent of 1973 months. The mean duration of therapy (and standard deviation) with an unlicensed medication was

Table 1. Method of Obtaining Unlicensed Medications through the Special Access Programme

Variable	No. (%) of Patients	
Method		
In person	37	(57)
By mail	21	(32)
In person and by mail	7	(11)
Renewal of unlicensed medication		
Monthly	27	(42)
Every 2 months	16	(25)
Every 3 months	20	(31)
Other interval	2	(3)
Specialist who prescribed the unlicensed medication		
Gastroenterologist	24	(37)
Geneticist	21	(32)
Neurologist	10	(15)
Nephrologist	5	(8)
Pediatrician	2	(3)
Infectious disease specialist	2	(3)
Immunorheumatologist	1	(2)
Medication insurance coverage		
Public (through RAMQ)	19	(29)
Private (through employer)	45	(69)
Unknown	1	(2)
No. of family doctors or pediatricians seen by patient outside the study hospital		
0	24	(37)
1	40	(62)
2	1	(2)
No. of pharmacists involved in dispensing patient's medications		
0	2	(3)
1	60	(92)
2	2	(3)
3	1	(2)

RAMQ = Régie de l'assurance maladie du Québec.

30.4 ± 30.1 months. However, access to the community pharmacists' files was available for a total of only 1351 months. Of that subset, 474 (35%) months of treatment involved unlicensed medications known to have level I, II, or III interactions (Table 2), and interactions actually occurred in 4 (0.8%) of those months (Table 2). These interactions occurred in a total of 3 patients, all of whom were taking cisapride. This represents 12% of the patients who used this medication, 8% of all patients who took a medication with known interactions, and 2% (4/243) of the total number of months during which cisapride was taken. Three (8%) of the 39 patients who took a medication with a known interaction were in fact exposed to a potential drug interaction.

The potential interactions detected involved cisapride and either erythromycin, clarithromycin, or amitriptyline. Interactions between cisapride and either erythromycin or clarithromycin are considered major. Such interactions are caused by inhibition of the metabolism of cisapride by each antibiotic; this could in turn increase the plasma concentration of cisapride and the potential for toxic manifestations such as arrhythmias.[25] The interaction between cisapride and amitriptyline is classified as a level I interaction in *Drug Interaction Facts*[24] and is judged as major in *Micromedex MD*.[25] The risk associated with the latter interaction would be due to the potential additive increase in QT interval from the combination of the two agents.[26]

The 3 cases of potential interactions observed in this study are described briefly here.

Summary of Potential Interactions

In the first case, the community pharmacy file indicated 30 days of erythromycin use that overlapped with 2 months of use of the unlicensed medication. According to the hospital file, cisapride use was stopped at the beginning of the erythromycin therapy, but the exact date was not indicated. After validation, it was determined that the patient has been exposed to the potential interaction for a total of 2 days, not 2 months.

In the second case, the patient's community pharmacy file indicated that a 10-day tritherapy treatment against *Helicobacter pylori*, which included clarithromycin, had been dispensed. The note in the hospital file indicating the initiation of treatment with clarithromycin did not mention use of cisapride. The parents confirmed that the patient had been in fact been concomitantly exposed to the 2 medications for 10 days.

In the third case, the patient's community pharmacy file indicated a 14-day course of amitriptyline treatment a few days before the study interview with the community pharmacist. The pharmacist had noted the use of cisapride in the patient's file and recognized the potential interaction with the amitriptyline, yet had dispensed the medication, asking the parents to wait for his telephone call before starting use of the cisapride. However, it could not be determined whether the parents had followed this advice.

In all 3 cases, the physician had enough information to prevent concomitant administration of potentially interacting medications with cisapride. In 2 of the

Table 2. Potential Drug Interactions Detected

Medications	*n*	Duration of Medication Intake† (months, min–max)	Mean No. of Concurrent Medications‡ (± SD)	Total Period Analyzed (months)	Total Duration with Potential Interaction (months)	% of Months with Potential Interaction
All drugs	63	2–84	7.4 (4.2)	1351	4	0.3
Drugs with known interactions	39	2–38	6.8 (4.0)	474	4	0.8
Cisapride*	25	4–28	7.2 (4.8)	243	4	1.6
Nitisinone	8	35–84	7.8 (3.8)	469	0	0
Hydroxocobalamin	8	4–40	7.9 (5.2)	217	0	0
Cysteamine	5	3–47	10.4 (5.4)	145	0	0
Melatonin*	4	5–28	4.3 (1.3)	54	0	0
Divalproex sodium*	4	6–30	7.3 (2.2)	71	0	0
Interferon gamma*	4	6–38	5.5 (1.9)	94	0	0
Stiripentol*	2	2–10	8.0 (1.4)	12	0	0
Phenylbutyrate	2	6	7.5 (2.1)	12	0	0
Methylcobalamin	1	34	10 34	0	0	

SD = standard deviation
*Drugs with known drug–drug interactions.
†Period (in months) for which authors had access to the community pharmacist file.
‡Number of medications taken at least once during the study period.

3 cases, the pharmacist also had the information necessary to intervene, but in only 1 case was this done. Fortunately, none of the patients appeared to experience any negative effects from the potential drug interactions.

Survey Results

A total of 66 (99%) of 67 pharmacists and 38 (90%) of 42 physicians responded to the study questionnaire. Only 11 (17%) of the pharmacists had noted use of an unlicensed medication in patients' files, but 34 (89%) of the physicians had inserted a note.

DISCUSSION

Although this study had a limited number of observations, it was possible to define certain important problems with medications obtained through Health Canada's SAP, including the non-negligible risk of drug interactions.

All of the potential interactions detected through pharmacy files were associated with the use of cisapride. This is not surprising, given that cisapride is known to interact with many other medications. Studies of interactions involving cisapride occurring in adults, conducted before withdrawal of this drug from the market in 2000, reported rates of interaction with macrolides, azole antifungal agents, and some antihistamines of 3%[27] and 5%.[8] More recently, Jones and others[26] determined that patients in the United States receiving cisapride (a sample consisting of 38 757 patients, 97% adults and 3% children 15 years of age or younger) were exposed to potential interactions with other medications during 3.4% of the months of cisapride therapy. These interactions involved clarithromycin, erythromycin, and fluconazole in 43%, 26%, and 22% of cases, respectively.[26]

In the study reported here, potential interactions with cisapride were identified in 2% of the total number of months during which this drug was taken, less than the rate identified by Jones and others.[26] However, in the latter study, 2% of the interactions occurred in the 3% of the population that was 15 years of age or younger, which suggests that drug interactions were less frequent in children. The finding from the current study is particularly alarming because it indicates that withdrawal of cisapride from the market did not reduce the risk of a drug interaction, even with all the precautions specified by the SAP. Contrary to Jones and others,[26] there was no access to a complete database for the current study. In fact, the complete list of patients' medications was not necessarily available, because the regulations governing pharmacies require retention of prescriptions for only 2 years,[28] and some parents may not have remembered all of the pharmacists who were consulted since the beginning of their children's use of an unlicensed medication. Therefore, there might have been potential interactions that were not identified.

This study had many limitations. For example, it would have been better to have a higher number of months of exposure. An observation period of 5 to 10 years might have generated stronger data. The drug interactions identified were all theoretical interactions; however, only those drug interactions that would ideally need to be avoided were taken into account. Each detected interaction was also documented clinically. A variety of factors might have led to underdetection of potential interactions. Certainly, some interactions might have been detected by the parents at the physician's office. In fact, each parent received a list of medications contraindicated with cisapride from the pharmacy department at the time the medication was dispensed. However, when a medication with a potential interaction was prescribed, it was not possible to determine whether the community pharmacist detected the potential interaction and contacted the physician to request a modification of therapy. Another possible reason for a potential interaction being overlooked is that cisapride is no longer itemized in pharmacy computers since its withdrawal from the market. To correct this problem, Health Canada should develop a list of the unlicensed medications obtained through the SAP and make it available to clinical database providers. Also, pharmacists do not have access to the necessary clinical information needed to identify all potential drug interactions. For example, many clinical database providers do not carry or update information on SAP medications, a situation well described by McMullin.[29] Finally, few pharmacists made notes in their patients' files about the use of unlicensed medications, which further decreases the chance of detecting potential interactions.

From a clinical perspective, the proportion of patients exposed to a potential interaction with cisapride is worrisome. In a retrospective study involving both adults and children, the rate of exposure to a potential drug interaction with cisapride was 3%.[27] In the current study, 12% of patients who took cisapride were exposed to a potential interaction. Given that such potential interactions could be prevented and given that the consequences may be fatal, it is clear that improvements are needed.

The fact that most patients consult a limited number of health care professionals should in itself ensure adequate transmission of information. However, this was not confirmed by the current study. Although the examination of transmission of information was based on a telephone questionnaire, it is important to note that the rate of transmission was disappointing. Physicians had recorded information about the use of an unlicensed drug obtained through the SAP in the patient's file in only 89% of cases. In the pharmacists' files, the proportion fell to just 17%. It seems reasonable to expect that such important information would be known by all pharmacists and all physicians. Furthermore, knowledge about drugs and their interactions may be an issue. In a study examining knowledge of cisapride, only 22% of family doctors and 50% of pediatricians were aware of possible interactions with this drug.[30]

Finally, efforts are necessary to inform physicians about the use of unlicensed medications obtained through Health Canada's SAP and its implications. Completion of the request forms is considered an administrative annoyance, and the task is commonly delegated to secretaries or other health care professionals such as hospital pharmacists. It would be desirable to modify the procedure to emphasize the clinical consequences of potential interactions and the responsibilities of the physician. A requirement to obtain written consent from the patients who receive SAP medications would help to ensure that they are aware of the risks and benefits. These measures could be useful in diminishing the risks associated with unlicensed medications.

In conclusion, 3 (8%) of the 39 patients taking unlicensed medications known to have drug interactions were exposed to a potential drug interaction during the study period. The interactions occurred in 4 (0.8%) of the 474 months of therapy with an unlicensed medication known to have one or more drug interactions. Measures should be taken to decrease the risk associated with the use of medications available through Health Canada's SAP. A similar study over a longer period is needed to draw stronger conclusions.

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