PAEDIATRIC ADVERSE DRUG REACTION REPORTING: UNDERSTANDING AND FUTURE DIRECTIONS

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ABSTRACT

Background
Severe adverse drug reactions (ADRs) are an important cause of childhood morbidity and mortality. 95% of ADRs are likely not reported, less than 25% of marketed drugs can be advertised as safe and effective in children; yet over 50% of Canadian children receive prescription drugs annually.

Objectives
To increase understanding of reported ADRs in Canadian children.

Methods
A retrospective analysis of 1193 suspected ADRs reported to Health Canada (January 1998 - May 2002). These data were a paediatric subset of the Canadian Adverse Drug Reaction Information System database.

Results
58.6% of ADRs were for children over 13 years. 61% of reports were defined by Health Canada as serious. Case outcomes include: death (n=41) and recovered with sequelae (n=14). 4 reports of interacting drugs had fatal outcomes. Drugs most frequently cited include: isotretinoin (n=56), paroxetine (n=42), methylphenidate (n=41), amoxicillin (n=40), and valproic acid (n=32). Most frequent reaction descriptors include: psychiatric disorders (isotretinoin and paroxetine) and nervous system disorders (valproic acid, bupropion and carbamazepine). Causal links between suspected ADRs and clinical outcomes have not been established.

Conclusions
Current ADR reporting is insufficient to improve patient safety. More detailed reporting, including case outcomes, is needed. Mandatory ADR reporting is unlikely to improve underreporting. Trained surveillance personnel located in major health centres and solely dedicated to ADR reporting may provide a more accurate determination of ADRs in Canadian children.

Key Words: *Adverse drug reactions, adverse drug reaction voluntary reporting, paediatrics*

Severe adverse drug reactions (ADRs) are recognized in North America and Europe as an important cause of childhood morbidity and mortality. Despite this, few reports in the literature describe the problem in the paediatric population.[1-3] A recent systematic review and meta-analysis of the incidence of ADRs in paediatric in/out-patients calculated an overall incidence rate for ADRs in hospitalized patients of 9.53% (range 4.37%-16.78%) and 1.46% for outpatients; and a rate of paediatric hospital admissions due to ADRs of 2.09% (39.3% of these were life-threatening).[4] A prospective study from a regional paediatric hospital in France

showed similar incidence rates: 1.53% of hospital admissions due to ADRs, and 2.64% of patients developing ADRs while in hospital.[5] Temple et al[6] calculated an ADR incidence rate of 0.85%, based on retrospective review of ADR reports from a 313 bed American paediatric, tertiary care hospital. The authors suggested that this lower rate was due to underreporting.

Health Canada defines a reportable Adverse Drug Reaction as a noxious or unintended response to a drug, which occurs with the use or testing for the diagnosis, treatment, or prevention of a disease. ADRs which should be reported to Health Canada include ones that are unexpected, regardless of severity; ones that are serious, whether expected or not; and ones that are to products marketed for less than five years.[7]

The Canadian and American health care systems have long relied on voluntary surveillance for the identification and reporting of severe ADRs; both countries using federal systems for reporting. In Canada all reporting is coordinated by the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) and is centralized in a database developed to provide information concerning suspected adverse reactions to Canadian marketed health products of pharmaceuticals, biologics (including blood products and therapeutic and diagnostic vaccines), natural health products, and radiopharmaceuticals. Despite the inclusiveness of the Canadian reporting system, a major criticism of voluntary surveillance by health professionals has been the high level of underreporting. Health-related accreditation bodies estimate that as many as 95% of all adverse drug events are not reported.[8] Mittmann et al[9] reported that only 4% of cases of toxic epidermal necrolysis (TEN) were reported to CADRMP when they conducted a retrospective review of TEN cases in Canadian burn treatment centres from January 1995 – December 2000. In 2000, the CADRMP received 7361 reports of suspected adverse drug reactions, of which 351 (4.8%) were for paediatric cases.[10] Statistics Canada data for the year 2001 shows that children 0-18 years of age make up approximately 25% of the total Canadian population (approximately 7.67 million children).[11]

In January 2004, the Pharmaceutical Outcomes and Policy Innovations Programme (POPi) at Children's and Women's Health Centre of British Columbia, in conjunction with the Canadian Pediatric Surveillance Program (CPSP), began active surveillance of serious and life-threatening ADRs in children. As background work for this project, POPi collaborated with Health Canada to review all paediatric ADR reports submitted to CADRMP from January 1, 1998 to May 31, 2002. Data to May 31, 2002 represented the most up-to-date ADR data available at this time. The purpose of this review was to increase understanding of suspected paediatric ADRs reported to Health Canada including: the age and gender of the children, the types of reactions, and the severity of reactions reported. Determination of ADR causation was not possible on the basis of the information contained on most ADR reports.

METHODOLOGY

This was a retrospective analysis of 1193 suspected ADRs in Canadian children reported to Health Canada between January 31, 1998 and May 31, 2002. The electronically supplied data was a paediatric subset of the information reported to CADRMP and contained in the Canadian Adverse Drug Reaction Information System (CADRIS) database.

CADRMP receives voluntary ADR reports from physicians, pharmacists, other health care professionals, and patients and mandatory reports from pharmaceutical manufacturers. These data are catalogued within the CADRIS database. An anonymized subset of these data containing 1305 reports of adverse drug reactions in children less than 19 years of age was provided to POPi and was entered into a central, integrated database. Note that POPi was not provided all Health Canada data for these adverse reaction reports. When Health Canada assesses ADR causality all the information in the ADR report is used.

All data were devoid of personal identifiers. Data fields supplied included: unique identification code, date received at Marketed Health Products Directorate, severity of report (serious report - yes or no), age, gender, drug name (generic or trade name), dosage form, route of administration, drug involvement (suspected, interaction, concomitant, or treatment), dose, frequency, duration, World Health Organization adverse reaction term (WHO-ART), date of onset,

date of resolution, and outcome at the time of report (recovered without sequelae, recovered with sequelae, died drug may be contributory, died due to ADR, died unrelated to drug, not yet recovered, or unknown).

For the purpose of this report, a *suspected drug* was defined as a drug or combination of drugs in a single drug product reported to be the suspected cause of the ADR. An *active ingredient* was defined as a pharmacologically active component of a suspected drug. The names of suspected drugs were converted to generic name(s). All active ingredients of combination products were included, as per the Drug Product Database (DPD). The DPD contains product specific information on approximately 20,000 drugs approved for use in Canada. The database is managed by the Therapeutics Products Directorate of Health Canada and includes human, veterinary and disinfectant products. Exceptions to this were the following combination products containing many active ingredients: Aminosyn, Ultra Thermaburn, Thermalean, Thermalift, Prolab ThermaPro, Pedialyte, Pedialyte Freezer Pops, Pollinex-T, and Nuxil, which were reported as suspected drugs under these trade names.

In reports where more than one suspected drug and/or more than one active ingredient was contained in the suspected drug, all active ingredients were included in the analysis. For example, when two active ingredients were contained in the suspected drug (e.g. Tylenol # 3®) both active ingredients (acetaminophen and codeine) were included in the analysis. No attempt was made to judge which ingredient was the most likely cause of the ADR.

Only suspected drugs were analyzed. The concomitant drugs' contributions to the ADR cited in the report and the treatment strategies were not evaluated as there was insufficient information to do this reliably and with demonstrated validity. Twelve ADRs which reported two or more interacting drugs, but no suspected drug(s), were analyzed separately (Table 1). Eleven cases were included in the analysis where the patient's age was not reported, but where it was judged (based on consensus of 3 clinicians - a paediatric clinical pharmacologist (PharmD), a licensed pharmacist (BSc Pharm, MSc), and a registered paediatric nurse BSc, RN) that the drug had been administered to a child.

TABLE 1 Interaction ADRs[1] with serious outcomes

Age (years)/Gender	Outcome at Time of Report	Interaction Drugs
15/ M	Not yet recovered	clarithromycin/digoxin
10/ F	Died drug may be contributory	amitriptyline/cambamazepine/morphine/gabapentin
11/ F	Recovered without sequelae	pethidine/pentobarbital
10/ unknown	Unknown	clarithromycin/tacrolimus
16/ F	Recovered without sequelae	venlaflaxine/St Johns Wort
17/ M	Died drug may be contributory	carbamazepine/lamotrigine
17/ F	Died drug may be contributory	hydromorphone/gabapentin/ olanzapine
18/ M	Died drug may be contributory	propofol/itraconazole

[1]Adverse Drug Reaction

Inconsistent reporting of generic drug names was a problem in six ADR reports where both generic and trade names were listed as suspected drugs or two dosage forms (e.g. regular and enteric coated tablets) were listed separately as the suspected drug. Because it is possible to have an ADR associated with the consumption of more than one product with similar ingredients, or two brand name pharmaceuticals with the same active ingredient, both suspected drugs were included as reported.

Of the 1305 reports provided, 112 were deleted from our analyses for the following reasons: drug administration was to the mother (i.e. fetal-transfer) (n=84); out-of-range age (n=12); interacting drugs only (n=12); or no suspected drug (n=4). In total, we examined 1193 reports of suspected paediatric ADRs that were reported to the CADRMP during the study period.

Missing values in many data fields were a significant challenge. Age was missing in 11 reports, dose was missing in 51% of reports, dosage form in 70% of reports, dosing frequency in 55%, route of administration was missing in 18% of reports, and patient outcome at the time of report was missing in 7 reports.

Reported Reactions

Reactions were described using 924 unique World Health Organization Adverse Reaction Terms (WHO-ART). POPi reclassified these WHO-ART terms into the 26 System Organ Class (SOC) allocations from The Medical Dictionary for Regulatory Activities (MedDRA) terminology.

RESULTS

Drugs Responsible for Adverse Drug Reactions

In 95 reports, more than one suspected drug was cited (Table 2). Note that drugs included any marketed Canadian health product, including prescription and non-prescription medications and natural health products. In addition, there may have been more than one active ingredient contained in a suspected drug. In total, 1451 active ingredients were associated with the 1193 reports of pediatric suspected adverse drug reactions. These active ingredients will be referred to as "drugs" for the remainder of this report. Table 3 shows the drugs most frequently associated with the reported suspected ADRs. Note that these 1193 reports include expected, unexpected, non-serious and serious suspected ADRs.

TABLE 2 Number of suspected drugs per ADRs[2] report

# of Suspected Drugs Reported	# of ADR Reports
1	1098
2	77
3	14
4	3
6	1
TOTAL	**1193**

[2]Adverse Drug Reaction

Patient Demographics

Of the 1193 reports of suspected paediatric ADRs the majority involved patients between 13 to 19 years of age (Table 4).

Patient Outcomes Resulting from Reported Adverse Drug Reactions

Sixty one percent (726/1193) of the adverse drug reactions were reported as serious reactions. Health Canada defines a serious reaction as a noxious and unintended response to a drug, that occurs at any dose and that requires in-patient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening, or results in death.[7] Table 5 shows the outcomes of the suspected serious ADRs, of which nearly 37 % (264/726) have an unknown outcome at the time of reporting.

TABLE 3 Drugs most frequently associated with suspected ADR[3] Reports

56 Reports	**11 Reports**	**6 Reports**
Isotretinoin	Azithromycin	Budesonide
42 Reports	Cisapride	Dextroamphetamine Sulfate
Paroxetine	Cyclosporine	Fentanyl
41 Reports	Vigabatrin	Fluvoxamine Maleate
Methylphenidate	**10 Reports**	Insulin Lispro
40 Reports	Enoxaparin Sodium	Iopamidol
Amoxicillin	Ethinyl Estradiol	Levofloxacin
32 Reports	Fluticasone Propionate	Meperidine
Valproic Acid	Mycophenolate Mofetil	Minocycline
26 Reports	**9 Reports**	Palivizumab*
Bupropion	Erythromycin	Phenylephrine
25 Reports	Immune Globulin (Human)	Phenytoin
Carbamazepine	Indomethacin	Sevoflurane
Fexofenadine	Morphine Sulfate	**5 Reports**
19 Reports	Olanzapine	Amitriptyline
Acetaminophen	Pseudoephedrine	Baclofen
Clarithromycin	Sertraline	Caffeine
18 Reports	Topiramate	Cefuroxime
Risperidone	**8 Reports**	Clindamycin
16 Reports	Acetylsalicylic Acid	Epinephrine
Sulfamethoxazole	Ibuprofen	Etoposide
Trimethoprim	Insulin NPH Human	Fluoxetine
15 Reports	Iohexol	Ganciclovir
Cefaclor	Permethrin	Gentamicin
Clavulanic Acid	Tacrolimus	Insulin Semi Synthetic Human
Medroxyprogesterone Acetate	Venlafaxine	Levonorgestrel
14 Reports	**7 Reports**	Midazolam
Cetirizine	Citalopram	Naproxen
13 Reports	Clobazam	Octocrylene
Lamotrigine	Clozapine	Penicillin G
12 Reports	Guaifenesin	Propofol
Dextromethorphan Hydrobromide	Metronidazole	Salbutamol
Lidocaine	Omeprazole	Somatropin
	Pegaspargase	Temozolomide
	Ranitidine	Tetracaine
		Tetracycline
		Titanium Dioxide
		Triamcinolone Acetonide

[3]Adverse Drug Reaction

TABLE 4 Number of reported ADRs[4] by age category and year

Year of Report						
Age of Child	**1998**	**1999**	**2000**	**2001**	**2002***	**TOTAL**
< 1 year old	37	34	37	19	15	142
1 - 3 years old	22	22	22	42	3	111
3 - 6 years old	3	2	4	7	1	17
6 - 13 years old	38	33	68	49	25	213
13 - 19 years old	124	131	193	181	70	699
Unknown age	1	2	4	3	1	11
TOTAL	**225**	**224**	**328**	**301**	**115**	**1193**

*Data from January 1, - May 31, 2002
[4] Adverse Drug Reaction

TABLE 5 Outcomes resulting from serious ADR[5] Reports

Outcome	**1998**	**1999**	**2000**	**2001**	**2002***	**TOTAL**
Undefined (No value in database)	5	0	0	0	0	**5**
Died - drug may be contributory	6	7	15	7	2	**37**
Died - unrelated to drug	1	2	2	0	1	**6**
Died due to adverse reaction	1	2	1	0	0	**4**
Not yet recovered	27	18	20	39	10	**114**
Recovered with sequelae	6	1	3	4	0	**14**
Recovered without sequelae	54	45	71	77	30	**277**
Unknown	36	38	61	93	41	**264**
TOTAL	**136**	**113**	**173**	**220**	**84**	**726**

*Data from January 1 – May 31, 2002
[5] Adverse Drug Reaction

Suspected Adverse Reaction Reports with a Fatal Outcome

Forty-one reports included a fatal outcome; of which 37 had outcomes reported as “died, drug may be contributory,” and 4 reports had outcomes reported as “died due to adverse reaction.” The active ingredients most commonly cited as suspected in ADRs where a fatal outcome was reported were: olanzapine (n=3), cisapride (n=2), enoxaparin (n=2), fentanyl (n=2), isotretinoin (n=2), propafenone (n=2), propofol (n=2), and venlafaxine (n=2). Table 6 shows the suspected drugs in reports with a fatal outcome. Table 1 shows that 4 additional reports of interacting drugs had outcomes of "died, drug may be contributory". Drugs reported in these 4 cases include: carbamazepine (n=2), gabapentin (n=2), amitriptyline, hydromorphone, itraconazole, lamotrigine, morphine, olanzepine, and propofol (n=1).

TABLE 6 Drugs reported in suspected ADRs[6] with a fatal outcome by frequency of times reported

ACTIVE INGREDIENT	# TIMES REPORTED
Olanzapine	3
Cisapride	2
Enoxaparin	2
Fentanyl	2
Isotretinoin	2
Propafenone	2
Propofol	2
Venlafaxine	2
Acetaminophen	1
Allopurinol	1
Alteplase	1
Amantadine	1
Aminoacid Solution	1
Amphotericin B	1
Clarithromycin	1
Clobazam	1
Cyclophosphamide	1
Cyclosporine	1
Dextropropoxyphene	1
Ethinyl Estradiol	1
Immune Globulin (Human)	1
Insulin Semi Synthetic Human	1
Lidocaine	1
Loratadine	1
Lung Surfactant	1
Mycophenolate Mofetil	1
Norgestimate	1
Phenoxybenzamine	1
Pseudoephedrine	1
Reviparin	1
Risperidone	1
Salbutamol	1
Sulfamethoxazole	1
Temozolomide	1
Topiramate	1
Trimethoprim	1
TOTAL	**45**

[6]Adverse Drug Reaction

Suspected Adverse Reaction Reports with the Outcome "Recovered with Sequelae"

Fourteen suspected ADR reports included the outcome "recovered with sequelae." These 14 cases involved 40 drugs, of which the most commonly reported were: isotretinoin (n=3), ethinyl estradiol (n=2), venlafaxine (n=2).

Reaction Types

Table 7 shows the most frequent MedDRA SOC terms used to describe the top suspected drugs. Psychiatric disorder was listed as a reaction descriptor in 46.4% of reports where isotretinoin was a suspected drug and 38.1% of reactions associated with paroxotine. Methylphenidate's most frequent reaction descriptors were lack of efficacy (43.9% of reactions) and psychiatric disorders (31.7% of reactions). Skin reactions were most common for amoxicillin (57.5%), while nervous systems disordersranked highest for valproic acid (37.5% of reactions), bupropion (34.6 % of reactions), and carbmazepine (44% of reactions).

TABLE 7 MedDRA SOC[4] terms most frequently reported for top 10 drugs

Drug	SOC Terms Reported	# of ADR's Reported	% of Cases
ISOTRETINOIN (n=56)	Psychiatric Disorders	26	46.4
	Musculoskeletal and Connective Tissue Disorders	12	21.4
	Nervous System Disorders	9	16.1
	Gastrointestinal Disorders	7	12.5
	Hepatobiliary Disorders	6	10.7
	Skin and Subcutaneous Tissue Disorders	6	10.7
PAROXETINE (n=42)	Psychiatric Disorders	16	38.1
	Nervous System Disorders	13	30.2
	Respiratory, Thoracic & Mediastinal Disorders	5	11.9
METHYLPHENIDATE (n=41)	General Disorders and Administration Site Conditions *Lack of Efficacy-18* *Death and Sudden Death-1* *Headaches-1* *Mood Disorders-1*	21	51.2
	Psychiatric Disorders	13	31.7
AMOXICILLIN (n=40)	Skin and Subcutaneous Tissue Disorders	23	57.5
	Gastrointestinal Disorders	10	25
	Immune System Disorders	10	25
VALPROIC ACID (n=32)	Nervous System Disorders	12	37.5
	Blood and Lymphatic System Disorders	9	28.1
	Gastrointestinal Disorders	6	18.8
	Psychiatric Disorders	6	18.8
BUPROPION (n=26)	Nervous System Disorders	9	34.6
	Psychiatric Disorders	8	30.8
	Cardiac Disorders	6	23.1
	Immune System Disorders	5	19.2
	Skin and Subcutaneous Tissue Disorders	5	19.2
	Gastrointestinal Disorders	3	11.5
CARBAMAZEPINE (n=25)	Nervous System Disorders	11	44
	Blood and Lymphatic System Disorders	6	24
	General Disorders and Administration Site Conditions *Lack of Efficacy-4*	4	16
	Respiratory, Thoracic, & Mediastinal Disorders	4	16
	Immune System Disorders	3	12
	Musculoskeletal and Connective Tissue Disorders	3	12
	Psychiatric Disorders	3	12
	Skin and Subcutaneous Tissue Disorders	3	12
FEXOFENADINE (n=25)	General Disorders and Administration Site Conditions *Lack of Efficacy-12* *Ocular Infection-1*	13	28

	Eye Disorder	6	24
	Gastrointestinal Disorders	4	16
	Respiratory, Thoracic, & Mediastinal Disorders	4	16
	Immune System Disorders	3	12
ACETAMINOPHEN (n=19)	Gastrointestinal Disorders	5	26.3
	Nervous System Disorders	5	26.3
	Hepatobiliary Disorders	4	21.1
	Cardiac Disorders	3	15.8
	Respiratory, Thoracic, & Mediastinal Disorders	3	15.8
	Skin and Subcutaneous Tissue Disorders	3	15.8
	Blood & Lymphatic System Disorders	2	10.5
	Eye Disorder	2	10.5
	Immune System Disorder	2	10.5
	Renal and Urinary Disorders	2	10.5
CLARITHROMYCIN (n=19)	Nervous System Disorders	5	26.3
	Skin and Subcutaneous Tissue Disorders	5	26.3
	Gastrointestinal Disorders	3	15.8
	Immune System Disorders	3	15.8
	Psychiatric Disorders	3	15.8
	Vascular Disorders	3	15.8
	Eye Disorder	2	10.5
	Musculoskeletal and Connective Tissue Disorder	2	10.5

[4] Medical Dictionary for Regulatory Activities, System Organ Class

Interaction ADRs

Eight suspected drug interaction ADRs of the 12 reported had serious outcomes. Details of these serious ADRs are presented in Table 1.

DISCUSSION

Data Limitations

Health Canada provides data with the following caveat:

The vast majority of reports on which this summary is based were submitted by health practitioners and to a lesser extent laypersons. Each report represents the suspicion, opinion or observation of the individual reporter. Cause and effect relationships have not been established in the vast majority of reports submitted. Similarly, descriptors for drug involvement and the outcome at the time of report do not imply causality. These reports contain raw information that has not been scientifically or otherwise verified as to cause and effect relationship by Health Products & Food Branch scientists.

In addition to the data quality issues highlighted by Health Canada, other issues of data quantity and quality are also important. The data submitted to Health Canada concerning suspected adverse drug reactions in children represents only a small percentage of all adverse drug reactions occurring in Canadian children; perhaps just 5%. Further, the information collected is severely limited by the quality of descriptive information collected. For example, in more than half of all reports the dose, dosage form, and frequency of medication administration was not provided.

Further, there is no information to indicate the temporal relationship between the time of drug administration and the time of the suspected

reaction. Our recent work with the Canadian Paediatric Surveillance Program confirms this problem; with only 27% (12/44) of the 2005 reports received being complete. Cause and effect relationships involving drug reactions are often difficult to establish, even given complete reporting. For example, some drugs' adverse effects are identical to the underlying disease state effects that they are used to treat. Current hypotheses about selective serotonin reuptake inhibitors (SSRIs) and suicidal ideation posit that treatment-induced akathisia[12], emotional blunting[13,14], or mania[15] may lead in some (e.g. more sensitive) patients to suicidal thinking and perhaps even to suicide.

Testing this hypothesis would be extremely difficult because of, 1) the small number of patients for whom data are available and 2) the overlap between suicidal ideation caused by the underlying disease versus ideation caused by drug treatment.

Reported Reactions

The reaction terminology systems referred to (i.e WHO-ART and MedDRA) are both widely used by regulatory bodies and are designed to allow precise description of an ADR using standardized terminology. WHO-ART contains more than 1700 unique terms and has been developed over more than 30 years to serve as a basis for rational coding of adverse reaction terms.[16] The structure of WHO-ART is hierachial, beginning with the body system/organ level (within which there are general and high level grouping terms) and including preferred terms (to provide precise identification of drug problems). However, to group the information in a more meaningful way, and at the request of Health Canada, POPi combined and reclassified the 1193 reported WHO-ART terms using the 26 System Organ Class (SOC) allocations from The Medical Dictionary for Regulatory Activities (MedDRA) terminology. MedDRA is another standardized dictionary of medical terminology, developed by the International Conference on Harmonization (ICH), to standardize the medical terminology used internationally.[17] Note that the SOC term is associated with the ADR report and not the specific drug.

This is important because ADR reports frequently included multiple suspected drugs as well as concomitant or interaction drugs; and therefore, any or all of these could be implicated in the occurrence of the specified reaction. For example, isotretinoin is a suspected drug in 56 reports. Many of these 56 patients were also receiving other drug therapy for a variety of disease conditions that may have been partially or fully responsible for the reaction. Also note that the SOC term is an aggregate term. We collapsed all reactions of a single type within the SOC terminology and recorded them only once for any unique ADR report. For example, a report that cited anxiety, suicidal ideation, and depression would be classified under the SOC "psychiatric disorder". Finally, there are more SOC terms reported than there are unique reports for a given suspected drug. This is because ADRs frequently present at more than one site of the body (e.g. rash and headache).

Drug interaction reports were surprisingly small in number, given the frequency of concomitant medication use reported in ADR cases. Note that these interactions are only those documented by the reporter, and many drug interaction-related ADRs may be present but not recognized.

Implications for Clinicians and Policy Makers

Drug therapy is increasingly becoming an integral part of the treatment of childhood disease.[18] A wide range of drugs are prescribed to children, many of which are being used outside the age range approved by Health Canada.[19] Pre-marketing trials often do not include children despite the fact that children may be at risk for unique ADRs and for an increased frequency of ADRs compared with the general population.[20-22] This was confirmed by a Boston collaborative study which showed that the potential adverse drug event rate is significantly greater in paediatric patients than in adult patients.[23] Factors that increase the risk of ADRs in children and make them more difficult to identify include the inability of many children to assess and express their own response to medications and describe adverse events.[22]

According to Health Canada and the U.S. Food and Drug Administration, less than 25% of marketed drugs can be advertised as safe and effective for use in infants and children.[19] Despite this, drugs are widely used. A recent analysis of

administrative data from Canadian private drug payment plans indicated there were over 1,000,000 Canadian paediatric claimants (representing approximately 50% of eligible children).[18] The magnitude of prescription medication use in this population is also shown by BC PharmaNet; BC's fully comprehensive prescription database (1998-2001) that indicates, on average, over 530,000 children (approximately 54% of BC children) were prescribed and dispensed at least one prescription medication annually. A survey of children's hospital wards in 5 European hospitals found almost half of all drug prescriptions were either unlicensed or off label.[23]

Given the dearth of ADR reporting and the known limitations due to data quality, it is often asked of us whether study of these existing data is worthwhile. If the Health Canada ADR reports represent just 5% of the total, should these statistics govern practice change? Should any decision-making be based on such incomplete data? The level of ADR reporting is clearly insufficient to understand the problem fully but does provide clues to the nature and magnitude of the issue. For example, our analysis shows that the drugs most frequently associated with suspected ADRs in children are isotretinoin, paroxetine, methylphenidate, amoxicillin, and valproic acid. BC PharmaNet data (2001), shows purchase of these drug for children as follows: isotretinoin (n=3,551), paroxetine (n=2,683), methylphenidate (n=7,945), amoxicillin (n=193,089), and valproic acid (n=352). However, without thorough accounting of the therapeutic outcomes for all children who take these medications, there is insufficient data to accurately calculate or even estimate true ADR incidence rates.

Health Canada currently uses these reports of suspected ADRs for *signal* generation. In this context the World Health Organization definition of "signal" is used: "reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously; or an increased frequency of a serious or severe adverse event previously known". History shows that even one reported case can make a difference**:** regulating authorities can respond to a single clinical report of a serious ADR leading to further investigation of a drug's safety. For example, the US Federal Drug Administration's response to one report ultimately led to the removal of terfenadine from the market.[24] This report potentially saved many lives and led to a better understanding of the mechanism involved in causing *torsades de pointes*. As a further result of this single case report, almost all drugs are now evaluated, prior to being released on the market, for their potential to induce cardiac arrhythmias.

Next Steps

Recent discussions concerning legislation for mandatory reporting of ADRs are interesting. However, our experience suggests that mandatory reporting might not generate accurate ADR rates because it relies on clinicians being able to both recognize ADRs and assess causality. A recent study suggests that many ADRs go unrecognized by clinicians, 25% of physicians have never diagnosed an ADR and two-thirds of physician state they did not file a report because of doubt about causality.[25]

In Italy, reporting of any ADR to the Ministry of Health has been mandatory for physicians, pharmaceutical companies, pharmacists, and patients since 1987. Despite this, under-reporting is high compared with other countries. Only 4 ADRs per 100,000 children were reported in 1994 and 1995.[3] Reporting rates also appear to vary significantly by region and results of a physician survey in one area showed half of the doctors did not report ADRs to anyone and less than 60% were aware of their statutory responsibility.[26] We therefore believe the time has come to address this problem through a large-scale epidemiological evaluation of ADR reporting through active surveillance. This strategy is distinct from the current voluntary approach (or in some jurisdictions, mandatory) and relies on reporters whose principal, even sole responsibility is the identification and documentation of ADRs. Our most recent work in active surveillance, supported by a pharmacogenomics grant from Genome Canada, has allowed us to establish a network of clinical ADR surveillors in eight paediatric teaching hospitals across Canada that serve more than 75% of Canadian children. The network is identifying and collecting clinical data and biological samples from patients with ADRs and matched controls. This surveillance model has proven to be more effective than voluntary ADR surveillance systems. Over the last 32 years, ADR

surveillance by Health Canada identified 4 reports of ibuprofen-induced Stevens Johnson syndrome (SJS),[27] while our new network identified 3 cases of ibuprofen-induced SJS in the first 6-months of operation.

In order to achieve better understanding of the risks involved with drug therapy in children more thorough individual ADR reports are needed, including fully detailed ADR outcomes for each case. Trained surveillance personnel with primary responsibility for reporting at each paediatric health centre in Canada would be a solid first step towards accurate determination of the incidence and prevalence of ADRs in Canadian children. Our collaborative study with CPSP and our Genome Canada supported work is a first step in this process. Well-trained surveillance personnel could also aid in determination of ADR causality and in preventability assessments. Currently the causal link between administration of the drug and the reaction or its preventability is rarely known or estimated with precision. Understanding causality and preventability of ADRs will significantly aid in better therapeutic monitoring for future children receiving the same therapy.

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