Does active surveillance of serious and life-threatening adverse drug reactions improve reporting?

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Adverse drug reactions (ADRs) are an important cause of illness and death (1). Of particular concern is the alarming lack of ADR data in the paediatric population, which, therefore, limits the ability to avoid or prevent these occurrences. Only a minority of prescribed pharmaceuticals on the market in North America have been tested in paediatric populations, and most of them are used without the benefits of adequate guidelines for safety or efficacy (2). Postmarketing surveillance is, therefore, essential for early detection of ADRs, and relies mainly on voluntary reporting. A major criticism of current voluntary surveillance by health professionals has been the high level of under-reporting. Health-related accreditation bodies estimate that 95% of all ADRs are not reported (3).

The Canadian Paediatric Surveillance Program (CPSP) launched a specific study to enhance reporting of serious and life-threatening ADRs in children, and has been collecting data since 2004. The first study objective is the identification of products most frequently causing ADRs in children, of the type of reactions encountered, and of any ADRs not currently captured by existing spontaneous reporting systems. Further objectives are quality data collecting, using 'ADR Tips of the Month' to build support and awareness of the study, facilitating case ascertainment, and impacting new information relating to the study or broader ADR surveillance topics. In 2008 and 2009, evaluations were conducted to collect more information on reporting practices of participants, and to assess the value of the CPSP surveillance methodology in supporting recognition/reporting of serious and life-threatening ADRs. Information was gathered on the ability of the CPSP to overcome documented barriers to reporting associated with passive surveillance, and the effectiveness of collaborative models in identifying solutions to improve ADR recognition and reporting. The current article presents study findings and results of the evaluative surveys.

METHODOLOGY

The serious and life-threatening ADRs study is conducted through the CPSP – a network of more than 2500 actively practicing paediatricians and paediatric subspecialists from across Canada – who report cases monthly according to a preset case definition (Table 1). For each reported case, participants complete a clinical questionnaire.

In 2008, a one-time survey was performed. Information was gathered online and via questionnaires mailed to CPSP participants. The survey aims were to understand the case definition, notion of rarity, patterns of ADR reporting, ease of completion of the clinical questionnaire, usefulness of feedback information, assiduity in reporting, and barriers and solutions to increase reporting. In 2009, one-time surveys on web-based reporting and paediatric antiviral drug use enabled the CPSP to gather additional information.

TABLE 1
Case definition of serious and life-threatening adverse drug reactions

- Report serious and life-threatening adverse drug reactions* associated with the use of prescription, nonprescription, biological (immunoglobulin) products, complementary medicines (including herbals) and radiopharmaceutical products in an infant or child who is 18 years of age or younger.
- Report even if you are not certain whether the product caused the adverse reaction or you do not have all the reporting details.
- Exclusion: Do not report reactions to medical devices, blood products (platelets, red cells and single donor plasma), vaccines, poisonings or self-administered overdoses.

**Noxious and unintended severe response to a drug, which occurs at any dose and results in emergency observation, hospitalization, persistent or significant disability, or death*

RESULTS AND DISCUSSION

The CPSP national reporting rate for all studies is 80%, and the response rate for completion of clinical detailed questionnaires is 94%. On average, 70 cases are reported per year; the serious and life-threatening ADRs study confirmed more than 40 suspected serious ADRs annually (Table 2). Through the years, product groups most commonly associated with suspected ADRs were anticonvulsant, anti-infective and antineoplastic agents (4). Of note, there was a change to antibacterial, psychoanaleptic and psycholeptic agents in 2010. Table 3 summarizes clinical data for deaths from suspected ADRs. Table 4 describes events reported through the CPSP that were not documented in standard reference sources for health products.

The ongoing serious and life-threatening ADRs study has described trends in suspected products causing either serious reactions or causing/contributing to death; in addition, it has also reported reactions not documented in standard reference sources for health products.

2008 one-time survey on the serious and life-threatening ADRs study

Reporting patterns: A one-time survey was conducted in 2008 (5). More than 700 survey responses were received, representing an approximate response rate of 28%, which is comparable with

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TABLE 2
Suspected adverse drug reactions (ADRs) and outcomes (2004 to 2010)

Suspected ADRs	2004	2005	2006	2007	2008	2009	2010
Reported	64	71	84	45	68	67	42
Confirmed*	42	44	60	41	35	45	32
Outcome							
Medically important†	–	–	18	11	12	21	17
Hospitalization/prolongation of hospitalization	32	25	25	19	18	28	19
Disability	1	4	1	0	0	3	2
Life-threatening	10	11	14	9	12	14	6
Death	0	1	2	0	3	1	0

*Data presented as n. *A confirmed case is one that meets the case definition; 'confirmed' does not equate to causality. †A medically important reaction is defined as one that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of these outcomes from occurring*

TABLE 3
Deaths from suspected adverse drug reactions (2004 to 2010)

Suspected product(s)	Known pre-existing disease	Adverse event(s)
Ceftriaxone	None	Hemolytic crisis
Clofarabine*	Acute relapsing lymphoblastic leukemia	Stevens-Johnson syndrome, hepatitis and pancytopenia
Succinylcholine	Cerebral palsy	Cardiac arrest due to hyperkalemia after induction for general anesthesia
Infliximab and azathioprine	Crohn's disease	Malignant hepatic tumour after several years of treatment
Fentanyl	None	Thoracic rigidity, desaturation, cardiac arrest after preintubation analgesia in a neonate
Olanzapine and sertraline	Autism and Tourette's syndrome	Sudden death three days after abrupt discontinuation of suspected agents
Clofarabine* and cytarabine	Resistant acute relapsing lymphoblastic leukemia	Pulmonary edema, renal failure and hypotension the day after receiving the final dose of a five-day course of clofarabine; died 48 h after completing

**Investigational product*

TABLE 4
Suspected adverse drug reactions not documented in standard reference sources for health product*

Suspected product(s)	Known pre-existing disease	Adverse event(s)
Somatotropin	Growth hormone deficiency	Pancreatic endocrine tumour with/without biliary tract obstruction
Propolis	No underlying condition	Acute renal failure
Clofabrine	Relapsing acute lymphoblastic leukemia	Stevens-Johnson syndrome
Piperacilline, tazobactam and cefatoxime	Empyema and pneumonia	Disseminated intravascular coagulation
Oseltamivir	Diabetic with flu-like illness	Hypertriglyceridemia with pancreatitis
Amoxicillin	Rheumatic fever	Small pericardial effusion
Cisplastin and fluorouracil	Metastatic hepatic cellular carcinoma	Hyperammoniac encephalopathy
Olanzapine and sertraline	Autism and Tourette syndrome	Sudden death three days after abrupt discontinuation of suspected agents
Isoretinoin	Acne	Polycythemia
Phenytoin	Not reported	Anaphylactic reaction following a single intravenous bolus
Prednisolone	Asthma	Dystonic-like posturing of arms, slurred speech and vacant gaze after oral administration
Methylphenidate	Obsessive-compulsive disorder	Aggravation of pre-existing symptoms
Olanzapine and granesitron	Anxiety and mood disorder	Serotonin syndrome

**The information source for this determination was the Canadian-approved product monograph. When an approved product monograph was not available, the source used was the Compendium of Pharmaceuticals and Specialties electronic version, the Micromedex Drug Information system (Thomson Reuters, Canada) or the American Hospital Formulary Service (AHFS) Drug Information (American Society of Health-System Pharmacists, USA) reference*

previous CPSP surveys with no reminders. The CPSP ADR study uses a regulatory definition to describe an ADR. Results confirmed that 96% of respondents agreed that it described a serious and life-threatening event. This was reassuring in view of the generality of the regulatory definition and the concern that it might limit identification and reporting.

The WHO defines rarity for serious and life-threatening ADRs in children at a ratio of 1:10,000; 68% of survey participants also agreed that serious and life-threatening ADRs are rare. However, 24% indicated that they had reported an event during the study period. Interestingly, 83% believed that the ADR study should continue. Comments received suggest that the CPSP makes the reporting of ADRs more accessible and meaningful for some members, and it had increased their likelihood of reporting ADRs. This reinforces the success of the program and highlights the benefits of working with a national active surveillance program that promotes ongoing involvement and commitment of front-line members.

At the end of 2004, a comparison of relative efficiency for reports received and entered into the Canada Vigilance Database, between January 1 and December 31, 2004, was performed. The results suggested that the Canada Vigilance Program received 1.7 reports of paediatric serious and life-threatening ADRs per 1000 health care professional reporters compared with 16.5 reports per 1000 reporters for the CPSP.

In 2004, 2005 and 2006, the CPSP's yearly reports of serious and life-threatening ADRs represented approximately 10% of the total paediatric serious ADRs received by the Canada Vigilance Program. Study results confirm the seriousness of the suspected ADRs with patient outcomes such as life-threatening events, hospitalizations, prolonged hospitalizations, disabilities and interventions to prevent damage and/or permanent impairment and deaths. Importantly, the quality of clinical information gathered via the CPSP is considered to be good to excellent according to the quality grading scale used by the WHO (6). The quality of the information reported is important to the assessment of possible relatedness between exposure to a drug and an adverse event. A strong case report will include information to assess a temporal association (time frame of therapy and onset of reactions), possible alternative explanations (concomitant medications and medical conditions) and dechallenge/rechallenge information.

Barriers impacting ADR reporting

Documented barriers identified with passive reporting systems include heavy workload, fear of liability and patient confidentiality. When asked about the barriers that impact reporting ADRs to the CPSP, heavy workload (51%), time to complete the detailed questionnaire (39%) and difficulty in determining whether the problem is associated with a drug versus a disease (53%) were identified as significant. The comments provided suggested that even a simple questionnaire represents an increased workload and that defining priorities for reporting would help manage workload issues, as would electronic reporting. The issue of perceived competing interests with different academic studies and one-time programs researching paediatric ADRs conducted concurrently was mentioned by some reporters. The protocol and expectations vary from study to study, leading to confusion and/or apathy.

More targeted surveillance of drugs was also recommended as a mechanism to reduce the burden of reporting and increase the utility of feedback for clinicians. Concerns about legal liability and fear of breaching patient confidentiality were not seen as barriers to the reporting of ADRs to the CPSP. This most likely reflects the awareness of CPSP participants that every study undergoes approval by an independent Canadian research ethics board, and that the program is committed to the rights to individual privacy and professional confidentiality.

Solutions to increase ADR reporting

Meaningful, targeted feedback is a critical measure of value, and is instrumental in building motivation and buy-in with active surveillance. All reporters, regardless of the reporting program, are looking for such feedback. The CPSP has recognized this important component of knowledge transfer (7), and created the 'ADR Tips of the Month' for participants as a step toward achieving this goal. In 2007, a decision was made to eliminate the tips for financial reasons. This educational strategy was quickly reintroduced when it was noted that the reporting rate dropped by more than 50% in 2007 compared with 2004, 2005 and 2006. The 2009 one-time survey on web-based reporting (8) identified that participants viewed these tips as relevant, effective and timely. Numerous comments and suggestions were provided supporting the short and simple format. In the present evaluation, CPSP participants viewed the tips as useful, with 60% of respondents indicating that they are a valuable tool in increasing ADR reporting. Other solutions to support increased reporting of CPSP participants included greater feedback (61%), more education on ADRs (61%) and a simplified questionnaire (53%).

CONCLUSION

Collaboration with a national specialty active surveillance program is an effective way to promote awareness and buy-in. Results indicated that the CPSP has been instrumental in building and maintaining a culture of reporting among members. It has simplified the reporting process and increased the likelihood of ADR reporting. The clinical information gathered is of high quality, as characterized by the quality of the grading scale used by the WHO. The CPSP, as an active surveillance tool, addresses some of the barriers of the current passive surveillance process and reinforces the importance of information sharing and feedback in building a culture of reporting. Postmarketing surveillance of ADRs and the ongoing sharing of safety information remain urgent public health needs and are key to enhancing the benefit-risk profile of health products used in the paediatric population.

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