Adverse Drug Reaction Reporting Program of the Ontario Medical Association: the first 3 years

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This paper describes the Adverse Drug Reaction Reporting Program developed and operated by the Committee on Drugs and Pharmacotherapy of the Ontario Medical Association. Analyses were done to demonstrate some of the trends derived from the reports. Some of the clinical observations based on the reports, which are published quarterly and circulated to physicians and to pharmacy, nursing and hospital organizations, are also reviewed.

Description du programme de déclaration des effets nuisibles des médicamants (Adverse Drug Reaction Reporting Program) conçu et réalisé par le Comité des médicaments et de la pharmacothérapie de l'Association ontarienne des médecins. Analyse de quelques tendances ressortant de l'étude des déclarations. Revue de certains aspects cliniques de ces observations, qui font l'objet d'une publication trimestrielle à l'intention des médecins et des organismes pharmaceutiques, infirmiers et hospitaliers.

Prompted by a suggestion from the Chief Coroner's Office in Ontario that the mechanism for reporting adverse reactions to drugs in the province should be reviewed, the Ontario Medical Association (OMA), through its Committee on Drugs and Pharmacotherapy,* launched an Adverse Drug Reaction Reporting Program in February 1981. The committee believed that encouragement of Ontario physicians by their own association to send in reports of suspected adverse reactions to drugs from their practices might lead to an improvement in reporting, heightened critical awareness and closer monitoring of drug effects. The overall objective of the program was to help physicians select appropriate therapeutic agents.

Methods

The committee defined a suspected adverse drug reaction as follows: "Any undesirable clinical response which might be due to any drug(s) and which is considered to merit reporting." The definition was printed on each reporting form. It was not intended to restrict reports to suspected reactions to new drugs or unexpected reactions to older agents. A "serious" reaction was defined by the committee as "an organic lesion or psychological or somatic symptom which requires significant medical attention and/or significantly interferes with the patient's usual activities."

A simple bilingual reporting form was devised that was compatible with that used in the Adverse Drug Reaction Program of the Health Protection Branch (HPB) of the Department of National Health and Welfare in Ottawa. Patients' anonymity was guaranteed since their identification included only a code number or their initials. The form asked for the prescriber's name and the reporter's name and address, as well as the age and sex of the patient, the suspected drug, a list of drugs taken concomitantly, and a description of the reaction, its onset and outcome. The form was sent to all members of the OMA and to over 200 hospitals; later it was published periodically in the *Ontario Medical Review*. Discussions about the program were arranged with representatives of Ontario's other health care professions. After the reporting forms had been studied, copies were sent to the HPB to be incorporated into its computer program for storage, retrieval and subsequent transmission to other agencies, such as the World Health Organization.

Convinced that feedback to the reporters was important, the committee decided that all the reports it received would be acknowledged by a letter from the OMA together with another reporting form; the HPB agreed to supply the reporter with information concerning similar suspected adverse reactions. The committee also issued regular reports of the Adverse Drug Reaction Reporting Program.

To establish a definite cause-and-effect relation between a drug and an unwanted clinical event is notoriously difficult[1-10] and requires that several criteria be met, as outlined by Achong,[5] Venning[8,9] and Naranjo and colleagues.[10] These criteria include a temporal sequence, improvement when the drug was discontinued, recurrence when the patient

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was re-exposed to the drug and exclusion of other causes, such as the condition for which the drug had been prescribed. Rechallenge with a suspected drug was rarely reported (and not always warranted), so the committee decided to use in its reports the HPB's term, "suspected adverse drug reactions". We will use the generic names of the drugs throughout this paper, although the drugs were frequently reported by trade name. The committee held regular monthly meetings to review the adverse drug reaction reports and to prepare summaries and comments.

Results

In the first 3 years of the OMA program there were 4918 reports of suspected adverse drug reactions. Table I shows the distribution by year of some of the most frequently reported drug classes. The number of reports increased yearly. Slightly more than half of all the suspected reactions met the criteria for "serious" reactions — that is, they required specific medical treatment or interfered with the patient's normal activities.

More than a quarter of the suspected reactions were to antimicrobials, and of these reactions up to half were defined as serious. Slightly less than 10% of all the reports involved nonsteroidal anti-inflammatory drugs (NSAIDs), but 74% of these reactions in 1982–83 and 85% of those in 1983–84 met the criteria for serious reactions. About 10% of the suspected adverse reactions were associated with psychotropic drugs and 7% to 8% with analgesics; between one half and two thirds of these reactions were designated serious. In the last 2 years of the program radiologic dyes were suspected of provoking 13% to 16% of the reported reactions, about one fifth of which were serious.

These five classes of drugs accounted for 66% to 70% of all the reported suspected adverse reactions and for 57% to 69% of all the serious reactions. In the first 12 months after the introduction of the program in February 1981 the number of reports of adverse drug reactions by Ontario reporters increased by 59% over the number that had been submitted directly to the HPB in the previous 12 months.

The 10 drugs or diagnostic agents most frequently reported to the OMA as being associated with suspected adverse reactions over the 3 years of this study are shown in Table II. After the HPB computer had identified the 25 agents in each year that were most often reported as being associated with adverse reactions the agents were grouped into drug classes. In 1981–82 and 1982–83 there were more antibiotics than drugs of other classes in the top 25. The next most frequently reported drugs were NSAIDs, followed by radiologic diagnostic agents and opioids. The drugs in these four classes made up 60% to 76% of the 25 most frequently reported drugs.

Further analysis revealed that of 347 adverse reactions suspected to be associated with NSAID therapy

Table I—Distribution of suspected reports of adverse drug reactions by year and drug class

Class of drug	Year;* no. (and %) of reports 1981–82	1982–83	1983–84
Antimicrobials†	349 (26)	407 (28)	558 (26)
Radiologic dyes	27 (2)	227 (16)	270 (13)
Psychotropics	147 (11)	152 (10)	217 (10)
Nonsteroidal anti-inflammatory drugs (NSAIDs)	126 (9)	125 (9)	204 (10)
Analgesics	119 (9)	116 (8)	137 (7)
Others	574 (43)	433 (30)	730 (35)
Total	1342	1460	2116

*Each year includes reports received from Feb. 1 to Jan. 31.
†Includes sulfonamides, trimethoprim–sulfamethoxazole and antifungals.

Table II—The 10 agents most frequently reported as being associated with suspected adverse reactions over the 3-year period

Drug	Total period: Total no. of reports	Total period: Frequency ranking	Year; frequency ranking* 1981–82	1982–83	1983–84
Meglumine and sodium diatrizoate	333	1	3 (3)	1 (2)	1 (2)
Co-trimoxazole	286	2	1 (4)	2 (4)	2 (3)
Ampicillin	236	3	2 (2)	3 (3)	3 (4)
Amoxicillin	129	4	4 (6)	4 (5)	4 (9)
Piroxicam	99	5	7 (21)	5 (12)	5 (8)
Zomepirac sodium	82	6	5 (10)	11 (13)	12 (11)
Sodium diatrizoate	79	7	6 (14)	8 (†)	14 (21)
Meglumine iothalamate	73	8	† (17)	7 (8)	7 (6)
Morphine	68	9	21 (9)	8 (9)	8 (12)
Naproxen	62	10	13 (†)	19 (†)	12 (†)

*The numbers in parenthesis are for Canada and are from the Health Protection Branch (HPB) program; the others are from Ontario Medical Association reports. (In each of the 3 years diphtheria–pertussis–tetanus adsorbed vaccine ranked first in the reports to the HPB.)
†Not among the top 25.

and reported up to mid-1983, 46 consisted of gastrointestinal bleeding, 36 of peptic ulceration and 38 of edema. Acute asthmatic attacks were associated with naproxen therapy in three patients known to be sensitive to acetylsalicyclic acid; dizziness, ataxia and double vision occurred in three patients who were taking indomethacin. Symptoms such as anorexia, nausea, confusion, depression, amnesia and hallucinations were also reported but were much less common. There were occasional reports of generalized pruritus and rashes. In addition, there were 36 reports of severe anaphylactoid reactions, angioedema, respiratory distress, severe rashes or erythema associated with the use of zomepirac sodium.

Of the reported reactions, about 20% were in people 70 years of age or older, and more than 33% were in people 60 years of age or older. Patients under 10 years old were involved in 6.2% of the reports. In the 3-year period 63.1%, 63.2% and 60.3% (average 61.9%) of the reports, respectively, concerned female patients.

Over the 3 years there were 51 deaths reported in which drug-induced adverse reactions were suspected to have contributed (Table III). The deaths were not included when intentional overdoses were implicated, when antineoplastic agents had been used alone or with other drugs or when the suspected drug had been given to a patient who was terminally ill from other causes. Also not included are the deaths of three elderly people who had been given influenza vaccines. The mean age at which the 51 deaths occurred was 62.9 (extremes, 8 and 97) years, and 26 (51%) were in people 70 years of age or older.

NSAIDs were implicated in 16 of the deaths. Gastrointestinal bleeding occurred in 12 of the patients, and gross edema leading to congestive heart failure in 2, fluid retention and liver congestion in 1, and "sideroblastic anemia" and leukemia in 1. Piroxicam was reported to be implicated in six of these deaths. Antimicrobial drugs were implicated in eight deaths, four of which involved antibiotics (two tobramycin, one moxalactam and one rifampin), one a sulfonamide, one dapsone, one benzyl benzoate and one an antifungal agent. Antipsychotic agents were implicated in four deaths (haloperidol in three and perphenazine/phenelzine sulfate/flurazepam hydrochloride in one), anticonvulsants in three (phenytoin in two and carbamazepine in one) and antiarrhythmics in three (procainamide hydrochloride in two and disopyramide in one). Two deaths each were associated with bupivacaine hydrochloride, allopurinol and oral contraceptives. The other 17 deaths were reported to be associated with a wide variety of drugs, ranging from benzyl benzoate to methysergide, and from acetaminophen to warfarin.

The quality of the adverse drug reaction reporting was assessed independently by two of the committee members, one a physician (M.B.) and the other a pharmacist (G.N.R.). They reviewed all the reports received in 1 month in 1981 and in the same month in 1982. The reports were scored for completeness as to the information requested on the form. Of the 117 reports received in November 1981 an average of 92% of the items requested were filled in; 43% of the forms were complete. The corresponding figures for the 140 reports in 1982 were 94% and 52%.

The reports were also assessed as to the probable accuracy of the suspected relation between the adverse reaction described and the drug product named by the reporter as the suspected agent. Of the 257 reports received in 1981 and 1982 the probable accuracy was scored as good/excellent for 86%.

Following the monthly reviews of the adverse drug reaction reports the committee prepared quarterly reports, which were published in the *Ontario Medical Review* until the middle of 1983. Since then they have been published by the OMA as *The Drug Report*.

Table III—Number of deaths reported to be associated with suspected adverse drug reactions over the 3-year period

Class of drug	No. (and %) of deaths	Mean age (and extremes) at time of death (yr)*
NSAIDs	16 (31)	77.4 (40, 95)
Antimicrobials	8 (16)	64.8 (8, 86)
Antipsychotics	4 (8)	60.0 (48, 97)
Anticonvulsants	3 (6)	50.3 (21, 85)
Antiarrhythmics	3 (6)	NK (68, 82)
Others	17 (33)	49.9 (8, 78)
Total	51 (100)	62.9 (8, 97)

*NK = not known.

Discussion

The aim of the Adverse Drug Reaction Reporting Program was not simply to accumulate more numbers or primarily to discover hitherto unsuspected adverse drug reactions but, rather, to foster an awareness of the potential for harm of powerful drugs, some of which were marketed before they were completely investigated. According to a 1982 editorial in the *British Medical Journal*:[11]

> Newness should not be seen as a virtue in a pharmaceutical product. Indeed, the crucial need is for doctors to think more carefully before prescribing a new . . . drug. If the new preparation really does seem to have advantages that outweigh the risks implicit in its novelty, then the prescribing doctor must accept that his decision should carry with it an obligation to be alert for all "events", to record them, and to report any possible adverse reactions quickly.

Karch and Lasagna[1] complained, and we agree, that the data on adverse drug reactions are incomplete, uncontrolled and lacking in operational criteria; hence, no quantitative conclusions can be drawn as to morbidity, mortality or the underlying causes of the reactions. The true frequency of adverse reactions to a given drug is rarely known because neither the exact number of adverse reactions nor the number of patients taking the drug over a given

period are available for analysis. At no time did our committee state that the incidence of severe reactions was known to be greater with one drug in a class (e.g., NSAIDs) than with others. Determining the true frequency of adverse reactions when two or more drugs are involved is even more difficult.[12] Even when there appears to be a relation between an adverse reaction and treatment with a pharmaceutical preparation it is sometimes difficult to decide whether the drug or one of the dyes or other pharmaceutical excipients was responsible.[13] Moreover, some patients are known to respond adversely in certain situations: reports of a wide variety of "adverse drug reactions" in patients given placebos during drug trials are common, and there are even reports of such reactions in patients who have received no drugs.[14]

Our results indicate that the reports of adverse drug reactions in elderly patients were disproportionately high considering the fraction of the population they represented. Indications of more potential harm than benefit in some elderly people were reported in association with oral hypoglycemics, NSAIDs, neuroleptics, antidepressants and benzodiazepines. The greater susceptibility of the elderly to the anticholinergic actions of antidepressant drugs and diphenhydramine was inferred from several of the reports.

The continuing reports of adverse drug reactions associated with the use of NSAIDs that were received over the first 3 years of our program suggested that elderly patients with arthritic symptoms were most at risk. The severity of the gastrointestinal hemorrhages, sometimes without premonitory symptoms, that were reported in association with these drugs led the committee to issue a warning to the medical profession, although it knew it did not have, and would be unlikely to obtain, sufficient firm data so that the true incidence of severe adverse drug reactions could be estimated for any one of the drugs. A table summarizing the reports of the adverse reactions suspected of being associated with NSAIDs that had been received over the first 23 months of our program was published in the *OMA Bulletin* in February 1983,[15] and subsequently a table of the serious reactions reported during the first 6 months of 1983 was published.[16] Linton[17] has recently warned of "potentially as dangerous" side effects of NSAIDs on renal function, electrolytes and blood pressure.

The task of relating adverse reactions to specific drug products is made even more difficult by the widespread use of "generic equivalents", and the prescriber may often not know which product the patient actually received. Several reporters attributed adverse effects to the patient's receiving a "generic" drug product and stated that no problems had been noted when the relevant trade-name preparation had been taken.

The analysis of how adverse reactions to new drugs are discovered revealed great variation,[2] but unsuspected adverse drug reactions were identified after marketing and were often attributed to case reports by alert physicians who had used spontaneous reporting mechanisms.[8,18–20] The extent of under-reporting is not uniform and may be subject to bias when there is publicity concerning a suspected adverse reaction that will contribute to more publicity.[9] This is probably what happened in our program with the reporting of suspected reactions to newer NSAIDs.

The incidence of fatal drug reactions in patients who met the criteria for definite or probable adverse reactions was estimated to range from 0 to 0.3% among medical ward patients.[1] Koch-Weser[21] claimed that the true number cannot be established without further large-scale epidemiologic studies. With careful analysis and with use of the validation criteria and the definition of the World Health Organization to rule out suicidal overdoses, errors, malignant conditions treated with cytostatics, and so forth Irey[22] found that only 220 of almost 2000 patients in whom autopsies had been done and for whom the findings had been submitted to the American Registry of Tissue Reactions to Drugs met the criteria for an adverse drug reaction "in the strict definitional sense". There was a wide range in the age distribution of the 200 patients, with about 50% of them being in the third to fifth decades; this is in contrast to the 51 deaths that we analysed, of which 22% occurred in people between 20 and 49 years of age.

Conclusions

In the first 3 years of the program 4918 reports of suspected adverse drug reactions were received. Of these about half were deemed serious enough to require medical attention or interfere with the patient's usual activities, or both. Five drug classes — antimicrobial/antifungal agents, NSAIDs, psychotropics, analgesics and radiologic dyes — accounted for nearly two thirds of the suspected drug reactions. Of all the reactions reported, about 20% were in patients 70 years of age or older, and 6.2% were in those under 10 years old; 61.9% involved female patients. Drug-induced reactions were suspected of contributing to 51 deaths, 26 of them in people 70 years of age or older.

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The power of the printed word

How is it possible to control man's mental evolution so as to make him proof against the psychoses of hate and destructiveness. Here I am thinking by no means only of the so-called uncultured masses. Experience proves that it is rather the so-called Intelligentzia that is most apt to yield to these disastrous collective suggestions, since the intellectual has no direct contact with life in the raw but encounters it in its easiest synthetic form — the printed page.

—Albert Einstein (1879–1955)