Canadian Adverse Drug Reaction Newsletter
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Adverse drug reaction reporting — 1996

More than 4000 spontaneous case reports in Canada were submitted to the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) in 1996. These reports were received from a variety of sources (Fig. 1). Most of the reports were from drug manufacturers, which are under regulatory obligation to systematically forward certain reports that come to their attention. A significant number of the reports also came from the 4 regional ADR centres affiliated with the CADRMP. Two of their objectives are to increase awareness and participation in ADR reporting in their respective regions. Other important sources of reports were hospitals, many of which have programs in place for identifying and reporting ADRs, and physicians, pharmacists and others who reported directly to the CADRMP.

In most cases, the people who initiate the reports are health professionals (physicians, pharmacists, nurses, dentists, coroners and others) who *suspect* that a drug has played a role in the adverse reaction and who voluntarily complete an ADR reporting form and forward it directly to the CADRMP or indirectly through one of the other sources. The CADRMP would like to thank all of you for your important contribution to

monitoring the safety of drugs in Canada and to encourage you to continue your efforts.

This article is under the responsibility of: Claire-Marie Wray, PhD, Bureau of Drug Surveillance

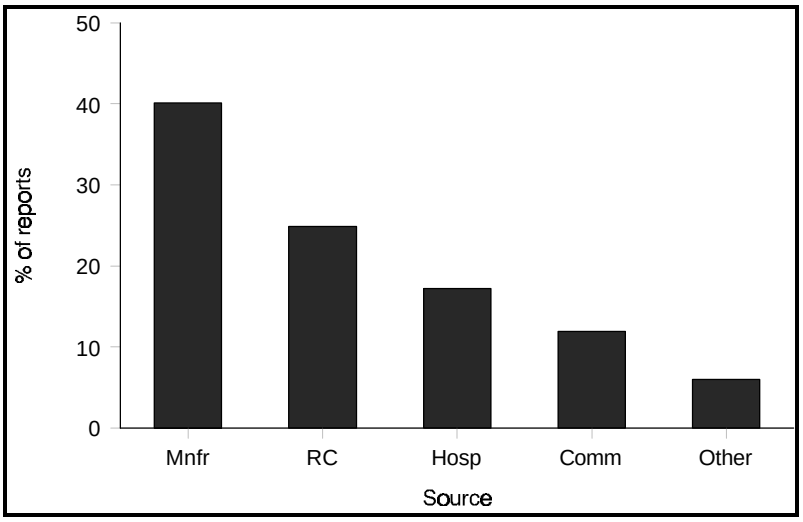

Fig. 1: Source of reports of adverse drug reactions (ADRs) in Canada in 1996. Mnfr = drug manufacturers, RC = regional ADR centres, Hosp = hospitals, Comm = pharmacists and physicians in the community, and Other = professional associations, nursing homes, Health Protection Branch regional inspectors, coroners, nurses, dentists and others.

Potential abuse of butorphanol nasal spray

Since November 1994 the CADRMP has received 48 reports of ADRs associated with the administration of butorphanol tartrate nasal spray (Stadol NS™). The CADRMP reviewed 15 reports that indicated suspected drug-seeking behaviour, drug abuse or addiction.

The age of the patients (9 women, 3 men, 3 sex not specified) ranged from 22 to 51 years (age was unknown in 6 cases). The reasons for use were stated as migraine and migraine headache (8 cases), headache (2 cases), and cluster headaches and intractable migraine (1 case); a reason was not documented in 4 cases.

Information on the total number of bottles used, the duration of therapy and any other significant comments in the reports is provided in Table 1. Significant findings from these reports include the receipt by 1 patient of 257 bottles of the nasal spray over 9 months and the receipt by 4 patients of prescriptions from 2 or more practitioners. One of the 4 patients received prescriptions from 34 practitioners and had them filled at 23 different pharmacies. In addition, 4 patients had been or were currently using opioid medications such as drugs containing codeine or oxycodone or meperidine, 2 had a history of opioid abuse, and 1 had a history of alcohol abuse.

In addition to these 15 abuse-related ADR reports, the Bureau of Drug Surveillance received 41 Psychoactive Drug Loss/Theft/Forgery reports indicating that, from February 1995 to May 1996, 2 units of butorphanol nasal spray were lost, 11 were obtained by forged prescriptions, and 53 were stolen (48 by break and entry on different occasions and 5 by armed robbery).

Furthermore, in January 1997 butorphanol nasal spray was added to one province's Prescription Practice Program. This program monitors prescriptions filled by pharmacists to screen for such anomalies as abuse, multiple prescribers and prescription forgeries.

Although butorphanol nasal spray may have a lower abuse potential than morphine, reports suggestive of possible abuse are mentioned in the precautions section of the current product monograph. The section also states that special care should be exercised in administering butorphanol to emotionally unstable patients and to patients with a history of drug misuse.

The CADRMP would like to remind health practitioners of its interest in receiving any report on abuse-related reactions. This information contributes to the determination of the relative potential for abuse of any drug. Furthermore, drug abuse or dependence is considered a serious ADR because it can be life-threatening or may result in persistent or significant disability.

Additional information on butorphanol nasal spray

Butorphanol nasal spray (Stadol NS™) is a controlled drug under Schedule G of the Food and Drugs Act and was approved for marketing in Canada in July 1994. It is indicated for the relief of moderate to severe acute pain. As stated in the product monograph, butorphanol acts as an agonist at kappa-opioid receptors and a mixed agonist-antagonist at mu-opioid receptors in the central nervous system to alter the perception of pain. Although, as a class, the mixed agonist-antagonist opioid analgesics have a much lower abuse potential than morphine, all such drugs have been reported to be abused.

The analgesic potency of butorphanol is about 4 to 8 times that of morphine, 30 to 40 times that of meperidine and 16 to 24 times that of pentazocine.<1> The onset of action and the

systemic bioavailability of butorphanol administered intranasally are similar to those achieved following parenteral administration.

Table 1: Details of 15 abuse-related adverse reactions to butorphanol nasal spray

Case	Age/sex	Duration of therapy	No. of bottles used*	Additional comments in report
1	30/F	20 d	23	Patient complained that 1 bottle contained water
2	44/F	4 mo	83	Prescriptions from 2 doctors; dependence problems
3	22/F	4½ mo	24	Prescriptions from several doctors; renewed every few days
4	NS+/F	6 mo	105	Prescriptions from 34 doctors; filled at 23 pharmacies
5	NS/M	7 mo	80	Concomitant use of drugs containing codeine or oxycodone; patient requested replacement of 6 bottles, negotiated the number of refills and reported problems with the seal and pump mechanism
6	42/F	8 mo	NS; use listed as "out of control"	History of similar use of drugs containing codeine; patient admitted to hospital for 11 d for withdrawal
7	30/F	9 mo	257	
8	51/M	l yr	1 every 1-2 wk	Concomitant use of drugs containing codeine; patient claimed lack of effect of butorphanol; patient requested replacement of 2 bottles
9	NS/NS	≥1 yr	≥ 2 per wk	
10	NS/M	NS	115	
11	33/F	NS	Peak use: 1 bottle or 10 doses daily	Use escalated quickly
12	Late 40s/F	NS	NS; drug used every day	Patient claimed that bottle was underfilled; physician doubts authenticity of patient's claim and believes that patient abuses butorphanol
13	28/F	NS	NS	Patient claimed that bottle had been diluted and requested replacement; name is on a pharmacists' network alert list of narcotic abusers; history of use of meperidine and a drug containing codeine
14	NS/NS	NS	2 per wk	Primary drug of abuse was an opioid
15	NS/NS	NS	3 per wk	Prescriptions from different doctors; history of alcohol abuse

*One 2.5 mL bottle provides 14-l5 intranasal doses of l mg each.
†NS = not stated.

This article is under the responsibility of: Pascale Springuel, BPharm, Bureau of Drug Surveillance

Reference

1. Gillis JC, Benfield P, Goa KL. Transnasal butorphanol: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in acute pain management. *Drugs* 1995;50:157-75.

Aminoglycoside ear drops and ototoxicity

Ototoxic effects are well-documented, clinically important side effects of parenteral aminoglycoside use.<1> However, not as well documented are ototoxic effects from topical aminoglycoside use.<2> Although aminoglycoside ear drops are generally considered safe when used in the presence of an intact tympanic membrane, controversy exists in the literature as to their safety in the presence of a membrane defect.<2–4>

Ear drops may pass into the middle ear through a perforation in the tympanic membrane and reach the inner ear through the round window membrane. The resulting ototoxicity is in the form of cochlear damage (tinnitus and hearing loss) or vestibular damage (vertigo and loss of balance), or both. The onset is variable. Ototoxicity may appear rapidly with short-term exposure, slowly during administration or some time after therapy has stopped. It begins with tinnitus (most often a high-pitched ringing) and progresses to high-tone sensorineural hearing loss and vestibular dysfunction, which may only be detected by special tests (audiography, speech tests and electronystagmography with air caloric). Because of the insidious nature of these effects and the minimal symptoms, significant functional hearing and vestibular loss may occur before ototoxicity is detected.

The CADRMP has received 7 reports in which the use of Garasone™ ear drops (gentamicin sulfate and betamethasone sodium phosphate) in the presence of tympanic-membrane perforation resulted in ototoxicity. A summary of the cases follows:

- The average age of the patients was 50 (range 32–66) years; 4 were women and 3 were men.
- Tympanic-membrane defects were due to an accidental perforation (1 case), chronic ear problems (4), and bilateral myringotomy and tube insertion (2).
- All patients were prescribed Garasone™ drops to treat middle-ear disorders with or without otorrhea. Some were also prescribed oral antibiotic therapy (those specified were cefaclor, cefixime, ciprofloxacin and amoxicillin–clavulanate). The ear drops were used for 10 days to 4 months, and in 1 case of chronic ear discharge they were used intermittently for 2 years.
- Complaints were of imbalance, vertigo, ataxia, oscillopsia (visual blurring with head movement), tinnitus and hearing loss.
- Subsequent investigations (vestibular testing and audiometry) confirmed the absence or reduction of vestibular function as well as high-frequency sensorineural hearing loss in all cases (bilateral in 5 cases, unilateral in 2).
- All patients were severely affected by the ototoxicity and some were incapacitated. The drops were stopped. At the time of reporting, there was no improvement in their symptoms. No other identifiable causes have been found that would explain their status.
- In all the cases the reporter felt that the adverse events were related to the ear drops.

Although the CADRMP has not received reports of similar ADRs for other aminoglycoside otic preparations, *all* aminoglycosides are capable of affecting both cochlear and vestibular function.<1> Some preferential toxicity is evident. Of the aminoglycosides commonly found in ear drops (gentamicin, neomycin and framycetin) neomycin and framycetin primarily affect auditory function, and gentamicin primarily affects vestibular function. In the absence of hearing loss, the vestibular toxicity of gentamicin is often missed or is assumed to be inadvertently due to labyrinthitis.<4,5>

Despite the widespread use of aminoglycoside ear drops, ototoxicity in the presence of tympanic-membrane defects appears to occur in a small percentage of patients.<3,4> However, its incidence and prevalence may be higher than reported because of the difficulty in distinguishing between the natural course of the disease and the drug's toxicity. Because hearing loss and vestibular paralysis are permanent in most cases, emphasis must be placed on prevention. In most of the cases summarized in this article, hearing loss occurred after prolonged use of the ear drops in the presence of tubes or tympanic-membrane perforation. The following precautions in the treatment of ear infections in such situations have been suggested:<2,4,5>

- The drops should be used for the shortest duration possible.
- Instruct the patient precisely regarding the dosage and duration of therapy.
- Have the patient apply the drops onto a carrier medium such as a gauze strip.

- Advise the patient to stop the treatment as soon as the discharge subsides.
- Advise the patient to stop the treatment if hearing loss, tinnitus, vertigo or imbalance is noted.
- Reassess the need for ear drops 5–7 days after the start of treatment.

For patients with tympanic membrane defects, the risks of using aminoglycoside otic preparations should be weighed carefully against the benefits.

This article is under the responsibility of: Amal Hélal, BSc Phm, Bureau of Drug Surveillance

References

1. Dukes M, editor. *Meyler's side effects of drugs*. 12th ed. Amsterdam: Elsevier; 1992.
2. Linder TE, Zwicky S, Brandle PB. Ototoxicity of ear drops: a clinical perspective. *Am J Otology* 1995;16:653-7.
3. Welling DB, Forrest LA, Goll F III. Safety of ototopical antibiotics. *Laryngoscope* 1995;105:472-4.
4. Rutka JA, Wong DLH. Do aminoglycoside otic preparations cause ototoxicity in the presence of tympanic membrane perforations? *Otolaryngol Head Neck Surg* 1997. In press.
5. Longridge DB. Topical gentamycin vestibular toxicity. *J Otolaryngol* 1994;23:444-6.

Spontaneous reporting of suspected adverse drug reactions (ADRs) is a critical ongoing source of drug-safety information. Thus, we encourage health professionals to report any suspected ADRs to one of the following addresses:

British Columbia

BC Regional ADR Centre

c/o BC Drug and Poison Information Centre

1081 Burrard St.

Vancouver BC V6Z 1Y6

fax: 604 631-5262; tel: 604 631-5625

Saskatchewan

Sask ADR Regional Centre

Dial Access Drug Information Service

College of Pharmacy and Nutrition

University of Saskatchewan

Saskatoon SK S7N 5C9

fax:306 966-6377;tel:306 966-6340 or 800 667-3425

Quebec

Quebec Regional ADR Centre

Centre d'information pharmaceutique

Hôpital du Sacré Coeur de Montréal

5400, boul. Gouin ouest

Montréal QC H4J lC5

fax: 514 338-3670; tel: 514 338-2961 or

338-2161 (collect calls accepted)

Nova Scotia, New Brunswick,

Newfoundland and Prince Edward Island

Atlantic Regional ADR Centre

Queen Elizabeth II Health Sciences Centre

New Halifax Infirmary Building

Level 200, Drug Information Centre

1796 Summer St.

Halifax NS B3H 3A7

fax: 902 473-8612; tel: 902 473-7171

Other provinces and the territories

Adverse Drug Reaction Reporting Unit

Continuing Assessment Division

Bureau of Drug Surveillance

Drugs Directorate

AL 4103B1

Ottawa ON K1A 1B9

fax 613 957-0335; tel 613 957-0337

Please Note: A voluntary reporting system thrives on intuition, lateral thinking and openmindedness. Eor these reasons, most adverse drug reactions (ADRs) can be considered only to be suspicions, for which a proven causal association has not been established. Because there is qross underreporting of ADRs and because a definite causal association cannot be determined, this information cannot be used to estimate the incidence of adverse reactions.

ADRs are nevertheless invaluable as a source of potential new and undocumented signals.