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15. WESTBURY RC: *The Content of a Calgary Family Practice, 1967-1971,* MD thesis, Cambridge U, Cambridge, England (submitted)
16. TARRANT M: What price admitting privileges? A study of hospital admissions by two family physicians. *Can Fam Physician* 23: 837, July 1977
17. *International Classification of Health Problems in Primary Care,* American Hospital Association, Chicago, 1975
18. HEBB AMO: Reports on Nova Scotia Fetal Risk Project, 1971–76, national health grant 602-7-147

Adverse drug reactions: uncommon or unrecognized?

Clinically important drug interactions that are predictably beneficial to the patient are the mainstay of optimal drug therapy for such disorders as malignant disease, hypertension, arrhythmias and infections. Harmful drug interactions have been unduly emphasized with respect to overall importance, and their mechanisms are considerably misunderstood.[1]

The reported frequency of interactions is dependent on the definitions and criteria applied. For example, when drug interactions were "diagnosed" by comparing patients' prescriptions with a computer bank of 24 000 drug interactions reported in the literature, it was found that every day 9% of patients had an adverse interaction.[2] When strict criteria for what is a potentially serious interaction were applied, the maximum predicted frequency was 1.2%. In contrast, in the Boston collaborative drug surveillance program only 0.28% of patients had a clinically recognized adverse interaction.[2]

For almost all specific adverse drug interactions the true frequency is not known since the frequency of coadministration of two drugs without interaction is not known; conversely, the frequency with which undetected interactions occur is also unknown. Even if the frequency of interaction is known, the concurrent prescription of two drugs with a potential for serious adverse interactions does not have any predictive value as to the likelihood of such an interaction in a particular patient. In the absence of more specific information, combinations of frequently implicated drugs should be avoided; for example, coumarin anticoagulants (e.g., warfarin), orally administered hypoglycemics (e.g., tolbutamide), antiseizure medications (e.g., phenytoin) and anti-inflammatory agents (e.g., phenylbutazone). However, drugs that are proven to frequently induce clinically important adverse drug interactions can safely be given, when it is essential, with dose adjustment or extra observation of the patient or both.

In this issue of the Journal (beginning on page 1261), Cass, Kadar and Stein focus attention on a large number of potential and often predictable interactions among drugs that affect the autonomic nervous system. Interactions among β-blockers, sympathomimetic agonists (e.g., ephedrine, phenylephrine and salbutamol), tricyclic antidepressants, phenothiazines and antihypertensive agents must occur commonly, and occasionally will be important. When drugs with such pharmacologic potential are given together, the patient should be watched carefully when administration of the second drug is started or stopped. For example, if phenylephrine is given to a patient taking reserpine or guanethidine, both α-adrenergic receptor sensitivity and blood pressure will increase.[3] The fatal outcome in the case reported by Cass and colleagues was due to the presence of an aneurysm, which made any increase in blood pressure dangerous for the patient. The administration of eye drops containing 10% phenylephrine can alone raise the blood pressure a little in some patients.[4] The magnitude of the increase and the probability that it will be clinically important are determined by the dose of phenylephrine, the technique used to instil the eye drops, whether there is conjunctival inflammation, whether the drops reach the nasal mucosa and whether the responsiveness of the cardiovascular system is altered. In the patient

described by Cass and colleagues 5 to 10 times the recommended intravenous dose of phenylephrine could have been absorbed.

Propranolol is effective and, in most instances, safe to use in the management of hypertension, angina pectoris and arrhythmias. However, its nonselective reversible blockade of β_1- and β_2-receptors can result in a variety of potential interactions with sympathomimetic drugs. The bradycardia produced by propranolol abolishes the reflex lowering of the heart rate if the blood pressure increases; with blockade of the β_2-receptor-mediated vasodilation in muscles one mechanism of decreasing peripheral vascular resistance is impaired. Since it is not known when Cass and colleagues' patient last took propranolol, the possibility of β-receptor hypersensitivity, which occurs 24 to 48 hours after propranolol is discontinued, might be considered.

Finally, because of the aneurysm and the decreased baroreceptor sensitivity associated with hypertension, the patient's reflexes may not have been called into play quickly enough to offset the rise in blood pressure.

Reports on drug interactions and adverse reactions generally do not critically evaluate the certainty of the suspected link between the drug or drugs and the untoward clinical event.[5] Several definitions of such events should be kept in mind:[6]

- Definite: An event that follows a reasonable temporal sequence from administration of the drug(s), or in which the concentration of the drug(s) has been established in body fluids or tissues; that follows a known pattern of response to the drug(s); and that is confirmed by improvement when administration of the drugs (dechallenge) is stopped and reappearance of the reaction when administration is begun again (rechallenge).
- Probable: An event that follows a reasonable temporal sequence from administration of the drug(s); that follows a known pattern of response to the suspected drug(s); that is confirmed by dechallenge; and that could not be reasonably explained by the known features of the patient's clinical state.
- Possible: An event that follows a reasonable temporal sequence from administration of the drug(s); and that follows a known pattern of response to the suspected drug(s); but that could readily have been produced by the patient's clinical state or other modes of therapy.
- Conditional: An event that follows a reasonable temporal sequence from administration of the drug(s); that does not follow a known pattern of response to the suspected drug(s); but that could not be reasonably explained by the known features of the patient's clinical state. This category allows for later reclassification of as yet undescribed adverse drug reactions when more information becomes available.
- Doubtful: An event that does not meet the above criteria.

On the basis of these definitions, the case reported by Cass and colleagues could be categorized as either a possible or a conditional drug interaction. If one accepts as sufficiently analogous the fact that the administration of epinephrine to volunteer subjects taking β-blockers will increase peripheral vascular resistance[7] the drug interaction could be considered possible. The reaction could be considered conditional because that particular drug interaction has not previously been reported. Most drug interactions are difficult to categorize unequivocally as to probability and cause because of the lack of uniqueness of the features of the reactions, and because definitive cause–effect tests cannot or have not been performed.

The case reported by Cass and colleagues may illustrate how a combination of drugs, local absorption factors and disease could result in a therapeutic misadventure. In this respect then, case reports are an important means of alerting others to clinically important interactions. However, such case reports, by their very nature, cannot indicate whether the combination of drugs caused the observed clinical problem, what the frequency of that interaction is or when that interaction is clinically important. For answers to these questions case reports must be followed up by scientific study. Unfortunately, case reports, in vitro studies and laboratory studies of interactions in animals have a tendency to become enshrined as scientific fact, are repeated by well meaning reviewers, lecturers and clinical pharmacists and entered into highly efficient and nonerasable computer retrieval systems.

This case report and evidence in the literature should prompt ophthalmologists to review the routine use of eye drops containing 10% phenylephrine. The smaller amounts of phenylephrine in over-the-counter preparations probably do not constitute a serious hazard for interaction with propranolol and other antihypertensive agents. Nevertheless, this is a conditional statement since a systematic study has not been done. Proper scientific study is needed to determine the clinical importance, absolute frequency and causality of drug interactions with propranolol. Extra care should always be taken when drugs with a potential to interact are administered.

E.M. SELLERS, MD, PH D, FRCP[C], FACP
Head, joint division of clinical pharmacology
Toronto Western Hospital
and Clinical Institute
Addiction Research Foundation
University of Toronto
Toronto, Ont.

References

1. SELLERS EM: The clinical importance of interactions based on displacement of protein bound drugs, in *Proceedings of the VIIth International Congress on Pharmacology* (in press)
2. GOUVEIA WA, MILLER RR: Drug interaction screening — a screen or sieve? (E). *Am J Hosp Pharmacol* 35: 667, 1978
3. KIM JM, STEVENSON CE, MATHEWSON HS, et al: Hypertensive reactions to phenylephrine eyedrops in patients with sympathetic denervations. *Am J Ophthalmol* 85: 862, 1978
4. MATTHEWS TG, WILCZEK ZM, SHENNAN AT: Eye-drop induced hypertension (C). *Lancet* 2: 827, 1977
5. KOCH-WESER J, SELLERS EM, ZACEST R: The ambiguity of adverse drug reactions. *Eur J Clin Pharmacol* 11: 75, 1977
6. KARCH FE, LASAGNA L: Adverse drug reactions: a critical review. *JAMA* 234: 1236, 1975
7. HARRIS WS, SCHOENFELD CD, BROOKS RH, et al: Effect of beta adrenergic blockade on the hemodynamic responses to epinephrine in man. *Am J Cardiol* 17: 484, 1966