Discovering Adverse Drug Reactions

Sophisticated, adj.: adulterated, complex, worldly-wise, knowing, subtle, intellectually appealing, devoid of the obvious traditional or popular appeal (Webster's Third New International Dictionary).

When a new drug is marketed, one can be sure that not everything (good or bad) about the drug is known. There are always some surprises in store. Sometimes they are pleasant surprises. When lidocaine was introduced as a local anesthetic, who would have dreamed that it would one day become a drug of choice for terminating cardiac arrhythmias? Diazepam used to carry labeling that its use was hazardous to epileptics; it went on to be recognized as a treatment for status epilepticus. Probenecid was first used to augment the effects of penicillin by preventing the tubular secretion of the latter drug; today it is useful as a uricosuric agent in the treatment of gout. Aspirin, first marketed as a simple analgesic, is now not only a major drug for treating arthritis but can prevent vascular thrombosis. These are just a few of the many examples one could cite.

The public, however, tends to be more concerned with the unpleasant surprises—the phocomelic babies whose mothers took thalidomide early in pregnancy; the hepatic and renal dysfunction in patients taking ticrynafen or benoxaprofen, which resulted in the withdrawal of these drugs from the market; the strokes in young women taking oral contraceptives; and the vaginal adenocarcinoma in young women whose mothers took diethylstilbestrol during pregnancy.

In recent years, there has been a growing tendency for manufacturers in the United States to agree to conduct formal postmarketing surveillance as a condition of approval of a new drug application. One of the earliest occurred in 1970, when levodopa was approved by the Food and Drug Administration (FDA), provided that the sponsor would obtain additional evidence on the drug's safety and efficacy.[1] There was good reason for this arrangement: the drug was a remarkable therapeutic advance; patients and physicians were clamoring for access to it, but the long-term animal toxicity studies were not yet completed, and no one knew what the long-term effects (beneficial or harmful) would be. Some 1,500 patients were followed for up to six years. No new adverse drug reactions (ADRs) were revealed by the study, which was reassuring to the manufacturers, the regulatory agency, the prescribing physicians, and consumers.

In this issue of THE JOURNAL (p 2226), Rossi et al describe the experience with three other so-called Phase IV studies. Each of these was considerably larger than the levodopa study referred to herein; approximately 10,000, 7,000, and 22,000 patients were involved. For two of the three drugs involved, new ADRs have been recognized since approval, but in no case did the new information come from the formal Phase IV data. Instead, the additional light was shed by that often deprecated source of insight—spontaneous reporting by physicians.

Rossi et al suggest that perhaps the trouble lay in expecting too much from sample sizes that were too small. They do not, however, go so far as to suggest that perhaps this numbers game cannot easily be won.

Wardell and colleagues[1,2] have made some sobering calculations. They point out that the sample size needed to detect a

difference between an incidence rate of 1/10,000 and 2/10,000 at the 90% power level (using a two-sided test, α=0.05) is 306,000 (for each group, eg, placebo [or no treatment] and new drug). Some serious toxic reactions—like the aplastic anemia of chloramphenicol—occur considerably less frequently than this, perhaps 1/20,000 to 1/40,000.

The sample size needed depends not only on the β-error chosen (ie, the risk of missing a real difference) and the α-error (ie, the risk of calling a difference real when it is not) but on the baseline incidence of the effect of interest. Hardly any drug effect is unique. The bad things a drug does almost always can be seen in the absence of the drug. Furthermore, we are also usually in a poor position to link a drug with an effect through laboratory tests or dechallenge-challenge experiments.

Suppose that we say we're interested in a "doubling" of the incidence of a given symptom or pathological effect. If the effect in question occurs not 1/10,000 people (as in the example above) but in 10/10,000, for a doubling of this effect by a drug (ie, to 20 per 10,000), the numbers needed drop from 306,000 per treatment group (for a power of 90%) to a tenth of this figure, ie, 30,600 per treatment group. These latter figures remain, however, formidable ones.

What can one conclude from all of this? First, I see little hope for identification of really rare serious ADRs from postmarketing surveillance schemes of the type analyzed by Rossi et al. This is infinitely more obvious if a new drug is to be used for relatively rare diseases or does not achieve notable popularity in the marketplace for other reasons.

Second, the imposition of formal Phase IV schemes, for whatever reason (such as a political one), must not lead physicians to underestimate their own importance in the discovery of new information about drugs. Spontaneous reporting by the alert and competent physician will, for the foreseeable future, remain the most important source of new leads about drugs. There is much information that cannot be completely assessed before marketing: How well do physicians and patients use a drug? Are the doses recommended on the basis of premarketing studies optimal? What is the impact of the drug's interactions with other drugs, with various disease states, and with genetic differences? Will the drug turn out to be abused by persons seeking nontherapeutic drug effects? What is the clinical picture in cases of massive overdose? Are there any important uses not predicted by earlier studies? It is essential, therefore, to study drugs after they are marketed, as well as before. But we must not equate this need with the need for formal monitoring of a given group of patients intended only to discover new ADRs, or even intended to check out premarketing estimates of observed toxicity. To do so is to fly in the face of all we know.

Rossi et al state that spontaneous reporting is usually viewed "as the least sophisticated and scientifically rigorous . . . method of detecting new adverse drug reactions." This may be true in Webster's dictionary sense of sophisticated meaning "adulterated," "devoid of the obvious traditional or popular appeal," or "complex," but I submit that spontaneous reporting is more "worldly-wise, knowing, subtle, and intellectually appealing" than grandiose, expensive Phase IV schemes that divert funds and manpower away from more useful pursuits and increase the price of drugs to consumers.

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1. Wardell WM, Tsianco MC, Anavekar SN, et al: Postmarketing surveillance of new drugs: II. Case Studies. *J Clin Pharmacol* 1979;19:169-184.
2. Wardell WM, Tsianco MC, Anavekar SN, et al: Postmarketing surveillance of new drugs: I. Review of objectives and methodology. *J Clin Pharmacol* 1979;19:85-94.