MEDICAL PRACTICE

Contemporary Themes

Postmarketing surveillance of adverse drug reactions in general practice**I: Search for new methods**

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Abstract

Spontaneous reporting of suspected adverse drug reactions through the yellow card system provides an effective means of early warning of potentially serious drug effects but occasionally fails because of under-reporting. Since more than 80% of medicines are prescribed by general practitioners we look to them to support new methods of postmarketing surveillance. No single method will be appropriate for all drugs, and yellow cards will always be required to detect rare events. It is proposed that adverse events experienced by the first 10 000 patients who receive certain new medicines should be recorded and transmitted to a monitoring centre and that a realistic target, which should be reached early in the market life of a new medicine, is the detection of any adverse event that occurs in more than one in 1000 patients.

Introduction

It has to be admitted that, two decades after the thalidomide tragedy which focused our attention on the need for vigilance, the present arrangements for monitoring adverse drug reactions are still far from satisfactory.

The well-tried yellow card system will continue to be in the front line of our defences, but experience with practolol and other drugs that produced effects not readily identified as

adverse drug reactions leads us to continue our search for new methods that will speed detection without adding appreciably to the burden of paperwork imposed on the profession.

The problem

Laboratory studies of animal toxicity sometimes eliminate otherwise promising drugs from trial in man but also, on occasions, fail to predict the toxicity that unfortunately, and perhaps inevitably, occurs from time to time when drugs are used in man.

Clinical trials may not detect uncommon adverse drug reactions—for example, those affecting less than 1% of those who take the medicine—because they are conducted in hundreds rather than thousands of patients or because they are often restricted to selected groups that do not include certain classes, such as pregnant women, the elderly, or the very young. Nor will premarketing studies identify adverse drug reactions that are long delayed. The issue of a product licence, however careful the scrutiny of animal or clinical trial data, does not ensure that a medicine will be safe in subsequent prescribing practice—no effective drug is totally safe. The licence merely means that, at the time of issue, no hazards unacceptable to the licensing authority have been identified.

The yellow card system has, over the years, brought to light many previously unsuspected adverse drug reactions and has also helped us to follow up clues from anecdotal case histories in medical journals or reports by manufacturers. Occasionally the yellow cards have indicated the need for a public warning or, more frequently, for “low-key” action to modify manufacturers’ claims or prescribing instructions. Occasionally they have led to advice to manufacturers to remove drugs from the market. On other occasions, field studies of the reports have been

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reassuring. Unfortunately the system has not always worked as fast as might be desired, either because adverse drug reactions were not suspected at an early stage in postmarketing experience or because those that were suspected were not reported.

Adverse drug reactions are usually indistinguishable from events that can occur spontaneously. Practolol, for example, caused many reactions resembling "psoriasis" or "conjunctivitis." Drugs may increase the incidence of common diseases such as thromboembolism—for instance, oral contraceptives—or peptic ulceration—for example, corticosteroids. Only in exceptional circumstances, such as the reappearance of symptoms after rechallenge with a drug, is it possible to prove a causal relationship between a drug and an effect in an individual patient. While spontaneous reporting would be unlikely to disclose a doubling or even greater increase in the incidence of a common disease such as cancer, it may on the other hand highlight rare events such as blood dyscrasias that are more likely to be attributed to drugs.

Even when they have been suspected, adverse drug reactions may not be reported. The practitioner may feel diffident about notification of a mere suspicion. He may wrongly believe that an adverse drug reaction is already well known. He may recoil from an admission that something intended for a patient's benefit may actually have resulted in harm.

More than 80% of drug treatment is prescribed by general practitioners, and the responsibility for early detection, especially of uncommon adverse drug reactions rests mainly on them. We need additional methods that will supplement, but certainly not replace, the yellow card system by providing a more complete record of events that occur among the first few thousands of patients who receive the drug, whether these events are thought to be adverse drug reactions or not.

Various proposals have been made for systems, described collectively as "postmarketing surveillance," but few have been put into effect. "Recorded release"¹ or "registered release"² are prospective methods in which doctors or pharmacists would be requested to notify a central agency that certain patients had started treatment with a drug that has been selected for special study, and to report adverse events to the centre.

Retrospective schemes have also been proposed, such as the Committee on Safety of Medicines' Retrospective Assessment of Drug Safety, which, mainly for economic reasons, has had to be shelved by DHSS. In a second article I shall describe a similar scheme that we have started this year from the Drug Surveillance Research Unit at the University of Southampton. I have reviewed the objectives and the barriers that have to be overcome³ and, in this short article, will merely touch on some of the important ones.

Objectives

Most patients with diseases or symptoms receive some form of treatment, and it is often difficult or impossible to determine the incidence of adverse drug reactions (or spontaneous illnesses that are indistinguishable from them) in untreated patients. The best we can usually hope to achieve is a comparison of the relative incidence of events in groups of patients who receive different medicines for similar complaints. We must organise our studies in such a way that long-term or long-delayed effects are detected. To avoid bias we must make our comparisons under normal prescribing conditions in a way that neither interferes with freedom to prescribe nor increases the medicolegal risks of prescribing. Moreover, the methods we choose must be simple, inexpensive, and not time-consuming.

The "numbers game"

No proposal for improved postmarketing surveillance may be made without a brief reference to the "numbers game." The figure may help the reader to understand the rules. The actual

figures are arbitrary and are intended merely to indicate the order of magnitude of the numbers concerned. To play the game we first have to decide what is an acceptable level of risk that a drug will cause a serious or perhaps fatal adverse drug reaction. This level is related to the severity of the illness for which the drug is given, ranging from 1% or more for a drug that is effective in life-threatening disease to a relatively minute risk—for instance, less than 1 in 100 000 treatments—for a drug used to relieve minor symptoms, such as those of the common cold, over-indulgence, or insomnia. Interestingly, we find that, as the level of risk increases, the number of patients required to detect it diminishes, roughly by one order of magnitude for every order of increasing risk. Risks in the order of 1% may be identified in a few hundred patients while those in the order of 0.001% will require studies involving millions. The cost of these studies is directly proportional to the numbers concerned.

The diagram also suggests that "enthusiasm" for participation in studies of drug safety is likely to vary in the same direction as that of the severity of the disease and the extent of the risk. There may be great enthusiasm to join in a trial of a drug that saves life, practically none for the much more massive exercise required to ensure safety of a cough linctus.

Because it might cost ten or one hundred times as much to assess the safety of the linctus than that of an effective remedy for gastric ulcer or severe hypertension and because enthusiasm for the former would be low or non-existent, I conclude that there is no alternative to the yellow card system for the detection of rare but nevertheless important risks. There is no way, at a price that any nation can afford, that all the minor remedies on the market could be successfully tested by one or other of the proposed new methods of postmarketing surveillance.

Clinical trials will enable us to assess large risks, and yellow cards may show important hazards at any level of risk, including the extremely rare event (although it will often be slow to do so and will miss some adverse drug reactions completely). Somewhere between these levels of risk lie those that should be detected reliably by new methods of postmarketing surveillance.

I suggest that a realistic target should be the detection of risks occurring at a frequency of 0.1% and that we should aim at recording events in the first 10 000 patients who receive the new drug. In the next article I shall describe a simple scheme that could achieve this.

References

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