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Key passages

Validity of anecdotal reports of suspected adverse drug reactions: the problem of false alarms

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Abstract

Suspected adverse drug reactions first reported in 1963 in the "British Medical Journal," the "Lancet," the "Journal of the American Medical Association," and the "New England Journal of Medicine" were reviewed 18 years later to assess their initial validity and subsequent verification. Of 52 first reports, five were deliberate investigations into potential or predictable reactions, and in each case causality was reasonably established; the other 47 reports were essentially anecdotal. Of these 47 reports, 14 related to categories of adverse reaction where false-positive reports were unlikely: immediate reactions, local reactions, and known reactions caused by a different mode of administration or a brand previously thought or claimed to be safe. The problem of false alarms rose in the remaining types of reactions: general reactions that did not occur immediately after administration and arose for the first time with a new chemical entity. Of 33 reports of such suspected adverse reactions, validity was satisfactorily established in 14 cases on the basis of rechallenge, predictability from known pharmacology, or the unique nature of the reaction. Of the remaining 19 reports, further verification still has not been satisfactorily established in 12. Seven of these possible false alarms were haematological reactions.

Although 35 of the 47 anecdotal reports were clearly correct, of the 19 reports that were not reasonably validated at the time of the report, only seven were subsequently verified. This suggests that agencies monitoring adverse drug reactions should adopt criteria for assessing the validity of first reports of suspected adverse reactions. Such criteria should include: reactions on rechallenge, a pharmacological basis for the adverse reaction, immediate acute reactions, local reactions at the site of administration, reactions with a new route of administration of a drug known to provoke such reactions by another route, and the repeated occurrence of very rare events.

Introduction

From time to time the validity of anecdotal reports of suspected adverse drug reactions is challenged, and not only by representatives of the pharmaceutical industry. Despite various mechanisms for identifying adverse drug reactions, however, the anecdotal report (perhaps of a single case) is often the first means of alerting doctors and regulatory agencies to a serious adverse reaction to a new drug. Unfortunately there is often a substantial time lag between the first alert and subsequent verification and further delay before any regulatory action occurs. A systematic policy of investigating first alerts, at any rate of serious reactions, might reduce the delays that occur. Any consideration of such a policy should, however, take into account the possibility of false alarms. It would be useful to know how often these occur, and the present review was undertaken to investigate this problem.

Methods

Four journals were reviewed for reports of adverse drug reactions in 1963. The journals reviewed—the *British Medical Journal*, the *Lancet*, the *Journal of the American Medical Association*, and the *New England Journal of Medicine*—were chosen because they publish anecdotal reports of adverse reactions and are widely read internationally. The year 1963 was chosen, firstly, because the adverse reaction yellow-card system was started in 1964, and, secondly, to allow as long a time as possible for verification. Reports were selected for further study where there was reason to think that these were the first alerts to the suspected reaction.

Each report was assessed for internal evidence of validity. When any reasonable doubt remained an attempt was made to assess whether or not each suspected reaction had been verified in the subsequent 18 years. For this purpose three text books of adverse drug reactions were consulted: D'Arcy and Griffin's *Iatrogenic Disease*, Davies's *Textbook of Adverse Drug Reactions*, and Meyler's *Side Effects of Drugs*.¹⁻³ A search of published reports was also made using the computerised data base BLAISE (British Library Automated Information Service). This data base covers 3000 journals from 1966 onwards. A further search was made using the Excerpta Medica computerised data base. Finally, the adverse reaction files in the Medicines Division of the Department of Health and Social Security were studied. These include all yellow cards and all death certificates in which a drug is mentioned. They cover the period 1964 to the present time, and for the period 1975-80 information is also available on the extent of general practitioner prescribing.

[Home](#)[Contents](#)