BIAS IN THE ELUCIDATION OF SUBJECTIVE SIDE-EFFECTS

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- 1 Subjective drug-related adverse effects need to be carefully scrutinized for accuracy and completeness. This should include inspection of patients' records and chemical evidence of drug intake.
- 2 The information necessary to attribute an adverse effect to a drug is suggested.

Introduction

THE past four decades have witnessed a revolution in the quantification of drug effects in humans. In past centuries, the delineation of such effects suffered from a lack of appreciation of the various factors that could distort assessment by patients or doctors, and so quantitative and qualitative errors were made. Therapeutic success was frequently exaggerated, and toxic effects were at times missed. Today, the methods for deciding whether a drug produces therapeutic benefit under carefully controlled conditions are generally agreed upon for most drug classes. The paradigm *par excellence* has become the randomized, double-blind comparative trial, pitting the new drug against one or more standards. Like all other techniques, these trials can come to the wrong conclusions, but they have the advantage that bias in allocation of patients and in the assessment of effects is, if not eliminated, at least minimized. The process of randomization helps to achieve groups that are comparable at baseline, and also provides the statistical basis for the estimates of confidence and error which are necessary at the conclusion of data analysis.

For the purpose of attributing untoward events to a treatment, comparison with a placebo is the most useful device, and controlled trials have often used a placebo as the standard (or at least one of the standards) for this very purpose. The placebo is now under ethical and legal attack in various quarters, (Lasagna, 1979) but there is no doubt about its scientific usefulness. The placebo effect is now widely discussed, but its ingredients not yet fully appreciated. Most students of the placebo have focused on its potential for benefit (Beecher, 1955), neglecting its capacity to be associated with undesirable effects as well. This double potential is readily appreciated if one remembers that both 'placebo benefit' and 'placebo harm' are derived from two different sources. The first is psychological attitude and the

second is spontaneous change. Some individuals are predisposed to have faith in medicines, therapeutic manoeuvres or the physician, whereas others are not, or are actually hostile. The power of medication (or a placebo) may therefore be augmented or diminished by such attitudes.

Spontaneous change can work in either direction. Diseases and symptoms often vary and many ills are self-limiting or episodic. Improvement or deterioration can occur irrespective of the medicine taken, but may be erroneously attributed to the medicine (or placebo) through a *post hoc ergo propter hoc* fallacy. Green (1964), for example, has reported symptomatic complaints in 13% of patients and 58% of healthy volunteers taking placebos. Reidenberg & Lowenthal (1968) have found that 81% of presumably healthy individuals not receiving medications had symptomatic complaints, during a 72 h period before questioning, of types that might be considered to represent adverse reactions to drugs. Such studies emphasize the importance of controls in any attempt to evaluate adverse reactions to drugs, and highlight the difficulties in unequivocally ascribing specific untoward events to drugs. As reports have appeared describing 'addiction' to placebos (Vinar, 1969; Mintz, 1977), we must not underestimate our ability to be misled by non-pharmacological factors.

Another dimension to the problem is contributed by the interaction between disease or baseline state and response to drugs or placebo. Lasagna & von Felsinger (1954) have reported an interaction between the personality of research subjects and their responses to both placebos and drugs. The basic psychological strengths, weaknesses and needs of individuals may contribute in important ways to the nature and magnitude of reported effects. At times this poses problems in dissecting drug from non-drug effects, and in differentiating spontaneous events or

suggestibility effects from a true interaction between a chemical and the personality of the subject. Von Felsinger, Lasagna & Beecher (1956) have found that the magnitude of a 'bad trip' from hallucinogens is related to the degree of psychological control of a group of volunteer subjects. It is impossible to say at times whether a prolonged psychiatric syndrome occurring after ingestion of a known psychoactive drug is due to a disturbance of a precariously balanced mental state, thus making the drug experience simply fortuitous.

In regard to hypnotics, it is well to remember that certain age groups may show 'paradoxical' reactions to drugs that in part represent merely the expected rate of agitation and confusion from which certain individuals suffer impairment of visual cues resulting either from sedation or simply from putting out the lights (Lasagna, 1978). The confusion seen in many blindfolded patients after ophthalmologic surgery of both eyes has led to changes in operative and post-operative techniques aimed at preventing such adverse effects. With antidepressant and antipsychotic drugs, it is well to remember that the side-effects often resemble closely some of the complaints that characterize the target disorders being treated.

As many patients today receive multiple drugs simultaneously, there is a serious problem in ascribing the blame for a suspected adverse effect. Are *any* of the drugs taken in the recent past to blame? If so, which one? Is there reason to suspect a drug-drug interaction? Might the reaction be the result of withdrawal of a drug taken previously rather than the ingestion of a newly substituted medicine? The techniques to decide this are far from perfect, and the tendency for even experienced clinical pharmacologists to disagree in these matters highlights the hazards in assigning an aetiological role to a given drug.

In eliciting adverse subjective effects in clinical trials, there are two fundamentally different approaches. One is to ask an open-ended question, such as 'Did you experience any unpleasant effects from the medicine you took?', and to rely on what is in essence a volunteered response. The second is to use a check-list of adverse effects (plus an open-ended question) which the patient or subject has to fill out. Both techniques have their advantages and disadvantages. The volunteered response tends to elicit the more important side-effect and the ones likely to be attributed by the patient (rightly or wrongly) to the drug. The check-list almost always elicits more adverse effects, including trivial ones and some that the patient will (if asked) ascribe to spontaneous change. The disadvantages of the check-list are largely eliminated by a post-questionnaire discussion to try to eliminate semantic confusion and errors due to misattribution, and by the inclusion of a placebo group or period. With the latter, the 'excess' and spurious reports can usually be distinguished, but in the ab-

sence of placebo controls, one has to anticipate a certain amount of background 'noise'.

The possible contribution of bias by both drug-takers and drug-givers must be watched. Communications between patients in a trial may produce a 'halo' effect, with an epidemic-like spread of an adverse effect, or at least of its reporting. In big cities in the United States, narcotics users have at times described themselves as 'hooked' on heroin that on chemical analysis it turned out to be almost totally heroin-free. Many years ago, a water fluoridation programme in an American city was opposed by individuals who described all the various putative adverse effects of excess fluoride intake. The city administrator announced widely a date for the start of fluoridation. The next days saw a barrage of phone calls and letters from people who described themselves as ill from the newly added fluoride. The city official then announced that due to unforeseen circumstances the fluoridation had not yet started. The programme proceeded without further trouble (Lasagna, 1962).

The reporting physician must also be checked for competence and bias. Irey (1966; 1967; 1968) has pointed out the reporting of so-called adverse drug effects in which the temporal sequence or the results of objective laboratory measurements have on careful scrutiny effectively ruled out the culpability of the accused drug. (A drug taken for the first time *after* the onset of an adverse effect, for example, is unlikely to be the cause.) Physicians often blame the one drug out of many taken by the patient that is associated in their minds with the adverse effect in question. Hence a pruritic rash will usually be blamed on penicillin, and aplastic anaemia on chloramphenicol. In a multi-hospital study carried out some years ago (Bianchine *et al.*, 1968), the Stevens-Johnson syndrome was found to be in fact rarely associated with sulphamethoxypyridazine, drugs blamed for the syndrome were often given after the advent of premonitory evidence of the later full-blown syndrome, and the rate of reported cases after the brand of the sulphonamide in question, which had been most often linked with the syndrome in the literature, was six times the reported rate of a competing brand of the same product.

In conclusion, reports relating to subjective drug related adverse effects need to be carefully scrutinized for accuracy and completeness, preferably with scrutiny of patient records and clinical chemistry corroboration of drug intake, to at least establish the possibility of a drug's culpability. After that, one must approach the attribution of specific blame with both humility and caution, in view of all the traps enumerated above. Controls, when available, are invaluable, but not likely to be present in the strictest sense when dealing with voluntary reporting by physicians. In their absence, one must make do with the available data from controlled trials and from experi-

ence with the basic disease or complaint when treated with other drugs.

The British voluntary system, for example, has proved useful in enabling a comparison to be made between different drugs of a given therapeutic class. If a group of anti-arthritis drugs all produce a similar incidence of rash or gastric distress, it may be difficult or impossible to decide if all, or some, or none of the reported side-effects are attributable to the drugs, as opposed to suggestibility or spontaneous change. But if one member of the therapeutic group has a rather high incidence of liver toxicity, that drug deserves serious consideration as an aetiological candidate for hepatic disease.

In published reports on adverse effects attributed to a given drug, the following kind of information would be helpful:

How far back in time did the drug history extend?

How many other drugs were being taken by each patient for whom an adverse effect has been reported?

On what grounds was it decided to indict a particular drug?

Was 'dechallenge' or 'rechallenge' invoked?

Was there any chemical assay corroboration of the presence of the incriminated drug?

Was the timing of drug intake reasonable for linking the drug aetiologically?

Were there attempts by different observers at judging the certainty of the association between drug and event?

Was any attempt made to assess the 'background noise' in the reports of patients, in order to control for symptoms due to the disease being treated?

Was the side-effect reported one already observed with other drugs in the same chemical class or are we dealing with a new effect?

Were the adverse reactions preventable by means of dose restriction, or avoidance of certain age groups or concomitant drug administration?

Medicine is still dependent on voluntary reporting to detect adverse drug effects. We cannot afford to ignore such reports, but it is imperative that the quality of our reporting of adverse reactions be as good as we can make it.

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