EDITORIAL

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Outliers and Patients with Adverse Drug Reactions

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Professor David Finney is arguably the initiator of global pharmacovigilance, and, in his 90th year, he can still provoke us to thought! A statistician by training, he has recently criticized the WHO for their removal of outliers[1] in producing normative calibration curves (for thromboplastin time).

The assertion in his paper is an important one for pharmacovigilance – ''Never discard an apparent outlier unless there is strong evidence that it was the product of a measurement or other form of observation that suffered a gross mistake or accident, this misfortune being unrelated to any experimental treatment under investigation.'' The statement can be seen as implying that data that 'fits in' can broadly be accepted as coherent, and that which does not should be scrutinized for reasons why it does not. I am not in agreement with the first putative implication in the sense that it is likely to be a balance of heterogeneous factors that determines belonging to a group; therefore, some important factors may be masked by a much greater predominance of others. The main point, however, is that one should never make an assumption that an outlier is an error, and there may well be significant gains to be made by looking for the reasons behind outliers.

In pharmacovigilance we make assumptions about outliers all the time – after all they are the few people who experience adverse events that are reported as adverse reactions. But the first person to consider these patients is the health professional reporter who, in sending the report, has effectively decided that there is a reasonable likelihood that the drug selected could have been causally related to the event the health professional reports. It would be most interesting to understand the decision process behind each adverse reaction diagnosis: why select such a relatively rare cause as a drug for a particular clinical symptom or disease? We often talk about the possibilities of various biases and confounding such as publicity about a drug reaction and the influence of high background disease rates, but we have very little real knowledge about how these influences operate in an individual case.

Reports of events after drug treatment are analysed from trials and studies on a statistical basis, comparing with controls, but serious adverse reactions following drugs are rare, usually at rates <1/1000 for marketed products. For such a small total number of outliers, surely one should be more interested in *why* they are outliers than trying to differentiate whether they are *statistically* more or less frequently related to the drug?

A doctor makes a diagnosis of myocardial infarction, a common disease. If the patient is young and fit with no family history, the doctor will consider underlying causes such as diabetes, hyperlipidaemia, Prinzmetal angina, cocaine abuse and coronary embolism from a septic heart valve, amongst many others. The possibility that a drug that is taken might be the cause is also given more consideration because the case is generally unusual in the health professional's training and experience.

Any health professional should know, and eliminate, the common causes of myocardial infarction, as well as thinking of a drug as the cause, but if the clinical event is rarer in prevalence, such as agranulocytosis, then the range of causes are less likely to be known by health professionals, and perhaps drugs will be more likely to be the cause than other rare clinical events. The point is that

medical diagnosis is partly a consideration of competing probabilities. Those probabilities are generated from the practitioner's prior knowledge and experience, and tempered by application to the particular attributes of the patient in question.

In most diagnostic situations, and perhaps also in a situation when one has a clinical feeling that the particular patient is unusual in some way, adverse drug reactions (ADRs) are rare outliers, carefully considered and evaluated only after excluding the common causes. We should always try to find out how carefully this diagnostic evaluation was made in such patients, and try to have written justification for the ADR diagnosis. This justification is not often given by the reporter; indeed, the information on an individual case safety report (ICSR) is often limited. So what do we do at the moment with ICSRs that have limited information? We make assumptions of bias and confounding if we think this could exist, and we tend to dismiss cases without enough data to satisfy us. This is to assume that possible bias and confounding *is* the cause, and that absence of information equates with poor probability of a causal ADR diagnosis. This is implausible, given that the reporter, if a busy health professional, has to undertake an additional work burden in sending in a report. If the reporter is a consumer, then the information is perhaps less likely to be complete.

In clinical trials, although there may be a clinical evaluation of every patient with an adverse clinical event as part of the trial monitoring, the results of those evaluations do not form part of publications other than in the most basic way. The adverse events are often only considered 'causal' if they are statistically different from a control/background. There is rarely any discussion about diagnostic evaluation of the patients. For example, was a firm alternative cause found for the event, and what were the results of investigations performed in the patient?

Not only do we miss information that may help with determining a causal relationship between the drug and a clinical event, we should be able to find a lot more about mechanisms or other reasons for adverse events related to drugs by closer examination of these outliers. Is there a dose issue? Are there drug interactions? Is there an at-risk group or groups? Is this medical error: what are the root causes if it is? What happened to the clinical event?

I feel sure that these detailed evaluations of patients with suspected ADR are done all the time as part of the patient's care, but the logic used and the detailed results obtained are not found except in case reports, which many medical journals will not publish. When case reports are published, the short length of the article sometimes limits the detailed analysis needed for independent review. The International Society for Pharmacoepidemiology published guidelines for submission of ICSRs in this journal,[2] and other authors have pointed to the usefulness of the detail in ICSRs[3-5] and of their general value to drug safety. Like these authors, I would like to stress the ongoing value of ICSRs, which cannot be replaced by controlled studies and trials – their function is different.

Professor Finney is right: no patient with an unusual clinical response after therapy should escape detailed scrutiny and we should positively determine, in their individual case, what the root cause was for them to be an 'outlier'.

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