

ADVERSE REACTIONS AND THE COMMUNITY

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The Highland Scots are renowned for their intuition and prescience. Thus it is not surprising that although this session was planned so much earlier in the year it should have become so unexpectedly topical. Its subject is one which has attracted enormous public attention since this meeting was originally planned. This situation, which so greatly enhances our Scots' reputation for accurate presentiments, nevertheless poses the speakers with a serious challenge. By November 1982 there is a feeling that it has all been said before. In accepting this challenge, I shall aim to do two things. First, to put the experience with benoxaprofen into a broader and cooler perspective. Secondly, to spell out a theoretical framework from which to develop a more rational attitude towards "adverse reactions" in the future.

Historically, two events stand out in relation to adverse reactions to medicines. The first was the thalidomide tragedy in 1961, and the second was with practolol in the mid-1970s. It has been suggested that benoxaprofen in 1982 represents a third event in this sequence. Although no parallel exists between the circumstances of these cases, the contrast between the three experiences highlights the development of attitudes towards adverse reactions over the

over the past 20 years.

In the 1960s, pharmacology was only just beginning to emerge from the galenical era, in which it had been generally accepted that medicines were poisonous. Antimony, mercury and strychnine were all in the 1958 British Pharmacopeia, and arsenic was still retained in the 1963 British Pharmaceutical Codex. Deaths from penicillin allergy and agranulocytosis with chloramphenicol were more or less taken for granted against this background. It was the horrific and totally unexpected nature of the effects of thalidomide which rocked the world. An apparently safe mild hypnotic turned out to have been having the most terrible effects on unborn children. While many other unsafe medicines remained on the market thalidomide was immediately withdrawn - but not before it had damaged about 500 children in Britain.⁽¹⁾

There are three factors of significance which mark out thalidomide as a milestone in the development of attitudes towards adverse reactions. First, its effects were reported initially by an astute physician who connected the characteristic thalidomide deformities with the medicine by observing its effects in children born to his own patients. There was at that time no attempt anywhere in the world systematically to monitor the effect of new medicines in order to provide early warning of suspicious events. Thus, the concept of monitoring for adverse reactions was introduced in response to the thalidomide tragedy.

Second, there was a heated debate as to whether the compound had been adequately tested before it was marketed, and whether the warning signs of peripheral neuritis had been taken sufficiently seriously. This led first to the introduction of the Dunlop Committee on Safety of Drugs in Britain in

1964, and then to the 1968 Medicines Act. In the United States, the 1962 Amendments to the Food and Drug Acts matched these British developments.

Third, there was a public outcry, spearheaded by The Sunday Times, for compensation of the victims. This more than anything else had the effect of alerting the public to the harm which could be done by modern medicines. The subsequent consumerist attacks on whooping cough vaccination and Debendox, for example, arose because public awareness of the dangers of medicines had been so vigorously stimulated by the media. The dangers of medication which had been taken for granted in the 1930s suddenly became a source of vituperative attacks on the companies who had developed effective modern medicaments, some of which still had a serious potential for hazard.

By the time that practolol was first marketed in 1970, therefore, there was already a widespread appreciation of the fact that medicines could have unexpectedly harmful effects. Machinery had been set up under the 1968 Medicines Act to monitor for adverse reactions, and companies were themselves on the alert for reports of unpredictable hazards. Hence the experience with practolol was a gradual build-up of reports first of an unusual rash, then of damage to the eyes and finally of reports of intestinal obstruction caused by sclerosing peritonitis of the stomach. Because the early use of the medicine had been fairly limited and the adverse reactions were slow to develop, the first reports did not appear until 1974.

At the end of that year, the company had had 164 reports of adverse effects, and wrote to all doctors warning them of the position.⁽²⁾ This was followed by a formal warning from the Committee on Safety of Medicines early in 1975.

As reports of adverse effects continued to build up, the company first advised doctors to restrict the use of practolol to those conditions where it was considered the medicine of first choice, and then in July 1975 restricted its use to hospitals only. Finally, in September 1976, all oral forms of the medicine were withdrawn from the market. Thus six years had elapsed between the first marketing of the medicine and the decision on balance to withdraw it. By that time there had been about one million patient years experience with the medicine, and somewhere over 1000 cases of damage had occurred. Unlike thalidomide, however, practolol had been a lifesaving medicine and the balance between benefits and harm had been more difficult to establish.

This brings the story up to date with the events of benoxaprofen between 1980 and 1982. Largely because it was backed by a strong marketing campaign its use grew much faster than that of practolol. By the end of its first year 250,000 patients had been treated in Britain, and by the middle of 1982 the number had risen to 500,000.⁽³⁾ In addition, its adverse reactions had been much more intensively monitored and publicised. It was one of two subjects of an experiment in "Prescription Event Monitoring", in which 9000 doctors were asked to report on experience with 16,000 patients.⁽⁴⁾ Over 7000 forms covering benoxaprofen and the other compound, Lederfen, were returned and studied by Dr Inman's Drug Surveillance Research Unit at Southampton University. There was also a crescendo of publicity surrounding its adverse effects, which undoubtedly hastened reporting to the Committee on Safety of Medicines. By 1962, the Committee had received 3500 reports of adverse reactions. Most of these were for the already known side-effects of photosensitivity, but they

included 61 deaths associated with the medicine. As a result, the Committee advised the government that it should temporarily suspend the product licence in August 1982.⁽⁵⁾ The company has subsequently voluntarily surrendered the licence.

The suspension raised an immediate controversy. Some critics said that the CSM had been too slow to act. Others accused it of being too hasty. Two things seem certain. First, the deaths which were unique to benoxaprofen occurred through liver damage in the elderly. This highlights the need to assess more carefully the specific effects of new medicines in this particularly vulnerable group. Second, the reports of adverse effects with benoxaprofen had come in more rapidly and probably much more comprehensively than with practolol. Bearing in mind that the deaths were mainly in elderly and frail arthritics, whose persistent pain was being relieved by the medicine, the balance of benefits and risks was probably also more difficult to assess. Perhaps if the company had had more convincing evidence of the relative efficacy of benoxaprofen compared to alternative therapies, the medicine could have been allowed to remain on the market. Certainly its withdrawal has prompted a great deal of anecdotal evidence of patients who were prepared to accept its adverse effects for the sake of its exceptional benefits. Two "satisfied patients", for example, subsequently wrote to The Times arguing that the relief obtained was so great that patients should still be able to take the medicine, and to accept individual responsibility for the risks involved.⁽⁶⁾

Against that brief history leading up to this year's events, it is useful next to look more broadly at the extent of the problem of adverse reactions, and then to discuss some theoretical approaches to assess a proper balance.

If the reported deaths in relation to benoxaprofen are in fact associated with the use of the compound, and if they include the majority of such fatalities, they imply a mortality of the order of one in 10,000 cases. It is interesting to compare this with the "accepted" mortality associated with phenylbutazone and chloramphenicol, two compounds which have long been known to cause some fatal reactions. For phenylbutazone, there appears to be about one death per 50,000 cases from agranulocytosis or aplastic anaemia.⁽⁷⁾ For chloramphenicol, the estimates range between one death per 20,000 cases and one per 100,000.⁽¹⁾

The first point is not so much whether it is "right" that one in 10,000 should be unacceptable and one in 50,000 acceptable - although that provides interesting grounds for speculation - but the inherent difficulty in setting up monitoring schemes which will quickly and accurately detect events of such very low incidence.

The problem in relation to phenylbutazone - and to some extent, benoxaprofen - relates partly to the contrast between a very high incidence of relatively minor adverse reactions and the very small number of serious ones. For phenylbutazone, for example, Martindale reports that between 25 and 40 per cent of patients report untoward effects. That is, minor reactions occur more than 10,000 times as frequently as fatal ones. To detect the one serious reaction from amongst the host of relatively unimportant ones is indeed like looking for a needle in a haystack.

Incidentally, oral contraceptives represent another example of the difficulty in detecting and measuring the incidence of potentially serious reactions. According to the

Royal College of General Practitioners' Oral Contraceptive Study in 1977, the excess mortality associated with the use of the contraceptives in young women was one in 20,000.⁽⁸⁾

Turning now to a theoretical discussion, it is useful initially to establish why adverse reactions must always be an unavoidable feature of medication. First, there are cases such as anti-cancer therapy where serious and potentially fatal reactions are well-known when the medicine is first introduced, but where the known risk is considered acceptable in relation to the seriousness of the condition being treated.

Second, and more important, unexpected adverse reactions must also inevitably occur. As Shapiro and Sloane from the Boston Drug Epidemiology Unit said in 1977:

"It is impossible to determine at the time of first introduction that any drug is "safe". Three possibilities have not been ruled out and indeed they cannot be. The first is that the drug may cause some effect which is uncommon; the second is that an effect may only become apparent following long-term use (e.g. chloroquine retinopathy); and the third is that there may be a latent interval lasting years or decades (e.g. adenocarcinoma of the vagina)."⁽⁹⁾

The questions are how to minimise the risks and, much more difficult, how to reach an appropriate balance between acceptable and unacceptable hazards. In the latter context, the pattern of use of the medicine may play an important part. For example, the dangers of chloramphenicol are clearly acceptable when it is used to treat typhoid, but remain

questionable when it is used to treat minor infections.

There are four broad methods by which adverse reactions may be detected. The first is from individual physician's case reports. In the past this was the only way in which dangers first came to light. This was true of thalidomide in 1961 and, more interestingly, was still true with practolol in 1974.⁽²⁾ The second method is by government monitoring schemes, such as the "Yellow Card" reports in Britain. It has already been suggested that this had become enormously more sensitive and effective in respect of benoxaprofen than it had been eight years earlier with practolol.

The third method of monitoring is within the innovating company itself. This has the enormous advantage that it brings together reports from every country, whereas government schemes must rely primarily on reports from within their own national boundaries. Finally, there is the use of an independent agency, characterised in Britain by Dr Inman's Drug Surveillance Research Unit. At least in theory an international agency could offer similar monitoring services, although in practice Dr Inman's Unit relies on the unique availability of British National Health Service prescriptions.

There is also a distinction to be drawn between schemes of "monitored release", which are often looking for specifically suspected adverse effects, and the much more general concept of "post marketing surveillance", which is on the lookout for any sort of unsuspected reaction. In both cases, however, the central problem depends on the huge numbers required to pick up very rare reactions, such as the suspected fatal liver damage with benoxaprofen.

Taking that specific example, in his experimental monitoring, Dr Inman picked up three cases of liver damage possibly associated

with the medicine. Two would have been expected in a population of the given age structure from natural causes. Hence there was an "excess" of one case which was clearly insufficient on which to base a general warning.

The "numbers game" has been spelled out by Shapiro and Sloane.⁽⁸⁾ Given the postulate that a particular event, such as agranulocytosis, will occur "naturally" in one in 100,000 people per year, in order to detect an excess frequency of one in 500 requires 4000 patient years of follow-up. An excess frequency of 1 in 10,000 needs about 100,000 patient years and an excess frequency of 1 in 50,000 requires over a million and a half patient years to detect the rogue occurrence of the reaction.

These theoretical estimates enable one to put an order-of-magnitude price on the lives which could be saved. Godfrey and Bowler have calculated that at 1977 prices it would cost in total £240 million a year to monitor 20 new chemical entities on 100,000 patients for three years.⁽¹⁰⁾ The equivalent figure at 1982 prices is £420 million. In the 20 years between 1962 and 1982, there have been three serious events which could have been picked up more quickly by this monitoring. Thus, according to these estimates, for £8400 million at 1982 prices these three episodes would have been detected with optimum speed. The current controversy on the safety of medicines centres on benoxaprofen, so it is reasonable to take that experience as a basis for further calculation. In that case "optimum" monitoring would have detected the fatalities after 10 deaths (one per 10,000 in 100,000 cases). In the event, with only the present arrangements for Yellow Card reporting, the decision to withdraw the medicine was taken after 61 reports of deaths, about half of which were due to liver failure. Thus, given all the limitations

of the mortality data, one can nevertheless postulate a hypothetical saving of 51 deaths. If Godfrey's estimates of costs for "thorough" monitoring are correct, and if three such episodes could be prevented over 20 years, the cost per life saved could be £55 million. If one cuts the monitoring time down from three years to one year - which would probably have failed to detect the adverse reactions to practolol - the cost per life saved falls to £18 million.

Although these figures are highly theoretical, their astronomical size puts the problem into perspective. £55 million spent on health education in the prevention of heart disease, for example, could probably save hundreds and perhaps thousands of lives. The same sum could virtually double the annual amount currently spent by the NHS on renal transplantation and dialysis.

Furthermore, the risks of adverse reactions to medicines need to be seen in two further perspectives. The first is a comparison between the risks of pharmacology and surgery. In 1974 Professor Girdwood estimated that the risk of fatality from relatively "dangerous" medicines was between 3 and 30 deaths per million prescriptions.⁽¹¹⁾ At an OHE meeting that year the American anaesthetist Bunker estimated that the immediate risk of post-operative mortality from surgery was in the range of 1.0 to 1.5 deaths per hundred operations.⁽¹²⁾ At the same meeting, the pharmacologist Wardell pointed out that this meant that the risk of surgery was between 300 and 5000 times as great as the risk of receiving a prescription for a 'dangerous' medicine.⁽¹³⁾ Despite repeated references to the very high risk of surgery compared to that of pharmacological treatment, it is still the deaths associated with medicines which receive such widespread publicity. References to deaths associated with anaesthesia and surgery continue

to be treated in a remarkably matter-of-fact way.

Secondly, as has already been pointed out, the risk of medicines needs to be judged in relation to their benefits. Traditionally, these benefits have been able to be estimated in terms of numbers of lives saved. For example, in the Whooping Cough Vaccination controversy, some indication of the benefits from vaccination can be judged from the fact that death rates in very young children were reduced from 500 per million in 1931 to virtually zero by the 1960s.⁽¹⁴⁾ It is hard to separate out the exact contribution of vaccination from the earlier major contribution of the antibiotics in this fall, but no-one can contest that vaccination is life-saving.

However, with many modern medicines, the picture is more complicated. Very often they contribute more to the quality of life than to its prolongation. Here the benefits are much harder to measure. But already many economists and clinicians have started to be concerned with these questions. As a result, the concepts of 'health indices' as measures of 'health status' have been introduced into economics and medicine to aid the process. One of the most comprehensive pieces of work in this connection was undertaken by Rosser and Watts in Britain in 1974.⁽¹⁵⁾ They used a 'matrix' of health status, based on eight categories of disability along one axis and four categories of distress down the other. This gave a total of 32 possible classes of 'health status' into which individuals could be placed.

More recently in Britain, the Department of Community Medicine in Nottingham has developed 'The Nottingham Health Profile'. This is described as 'a standard and valid measure of perceived health'.⁽¹⁶⁾ The profile is in two parts: part 1 contains 38 statements pertaining to problems in six areas -

pain, energy, physical mobility, sleep, social isolation and emotional reactions. Part 2 contains seven statements referring to the effects of health on occupation, ability to perform tasks around the home, personal relationships, sex life, social life, hobbies and holidays.

Although the profile is intended as a tool for the survey of health problems in a population, it is also useful as a means of evaluating the outcomes and as an adjunct to the clinical interview. It has been found to relate well to other indicators of health such as the presence of chronic illness and the frequency of medical consultations and it is sensitive to changes over time. It thus provides a valid and reliable means of measuring the patients' assessment of their health.

Apart from the general measurements of health status based on studies such as these, there have also been more specific attempts to measure disability or incapacity on quantitative scales. Some of these are 'all-purpose' measurements intended to cover a wide spectrum of disease. Others relate to a single disease. The development of both health indices and scales of disability in relation to pharmaceutical therapy is in an embryonic state, but significantly it has already started. One example was reported in Arthritis and Rheumatism at the beginning of 1980.⁽¹⁷⁾ This paper presented a paradigm of outcome based on five separate dimensions: death, discomfort, disability, drug toxicity and dollar cost. Each dimension, in the US context, represented an outcome directly related to patient welfare. The measurements were quantified by interview or patient questionnaire and the authors concluded that 'the techniques appear extremely useful for evaluation of long-term outcome of patients with rheumatic diseases.'

More recently, and more directly relevant to the pharmaceutical industry, the clinical trials now being undertaken by Smith Kline and French on their new gold preparation, auranofin, for rheumatoid arthritis, include specific measurements on its effects on the quality of life. These are based on interviews conducted by non-medical interviewers, using a standard questionnaire. It seems likely that a similar approach will be developed for other pharmaceutical innovations in the future. No one protocol or method of measurement will be appropriate for all new medicines; but it seems likely that the general principle will become established in the future, to demonstrate more clearly the positive benefits of medicines on the quality of life.

Such measures cannot be available at the time that a new medicine is first introduced, and it would, therefore, be wrong for the national licensing authorities to call for such evidence before granting permission for a medicine to be marketed. However, they are relevant when it comes to judging the acceptability of adverse reactions. If a medicine is bringing clear cut major improvements in the quality of life for large numbers of patients, even the risk of mortality in the very elderly may be acceptable. Medicine in the future needs to be much more concerned with the quality of life rather than mere survival. To put this in terms of economic jargon, "death may not be the zero point on a scale of wellbeing"; in other words, there may be states of agonised survival which are worse than death. Clearly this is a matter of philosophical and religious controversy, but these are new areas into which the debate on the safety of medicines should increasingly lead public discussion.

In conclusion, the argument in this paper has come a long way from the conventional views that the absolute safety of medicines could be attainable and that it is axiomatically desirable. If pharmaceutical progress is to continue into the 21st century, a new and much more rational approach to adverse reactions needs to be developed. It is unfortunate that in public discussion at present, modern medicines and their manufacturers are so often cast in the role of miscreants. Medicines have brought outstanding benefits to mankind over the past 40 years and have a potential to relieve untold suffering in the decades ahead. One of the prices which must be paid for these benefits is an occasional episode of harm. No innovation is without its costs, in this sense. Although advances in pharmacological science and epidemiology are likely to make medicines safer in the future, the balance will still always have to be struck between benefits and risks. The plea in this paper is that the benefits should be more scientifically quantified in the future and should be given more prominence in relation to the inevitable risks of modern medicines.

REFERENCES

- (1) Teeling Smith G (1980). A Question of Balance, Office of Health Economics.
- (2) Nicholls J T (1977). The practolol syndrome. In: Post-Marketing Surveillance of Adverse Reactions to New Medicines. Medico-Pharmaceutical Forum.
- (3) Shedden W I H (1982). Side effects with benoxaprofen; British Medical Journal 284: 1630.
- (4) Scrip (1982). PEM "works well", says Dr Inman. Scrip 676: 1.
- (5) British Medical Journal (1982). Benoxaprofen. BMJ 285: 459.
- (6) Duff C L (1982). Opren: balancing the risks. The Times, 23 August.
Constable G M (1982). Opren: balancing the risks. The Times, 8 September.
- (7) Inman W H W (1977). Study of fatal bone marrow depression with special reference to phenylbutazone and oxyphenbutazone. British Medical Journal (i): 1500.
- (8) Royal College of General Practitioners' Oral Contraceptive Study (1977). Mortality among oral contraceptive users. Lancet (ii): 727.
- (9) Shapiro S and Sloane D (1977). Post-marketing assessment of Drugs. In: Post-Marketing Surveillance of Adverse Reactions to New Medicines. Medico-Pharmaceutical Forum.
- (10) Godfrey D and Bowler E J (1977). Post-marketing surveillance - the commercial implications. In: Post-Marketing Surveillance of Adverse Reactions to New Medicines. Medico-Pharmaceutical Forum.
- (11) Girdwood R H (1974). Death after taking medicaments. British Medical Journal (i): 501-4.
- (12) Bunker J P (1974). Risks and Benefits of Surgery. In: Benefits and Risks of Medical Care. Ed. Taylor D G, Office of Health Economics.
- (13) Wardell W M (1974). Assessment of benefits, risks and costs of medical progress. In: Benefits and Risks of Medical Care. Ed. Taylor D G, Office of Health Economics.
- (14) Office of Health Economics(1962). The Lives of Our Children. OHE.
- (15) Rosser R M and Watts V C (1974). The development of a classification system of symptoms of sickness and its use to measure the output of a hospital. In: Impairment, Disability and Handicap. Ed. Lees D and Shaw S. Heinemann for SSRC.

- (16) Hunt S M, McEwan J, Mckenna S P, Backett E M and Pope C (1982). Subjective health of patients with peripheral vascular disease. Practitioner 226: 113.
- (17) Fries J F, Spitz P, Kraines R G and Holman H R (1980). Measurement of Patient Outcome in Arthritis. Arthritis and Rheumatism 23:2:137.

