Leading article

Two cheers for NSAIDs

The non-steroidal anti-inflammatory drugs (NSAIDs) have had a bad press in the past several years. Five new and two old NSAID products have been withdrawn. A spate of recent publications^{1–5} promote the inference, if they do not prove conclusively,^{6,7} that NSAID use increases the risk of gastrointestinal ulceration, bleeding and perforation.

This news has had a background obligato of *tsk's*, implying that the pharmaceutical industry has spent so much to develop more than two dozen 'me-too' NSAIDs, different chemical species of NSAID that can scarcely be distinguished from one another in controlled clinical trials.

To that bleakness, however, it may be useful to add several other perspectives, especially for readers whose specialised focus is on the diseases of the gut.

First, and most obvious, is that these drugs offer undeniable benefits to patients with osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and related conditions. This effectiveness is documented in many controlled clinical trials of various sizes, including a recent one with over 2000 patients.⁸ Nevertheless, many arthritic patients are dissatisfied with available NSAID treatment, as evidenced by a great deal of switching from one product to another, and by the fact that there is usually a relative rush to try each new NSAID. On this latter point there hangs a tale, discussed further on.

The controlled trials that can scarcely distinguish one NSAID from another aggregate data from dozens, or hundreds of patients who meet the trials' inclusion/exclusion criteria. As Guyatt, Sackett, and colleagues from McMasters recently pointed out,⁹ it is often difficult to extrapolate such averaged results to the individual patient – even those who meet the inclusion-exclusion criteria of published trials. The McMasters group have described a technique for adopting the principle of randomised trials to individual patients as a way to find optimum therapy for that individual – the 'N of 1 trial'. Non-steroidal anti-inflammatory drugs pose a strong challenge to this new technique, which may improve the match of drug, dose, and patient, and incidentally help resolve the controversy over whether the choice of NSAIDs really offers a variety of effect useful to individual patients.

A second perspective on NSAIDs is that there has recently turned up evidence that they may have unexpected benefits. A recent study suggests that NSAIDs, with the notable exception of indomethacin, may decrease the risk of developing cataracts.¹⁰ Potentially much more important for overall morbidity and mortality is Inman's finding that the risk of acute myocardial infarction was 30–80% less during, as compared with after, the use of NSAIDs he studied with the prescription-event monitoring

method.^{11 12} Inman has been properly cautious about these results, but if such an effect turned out to be real its benefit to NSAID-users would more than offset all the serious mischief attributed to them. After all, ischaemic heart disease in its various manifestations, including acute myocardial infarction, accounts for about 40% of all deaths in the English speaking countries and most of Northern Europe.

The idea of a drug's indirect benefits offsetting adverse effects is not new. For example, oral contraceptives appear to prevent more deaths than they cause,¹³ although it has taken two decades of controversy and serial waves of public and professional concern¹⁴ to arrive at this judgment. But of course in the matter of NSAIDs and myocardial infarction the available data are very slender and are badly in need of confirmation or denial.

One might think that clinicians would long ago have recognised a 30–80% reduction in incidence of something so common as myocardial infarction. Yet quite the opposite is true.¹⁵ Effects that play on rarely occurring conditions are more readily detected clinically. For example, the effect of smoking on lung cancer was detected clinically as this once infrequent tumour began to appear in increasing numbers, mostly among heavy smokers; but only with formal epidemiological studies was smoking's effect evident on ischaemic heart disease, and this, in men at least, has larger impact on overall mortality than does smoking induced lung cancer. Thus it is quite important that Inman's findings be tested and either confirmed or refuted. Resolution may require both epidemiological studies and clinical trials: to show differences in incidence of acute myocardial infarction requires numbers of patients and trial lengths that tax the clinical trials method. Large numbers and long times also tax those who have to pay for the trials.

A final perspective is that the past several years' turmoil with so many withdrawals of new NSAIDs has preceded a new understanding of the dynamics of the reporting of adverse drug reactions (ADRs) by individual physicians, *via* the Yellow Card system and its counterparts elsewhere. First, the total number of reports of ADRs has increased markedly in recent years,^{16 17} but especially since 1982, not just for NSAIDs, but for all categories of drug.¹⁷ A second and much larger effect is that the reporting of ADRs has recently become strikingly higher in the first two to three years after a new drug's introduction, than thereafter.^{16 17} This recently occurring initial surge in ADR reports is raw material for making the new drug look like a brewing disaster, but of course the critical comparison of one drug to another has to be based not on raw numbers of ADR's but on their rate; the ratio of the number of each type of ADR (the numerator) to the number of people exposed to the drug (the denominator). It is also essential to assess and compare these rates between groups similar with respect to age, sex, duration of exposure to the drug, concomitant disease, use of other drugs, etc. For example, some of the NSAIDs are labelled for use strictly in chronic arthritic conditions, while others are indicated as well for various acute conditions that include athletic injuries. If that distinction and its influence on the demography of the patient population goes unrecognised, one can unwittingly be comparing ADRs among one drug's consumers who include many young, short term users – for example, for tennis elbow, *vs* ADRs among another drug's consumers who mostly are older, chronic users – for example, for chronic arthritis.

If the foregoing sounds too elementary for a learned specialty journal's leading article, take note of the fact that people from the general and financial news media also follow the medical literature and interpret it to their audiences. Bad news sells: media reporting is victim orientated and raw numbers of victims are a media staple.^{15 18} It is strenuous mental exercise for most people to go from simple counts to rates, in which transition much putative bad news may evaporate. For this reason, Heilmann, Struyker-Boudier and I have developed the Safety-Degree Scale to simplify the reporting of risk related information, formatting risk related information as rates rather than raw counts, and avoiding the sometimes lurid shock/horror effects that arise when a large relative risk plays on a tiny absolute risk.^{15 19-21}

This first two to three year surge in ADR reporting has been observed in, among other places, the United Kingdom, the United States and Norway. Part of this surge is related to the novelty, special interest and extra attention that a new product gets. Perhaps another source of this initial surge in ADR reporting are the dissatisfied problem patients who tend to flock to a new drug. Inman has pointed out that such patients bring their special problems into association with the new drug and may confuse its evaluation, unless the evaluators understand the prescribing dynamics and take pains to compare like with like.

The timing of new drug entries into the market since 1980 was such that many new NSAIDs appeared and so they have provided much of the experience that has taught these recently learned lessons about ADR reporting. One is left to wonder if any of the withdrawn NSAID products was a victim of prior misunderstanding of ADR reporting dynamics. One can only speculate, because the Committee for Safety of Medicines is less than forthcoming in making public the basis for its actions. Yet once a drug is withdrawn from the market, whether for good reason or not, it is a certified disaster for ever after.

Misunderstanding of recent developments of ADR reporting dynamics recently led an American activist group to petition for a ban on the use of piroxicam in patients over age 60, on the grounds of supposed increased gastrointestinal ADRs in older patients. That petition was decisively rejected this past July by the United States Secretary of Health and Human Services on the strength of an authoritative and thorough analysis by the Food and Drug Administration (FDA) of controlled trials and epidemiological studies comparing piroxicam with other widely used NSAIDs and with the background incidence of morbidity and mortality.¹⁷ Other drug regulatory agencies would do well to emulate the standard the FDA has set in dealing with this matter from the scientific and public disclosure points of view.

The FDA's analysis of piroxicam also highlighted an important point for improved understanding of drugs and their actions: while controlled clinical trials provide a basic definition of drug efficacy, they give only a limited definition of drug related risk. This limitation occurs because, for many good reasons, controlled trials can rarely involve more than 3000 patients, and so they can define the per treatment cycle risk of an adverse reaction to the level only of one in less than 1000.²² Yet many drugs have been withdrawn for ADRs whose risk appears to have been from one in 5000 to as low as one in 50 000, per treatment cycle.²⁰⁻²² These are levels of

risk which have been difficult to quantify with any certainty. The FDA has now put itself on record that epidemiological studies provide the best available means for reaching beyond the limits of controlled trials to measure the risk of clinically important, low incidence events.

Focus on what the FDA says and does is not as parochial as it might appear at first glance. The vast size of the American market for healthcare products necessarily gives international significance to the FDA's actions. In a very practical sense, it signals to the whole pharmaceutical industry that epidemiological studies have achieved regulatory standing. One can therefore expect to see growth in industry support of the subdiscipline for which Inman coined the term 'pharmaco-epidemiology'.

Sidney Truelove's and Richard Doll's pioneering gastroenterological work of three decades ago introduced the era of controlled clinical trials. We are now entering a new era of pharmaceutical risk analysis, in which Inman, Jick, Shapiro, Tilson and others are developing and testing pharmaco-epidemiological methods that complement and extend controlled clinical trials in quantifying low level, but important risks of drug therapy.

Non-steroidal anti-inflammatory drugs have taught important lessons and helped usher in this new era to a considerable extent. Pessimists and specialists whose clinical focus is remote from the daily tribulations of arthritics can say NSAIDs have had a lot to teach because they cause so much mischief. Most arthritics and their GPs can say that the benefit risk trade off is worthwhile in lieu of something better. There is hope that 'N of 1' trials will help some patients find something better among presently available NSAIDs. There is also hope that routine, careful application of the new techniques of pharmaco-epidemiology will give better understanding sooner in a new drug's history, by measuring risks and benefits in populations 10–100 times larger than can be recruited, or managed in clinical trials.

Of course sheer numbers cannot compensate for faulty study designs. So while it is natural to vest great hopes in pharmaco-epidemiology, perhaps it is not unreasonable to suggest an initiation rite for those who would work in this field: be able to recite reference 7 from memory.

The NSAIDs continue to help many patients. They cause some mischief, but may harbour some still-to-be proven benefits. Most arthritic patients want something better, but each of the many NSAIDs is the choice, for real or imaginary reasons, of some patients and their physicians. Two cheers.

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- 18 Documenting this assertion is a book in itself, but one may get the spectrum of flavours from the titles of the following recent press stories on NSAIDs: (a) Ferriman A, Arthritis drug alert after 77 patients die, *The Observer*, 22 December, 1985; (b) Veitch A, Doctors get warning of drug hazard, *Guardian* 23 December 1985; (c) Anonymous, 182 arthritis deaths laid to Feldene, *Los Angeles Times*, 11 January, 1986; (d) Rothschild, M, Death by prescription, *The Progressive*, June 1986: 18–22.
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- 21 Urquhart J. Perceptions of risk. In: Walker SR, Asscher AW, eds. *Medicines and risk benefit decisions*. Lancaster UK: MTP Press, 1986 (In press).
- 22 There are a few exceptions – for example, there were 16 027 patients in the recently published ISIS-1 trial of atenolol's use in acute myocardial infarction (*Lancet* 1986; **ii**: 57–66); the scope of the management problems may be inferred from the fact that the trial involved 245 centres in 10 countries, ran for 3.5 years plus 1.5 years from trial's end to publication, and cost about £1 million. Discussion of the limits on risk detection in clinical trials can be found in: Urquhart, J. The unfulfillable promise of drug safety. *Pharm Tech* 1985 (December): 14–15.