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EDITORIAL

THE RISE AND FALL OF BENOXAPROFEN

THE shock waves that were generated by the suspension of the UK product licence of benoxaprofen* by the Committee on Safety of Medicines (CSM) on 3 August 1982 continue to reverberate throughout the rheumatological world. As we go to press, the matter is still being hotly debated both in the medical press and in the lay media. Did the CSM act too late, or was its action precipitate and, perhaps, even unjustified?

Benoxaprofen was released for marketing in the UK in 1980 (and in the USA only in May 1982). It remained a controversial drug throughout its brief career. It was clear from the outset that this was a propionic acid derivative with a difference. It was only a weak inhibitor of prostaglandin synthesis, which in theory should cause less gastric irritation. Instead, it inhibited the lipoxygenase enzyme which converts arachidonic acid to hydroxy derivatives and the leucotrienes, which are potent mediators of inflammation and hypersensitivity reactions (1). It was never in doubt that the drug had anti-inflammatory and analgesic properties, clearly demonstrable in conventional experimental models and also in patients with rheumatoid arthritis (2), ankylosing spondylitis (3) and osteoarthritis (4). Its greater claim to fame—implied more often than expressed—that it had disease-modifying (remission-inducing) potential in chronic inflammatory joint diseases was based on evidence that was tenuous to say the least (5). It is true that benoxaprofen is capable of inhibiting migration of monocytes to sites of inflammation (6). It is also true that it can suppress experimentally-induced arthritis (7). What are lacking, however, are convincing clinical trials indicating a range of activities more generally associated with drugs like gold or D-penicillamine than with nonsteroidals.

Yet it was largely on the basis of this latter assumption that the drug was launched in 1980. The nature of the launch, directed as it was as much towards the general public as to the medical profession, was in clear breach of the agreed Code of Practice for the Pharmaceutical Industry (8). Patients were soon flocking to their general practitioner or their specialist requesting treatment with the new 'wonder-drug'. The reaction from members of the profession was angry (9). A formal complaint was made by the President of B.A.R.R. to the Association of the British Pharmaceutical Industry. Yet the promotion was highly successful and half a million patients received the drug in Britain alone.

*Benoxaprofen was marketed as Opren by Dista Products Ltd. in the UK and as Oraflex by Eli Lilly & Co. in the USA.

It was clear from the early trials that the drug produced unusual side-effects including the frequently seen increased skin and nail sensitivity to sunlight. These were troublesome but to some extent avoidable and certainly not dangerous (10). There was no hint of life-threatening complications (11). It was only in May 1982 that there emerged the first solid evidence linking benoxaprofen with death from hepato-renal failure in (mainly) elderly subjects (12). In June a recommendation was issued to halve the dose in patients over 65 years. Despite this, the numbers of deaths in patients taking the drug rose, and when it reached 61 the CSM acted.

It is always easy to be wise after the event. The question is how do we prevent a similar calamity from occurring in the future. The need for really effective therapeutic advances in rheumatology (as well as in other areas of medicine) is such that we can hardly blame our patients for grasping at the prospect of a brighter future. As physicians, we too are excited at the thought of major improvements in treatment. Yet, our critical faculties and vigilance must protect us (and our patients) from being carried away by the enthusiasm of others. The manufacturers by their over-zealous promotion of the drug may have sown the seeds of its downfall. Capturing the market so effectively and so rapidly may, indeed, have been the very factor that caused a crop of what are, clearly, rare complications. What would otherwise have been a few sporadic serious idiosyncratic reactions assumed alarming proportions, with the result that the CSM felt that the time had come to take action. The CSM have been criticized for the suddenness of their reaction, and for the fact that the decision was initially communicated to the press. (Ninety-eight thousand doctors were sent individual letters, but for logistic reasons these arrived several days later.) Having made the decision to suspend, the CSM had little choice but to ensure that the news of their decision was disseminated as widely and as speedily as possible. We do not share the view, held by some of our colleagues (13), that the CSM should be replaced.

Looking back, it seems strange that the knowledge concerning the pharmacokinetics of benoxaprofen in elderly subjects—a half-life that is three times that of younger adults (14, 15)—was not given practical expression at an earlier stage either by carrying out more extensive clinical trials in elderly patients, or by more stringent pre- and post-marketing monitoring in this vulnerable age group.

The CSM itself, is, no doubt, in the process of overhauling its machinery for the monitoring of side-effects using the 'Yellow Card' system. The kind of initiative recently taken by the CSM involving members of B.A.R.R. and the Heberden Society, whereby unusual adverse reactions associated with anti-rheumatic drugs are reported on a specially-tagged Yellow Card, is a welcome innovation and is the kind of measure that could forestall another tragedy.

Many patients found benoxaprofen to be an effective drug in relieving their rheumatic symptoms and are distressed to find that it is no longer available to them.

R.G.

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HIP REPLACEMENT—A FINANCIAL EMBARRASSMENT?

A RECENT publication—*Hip Replacement and the N.H.S.* (1)—states that, with the exception of abortion, no other surgical procedure has increased in number so rapidly over the course of the seventies. There is no doubt that total hip replacement has revolutionized the treatment of arthritis of the hip joint. No longer do those affected have to retire early, be confined to wheelchairs, struggle with crutches and sticks, become dependent on relatives and the social services, or, as so often happened, undertake repeated visits to a physiotherapy department in the vain hope of some relief.

Following a total hip replacement, a patient commented: 'It is like a dream come true'. Sadly, this is not the case for all; at least not within the National Health Service. Operative skills are widely available, but the facilities are not. The average time on waiting lists for arthroplasty of the hip is greater than for any other operation (1). In some units this waiting time extends to several years. Should patients in pain, often severely incapacitated, have to wait so long for what is now a relatively routine procedure? The answer is, of course, NO! The solution is simple, or at least appears so, and is that more resources have to be made available for this type of surgery.

It has been argued that many surgical procedures are not cost-effective. In the case of total hip replacement the operative costs are low, and the gains to the patient, and to society, are high. Taylor (2) calculated the benefit/cost ratio of at least 10:1 for the under-60 age group, and at least 2:1 for the 60–70-year-olds (2). A good example of community economic gain for monetary investment. To solve the problem of the enormous waiting lists, from where can this monetary investment come? There are several possibilities. The establishment of more hip surgery centres, financed directly from the Department of Health, or financial grant to District General Hospitals and Orthopaedic Centres for the specific purpose of joint replacement? Most orthopaedic surgeons would be against the former, and support the latter. However, in the present climate of economic restraint, only