Conference report

Drug toxicity and compliance

The annual day conference organised by the Clinical Pharmacology Unit at the Royal Bath Hospital, Harrogate, in the series 'Growing points in the treatment of rheumatic diseases' was this year devoted to 'Drug toxicity and compliance'. An audience of 100, including clinicians, basic scientists, and representatives from the pharmaceutical companies, met on 1 May in the Yorkshire Regional Health Authority's conference centre and 15 papers were presented.

Three papers served to highlight typical side effects of non-steroidal anti-inflammatory drugs (NSAIDs). Dr Marks (Stockport) found that although perforation of duodenal ulcers was more common than that of gastric ulcers, when patients had been receiving NSAIDs perforation became more common in gastric ulcers and was also more prevalent in women than men. Gastric ulcer perforation associated with NSAIDs was independent of age. Cutaneous photosensitivity was reviewed by Dr Diffey (Durham). Ibuprofen, indomethacin, azapropazone, and ketoprofen cause no phototoxic response. Benoxaprofen, naproxen, tiaprofenic acid, and piroxicam were more likely to be associated with skin reactions. A mathematical model has been devised to predict the likelihood of photosensitivity which relates to the normal dose of drug, its spectral absorption characteristics, and the sunlight exposure likely to be experienced. This may lead to prospective evaluation of new NSAIDs before they reach the market. The method might also prove useful in measuring the protective effect of barrier creams. Dr Richards (Glasgow) had studied the prevalence of renal disease in rheumatoid patients. Thirteen of 167 patients had significant renal problems, but no clear offender emerged amongst the four most commonly used NSAIDs. The difficulty of finding a measure of renal impairment that reflected drug effect rather than disease or aging was discussed. Eighty five of 167 patients had been receiving disease modifying drugs.

In a section devoted to epidemiological aspects the principal speaker was Dr R D Mann, the principal medical officer to the Committee on Safety of Medicines (CSM) at the DHSS. The yellow card

reporting scheme for adverse drug reactions (ADRs) had been introduced in 1964. Data on the frequency of prescribing had only been available from the prescription pricing authority since 1968. This made analysis of earlier trends difficult. There was a clear variation in the frequency with which ADRs were reported arising from many factors. The peak of ADRs in young children probably reflected increased general practitioner surveillance in this group. A peak of reporting in young women probably reflected the greater surveillance provided for such patients on prescription of the contraceptive pill. Overall, women were also more frequent attenders at the practitioners' surgeries than men. In spite of this a clear peak of ADRs emerged in late middle age and in the elderly. Data were sometimes hard to extract from ADRs. Gastrointestinal side effects from NSAIDs, for example, might be coded as haematemesis, gastrointestinal bleeding, or melaena. The CSM constantly reviewed its data base but remained cautious in the outright condemnation of drugs. Those drugs for which there was a large number of total serious reactions per million prescriptions (benoxaprofen, fenclofenac, feprazone, indoprofen, and Osmosin) were no longer marketed, though international data had also been reviewed in each case before coming to a decision. Apart from an impression that ibuprofen was significantly safer than the remaining NSAIDs, no particular drug had emerged as being more toxic than the others when data received were corrected for a variety of factors, including media attention. It was accepted that the 'softness' of these data prevented an accurate comparison between the toxicity of any two named drugs. In discussion it was noted that only 5% of total ADRs were reported to the CSM, though this figure might be higher for the more serious reactions. The system did not yet allow correlation with diagnosis. It remained a possibility that when a drug was withdrawn the side effects reported as arising from that drug were simply redistributed among remaining drugs. There was also heated discussion on whether generic preparations manufactured in many different countries did or did not have the same degree of product reliability

as the more expensive proprietary brand names. Professor Bjelle (Gothenburg, Sweden) then described his survey of variation in prescribing habits in rural and urban parts of Sweden. Even though fewer antirheumatic drugs were available in that country (only nine NSAIDs), clear patterns in prescribing preferences emerged in local areas. All of this would need to be accounted for in interpreting any data on the frequency of ADRs. Dr Pal (Durham) had surveyed 100 general practitioners in his area. There was much lack of awareness on the availability of some NSAIDs, particularly those bought by the patients 'over the counter' in addition to the medicines prescribed by their physicians. The extent to which products available in health food stores should be subject to CSM surveillance was also discussed.

After lunch two papers considered compliance. Dr Feely (Leeds) described the use of phenobarbitone as a chemical marker that could be incorporated into tablets (such as D-penicillamine) in order to determine whether patients were truly compliant. The drug had a long half life and in the dose used caused no side effects. Its presence could easily be detected in the blood. Sister le Gallez (Harrogate) reviewed the improved compliance when patients were trained to administer their own drugs during hospital admission. This scheme had worked with success in many specialties, including psychiatry.

Two papers discussed the toxicity of novel clinical approaches. The combined use of sodium aurothiomalate and D-penicillamine was described by Dr McKenna (Leeds). Twenty one of 45 patients had dropped out of his study, and, unlike previous reports, side effects had been troublesome, particularly in those patients receiving both compounds. Dr Rudge (London) had used sodium thiomalate in a dose of 100 mg/day for six months as a possible disease modifying agent. Four of 10 patients had withdrawn because of side effects and there had been little improvement in subjective and objective measures of arthritis.

The three papers devoted to sulphasalazine formed a 'mini symposium' which provided an update on our increasing knowledge of the use of this drug in rheumatoid arthritis. Mrs Astbury (Harrogate) had studied the pharmacokinetics of sulphasalazine and sulphapyridine, the metabolite normally held responsible for side effects. No difference in steady state plasma concentrations of combined sulphapyridine and acetylsulphapyridine had been seen in responders and non-responders, the slow acetylators not experiencing greater side effects. The concomitant administration of NSAIDs had no effect on the majority of pharmacokinetic parameters of

sulphasalazine or sulphapyridine, and the metabolism of the drug appeared similar in ulcerative colitis and rheumatoid arthritis. Dr Farr (Birmingham) reviewed side effects in 166 patients with RA, of whom 118 were seropositive. Hepatitis was occasionally seen. Side effects were similar to those seen in inflammatory bowel disease but were more frequently seen in rheumatoid patients. There was no evidence that eosinophilia gave an indication to those at risk, and the use of enteric coated tablets with antiemetics as required circumvented the gastrointestinal toxicity that was frequently seen. Dr Pullar (Leeds) reviewed the combined experience of Glasgow, Sheffield, and Birmingham in treating 774 patients with rheumatoid arthritis for at least one year. Between 25% and 30% of patients withdrew from treatment during one year, mainly because of gastrointestinal side effects. The nausea, central nervous system side effects, and mucocutaneous side effects were usually seen within one month of initiating therapy. The leucopenia could be seen within three months of initiating therapy and it was suggested that the most concentrated monitoring was required during this time, the manufacturers recommending at least monthly full blood and platelet counts for three months after the initiation of therapy.

The final two papers on immunosuppressive therapy both balanced the equation of disease remission against the undoubted side effects. Dr Kay (London) presented data from 96 rheumatologists in 15 countries on 1348 patients. Drugs were prescribed in the 16-88 year age range, azathioprine, chlorambucil, and cyclophosphamide being the most commonly prescribed in Europe. Two malignancies emerged six years after the start of treatment, but overall, side effects were not as great as might have been expected. Dr D G I Scott (Birmingham) argued that cytotoxic drugs were more frequently needed for patients with connective tissue disorders, particularly vasculitis. His series of 120 such patients had received 135 immunosuppressive drugs, cyclophosphamide, methotrexate, and azathioprine being most commonly used. Malignancies were rare with these drugs, though pneumonitis had been a problem with methotrexate. Overall, cyclophosphamide was associated with gastrointestinal side effects and methotrexate with liver dysfunction. Azathioprine and methotrexate were perhaps less efficacious than cyclophosphamide, and the deaths occurring during treatment with cyclophosphamide were attributed to severe disease rather than drug therapy.

The next conference in the series will be held on Thursday, 7 May 1987 at Harrogate, with the title 'Pain and its treatment'.

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