ANTI-INFLAMMATORY ANALGESIC DRUG RESPONDERS AND NON-RESPONDERS: A CLINICO- PHARMACOLOGICAL STUDY OF FLURBIPROFEN

It is common clinical experience in rheumatological practice for patients to find one drug effective in relief of their pain and another apparently ineffective. Indeed, the studies of Huskisson, Woolf, Balme, Scott & Franklyn (1976) suggest that this may be the case. We, therefore, considered it of interest to study the serum concentrations of flurbiprofen in patients with rheumatoid arthritis, some of whom had a satisfactory response with the drug and others not.

In order to identify 'responders' and 'non-responders', a number of out-patients with 'definite' rheumatoid arthritis as defined by the diagnostic criteria of the American Rheumatism Association (Ropes, Bennett, Cobb, Jacox & Jessar, 1959), who

were taking the drug, were studied in the following manner. Placebo was prescribed in place of flurbiprofen for 2 days, and then those who had an exacerbation of their arthritis were prescribed flurbiprofen in the dose they had previously been taking (150–300 mg/day). Where joint pain was not controlled, flurbiprofen was increased to the maximal allowable dose of 300 mg daily, and this was continued for a period of at least 7 days. If joint pain was still not controllable patients were categorized as 'non-responders'. Those patients who immediately responded to flurbiprofen after placebo were defined as 'responders'. In this way, six 'responders' and six 'non-responders' were identified.

Figure 1 Serum levels of flurbiprofen in (a) six 'responders' and (b) six 'non-responders'. The dotted line indicates the mean result.

The nature of the study was explained to each patient, who consented to participate. The patients were admitted to hospital and prescribed placebo for 24 hours. The mean pain rating after 24 h on placebo was 52.2 in the 'non-responders' (individual scores were 16, 22, 40, 50, 92, 93) and 40.5 in the 'responders' (scores of 22, 27, 30, 48, 49 and 67). The mean articular index (Ritchie *et al.*, 1968) on placebo was 18.5 (5, 10, 19, 23, 24, 30) in 'non-responders' and 13.7 (6, 8, 11, 15, 18, 24) in 'responders'. There was no significant difference between the two groups when the results were analysed by the Mann-Whitney U test. A 50 mg flurbiprofen oral test dose was given at 09.00 h after an overnight fast. Serum samples were collected at 0, 0.75, 1.5, 3, 6, 9 and 12 hours. The only drug given during the study was paracetamol, if required. Serum was stored at -20°C until analysed. Flurbiprofen was assayed as its methyl ester by gas chromatography using an internal standard technique (The Boots Company Limited).

The results are summarized in Figure 1. It can be seen that there is no significant difference in serum concentrations of flurbiprofen in 'responders' and 'non-responders'. There was also no difference in the amount of drug absorbed as reflected in the mean $\pm$ s.e. mean areas under the serum concentration versus time curves; $35.55 \pm 3.50 \mu\text{m ml}^{-1} \text{ h}$ for 'responders' and $34.08 \pm 4.45 \mu\text{g ml}^{-1} \text{ h}$ for 'non-responders'. The half-life of elimination of the drug from the serum of 'non-responders', $2.9 \pm 0.1 \text{ h}$, was not significantly different from that in 'responders', $3.0 \pm 0.4 \text{ hours}$. Although serum profiles in this study were obtained after ingestion of a single dose, it has been previously shown by Cardoe, Daymond, Risdall

& Glass (1975) that single dose data can reliably predict multi-dose levels. Since the amount of drug absorbed and its rate of elimination from serum were very similar for both groups it is very unlikely that there would be any difference in the mean serum profiles of the two groups when repeated doses of flurbiprofen were taken.

In this study we attempted to identify differences in metabolism of flurbiprofen in two groups of patients with different clinical responses. Metabolites of flurbiprofen are not present in serum of healthy volunteers (Adams, Crampton, Nicholson & Risdall, 1973), and we could not demonstrate differences in serum concentrations of unchanged flurbiprofen in the patients studied.

The authors wish to thank the Arthritis and Rheumatism Council for Research in Great Britain for financial support. Dr Fiona Sheldrake kindly supplied the flurbiprofen. The manuscript was typed by Miss E. Cameron. One of us (H.A.C.) was in receipt of a Carlo Erba Fellowship.

H.A. CAPELL & B. KONETSCHNIK

The Centre for Rheumatic Diseases, University of Glasgow, Department of Medicine, Royal Infirmary, Glasgow, Scotland

R.C. GLASS

Research Department, The Boots Company Ltd, Nottingham NG2 3AA

Received March 30, 1977

References

- ADAMS, S.S., CRAMPTON, E.L., NICHOLSON, J.S. & RISDALL, P.C. (1973). Metabolism of flurbiprofen in man. *XIII Int. Congress of Rheumatology*, Kyoto, Japan, pp. 173-177. The Boots Company Ltd., Internal Report, Research Department.
- CARDOE, N., DAYMOND, T.J., RISDALL, P.C. & GLASS, R.C. (1975). Serum concentrations of flurbiprofen in rheumatoid patients receiving large doses of flurbiprofen for long periods. *Curr. Med. Res. Opin.*, 3, (Suppl. 4), 15-19.
- HUSKISSON, E.C., WOOLF, D.L., BALME, H.W., SCOTT, JANE & FRANKLIN, SUE (1976). Four new anti-inflammatory drugs: responses and variations. *Br. med. J.*, 1, 1048-1049.
- RITCHIE, D.M., BOYLE, J.A., McINNES, J.M., JASANI, M.K., DALAKOS, T.G., GRIEVESON, P. & BUCHANAN, W.W. (1968). Clinical studies with an articular index for the assessment of joint tenderness in patients with rheumatoid arthritis. *Q. J. Med.*, 37, 393-406.
- ROPES, M.W., BENNETT, G.A., COBB, S., JACOX, R. & JESSAR, R.A. (1959). Revision of diagnostic criteria for rheumatoid arthritis. *Arthritis Rheum.*, 2, 16-20.