PATTERNS OF SIDE-EFFECTS

Of 88 patients with disorders of the locomotor system treated with indomethacin, 40 (45.4%) suffered side-effects. These effects were commoner in patients with rheumatoid arthritis (59.6%) than with gout (20%). Side-effects included headache, giddiness, faintness, muzziness, mental change, anorexia, nausea and vomiting, dyspepsia, diarrhoea, drowsiness, and blurred vision. More than one symptom occurred in all patients. Headache was improved by antihistamines, and drowsiness by coffee. Seven patients with rheumatoid arthritis and one with ankylosing spondylitis who had side-effects on relatively high initial dosage were found to be symptom-free on a lower dose more gradually introduced. It is probable, therefore, that with a starting dose of indomethacin 50 mg. daily and gradual increase by 50 mg. every third day to a maximum of 200 mg., the incidence of side-effects may be much lower than this figure. A dosage of 300–500 mg. daily may occasionally be used, but side-effects are likely to be frequent. There was no evidence of toxic effect on the blood, liver, or kidneys.

Side-effects occurred in four patterns: (1) Within a few hours the patient experienced severe symptoms independent of the dose. (2) Side-effects developed most often between 48 and 72 hours and were reduced by adjusting the dose. This appars to be a cumillative effect. (3) A small number of patients developed symptoms after seven days, as in two of the four cases of dyspepsia. (4) Some patients experienced muzzy feelings and mild headache about two hours after each dose, which wore off after an hour and did not progress. This occurred only with the 100-mg. tablet, never the 50 mg.

DISCUSSION

It is clear that in indomethacin we have an agent that will reduce swelling and also relieve pain. As an anti-inflammatory agent it is less effective than the corticosteroids and corticothrophin, but it is the only non-steroid agent we have used to date which has produced measurable reduction in finger-swelling in active rheumatoid arthritis. In this disorder those cases with measurable inflammatory swelling did appreciably better and had fewer side-effects than those with less inflammatory change. In two cases the dose of corticosteroids previously needed to control symptoms was gradually reduced under cover of the new drug, but in 12 others it proved ineffective. The response in acute gout is, in our opinion, better than with any other therapeutic agents at present available, for its action is more rapid than is that of phenylbutazone and the patient is less subject to rebound attacks than with corticotrophia. The definite relief of pain in the few cases of osteoarthritis assessed makes it seem likly that the drug has analgesic properties independent of its anti-inflammatory ones, and its use in a few febrile cases demonstrated that it is also an effective antipyretic: in one case of glandular fever treated with indomethacin there was rapid improvement in symptoms and signs, with relapse as soon as it was discontinued.

As regards toxicity, it is clear that our initial dosage was too high and we now seldom use 100-mg. tablets, but favour 50 mg. one to four times daily. On this lower dosage side-effects are much less troublesome and the headache and muzziness which are the commonest complaints often pass off on continuation of low-dosage therapy. Many patients intolerant of other drugs because of gastrointestinal side-effects are tolerant of indomethacin, which in our hands has proved relatively non-toxic in this respect to man, unlike the results in experimental animals. Time will show if there are any other side-effects, but at present no changes in blood counts or liver- or renal-function tests have been noted, nor were skin reactions seen. We have not used it in children or in pregnant women. On present evidence we consider that indomethacin, in spite of its tendency to cause headaches and dizzy feelings, has a definite part to play in the treatment of the chronic rheumatic disorders, and we regard it as the drug of choice in acute gout. In ankylosing spondylitis, osteoarthritis, and active rheumatoid arthritis it has also much to offer.

SUMMARY AND CONCLUSIONS

Indomethacin (1-*p*-chlorobenzoyl)-5-methoxy-2-methylindol-3-acetic acid) has proved to have anti-inflammatory and pain-relieving effects in gout and rheumatoid arthritis. It has also proved effective in the treatment of ankylosing spondylitis and osteoarthritis. As a dosage about 200 mg. a day headaches and dizziness were frequent, occurring in over 50% of those treated. At a daily dosage of 50–200 mg. side-effects occurred in 43%.