HOW FREQUENTLY SHOULD ANTI-INFLAMMATORY DRUGS BE GIVEN?
A STUDY WITH INDOPROFEN

BY E. C. HUSKISSION, J. SCOTT AND N. CHRISTOPHIDIS
Department of Rheumatology, St. Bartholomew's Hospital, London, EC1A 7BE

SUMMARY
Indoprofen, despite its relatively short plasma half-life, was just as effective given twice daily as when the same daily total was given in four divided doses. There was a trend in favour of the twice daily regime for changes in morning pain and the duration of morning stiffness. Preferences were equally divided between the two regimes and efficacy was the usual reason for patients preferring one or other. Side-effects were no more frequent with the twice daily regime. Pharmacokinetics are no substitute for clinical experiment in planning the dosage regime of a non-steroidal anti-inflammatory drug.

The frequency of administration of non-steroidal anti-inflammatory drugs is usually based on pharmacokinetics. It is supposed that anti-inflammatory drugs are like antibiotics and that those with short plasma half-lives must be given frequently in order to maintain an effective plasma level. But there is very little evidence to link plasma levels with response. It has not been possible to show correlations between plasma levels and response; differences in pharmacokinetics do not explain the wide individual variation in response to drugs of this class (Huskisson et al., 1979). There are striking examples of drugs whose action is not related to plasma levels. Indomethacin is very effective on the morning after a large night-time dose when plasma levels have declined to a low level (Huskisson, 1970). The effect lasts into the following afternoon and its time course bears no relation to that of plasma levels (Huskisson, 1976).

One of the great advantages of the latest anti-inflammatory drugs is their long plasma half-lives, which allow twice or even once daily administration. If plasma half-life isn't related to effect, drugs with short plasma half-lives may perhaps be just as effective given once or twice daily. This study was designed to look at indoprofen, a compound with a short plasma half-life which has been extensively investigated using three or four times daily administration (Bruni et al., 1980).

METHODS
Twenty patients with definite or classical rheumatoid arthritis by the A.R.A. criteria were admitted to a cross-over study comparing a total daily dose of 800 mg of indoprofen given either as 200 mg q.d.s. or 400 mg b.i.d. The study was double-blind, each patient receiving a total of four tablets daily in each treatment period but at different times. Each treatment regime was continued for one week and the order of administration of the two regimes was randomized and balanced.

Measurements made at the start of the study and at the end of each treatment period included pain at 8–10 a.m. pain at 4–6 p.m. using visual analogue scales, the duration of morning stiffness in minutes, and articular index using the method of Ritchie et al. (1968). Analgesic requirements were noted during the two treatment periods and the consumption

Accepted for publication April 1981.
Requests for reprints to Dr. E. C. Huskisson.

174
of indoprofen was monitored by returned tablet counting. Preference for one or other treatment period was noted with reasons. Side-effects were recorded at the end of each treatment period in response to a standard question, ‘Has the treatment upset you?’ All assessments were made by an observer who was not aware of the treatment regime at the time of seeing the patient.

The results were analysed using Student’s t test applied to paired data, except for morning stiffness for which the Mann–Whitney test was used and preference, for which a χ² test was used.

At the end of the cross-over trial, patients continued the regime of their choice with attempts made at monthly intervals to reduce the dose by one 200 mg tablet daily. The minimum maintenance dose was continued with assessments at regular intervals.

RESULTS

Nineteen patients completed both treatment periods. The mean results at the end of each treatment period are shown in the Table. There were no statistically significant differences between the efficacy of indoprofen given either twice or four times daily. There was, however, a trend in favour of the twice daily regime, especially in terms of pain in the morning and the duration of morning stiffness. Compliance with the two regimes, reflected in the returned tablet count, was identical. Eight patients expressed a preference for the twice daily regime, nine for the four times daily regime and two expressed no preference. Twelve patients gave reasons for their preference and all included greater efficacy with a particular regime. One patient mentioned in addition the convenience of a twice daily regime and one the lack of indigestion with this regime. Patients preferring four times daily administration tended to have more pain (t = 2.1; 0.1 > P > 0.05) than those who preferred twice daily administration.

Four patients had side-effects with the twice daily regime (headaches, dry throat, constipation and gritty eyes). Seven had side-effects with the four times daily regime (constipation in two, indigestion and nausea, headaches, dry throat, giddiness and dizziness).

One patient was withdrawn from the study during the first treatment period.

Fourteen of the 19 patients elected to continue treatment with indoprofen. Of these, five (36%) continued the full dose of 800 mg daily; five took 600 mg daily, 200 mg in the morning and 400 mg at night without relapse; four patients managed with maintenance doses of 200–400 mg daily.

<table>
<thead>
<tr>
<th>TABLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEAN RESULTS AT THE START OF THE STUDY AND AT THE END OF EACH TREATMENT PERIOD, INDOPROFEN 400 mg TWICE DAILY AND INDOPROFEN 200 mg FOUR TIMES DAILY</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>Pain (VA scale)</td>
</tr>
<tr>
<td>8–10 a.m.</td>
</tr>
<tr>
<td>4–6 p.m.</td>
</tr>
<tr>
<td>Duration of morning stiffness (min)</td>
</tr>
<tr>
<td>Articular index</td>
</tr>
<tr>
<td>Analgesic requirements (tablets/week)</td>
</tr>
<tr>
<td>Returned indoprofen tablets*</td>
</tr>
</tbody>
</table>

* Twelve tablets should have been returned at the end of each period.
There were no statistically significant differences between the two treatment periods.
DISCUSSION

The results of this study suggest that indoprofen, despite its relatively short plasma half-life can be given twice daily with as good an effect as when it is given four times daily; side-effects were no more frequent with this regime. There may even be an advantage to a twice daily regime apart from the obvious convenience. A larger dose of an anti-inflammatory drug taken at night is likely to produce good relief of pain at night, pain the next morning and morning stiffness, these benefits lasting well into the following day (Huskisson, 1976). Efficacy was overwhelmingly the commonest reason for patients preferring a particular regime. Patients preference for a four times daily regime may be explained by the analgesic action of indoprofen (Huskisson and Scott, 1979). This sometimes forgotten action of non-steroidal anti-inflammatory drugs may be a particular advantage for some patients while the anti-inflammatory action may be more important for others. The different time course of analgesic and anti-inflammatory effects of drugs like indoprofen has been emphasized by Huskisson (1977). Flexibility of dosage with these drugs may also be an advantage. Indoprofen can either be taken in full dosage twice daily for a full anti-inflammatory effect or in single doses on demand for pain relief. Maintenance doses required for patients who respond vary widely and attempts should be made to reduce the dose to the lowest which continues to achieve symptomatic control. It is surprising that compliance was not affected by the dosage regime but a study of longer duration might produce different findings.

The conclusions of this study are supported by similar findings with other anti-inflammatory drugs such as flurbiprofen which also has a short plasma half-life. It is clearly a mistake to think that plasma levels necessarily parallel clinical action; in the case of non-steroidal anti-inflammatory drugs, they do not.

ACKNOWLEDGEMENT

Dr. N. Christophidis is an overseas fellow supported by the National Health and Medical Research Council of Australia.

REFERENCES

Autumn mobility

To ease arthritic stiffness. To relieve arthritic pain.
For patients in the autumn of their years Benoral is especially acceptable and particularly well tolerated. Penetrating, easing, pain relieving...

Benoral benorylate suspension especially for the elderly arthritic

Benoral is a registered trade mark. Full Information from Winthrop Laboratories, Surbiton-upon-Thames, Surrey.
What you see above is the Medelec MS92:
2 channel, full function clinical EMG system.

This is all of it. Complete, in total.

Unlike other EMG systems, there are no setting-up routines to master, no technology to be learned. Microprocessor controls, flicker-free display and normalised averaging ensure that all the information you need is exactly where you want it. The results are displayed just as simply, with control settings printed on a paper read-out, and two cursors indicating accurate latency for velocity measurements. You would be offended if it were made any easier.

Despite its simplicity, the MS92 provides the complete range of tests required for clinical EMG—from volitional EMG to nerve conduction to single fibre studies—whilst its powerful averaging facilities make it just as useful for evoked potentials. It can also be connected to a hospital or laboratory computer system to analyse data, store results or even compile a record of the examination.

Although better, the MS92 still offers far greater value for money than comparable equipment (as does its single channel version, MS91). And the unit is so compact and portable, it can be carried with ease from clinic to intensive care to patient's bedside.

If that were not enough, both MS92 and MS91 are backed by Medelec's worldwide distribution network and the reputation of one of the most respected medical products organisations.

Call us. And make EMG easier for yourself.