Assessment of analgesic drugs in soft tissue injuries presenting to an accident and emergency department—a comparison of antrafenine, paracetamol and placebo

C. DE GARA
M.B., B.S., F.R.C.S. (Edin.)

M. TAYLOR
M.B., B.S.

A. HEDGES
Ph.D.

Accident and Emergency Department, and Department of Clinical Pharmacology, St Bartholomew's Hospital, London EC1A 7BE

Summary

In a preliminary dose-finding study in patients following abdominal hysterectomy, antrafenine was found to be an effective analgesic in single oral doses of 300-600 mg.

A double-blind controlled between-patient study was carried out to compare antrafenine (up to 1200 mg daily), paracetamol (up to 4 g daily) and placebo as analgesic in the control of pain produced by ligamentous knee or ankle injuries, low back pain or rib injuries. The only significant difference ($P < 0.05$) noted between drug treatments was a longer duration of analgesic activity following antrafenine.

The implications of these results for the study of potential analgesic drugs in soft tissue injuries are discussed.

Introduction

Antrafenine, an ester derivative of anthranilic acid, is a non-narcotic analgesic agent. Pharmacological studies have demonstrated analgesic and some anti-inflammatory activity; the activity is associated with inhibition of prostaglandin synthesis and has been confirmed in controlled clinical studies (Berry *et al.*, 1980; Manoury *et al.*, 1979; Wisanto *et al.*, 1981). The faecal blood loss after antrafenine 450 mg/day or 900 mg/day was similar to that after placebo and significantly less than after aspirin 1.8 g/day (Bown *et al.*, 1980).

This clinical trial, which was carried out in two separate parts, was designed first to establish an effective analgesic dose for antrafenine, and then to compare the efficacy of antrafenine, paracetamol and placebo in the relief of pain following soft tissue injury.

The first part of the study was carried out in female patients admitted to St Bartholomew's Hospital for

total hysterectomy and the second part was carried out in out-patients, admitted to the hospital Accident and Emergency department.

First study—to establish an effective analgesic dose for antrafenine

Materials and methods

Twenty-two female patients who had undergone total hysterectomy in the preceding 72 hr volunteered to participate in this part of the study. After narcotic intramuscular analgesics were discontinued, each patient was given a single dose of antrafenine as the first dose of oral analgesic medication in the post-operative period.

The doses of antrafenine used were 150 mg, 300 mg, 450 mg and 600 mg; it was planned to administer each dose to 5 patients. The strength of the antrafenine used was 150 mg and to ensure controlled conditions matching placebo tablets were used so that each dose of test analgesic consisted of four identical tablets.

Each analgesic dose was given to all patients at the same time of day and assessment of pain relief was made hourly for 3 hr following the dose and finally when another dose of oral analgesic was requested. Pain relief was estimated by the patients using visual analogue scales, and the investigator assessed pain relief by direct question using a pain score (Hedges *et al.*, 1977).

Results

In total, 22 patients were involved in the study—3 patients at 150 mg dose, 6 patients at 300 mg dose, 7 patients at 450 mg dose and 6 patients at 600 mg dose. A satisfactory analgesic effect was demon-

strated in all patients taking 300 mg, 450 mg and 600 mg. The pain analogue results are shown in Fig. 1. Antrafenine at all dose levels was well tolerated; any side effects noted were mild.

FIG. 1. Visual analogue scores at various times after administration of single oral doses of antrafenine 150 mg, 300 mg, 450 mg or 600 mg to patients who had undergone hysterectomy operations. The number of patients in each group is shown in brackets. Visual analogue scale: 0, no pain at all; 100, the most pain ever experienced.

Second study—comparison of antrafenine, paracetamol and placebo

Following the initial study in post hysterectomy pain, it was decided to investigate further the efficacy of antrafenine in a comparative study in patients with soft tissue injury. All patients entered in this part of the study were out-patients attending the Accident and Emergency Department at St Bartholomew's Hospital. It was considered that this study would permit evaluation of this method of screening analgesic drugs in a casualty department. The approval of St Bartholomew's Hospital ethical committee was obtained to carry out this study.

Materials and methods

The patients admitted to the second part of this study were treated for ligamentous knee or ankle injury, low back pain or rib injury. Absence of bone injury was determined by X-ray and confirmed by the radiology registrar. All patients entered the study voluntarily and written informed consent was obtained. We excluded patients with a history of acute or chronic hepatic insufficiency, mental retardation, pregnancy, history of alcoholism or drug dependence or long-term treatment with other analgesics.

The study was carried out under double blind conditions using a random block design. Patients were allocated into one of the three drug treatment

groups, i.e. antrafenine, paracetamol or placebo, according to a randomization sequence.

Each patient was given a bottle containing 80 tablets of either antrafenine, paracetamol or placebo and a record card to note daily pain intensity, pain relief and number of tablets taken (Fig. 2).

Day

1) Did the tablets help you? ☐ yes ☐ no

2) How bad was your pain today?

No pain at all The most pain ever experienced

3) How much did the tablets help your pain?

Helped a lot Did not help

4) How many tablets have you taken today? ☐

5) Have you taken tablets today:
(Please tick correct box)

Once ☐
Twice ☐
Three times ☐
Four times ☐
More than four times? ☐

6) How soon did the pain return?
(Please tick correct box)

Pain was not helped ☐
Less than one hour ☐
One to two hours ☐
Two to three hours ☐
Three to four hours ☐
More than four hours? ☐

FIG. 2. An example of the daily record card the patients were asked to complete.

The patients were asked to complete the booklet at the end of each day answering the questions:

- 'Did the tablets help you?'
- 'How many tablets did you have to take?'
- 'How often did you have to take the tablets?'
- 'How soon did the pain return?'

They were asked to complete an analogue rating scale by marking a cross on a 10 cm line in answer to the questions:

- 'How bad was your pain today?'
- 'How much did the tablets help your pain?'

Careful instruction was given to all patients on dosage and how to complete the pain relief scores and analogue scales. After 10 days the patients were asked to return and were examined by one of the two investigators (M.T. or C. de G.) who assessed the degree of improvement, noted any side effects and counted the number of tablets returned.

Dosage used

From the first study, it was considered that single doses of antrafenine 300 mg would be most satisfactory. A previous study in osteoarthritis (Berry *et al.*, 1980) has also demonstrated significant analgesic activity in daily divided doses of 450 mg/day and 900 mg/day.

In this part of the study a flexible dosage was considered necessary in order that patients could take their analgesic according to their individual needs. Also, to maintain double-blind conditions, a comparative analgesic agent had to be chosen which would be effective in this indication and could also be given in the same dosage regimen as antrafenine. Paracetamol was considered to be such a suitable analgesic and patients were instructed to take one or two tablets every 4–6 hr, to a maximum of 8 tablets per day,

e.g. for antrafenine: 150–300 mg 4–6 hourly as required.

for paracetamol: 500–1000 mg 4–6 hourly as required.

As a placebo group was also included in the design, patients were permitted to take a 'rescue' analgesic. Patients were instructed to take aspirin if they obtained inadequate relief from the trial drug.

Analysis of data

Many patients entered in the study did not require analgesic therapy for the suggested 10 days. Statistical analysis was therefore carried out on the pain relief scores and analogue scales obtained from the first 3 days of drug treatment only.

A second analysis was also performed on the data obtained from all subjects from day 1 to day 8. If patients did not take their tablets for all days, but provided data for a minimum of 3 days, the results from the patients' last day of treatment were repeated up to day 8, to account for the missing data.

The statistical analyses of pain scores and pain relief data were carried out by computing a global measure of pain intensity and analgesic relief, considering the area under the curve obtained from the individual pain and relief scores from day 1 to day 3 and day 1 to day 8. The global measures of pain intensity and pain relief were analysed using a one factor analysis of variance.

The homogeneity of the three drug treatment groups was tested comparing age, sex, diagnosis and initial pain intensity by means of a one factor analysis of variance or χ^2 squared test.

Mean duration of analgesic activity, daily tablet intake, patient and doctor overall assessment of analgesic activity were compared in the three drug treatment groups using non parametric analysis of variance (Kruskall-Wallis test).

Results

Of the 166 patients who entered the study, it was possible to evaluate results of only 91. Fifty-nine patients failed to return for follow up and their final assessment was incomplete. Of the 107 patients who did complete the study, the results of 15 of these patients could not be analysed because of inadequate records.

A summary of the number of patients in each diagnosis category and the analgesic treatment administered is given in Table 1. There was no significant difference in the homogeneity of the three drug treatment groups, comparing age, sex, initial pain intensity or distribution of diagnosis.

TABLE 1. Diagnosis and analgesic treatment (number of patients)

	Antrafenine	Paracetamol	Placebo	Total
Sprained ankle	15	16	17	48
Low back pain	4	11	10	25
Rib cage injury	—	3	3	7
Other	6	4	2	11
Total	25	34	32	91

In the analysis of pain relief data, the results of 88 patients were included in the 1–3 day analysis and 90 patients were included in the 1–8 day analysis. (1 patient included in the 1–3 day analysis was not included in the 1–8 day analysis).

Assessment of pain relief

The duration of analgesic activity was longer for antrafenine than paracetamol and placebo ($P < 0.05$ —see Table 2). Otherwise no significant differences between drug treatments were found.

TABLE 2. The duration (mean $\pm$ s.e. mean) of analgesic activity after antrafenine, paracetamol or placebo

Duration of analgesic activity (hr)	
Group 1—Antrafenine	3.2 (0.3)*
Group 2—Paracetamol	2.4 (0.3)
Group 3—Placebo	2.4 (0.3)

*The duration of activity in Group 1 was significantly longer than in groups 2 and 3 ($P < 0.05$) Kruskal-Wallis test.

The mean cumulative scores for pain intensity over the 3-day and the 8-day periods indicate a modest reduction in pain for the antrafenine group, com-

TABLE 3. Mean cumulative pain scores (mean $\pm$ s.e. mean) after antrafenine, paracetamol or placebo

	Number of patients		Cumulative pain score	
	days 1-3	days 1-8	days 1-3	days 1-8
Group 1—Antrafenine	25	25	93.2 (7.4)	257.3 (25.9)
Group 2—Paracetamol	33	34	106.7 (6.6)	271.2 (24.9)
Group 3—Placebo	30	31	111.0 (7.0)	308.3 (29.3)
Totals	88	90		

pared with paracetamol and placebo, but this did not reach statistical significance (Table 3).

Side effects

The distribution of total number of side effects in the 3 treatment groups was not significantly different. Drowsiness was the most frequently reported adverse effect, noted by 4 patients in the placebo and paracetamol groups and 7 patients in the antrafenine group.

Discussion

There is a need for more effective, safe analgesics for use in clinical practice. With the results of the initial study in postoperative pain, together with information from other clinical studies, it was considered justified to investigate antrafenine in a comparative study in patients with soft tissue injury, who often need non-narcotic analgesics.

An Accident and Emergency Department should be a good centre for such a study with a large number of patients presenting who actually need such drugs. However, the results of the study which indicated no significant difference between any of the 3 treatments, (antrafenine, paracetamol and placebo) require comment. Analgesic activity of antrafenine had been shown in the first part of this investigation. A single dose of 300 mg provided adequate pain relief for a period of 4-6 hr in patients with postoperative pain. This activity has been confirmed in double-blind clinical trials. Paracetamol is a frequently prescribed analgesic which should provide sufficient pain relief in the majority of patients with this indication. If paracetamol had not been included, then it might have been concluded that antrafenine was ineffective.

However, the absence of a significant difference between paracetamol and placebo indicates that this investigational model using these types of soft tissue injury is insensitive to screen such analgesic compounds. This emphasizes the importance of using a

known analgesic as well as placebo in the investigation of the efficacy of a new analgesic agent.

Patient compliance in this study was poor; 30% of the patients did not return for follow-up, despite telephone requests and postal communication with stamped-addressed envelopes. Of the patients who did complete the study 15 patients' results had to be rejected because of inadequate records.

The results of this study suggest that it may be unnecessary to prescribe routinely an analgesic for minor soft tissue injury and follow up appointments for further consultation may not be required. Also, it would appear that patients recruited in a casualty department are unlikely to be suitable for a clinical trial of this nature.

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