An evaluation of different doses of soluble aspirin and aspirin tablets in postoperative dental pain

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1 The efficacy of three different single doses (600, 900 and 1200 mg of soluble aspirin and aspirin tablets) was determined in a randomized placebo-controlled parallel study in 140 patients (70 females) with postoperative pain after removal of impacted third molars.

2 Patients treated with soluble aspirin 600 mg, 900 mg, 1200 mg and aspirin tablet 1200 mg reported significantly less pain ($P < 0.01$) throughout the investigation period than those treated with placebo.

3 Overall pain scores after treatment with aspirin tablets 600 and 900 mg did not differ significantly from those after treatment with placebo ($P > 0.05$).

4 On a comparative dose basis, soluble aspirin was significantly more potent ($P < 0.05$) than aspirin tablets.

Keywords soluble aspirin aspirin postoperative pain

Introduction

Postoperative pain after removal of impacted third molars is an acute inflammatory pain, usually of short duration (Seymour *et al.*, 1985). It is now well established that drugs which possess both analgesic and anti-inflammatory properties are effective in treating this type of pain (Seymour & Walton, 1984). Aspirin (acetylsalicylic acid, ASA) has been extensively evaluated in postoperative pain after third molar surgery (Cooper & Beaver, 1976; Henrikson *et al.*, 1979; von Graffenried *et al.*, 1980; Skjelbred, 1984), and a previous study (Seymour & Rawlins, 1982) demonstrated that 1200 mg soluble aspirin was more efficacious than 600 mg. Recently, it has also been shown that a single dose of soluble aspirin 1200 mg provided a more rapid onset, and a longer duration of analgesia, than the same dose of conventional aspirin (Seymour *et al.*, 1986). The aim of the present study was to investigate the dose-response relationship of soluble and conventional preparations of aspirin in patients with postoperative pain after removal of impacted third molars.

Methods

One hundred and forty adult patients (70 females) age 18–35 years who required the removal of all four of their impacted third molars, participated in the study, which had received prior ethical approval from the local Health Authority Ethics Committee. Informed written consent was obtained from all patients prior to the study in accordance with the Declaration of Helsinki, 1975. Patients who participated in the study were from the waiting list of the Department of Oral Surgery and had been admitted for routine third molar surgery.

Impacted third molars were removed under general anaesthesia. Oral diazepam 10 mg was given to all patients 2 h before surgery as a pre-medication. Anaesthesia was induced in each patient by the intravenous administration of 4–6 ml of thiopentone sodium 2.5%, and muscle relaxation achieved with intravenous suxamethonium chloride 100 mg. The third molars were removed following a standard technique and bone removal was carried out with a drill under saline spray. Operating time was recorded from first incision to completion of last suture.

Table 1 Patient and operative variables for each group ($n = 20$). Results are expressed as medians and ranges

	Placebo	Aspirin tablets			Soluble aspirin		
		600 mg	900 mg	1200 mg	600 mg	900 mg	1200 mg
Age (years)	22 (19–33)	23 (19–28)	22 (20–34)	22 (18–35)	21 (29–25)	22 (19–30)	21 (19–26)
Operating time (min)	26 (14–43)	25 (15–48)	27 (15–47)	26 (14–50)	28 (16–50)	27 (18–55)	24 (20–52)
Initial pain scores (mm)	78 (35–100)	75 (45–98)	69 (33–100)	70 (36–96)	78 (52–98)	69 (42–95)	70 (34–95)
Overall pain scores (mm h)	313 (28–474)	242 (44–476)	234 (34–467)	163* (14–537)	182* (7–404)	150* (15–300)	112* (5–37)

*Significantly different ($P < 0.01$) from placebo.

On completion of surgery, patients were returned to the ward and time was allowed for them to recover from the effects of the general anaesthetic. When patients' pain reached an intensity where they requested an analgesic, they were entered into the study. They then received in random, double-blind order, either a single dose of soluble aspirin (600, 900 or 1200 mg) (Solprin, Reckitt & Colman Ltd) in a raspberry flavoured solution, aspirin tablets BPC (600, 900 or 1200 mg), or matched placebo. Randomization ensured that there were 20 patients (10 females) in each of the seven treatment groups. To achieve double-blind conditions and ensure that patients were unaware of which treatment they received, the double-dummy technique was used. That is all patients were given tablets (aspirin 300 mg or matched placebo) and a 200 ml raspberry flavoured solution (with or without soluble aspirin). Patients received their drugs whilst sitting up in bed and were allowed to consume fluids and food some 2 h after dosage. Relief analgesics (paracetamol) were available for each patient if the medication failed to provide satisfactory pain relief.

Patients registered their pain experience on serial, plain horizontal visual analogue scales at 0, 15, 30, 45, 60, 90, 120, 180, 240 and 300 min after dosage. The boundaries of the scale were marked 'no pain' and 'unbearable pain'. The pain scales were presented by the same observer [I.H.]. The area under the graph of pain (mm) against time (h) was calculated by the trapezoidal method to provide an integrated measure of pain (AUC_{300}) experienced in units of mm pain h throughout the 5 h investigation period. The incidence and severity of adverse effects during the investigation period were recorded separately.

Statistical analysis

Treatment efficacy was assessed by comparing the pain curve for placebo with all aspirin treatments at each time point up to 300 min after dosage. A two-way analysis of covariance was used with treatment, sex and interaction effects and initial pain score (time 0) as covariate, in order to adjust for variation in initial pain. A similar, non-parametric analysis using the MRANK (Sarle, 1983) procedure of SAS (SAS users guide, 1982) was also performed to avoid assumptions about the form of the distribution of errors. A type I error probability of $P < 0.05$ was used to indicate statistical significance. The dose-response relationship and potency ratios of the soluble formulations relative to the tablets as standard was determined using standard methodology for a six-point assay (Finney, 1978), with validity tests as shown in Table 2.

Results

Demographic details of the patients together with the duration of surgery for each treatment group are shown in Table 1. Age and duration of surgery were comparable for the seven groups of patients. All patients in the study requested an analgesic within 2 h of completion of surgery, and 97% of patients had a baseline pain score in excess of 33 mm on the VAS. The incidence of adverse effects throughout the study was low. One patient in the 900 mg aspirin tablet group reported slight dyspepsia of short duration, and two patients in the 1200 mg soluble aspirin group noticed transient tinnitus.

Figure 1 (a) Mean pain scores (mm) $\pm$ s.e. mean compared with placebo (●) after treatment with soluble aspirin (○ 600 mg, ■ 900 mg, □ 1200 mg). (b) Mean pain scores (mm) $\pm$ s.e. mean compared with placebo (●) after treatment with aspirin tablets BPC (○ 600 mg, ■ 900 mg, □ 1200 mg).

Pain scores at each time point

Mean pain scores ($\pm$ s.e. mean) at each time point for all the six aspirin treatments compared with placebo are shown in Figures 1a and 1b. At no time throughout the 5 h investigation period did patients treated with aspirin tablets 600 mg report significantly less pain ($P > 0.05$) than those treated with placebo. Similarly, patients treated with aspirin tablets 900 mg reported significantly less pain ($P < 0.05$) than the placebo group at 60 and 90 min after dosage. For all three soluble aspirin treatments (600, 900 and 1200 mg), and for aspirin tablets 1200 mg, a significant difference in pain scores from placebo ($P < 0.01$) was observed at all time points between 60 and 300 min after dosage.

Overall pain scores

Mean overall pain levels, as assessed from the area under the pain time curve (AUC_{300}) are

shown in Table 1. A significant reduction from the placebo group was observed in patients treated with aspirin tablets 1200 mg and all three doses of soluble aspirin ($P < 0.01$). There was no significant difference ($P > 0.05$) in mean overall pain levels between the placebo group and patients treated with aspirin tablets 600 and 900 mg.

Dose-response

The six-point assay for determining the dose-response of both aspirin preparations using the overall pain levels (AUC_{300}) is shown in Table 2 and Figure 2. On a comparative dose basis, soluble aspirin was significantly more potent ($P < 0.05$) than aspirin tablets, as shown by the confidence intervals in Table 3. The estimated potency ratios between the two aspirin preparations at various time points are shown in Table 3. As assessed by the overall pain levels, the doses of soluble aspirin were approximately 1.7 times

Table 2 Parallel line assay assessing overall pain scores (AUC 0–300 min) for soluble aspirin and aspirin tablets

Nature of variations	d.f.	Sum of squares	Mean square	Significance
Preparations	1	186906.2	186906.2	$P < 0.001$
Regression	1	221963.5	221963.5	$P < 0.001$
Parallelism	1	14519.1	14519.1	NS
Linearity	2	6469.5	3234.7	NS
Between doses	5	429858.3		
Error within	114	1398760.4	12269.8	
Total	119	1828618.7		

Table 3 Potency ratios with 95% confidence limits between soluble aspirin and aspirin tablets (standard) at various time intervals throughout the investigation period

Time (min)	Estimated ratios	95% confidence interval
30	1.63	1.02–2.62
60	1.82	1.19–2.78
90	1.87	1.23–2.85
Overall	1.69	1.17–2.47

The above potency ratios are estimated on the assumption that the linear dose-response relationship holds over an extended dose range, as indicated by the consistent difference shown between preparations (Table 2).

Figure 2 Comparison of overall pain score (mm pain h $\pm$ s.e. mean) 600 mg, 900 mg and 1200 mg of soluble aspirin (●) and aspirin tablets BPC (○).

more potent than the same doses of aspirin tablets.

Discussion

This study has demonstrated that on a dose per dose basis, single doses of soluble aspirin are more efficacious than aspirin tablets when given in the immediate postoperative period to patients with pain after third molar surgery. Clinically, the results showed that the efficacy of aspirin tablets 600 and 900 mg in postoperative dental pain was poor when compared with the placebo group (Figure 1b). The size of the study (20 patients in each treatment group) and the variability in overall pain score (AUC₃₀₀) after aspirin tablets 600 and 900 mg resulted in a low power for the comparison with placebo. Obviously increasing the number of patients may show a difference between these treatment groups and placebo which could be statistically

significant. However better pain relief was demonstrated by the 1200 mg dose of aspirin tablets and all the doses of soluble aspirin.

Total and peak plasma concentrations of acetylsalicylic acid (ASA) have been shown to be an important determinant of the drug's efficacy in postoperative dental pain (Seymour *et al.*, 1984). Soluble aspirin provides higher peak and greater total (AUC) plasma concentrations of ASA than aspirin tablets (Levy, 1965; Rance *et al.*, 1975). Using the same doses, it has been shown that peak plasma concentrations of ASA after soluble aspirin are double those after aspirin tablets (Muir & Nichols, 1987, unpublished data). Aspirin is mainly absorbed in the upper part of the small intestine, thus the rate of gastric emptying is one factor which will determine the absorption of aspirin. After a general anaesthetic there may be a degree of gastrointestinal stasis, especially if atropine or an opioid is administered as a premedication (Bateman, 1985; Beatson, 1982). Any alteration in gastrointestinal mobility is likely to have a more pronounced effect on the absorption of a drug in tablet form than the same drug in solution. An alteration in gastrointestinal mobility after a general anaesthetic may contribute towards the poor efficacy that we observed after the 600 and 900 mg doses of aspirin tablets.

Soluble aspirin has also been shown to be more effective than the same dose of aspirin

tablets in the treatment of postoperative pain after orthopaedic surgery and general surgery (Dixit *et al.*, 1984), and have a more pronounced effect on platelet aggregation and bleeding time (Roos-Lee *et al.*, 1982; Proost *et al.*, 1983).

Postoperative pain after removal of impacted lower third molars is now a standard model for evaluating analgesic efficacy. This pain model appears to have sufficient sensitivity to discriminate between different doses of aspirin and different aspirin preparations. The dose-response obtained with aspirin in this model would suggest that a single 1200 mg dose of soluble aspirin provides a satisfactory reduction in pain. Similar dose-responses to aspirin have been reported in patients with non-migrainous headache (von Graffenried & Hill, 1979).

We can conclude from this study that on a dose per dose basis, soluble aspirin is more efficacious than aspirin tablets. A dose-response relationship with both aspirin preparations could be elicited in patients with postoperative pain after third molar surgery. All doses of soluble aspirin (600, 900 and 1200 mg) and aspirin tablet 1200 mg provided significant pain relief, with the maximum reduction in pain occurring approximately 90 min after administration.

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