EFFICACY AND PHARMACOKINETICS OF ASPIRIN IN POST-OPERATIVE DENTAL PAIN

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1 Soluble aspirin, 600 mg and 1200 mg, and placebo were compared in a double-blind, cross-over study in 12 patients with post-operative pain following removal of impacted lower third molars.

2 Significant analgesia after 600 mg aspirin occurred only at 45 min after administration, whereas significant analgesia after 1200 mg aspirin occurred from 45 to 240 min. The 1200 mg dose produced greater analgesia than the 600 mg dose and is to be recommended in clinical practice.

3 Plasma concentrations of salicylate and acetylsalicylate were measured after both doses. A significant correlation ($r^s = 0.876$, $P < 0.01$) was observed between analgesia and plasma salicylate concentration after 1200 mg aspirin.

Introduction

Despite extensive studies, the efficacy of aspirin in post-operative dental pain is uncertain. Indeed, the only placebo-controlled cross-over study failed to show any benefit from 2,000 mg/day aspirin orally (Hepso *et al.*, 1976). Moreover, although the pharmacokinetics of aspirin have been extensively studied (Levy, 1965, 1976, 1979; Leonards, 1962; Rowland *et al.*, 1972), there have been few attempts to investigate the relationship between the drugs kinetics and its analgesic properties. The present study was therefore undertaken to investigate the analgesic effect of aspirin, and in relation to its kinetics in plasma, in post-operative dental pain.

Methods

Twelve adult patients (six females) with clinical and radiographic evidence of symmetrical, bilateral, impacted lower third molars, which required surgical removal, agreed to participate in the trial which had received prior approval from the Area Health Authority Ethical Committee. All patients denied consumption of analgesics in the week preceding operation. Each impacted lower third molar was removed on separate occasions with at least four weeks between each operation.

Surgery was carried out by the same operator

(RAS) at 09.00 h. Local anaesthesia was produced by infiltration of the inferior dental and long buccal nerves with 2% lignocaine. The operating time (from first incision to completion of last suture) was recorded for every operation. On completion of surgery, time was allowed for lingual and mental nerve sensations to recover. When these were reported as normal (confirmed by response to pin prick and light touch on the lower lip and operation site), the patients received orally either soluble aspirin (600 mg or 1200 mg) in a strawberry flavoured solution (200 ml) or an identical tasting placebo. Six patients (three females) received 600 mg aspirin, and the remaining six received 1200 mg aspirin. Each patient received either aspirin, or placebo, in random order and thus acted as their own control.

An indwelling catheter was placed in a convenient forearm vein prior to aspirin or placebo administration, and a 10 ml venous blood sample was withdrawn at 0, 15, 30, 45, 60, 90, 120, 180, 240 and 300 min after the oral dose. The blood samples were placed in lithium-heparin tubes (Searle) each containing 200 μ l of a 50% (w/v) potassium fluoride solution. The blood tubes were kept in ice so as to further reduce the hydrolysis of acetylsalicylate (Rowland & Reigleman, 1967). Plasma was separated by centrifugation and stored at -20°C before analysis in duplicate for acetylsalicylate and salicylate

by high performance liquid chromatography (Lo & Bye, 1980). Patients registered their pain experience on a 100 mm visual analogue scale immediately after each blood sample had been withdrawn. The boundaries of the scale were 'no pain' and 'unbearable pain'.

Analgesia (in mm) was calculated by subtracting the pain score after aspirin, from the pain score after placebo, at each time point. The significance of the difference between means was assessed by Wilcoxon's signed rank test.

Plasma half-life was determined thus:

$$T_{1/2} = \frac{0.693}{k_{el}} \quad (1)$$

where k_{el} is the elimination rate constant calculated by least-squares regression analysis of the mono-exponential decay of plasma acetylsalicylate concentration.

Results

Mean pain scores after placebo and both doses of aspirin are shown in Figure 1. After 600 mg aspirin, the mean pain score was significantly ($P < 0.05$) less

Figure 1 Mean pain scores $\pm$ s.e. mean after aspirin and placebo. * = significant difference ($P < 0.05$) in pain scores. (a) --- placebo, — aspirin 600 mg, (b) --- placebo, — aspirin 1200 mg.

than placebo at 45 min only. After 1200 mg aspirin, the mean pain score was significant ($P < 0.05$) from 45 min to 240 min. The mean placebo pain scores in the two groups did not differ significantly at any time point. Figure 2 shows the analgesia (placebo score minus aspirin pain scores) after both doses of aspirin.

Figure 2 Analgesia after 600 mg (---) and 1200 mg (—) aspirin * = significant analgesia ($P < 0.05$) compared with placebo.

The mean maximum reduction in pain which occurred at 90 min after 1200 mg aspirin was 48% (Figure 2). No significant order effect was observed and the mean duration of surgery was the same (23 min, range 17–45 min) for each treatment.

Mean ($\pm$ s.e. mean) plasma acetylsalicylate and salicylate concentrations after the two doses of aspirin are shown in Figure 3. Peak acetylsalicylate concentrations were observed at 15 min after dosing and the mean concentration at this time after 1200 mg

Figure 3 Plasma salicylate (●) and acetylsalicylate (○) concentrations after 600 mg (---) and 1200 mg (—) soluble aspirin (mean $\pm$ s.e. mean).

Table 1 Pharmacokinetics measurements (mean $\pm$ s.e. mean)

	600 mg aspirin		1200 mg aspirin	
	Peak plasma concentration (mg/l)	Elimination half-life (h)	Peak plasma concentration (mg/l)	Elimination half-life (h)
Acetylsalicylate	14.4 $\pm$ 1.1	0.31 $\pm$ 0.01	25.6 $\pm$ 1.3	0.29 $\pm$ 0.02
Salicylate	41.1 $\pm$ 3.8	—	80.7 $\pm$ 6.5	—

(25.0 $\pm$ 1.3 mg/l) was not significantly different from that predicted by assuming linear kinetics after 600 mg aspirin (Table 1). Plasma acetylsalicylate concentration declined monoexponentially with a half-life of 0.31 $\pm$ 0.01 h and 0.29 $\pm$ 0.02 h after 600 mg and 1200 mg aspirin respectively (Table 1). Peak plasma salicylate concentrations were observed at 60 to 90 min after administration of both doses of aspirin. Thereafter, plasma salicylate concentrations decline linearly with respect to time.

Spearman rank correlation coefficients were calculated between analgesia and plasma concentrations of both acetylsalicylate and salicylate after each dose. The only significant correlation (Figure 4) was between salicylate concentration after 1200 mg aspirin and analgesia ($r^s = 0.786$, $P < 0.01$).

Discussion

In this study the same operation was performed on the same individual on two separate occasions. The

extent of operative trauma is independent of site, since the procedure is performed with the dental surgeon seated behind the patient. Post-operative pain is thus broadly comparable on each occasion, the patient can therefore act as his own control (Seymour & Rawlins, 1981). Patients who have had their lower third molars removed experience their most marked pain in the first 12 h after surgery (Sven & Gilhuus-Moe, 1975; Album *et al.*, 1977; Skjelbred *et al.*, 1977, 1979) and it is at this time that analgesics are required. Post-operative dental pain has an important inflammatory component (Szmyd *et al.*, 1965) and aspirin, with its known anti-inflammatory and analgesic properties (Ferreira & Vane, 1974) might be expected to be an effective analgesic. This study shows that the analgesia produced by aspirin is dose related and that 1200 mg produces effective control of pain for up to 4 h. Similar dose response relationships have been shown in post-operative orthopaedic pain (Parkhouse *et al.*, 1968) and in relieving headaches (Murray, 1963).

Although aspirin has been extensively studied in the treatment of post-operative dental pain, the only placebo-controlled cross-over trial was that reported by Hepso *et al.* (1976). These workers showed that in patients who had undergone bilateral removal of impacted lower third molars, the post-operative pain scores, as assessed once daily on a 4-point descriptive pain scale, were unaffected by 2000 mg aspirin daily. The difference in results between the present study and that of Hepso *et al.* (1976) is partly due to the superior sensitivity and reliability of the visual analogue scale as compared to the 4-point descriptive pain scale (Aitken, 1969; Joyce *et al.*, 1975; Ohnhaus & Adler, 1975; Revill *et al.*, 1976; Downie *et al.*, 1978).

Haemorrhage is potentially the most serious adverse effect of aspirin in the management of post-operative dental pain. In the study of Hepso *et al.* (1976) a high incidence of post-operative haemorrhage was reported by the patients after treatment with aspirin. However, in their trial, patients received their first dose of aspirin (1 g) on the night before their operation. Such a procedure is of little value and would be difficult to ensure in clinical practice. In the present study, aspirin was given approximately 2 h after completion of the surgery. After such a time, haemostasis is usually well estab-

Figure 4 Hysteresis loop for analgesia and plasma salicylate concentration after 1200 mg aspirin.

lished, and none of the patients in the present study reported untoward bleeding either during the 5 h investigation period or in the subsequent week.

The analgesia produced by 1200 mg aspirin appears to be greater than that achieved with 1000 mg intravenous paracetamol as assessed by the same technique (Seymour & Rawlins, 1981), and the former is therefore to be recommended in clinical practice.

Peak plasma concentrations of both acetylsalicylate and salicylate occurred at 15 and 90 min respectively after both doses. The concentrations obtained are similar to those previously reported (Rowland *et al.*, 1972; Rance *et al.*, 1975; Lo & Bye, 1980) and the half-life of acetylsalicylate was also similar to those observed by Rowland *et al.* (1972).

The correlation between analgesia and plasma salicylate concentrations (Figure 4), which we have observed, may be fortuitous. Although the pharmacological basis for the analgesic efficacy of 1200 mg aspirin is uncertain, it may be due to inhibition of cyclo-oxygenase activity by aspirin (Burch *et al.*, 1978). This action, which occurs as a result of acetylation of the enzyme is persistent and would not be expected to decline with the fall in plasma acetylsalicylate concentrations.

In conclusion, this study demonstrates that 1200 mg aspirin (but not 600 mg) is an effective analgesic in post-operative dental pain, but that the correlation with plasma salicylate concentration may be fortuitous.

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