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The efficacy and pharmacokinetics of sodium salicylate in post-operative dental pain

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1 Sodium salicylate, 537 mg and 1074 mg were compared in a double-blind cross-over study in 24 patients with post-operative pain following removal of impacted lower third molars.

2 No significant analgesic effect was observed after either dose of sodium salicylate, either overall or at any time point during the 5 h investigation period.

3 Peak plasma concentrations of salicylate after 537 mg were observed at 30 min after dosage, whereas peak plasma salicylate concentrations after 1074 mg sodium salicylate occurred at 45 min after dosage.

Keywords sodium salicylate dental pain pharmacokinetics

Introduction

In a recent study we determined the dose-dependent analgesic action of soluble aspirin (600 mg and 1200 mg) in patients with post-operative pain after bilateral third molar surgery (Seymour & Rawlins, 1982). This study also reported on the relationship between analgesia and plasma concentrations of acetylsalicylate and salicylate. A significant correlation was observed between analgesia after 1200 mg aspirin and the corresponding plasma concentrations of salicylate (r_s = 0.786, $P < 0.01$), but we commented that the biological basis for this was uncertain because the mechanism of the analgesic efficacy of aspirin in post-operative pain remains unclear. The present study was carried out to evaluate the analgesic actions of sodium salicylate at similar molar doses to 600 mg and 1200 mg aspirin.

Methods

Twenty four adult patients (12 females), who required removal of their bilaterally similar impacted lower third molars, agreed to participate in the trial. The protocol for the study was approved by the Area Health Authority Ethics Committee. All patients denied taking analgesics in the week preceding operation. Each impacted lower third molar was removed on separate occasions with at least 4 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, and 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 sodium salicylate (537 mg or 1074 mg) in a strawberry flavoured solution (200 ml), or an identical tasting placebo in random order. Twelve patients (six females) received 537 mg sodium salicylate, and the remaining 12 received 1074 mg sodium salicylate. Patients thus acted as their own (placebo) controls.

An indwelling catheter was placed in a convenient forearm vein prior to sodium salicylate or placebo administration, and 10 ml venous

blood was withdrawn at 0, 15, 30, 45, 60, 90, 120, 180, 240 and 300 min after dosing. Blood samples were placed in lithium-heparin tubes, plasma separated by centrifugation, and stored at −20°C before analysis in duplicate for salicylate by high performance liquid chromatography (Lo & Bye, 1980). Patients registered their pain experience on separate, vertical, 100 mm visual analogue scales immediately after each blood sample had been withdrawn. The boundaries of the scale were 'no pain' and 'unbearable pain'.

Analgesia (in mm) was calculated, for each patient, by subtracting the pain score after sodium salicylate, 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. Areas under the graphs for pain against time for each patient were calculated according to the trapezoidal rule, in units of mm.h.

Results

Mean pain scores after both doses of sodium salicylate are shown in Figures 1a and 1b. Pain

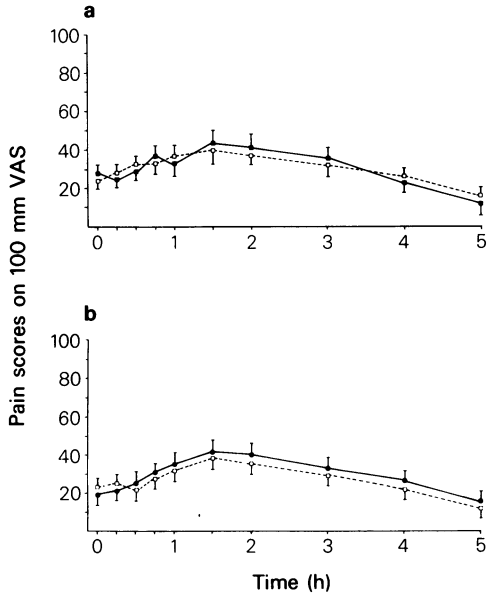

Figure 1 (a) Mean pain scores (mm) ± s.e. mean after 537 mg sodium salicylate (□----□) and placebo (■—■).
(b) Mean pain scores (mm) ± s.e. mean after 1074 mg sodium salicylate (□----□) and placebo (■—■)

scores after placebo, and after salicylate, were similar in the four groups, and at no time point did the difference reach conventional levels of statistical significance ($P < 0.95$). Mean (± s.e. mean) plasma salicylate concentrations after the two doses of sodium salicylate are shown in Figure 2. Peak salicylate concentrations (Table 1) after 537 mg sodium salicylate were observed at 30 min after dosage, whereas plasma salicylate concentrations after 1074 mg sodium salicylate occurred at 45 min after dosage.

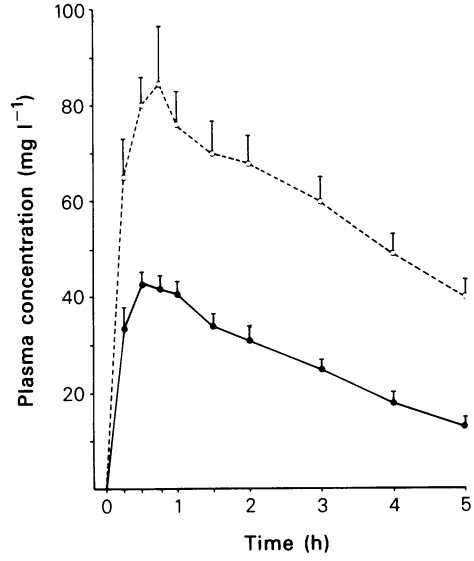

Figure 2 Plasma salicylate concentrations (mg/l) ± s.e. mean after 537 mg (●——●) and 1074 mg (O----O) sodium salicylate.

Discussion

After removal of impacted lower third molars, and in the absence of analgesia, localised pain increases in intensity and reaches a maximum at 3 to 4 h after the end of surgery (Cooper & Beaver, 1976; Seymour *et al.*, 1983). Thereafter, pain intensity declines after the following 12 to 24 h, although the rate varies widely between individuals. We have previously shown that intravenous paracetamol (Seymour & Rawlins, 1981) and oral aspirin (Seymour & Rawlins, 1982) are effective at reducing pain intensity when given at approximately 90 min (depending on the return

Table 1 Pharmacokinetic measurements (mean ± s.e. mean)

	Peak plasma salicylate concentration (mg/l)	*Area under plasma salicylate time concentration curve ($\mu g\ l^{-1}\ h$)*
1074 mg sodium salicylate	84.7 ± 12.8	543 ± 59
537 mg sodium salicylate	42.6 ± 2.8	203 ± 18

of lingual and mental nerve sensations) after the operation had been completed. In the latter study (Seymour & Rawlins, 1982), it was shown that the analgesic efficacy of aspirin was dose related, with 1200 mg aspirin providing greater analgesia than 600 mg over a 5 h observation period. In the present study we observed no significant analgesic effect of sodium salicylate after either 537 mg or 1074 mg. These doses are equimolar with those used in our previous study of the analgesic action of aspirin. Additionally, plasma concentrations of salicylate after both doses of sodium salicylate were similar to those obtained after 600 mg and 1200 mg aspirin.

The results of this study have two important implications. Firstly, the correlation between plasma salicylate concentrations and analgesic efficacy after 1200 mg aspirin in post-operative dental pain, which was reported previously (Seymour & Rawlins, 1982) is clearly not causal. Secondly, although the mechanism of aspirin induced analgesia in post-operative dental pain remains unclear, it has been suggested that the inhibition of cyclo-oxygenase by acetylation of the active site of the enzyme (Roth & Marjerus, 1975; Burch *et al.*, 1978) plays a crucial role. The poor efficacy of sodium salicylate, as compared to aspirin, may thus be due to its weak inhibitory effect on the synthesis of PGE_2 and $PGF_{2\alpha}$ (Vane, 1971). However, aspirin and sodium salicylate are equipotent in inhibiting the formation of 12-HETE from 12-HPETE *in vitro*, and have been reported to possess equipotent and anti-inflammatory properties *in vivo* (Siegel *et al.*, 1979). Our observations on the comparative analgesic efficacy of aspirin and sodium salicylate would therefore be compatible with the hypothesis that post-operative dental pain is primarily mediated by products of the cyclo-oxygenase pathway, and with less (or little) from lipoxygenase products.

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