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Aspirin metabolism and efficacy in postoperative dental pain

R. A. SEYMOUR[1], FAITH M. WILLIAMS[2], A. WARD[2] & M. D. RAWLINS[2]
[1]Department of Operative Dentistry and [2]Wolfson Unit of Clinical Pharmacology, The University, Newcastle-upon-Tyne

1 Aspirin 1200 mg was compared with placebo in a randomised, double-blind, crossover study in 15 patients with postoperative pain after removal of impacted lower third molars.
2 Over a 5 h investigation period, patients reported significantly less pain ($P < 0.01$) after treatment with aspirin, than after treatment with placebo.
3 Peak concentrations of aspirin occurred at 15 min after dosage.
4 Significant negative correlations were observed between plasma aspirin esterase activity and both AUC aspirin ($r = -0.904$, $P < 0.001$) and AUC analgesia ($r = -0.91$, $P < 0.001$). Similarly, a significant correlation was observed between AUC aspirin and AUC analgesia ($r = 0.96$, $P < 0.001$).
5 Evidence from this study would suggest that an individual's pain relief in postoperative dental pain is determined by the rate of aspirin hydrolysis to salicylate.

Keywords aspirin postoperative pain dental pain

Introduction

Aspirin (acetylsalicylic acid) is an effective analgesic for treating postoperative pain after the removal of impacted lower third molars (Von Graffenried *et al.*, 1980; Seymour & Rawlins, 1982). Its efficacy is dose-dependent, with 1000 mg to 1200 mg providing significantly greater analgesia than 300 mg–600 mg (Von Graffenried *et al.*, 1980; Seymour & Rawlins, 1982; Henrikson *et al.*, 1979; Cooper & Beaver, 1976). Sodium salicylate, when given at equimolar concentrations to 600 mg and 1200 mg aspirin, produced no significant analgesia when compared with placebo, after third molar surgery (Seymour *et al.*, 1984). This indicates that the acetyl moiety is essential for analgesia in postoperative dental pain. *In vivo*, aspirin is rapidly hydrolysed to salicylate by esterases (Menguy *et al.*, 1972) whose activity might be expected to be an important determinant of its analgesic effect. We have therefore investigated the relationship between plasma aspirin esterase activity, plasma aspirin concentrations, and analgesic efficacy after aspirin 1200 mg in patients who have undergone removal of their impacted lower third molar teeth.

Methods

Fifteen adult patients (eight females) aged 17–32 years with clinical and radiographic evidence of symmetrical, bilateral impacted lower third molars, which required surgical removal, agreed to participate in the trial. The protocol for the study was submitted to and approved by the Health Authority Ethical Committee. All patients denied consumption of analgesics in the week prior to surgery. Each impacted lower third molar was removed on separate occasions at least 4 weeks apart.

Surgery was performed 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 (without vasoconstrictor). The operating time (from first incision to completion of last suture) was recorded for each operation. At the end of surgery, time was allowed for lingual and mental nerve sensations to recover and 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 1200 mg in a raspberry flavoured solution (200

ml) or an identical tasting placebo. At least 1 month elapsed between operations and patients received either aspirin or placebo in random, double-blind order, and thus acted as their own control. An indwelling catheter was placed in a convenient forearm vein and venous blood was withdrawn at 0, 5, 10, 15, 20, 30, 40, 50, 60 and 75 min after dosage. Blood samples were placed in lithium-heparin tubes (Searle) each containing 50 μl of a 50% (W/V) potassium fluoride solution and immediately placed on ice. Plasma was separated by centrifugation and stored at −20°C before analysis in duplicate the following day.

Plasma aspirin esterase activity was measured in the pre-drug sample by a modification of the method of Harris & Riegelman (1967). Plasma (0.9 ml) was incubated for 30 min at 37°C with 0.1 ml of a freshly prepared aqueous solution of acetylsalicylic acid giving a final concentration of 10 mg/l. The reaction was stopped by adding acidified ether and placing the tubes on ice. Salicylate concentrations were measured fluorometrically after solvent extraction. Spontaneous (non-enzymatic) hydrolysis was measured in parallel by incubating aspirin in buffer (pH 7.0) and corrections were made for the presence of fluorescent material in plasma by co-incubating blank plasma from each patient. Plasma aspirin esterase activity was expressed by μmol salicylate formed ml^{-1} plasma min^{-1} (μmol ml^{-1} min^{-1}).

Plasma aspirin concentrations were measured directly by reversed phase high performance liquid chromatography after protein precipitation with 30% perchloric acid (Rumble & Roberts, 1981). Acetylsalicylate was separated from salicylate and other metabolites on a C18 column using 50% methanol/50% (0.072%) orthophosphoric acid as the mobile phase (flow rate 2.5 ml/min). P-toluic acid was added as an internal standard. The retention times for acetylsalicylate and *p*-toluic acid were 2.1 and 4.2 min respectively.

Patients registered their pain experience on separate, horizontal, 100 mm visual analogue scales, at 0, 15, 30, 45, 60, 90, 180, 240 and 300 min after dosage, without reference to their previous recordings. The boundaries of the scale were 'no pain' and 'unbearable pain'. The significance of the difference between placebo and aspirin 1200 mg was assessed by Wilcoxon's signed rank test (two tailed). Analgesia (in mm) was calculated by subtracting the pain scores after aspirin 1200 mg from the pain scores after placebo at each time point. The areas under the graphs for analgesia against time (AUC analgesia) and plasma aspirin concentration against time (AUC aspirin) were calculated by the trapezoidal method (with units of mm.h and mg l^{-1} h respectively). Results are expressed as means ± s.e. mean, and correlations (r) were assessed by least-squares regression analysis.

Results

Mean pain scores after aspirin 1200 mg and placebo are shown in Figure 1 and significant analgesia was observed at all time points between 30 min and 5 h, with maximum analgesia occurring at 90 min. The mean operating times after both treatments were similar (placebo = 20 ± 1.5 min, aspirin 1200 mg = 21 ± 2 min) and no significant order effect was observed ($P > 0.05$). The areas under the pain-time curves were significantly less ($P < 0.01$) after aspirin 1200 mg than placebo (27.3 ± 2.3 and 51.1 ± 4.8 mm.h respectively) and AUC analgesia was 23.8 ± 4.6 mm.h (range 0.3–57.5 mm.h) (Table 1). Peak plasma concentrations of aspirin (26.2 ± 3.2 mg/l)

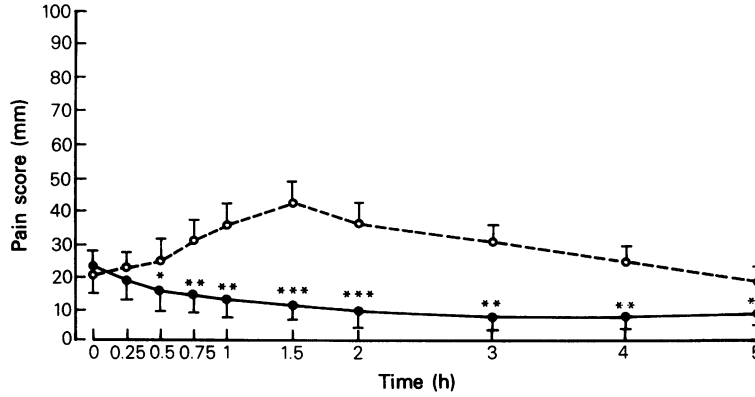

Figure 1 Mean pain scores (mm) ± s.e. mean for placebo (○) and aspirin 1200 mg (●). $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.

Table 1 Variables obtained for each patient in the study.

Patient	*Age (years)*	*Sex*	*Aspirin esterase activity (μmol salicylate ml⁻¹ plasma min⁻¹)*	*AUC analgesia (mm.h)*	*AUC acetylsalicylate (mg l⁻¹ h)*	*Peak plasma concentrations of acetylsalicylate (mg/l)*
1	20	M	0.68	10.5	5.7	15.7
2	21	M	0.58	12	7.7	17.2
3	23	F	0.58	15.7	10	27.2
4	32	M	0.56	28	13	19.2
5	18	F	0.49	22.5	13.7	46.2
6	17	M	0.53	25.2	14.4	31.6
7	25	F	0.425	32	16.4	33.6
8	24	F	0.43	46	17.7	28.8
9	22	F	0.40	57	24	37.8
10	21	M	0.38	57.5	22.3	44
11	19	F	0.54	26	15	12
12	27	M	0.62	11	6.4	16.4
13	28	M	0.73	5.7	4.8	8.0
14	22	F	0.83	0.3	3	8.4
15	23	F	0.72	8	5	14

(Figure 2) were seen at 10–20 min after dosage, and the AUC aspirin was 11.94 ± 1.68 mg l^{-1} h (Table 1). Mean plasma aspirin esterase activity was 0.57 ± 0.03 μmol ml^{-1} min^{-1} (range 0.38–0.83 μmol ml^{-1} min^{-1}) (Table 1). Spontaneous hydrolysis of aspirin under the incubation conditions employed was equivalent to only 10% of the measure esterase activity. Reproducibility of the assay was 5.6% (coefficient of variation, n = 4), and repeat plasma sampling from 2 patients over 3 months gave in both cases a coefficient of variation of 11% (5 samples), suggesting that there is little intra-individual variation in plasma aspirin esterase activity with time.

Significant negative correlations were observed between plasma aspirin esterase activity and AUC aspirin ($r = -0.904$, $P < 0.001$) (Figure 3) and between plasma aspirin esterase activity and AUC analgesia ($r = -0.91$, $P < 0.001$) (Figure 4). Similarly, a significant correlation was observed between AUC aspirin and AUC analgesia ($r = 0.96$, $P < 0.001$) (Figure 5). There was also a significant correlation between peak plasma aspirin concentrations and both plasma aspirin esterase activity ($r = -0.83$, $P < 0.001$) and AUC analgesia ($r = 0.74$, $P < 0.001$) (Table 1).

Discussion

The efficacy of a single dose of aspirin 1200 mg in postoperative dental pain shows marked variation between individuals (Table 1). Aspirin undergoes presystemic metabolism (Rowland *et al.*, 1972; Levy, 1979) and only 68% of an oral dose reaches the systemic circulation. The close correlation that we have observed between plasma aspirin

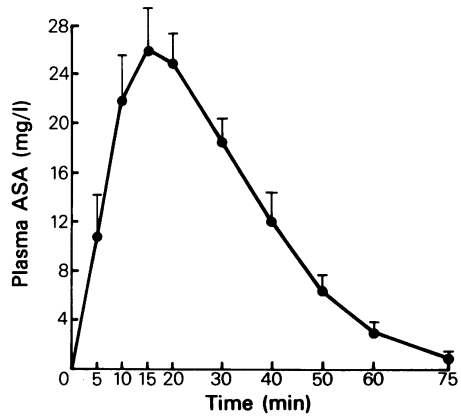

Figure 2 Plasma aspirin concentrations (mg/l) ± s.e. mean.

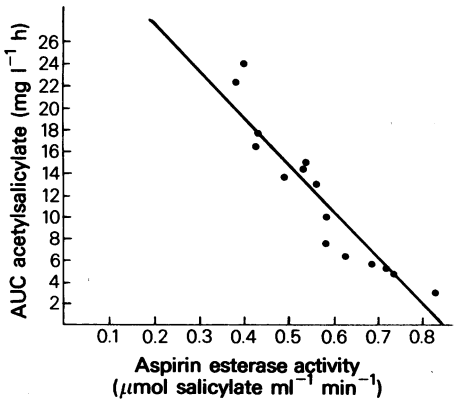

Figure 3 Correlation between plasma aspirin esterase activity (μmol salicylate ml^{-1} min^{-1}) and AUC acetylsalicylate (mg l^{-1} h). $r = -0.904$, $P < 0.001$.

esterase activity, peak plasma aspirin concentrations, AUC aspirin (Figure 3) and AUC analgesia (Figure 4) suggests that the rate of aspirin hydrolysis is a major determinant of its analgesia efficacy.

It has also been suggested that the absorption rate of aspirin may be a determinant of its analgesic efficacy (Levy, 1965). All patients in the present study were given aspirin under conditions of optimal absorption rate, with the drug in solution and administration some 3–4 h after a light breakfast. Furthermore, peak plasma aspirin concentrations (Table 1) were achieved between 10 and 20 min after dosage. It is unlikely that variation in apsirin absorption accounts for variability in efficacy in our patients.

Although plasma and liver esterases capable of hydrolysing aspirin have not been purified, Rainsford *et al.* (1980) has separated two components from plasma. One component appears to be similar to plasma cholinesterase, and the other is an aryl esterase.

The relationship between the hydrolysis of aspirin to salicylate, and its analgesic efficacy, has only been evaluated in pain after removal of impacted lower third molars. Further work is required to establish whether such a relationship applies to other actions of aspirin (e.g. platelet adhesion, other types of pain), and during its chronic administration.

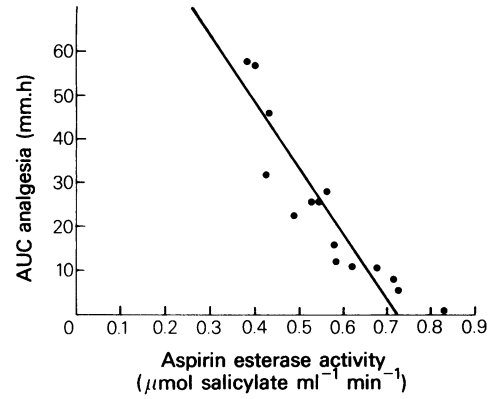

Figure 4 Correlation between plasma aspirin esterase activity (μmol salicylate ml^{-1} min^{-1}) and AUC analgesia (mm.h). $r = -0.91$, $P < 0.001$.

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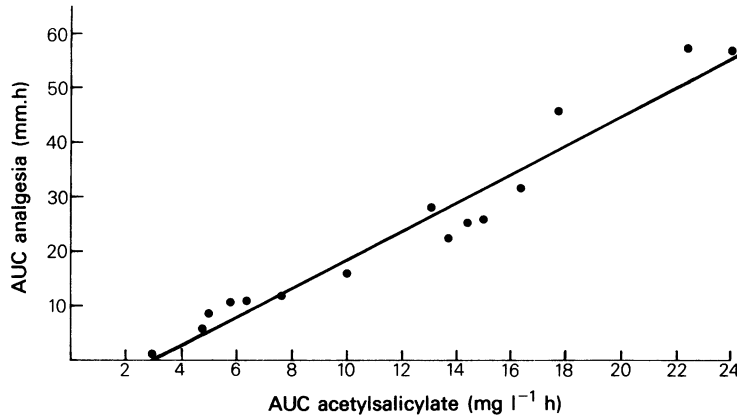

Figure 5 Correlation between AUC acetylsalicylate (mg l^{-1} h) and AUC analgesia (mm.h). $r = 0.96$, $P < 0.001$.

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