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The effects of acetylsalicylic acid on swelling, pain and other events after surgery

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1 In a double-blind crossover study acetylsalicylic acid (ASA) in low (2 g daily) or high (4 g daily) dosage was tested against placebo in two groups of 20 patients who each underwent identical oral surgical procedures on two separate occasions. Medication started 3 h post-operatively and continued for 3 days.
2 ASA in low dosage tended to increase the postoperative swelling, which on day 3 and 6 averaged 109 and 133% respectively of that with placebo ($P > 0.05$). In contrast, ASA in high dosage tended to reduce the swelling, which on day 3 and 6 averaged 85 and 90% respectively of that with placebo ($P > 0.05$).
3 Comparison of the two groups receiving ASA in low or high dosage revealed a significant difference in their effect on swelling; day 3, $P = 0.05$.
4 Pain was significantly reduced with ASA, but there appeared to be no greater analgesic effect with 4 g ASA daily than with 2 g ASA daily. There was, however, a substantial increase in the number of patients who reported tinnitus after taking 4 g ASA daily.
5 Subjective postoperative bleeding scores were significantly increased with 2 g ASA daily, but not with 4 g ASA daily.
6 None of the dosages of ASA appeared to reduce the swelling as efficiently, give better pain relief, or as high preference scores as previously obtained in studies when paracetamol and short term glucocorticoid administration were tested against placebo in this model.

Keywords acetylsalicylic acid pain swelling surgery

Introduction

Acetylsalicylic acid (ASA) has been shown to exert an objectively demonstrable anti-inflammatory effect when given in large regular doses to patients with active rheumatoid disease (Fremont-Smith & Bayles, 1965). In other inflammatory conditions, controlled clinical trials which demonstrate anti-inflammatory activity with ASA seem to be lacking, at least with swelling as a measure of inflammation. The present clinical model allows assessments on how drugs may modulate cardinale signs and symptoms of an acute inflammation such as swelling, pain, heat and loss of function (Løkken *et al.*, 1975). The findings in this model may also apply to traumatology. The purpose of the present trial was to investigate the effects of low and high dosage of ASA on swelling, pain and other events after surgery.

Methods

Patients

Healthy outpatients volunteered for the trial. They were in need of prophylactic surgical removal of bilateral, asymptomatic, impacted

third molar teeth of similar shape and position as evaluated clinically and by means of orthopantomograms. Forty patients completed the trial, 18 females and 22 males (mean age 22 years, range 17–27 years). Two other patients entered the trial, but had to be excluded as they were unable to follow the instructions given.

Drugs

At one operation they were given tablets containing 0.5 g ASA (Nyegaard & Co. A/S, Oslo, Norway), and at the other matching placebo tablets. The patients were allocated to two groups, and the randomization system ensured that half of the patients in each group received ASA at the first operation. The day of operation 20 patients were taking 1 tablet 3, 6, 9 and 12 h after surgery; the following two days 1 tablet at 08.00, 12.00, 16.00 and 20.00 h. The other 20 patients were taking two tablets at the corresponding times. No other drugs were permitted during the observation periods and 10 days prior to surgery.

Operations

Surgery was performed with a standardized technique (Skjelbred *et al.*, 1977). The interval between the two operations was 2, 3 or 4 weeks. For each patient the amount of local anaesthetic (Xylocain® andrenaline, Astra, Sweden) was the same at the two operations (3.6, 5.4 or 7.2 ml). In the 2 g group the average duration of the operation when ASA was given was 10.2 min (range 5–17 min) and 10.3 min (range 5–17 min) when placebo was given. In the 4 g group the corresponding durations were 10.2 min (range 5–17 min) and 9.5 min (range 5–15 min).

Assessments/statistical analyses

The facial *swelling* was measured with a mechanical device designed in our department (Løkken *et al.*, 1975). The *mouth-opening* ability was measured between the central incisors with a vernier gauge (Løkken *et al.*, 1975). The probe of an electronic thermometer (Omron MC-320®, Japan) registered the *oral temperature* distobuccal to the second lower molars (Skjelbred *et al.*, 1977). *Pain* was rated on a visual analogue scale with lines that ran from 'no pain' (0 mm) to 'pain cannot be worse' (100 mm). Assessments were made each hour during the first 9 h after surgery, and at bedtime the day of operation and for the following 5 days. The patients recorded *bleeding* 4 h postoperatively and in the evening of the day of operation and the following 5 days. The grading was none, slight (taste of blood), moderate (some blood in the mouth), and strong (much blood in the mouth). On the 3rd and 6th postoperative day the patients were examined for *haematoma/ecchymosis* (Hepsø *et al.*, 1976). *Complaints* ascribed to the medication were registered (Skjelbred & Løkken, 1982c), and after the second operation the patients gave an overall *preference* assessment of the course after this operation compared to the previous one (Skjelbred & Løkken, 1982c). *Statistical analyses* were performed with a two-sided Wilcoxon signed rank test with correction for ties (Lehmann & d'Abrera, 1975). A significance level of 5% was used.

Results

Swelling

ASA in low dosage tended to increase the postoperative swelling, which on day 3 and 6 averaged 109 and 133% respectively of that with placebo ($P > 0.05$). In contrast, ASA in high dosage tended to reduce the swelling, which on day 3 and 6 averaged 85 and 90% respectively of that with placebo ($P > 0.05$). Comparison of the two groups receiving ASA in low or high dosage revealed a significant different effect on swelling; day 3 $P = 0.05$ (Table 1).

Pain

Less pain was experienced when ASA was given, but there appeared to be no greater analgesic effect with 4 g ASA daily than with 2 g ASA daily (Figure 1).

Mouth-opening

The mean reduction in mouth-opening ability, expressed as percentage of the preoperative performance were:

2 g ASA daily vs *placebo*: third postoperative day 40 *vs* 45%, $P = 0.04$; sixth day 26 *vs* 26%.

4 g ASA daily vs *placebo*: third day 35 *vs* 38%, $P > 0.05$; sixth day 21 *vs* 19%, $P > 0.05$.

Oral temperature

The mean temperature difference between the operated and non-operated side were:

Table 1 Swelling after oral surgery in a crossover trial with 2 g daily or 4 g daily dosages of ASA tested against placebo in two groups of 20 patients. Medication started 3 h postoperatively with 0.5 and 1.0 g respectively and continued for 3 days.

	Swelling (Number of patients with)			*Measured swelling (mean)*		
	less after ASA	*same*	*less after placebo*	*ASA*	*Placebo*	*ASA vs placebo*
ASA—2 g daily						
Third day after operation	6	0	14	36 mm	33 mm	$P > 0.05$
Sixth day after operation	7	2	11	12 mm	9 mm	$P > 0.05$
ASA—4 g daily						
Third day after operation	14	0	6	34 mm	40 mm	$P > 0.05$
Sixth day after operation	12	0	8	9 mm	10 mm	$P > 0.05$

ASA 2 g daily *vs* ASA 4 g daily: Day 3: $P = 0.05$, Day 6: $P > 0.05$

2 g ASA daily vs *placebo*: third day 0.3 *vs* 0.3°C; sixth day 0.3 *vs* 0.4°C, $P = 0.02$.

4 g ASA daily vs *placebo*: third day 0.5 *vs* 0.9°C; $P = 0.004$; sixth day 0.5 *vs* 0.4°C, $P = 0.02$.

Bleeding

Subjective bleeding scores revealed a significant increase in postoperative bleeding with 2 g ASA daily, but not with 4 g ASA daily (Table 2).

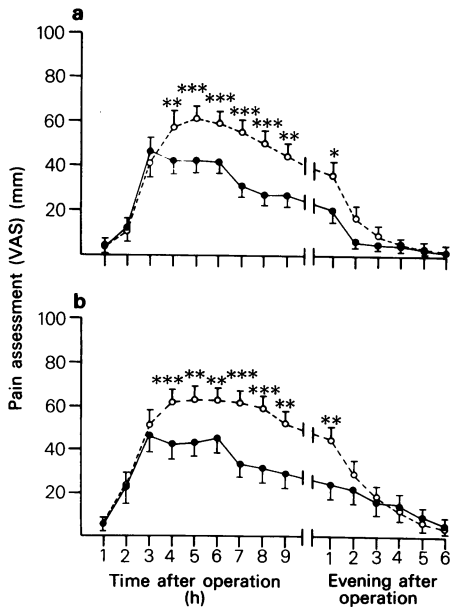

Figure 1 Pain assessments (mean ± s.e. mean) after oral surgery in a crossover trial with 2 g daily (a) or 4 g daily (b) dosages of ASA tested against placebo in two groups of 20 patients. ●—● ASA; ○- -○ placebo. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Haematoma/ecchymosis

The number of patients with visible discolouration were:

2 g ASA daily vs *placebo*: third day 12 *vs* 8, $P > 0.05$; sixth day 9 *vs* 7, $P > 0.05$.

4 g ASA daily vs *placebo*: third day 8 *vs* 7, $P > 0.05$; sixth day 6 *vs* 6.

Wound-healing

No clinically apparent complication was found after any operation.

Complaints

Tinnitus was frequently reported among the patients who received 4 g ASA daily, and in some of these tinnitus persisted 1–2 days after termination of the medication (Table 3).

Preference

According to the overall assessment after the second operation there was a significant preference for ASA in both groups on the day of operation (2 g ASA daily *vs* placebo: $P = 0.02$; 4 g ASA daily *vs* placebo: $P = 0.01$), but on the following days the preference did not reach a significant level in either of the two groups. Individual preference assessments are presented in Figure 2.

Discussion

In certain types of experimental inflammation in

Table 2 Bleeding after oral surgery in a crossover trial when 2 g daily or 4 g daily dosages of ASA tested against placebo in two groups of 20 patients. Medication started 3 h postoperatively with 0.5 and 1.0 g respectively and continued for 3 days.

	Bleeding (Number of patients reporting)			*Mean bleeding scores**		
	less after ASA	*same*	*less after placebo*	*ASA*	*Placebo*	*ASA vs placebo*
ASA—2 g daily						
4 h	1	12	7	2.1	1.6	$P = 0.02$
First evening	2	11	7	1.6	1.2	$P = 0.04$
Second evening	1	11	8	1.3	0.7	$P = 0.01$
Third evening	2	10	8	0.8	0.3	$P = 0.02$
Fourth evening	4	13	3	0.3	0.3	$P > 0.05$
Fifth evening	3	13	4	0.3	0.2	$P > 0.05$
Sixth evening	3	16	1	0.1	0.2	$P > 0.05$
ASA—4 g daily						
4 h	6	13	1	2.0	2.2	$P = 0.03$
First evening	3	15	2	1.5	1.6	$P > 0.05$
Second evening	3	12	5	1.2	1.1	$P > 0.05$
Third evening	1	14	5	0.7	0.4	$P > 0.05$
Fourth evening	3	14	3	0.3	0.3	$P > 0.05$
Fifth evening	3	16	1	0.1	0.3	$P > 0.05$
Sixth evening	1	19	0	0.1	0.1	$P > 0.05$

* 0 = none, 1 = taste of blood, 2 = some blood in mouth, 3 = much blood in mouth

animal models ASA exerted anti-inflammatory activity, and reduced swelling (Winter *et al.*, 1962; Winter & Nuss, 1966). In rheumatoid arthritis ASA in high daily dose was found to reduce joint swelling (Fremont-Smith & Bayles, 1965). This was also observed with salicylate at 5.3 g per day, but not at 2.6 g daily (Boardman & Hart, 1967). Controlled clinical trials which demonstrate the effects of ASA on swelling associated with a postoperative or traumatic inflammation seem to be lacking (Løkken & Skjelbred, 1981). In the present trial, a non-significant tendency toward increased swelling with 2 g ASA daily and decreased swelling with 4 g ASA daily compared to placebo was observed. Comparison of the two ASA treatments revealed, however, a significant different effect on swelling on the third postoperative day. A possible mechanism for these results was found with experimental inflammation in rats (Higgs *et al.*, 1980). ASA seems to have differential effects according to dose; at low dose the entry of leukocytes into the inflamed area was potentiated, while the leukocyte accumulation was inhibited at a higher dose which reduced oedema. The possibility was suggested that ASA at a low dose selectively inhibited the cyclooxygenase resulting in a diversion of arachidonic acid substrate through the lipoxy-

Table 3 Complaints related to the medication after oral surgery in a crossover trial with 2 g daily or 4 g daily dosages of ASA tested against placebo in two groups of 20 patients. Medication started 3 h postoperatively with 0.5 and 1.0 g respectively and continued for 3 days.

	ASA—2 g daily	*Placebo*
Day of operation	3 sleepiness, 1 nausea	1 sleepiness, 1 headache, 1 nausea
First day after	1 tinnitus, 4 sleepiness, 1 nausea	1 headache
Second day after	2 tinnitus, 2 sleepiness	1 headache
Third day after	–	–
Fourth day after	–	–
Fifth day after	–	–
	ASA—4 g daily	*Placebo*
Day of operation	4 tinnitus, 3 sleepiness, 1 cardialgia	3 sleepiness, 1 headache, 1 fever
First day after	8 tinnitus, 1 sleepiness, 1 cardialgia	1 sleepiness, 1 dyspepsia
Second day after	9 tinnitus	1 sleepiness
Third day after	3 tinnitus	–
Fourth day after	1 tinnitus	–
Fifth day after	–	–

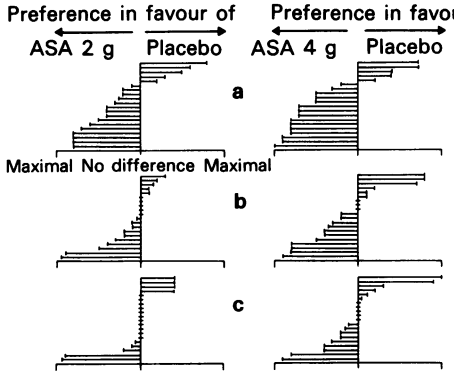

Figure 2 Preference for postoperative course on the day of surgery (a), day 1 and 2 (b) and day 3, 4, and 5 (c) after oral surgery in a crossover trial with 2 g daily and 4 g daily dosages of ASA tested against placebo in two groups of 20 patients. Abscissa: assessments by a visual analogue scale. Ordinate: each patient ranked according to preference.

genase pathway, resulting in increased production of chemotactic products and increased inflammatory response. At higher dose there was a dual cyclooxygenase and lipoxygenase inhibition resulting in reduction of the inflammatory reaction.

In a previous study 50% increase in swelling was measured after 2 g ASA daily compared to paracetamol (Skjelbred *et al.*, 1977). The difference in swelling might reflect a drug effect on the postoperative inflammatory reaction, or it might depend on bleeding within the tissue caused by ASA. The former explanation would mean that the inflammation was reduced by paracetamol and/or increased by ASA. This was, however, not consistent with the common view that paracetamol in contrast to ASA has little or no anti-inflammatory effect. The results of 3 follow-up studies have proved that paracetamol reduces swelling with about 30% compared to placebo (Skjelbred & Løkken, 1979, 1982c; Skjelbred & Løkken, unpublished results). The modest effect on swelling found with ASA in the present study is in accordance with results obtained with other non-steroid anti-inflammatory drugs in this model. Compared to placebo the mean reduction in swelling was 11% with ibuprofen (Løkken *et al.*, 1975), and 15% with oxyphenbutazone (Album *et al.*, 1977). With corticosteroids the reduction was about 50% (Skjelbred & Løkken, 1982a, 1982b, 1983).

A significant increase in postoperative bleeding was registered in the medication period with 2 g ASA, but not with 4 g ASA daily. A paradoxical effect on bleeding-time after ASA in low and high dose has been described (O'Grady & Moncada, 1978), and may be explained by a different sensitivity of platelet and vessel wall cyclooxygenase to ASA, disrupting the balance between the proaggregating thromboxane A_2 and the antiaggregating epoprostenol. Bleeding within the tissue caused by low dose ASA may have contributed to the increased swelling presently observed. There was, however, no connection between the occurrence of visible haematoma/ecchymosis and recorded swelling.

There appeared to be no increase in analgesic effect with 4 g ASA daily than with 2 g ASA daily. This is consistent with the clinical impression that a rather low ceiling exists for the analgesic action of ASA (Beaver, 1965).

The question of the relative efficacy and safety of ASA and paracetamol is a matter of considerable importance considering the extensive use of these drugs. They have about the same antipyretic (Yaffe, 1981) and analgesic (Skjelbred *et al.*, 1977) properties, but for the alleviation of inflammation ASA has been the preferable drug (Hollister, 1981). Previous studies indicate, however, that in inflammatory conditions other than rheumatoid arthritis, paracetamol reduces swelling more efficiently than ASA, and the present study gives additional evidence to suggest that ASA is not the drug of choice if swelling is to be prevented or reduced after surgery or accidental trauma.

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