COMPARISON OF INFUSIONS OF MORPHINE AND LYSINE ACETYL SALICYLATE FOR THE RELIEF OF PAIN AFTER SURGERY

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Lysine acetyl salicylate (LAS) is a water soluble salt of acetylsalicylic acid which may be given parenterally (LAS 1.8 g is equivalent to acetylsalicylic acid 1 g). The results of previous studies with LAS have been conflicting: some investigators suggest that its analgesic efficacy is comparable to that of opioids (Kweekel-De Vries et al., 1974; Blendinger and Eberlein, 1980; Korttila, Pentti and Auvinen, 1980), while others believe that, although LAS has some analgesic effect, it may not be comparable to opioids (McAteer and Dundee, 1981).

We are unaware of any previous studies which have used a constant i.v. infusion of LAS to provide analgesia after surgery. A double-blind comparison of the effectiveness of an infusion of LAS with an infusion of morphine has been undertaken following unilateral inguinal herniorrhaphy.

PATIENTS AND METHODS

Thirty patients (ASA class I/II) undergoing elective repair of an unilateral inguinal hernia were studied. The study was approved by the local ethics advisory committee and written informed consent obtained from each patient. Patients with a known intolerance or sensitivity to salicylates, an abnormal bleeding tendency or with a past history of peptic ulceration were excluded. Bleeding times were estimated in all patients before surgery. The patients were allocated randomly to one of two treatment groups to receive either LAS or morphine. The trial was conducted double-blind, with all assessments of pain being made by a single observer. A five-point verbal pain scoring system was used to grade the intensity of pain: none = 0; mild = 1; moderate = 2; severe = 3; very severe = 4 (Dundee, 1980). Analogue rating scales were used to assess the following side effects in the period after operation: drowsiness, dizziness, nausea, vomiting and sweating.

Anaesthesia was standardized in both groups. Premedication was with diazepam 10 mg orally and atropine 0.6 mg i.m. Anaesthesia was induced with thiopentone 4 mg kg⁻¹ and maintained with halothane and nitrous oxide in oxygen (2:1). The severity of pain was assessed immediately the patients arrived in the recovery area. Patients were then allocated randomly to one of two treatment groups to receive either LAS or morphine. The trial was conducted double-blind, with all assessments of pain being made by a single observer. A five-point verbal pain scoring system was used to grade the intensity of pain.

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SUMMARY

The effect of a constant i.v. infusion of lysine acetyl salicylate (LAS) on pain after operation was compared with that of a constant infusion of morphine in 30 patients undergoing unilateral inguinal herniorrhaphy. LAS provided analgesia equivalent to that provided by morphine and was associated with significantly less drowsiness, nausea and vomiting. No patient in either group was noted to suffer from respiratory depression. No untoward side effects were noted during or following the administration of LAS.
10–15 mg i.m. was prescribed as rescue analgesia. In a pilot study, the analgesic requirements of 10 patients undergoing unilateral inguinal herniorrhaphy were assessed. All of these patients were prescribed opioid analgesia to be administered as required. We found that seven patients received an analgesic at some time after surgery, and that of the three who did not, all had received an opioid as part of their pre-anaesthetic medication. In view of this, a placebo group was not included in the present study.

Results are expressed as mean (SD). Comparison between the groups has been made using the unpaired Student's t test. Pain scores were analysed statistically using the Mann–Whitney U test for non-parametric data. The incidence of side effects was compared using the chi-squared test with Yates' correction factor. Values of \( P < 0.05 \) were considered statistically significant.

### RESULTS

The two groups were comparable with regard to age, weight and duration of surgery (table I). No patient had a bleeding time before surgery greater than 240 s.

The results are represented graphically in figures 1 and 2.

The mean pain scores did not differ significantly at any time. The mean pain scores when the patients arrived in the recovery area were 1.47 in the LAS group and 1.60 in the group who received morphine.

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Duration of surgery (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAS (( n = 15 ))</td>
<td>52.5 (14.8)</td>
<td>75.3 (9.9)</td>
<td>49.6 (19.0)</td>
</tr>
<tr>
<td>Morphine (( n = 15 ))</td>
<td>49.3 (14.4)</td>
<td>74.1 (10.5)</td>
<td>47.7 (13.3)</td>
</tr>
</tbody>
</table>

Either analgesic agent effected a significant decrease in the severity of pain after 30 min (0.93 LAS group and 0.80 morphine group), but after 3 h the pain scores had increased (1.73 LAS group and 1.53 morphine group). After the infusion had been in progress for 3 h, the pain scores had again decreased significantly (0.53 LAS group and 0.67 morphine group), and remained low at 18 h (0.13 LAS group and 0.20 morphine group) and on completion of the infusion (0.07 LAS group and 0.20 morphine group). There was no difference in the patients' overall assessment of pain during the period of the investigation (0.67 LAS group and 0.77 morphine group).

Two patients in the LAS group required papaveretum i.m., one of them twice. Two patients in the morphine group received papaveretum i.m., one of them more than twice. Three patients in the LAS group complained of mild nausea, one of whom vomited, as did one other patient in this group. Eleven patients in the morphine group complained of nausea, which was mild in eight and of moderate severity in three; three of these 11 patients experienced vomiting. This difference between the two groups was significant (\( P < 0.05 \)). One patient in the

![Fig. 1. Cumulative frequency histogram of the pain scores in the two groups. Black columns = no pain; dotted columns = no or mild pain; open columns = no, mild or moderate pain; cross-hatched columns = no, mild, moderate or severe pain.](https://academic.oup.com/bja/article-abstract/57/3/255/387632/fig1?download=1)
LAS group and eight patients in the morphine group complained of drowsiness ($P < 0.05$). Furthermore, all of the patients in the LAS group were assessed by the observer as being awake and alert during the infusion, while seven of the patients in the morphine group were rated as being drowsy at some stage during the infusion ($P < 0.01$). No patient in either group was noted to suffer from respiratory depression.

DISCUSSION

Morphine and other opioid analgesics are used commonly to provide analgesia after surgery. However, there are several undoubted disadvantages associated with their use (Editorial, 1978). These include respiratory depression, nausea and vomiting. Other considerations include drowsiness—which may or may not be a disadvantage, depending upon its degree—as well as legislative restrictions and the possibility, albeit remote, of drug dependence. Non-opioids, such as the salicylates, have the advantage of being free from these side effects and have much to commend their use, provided that the analgesia produced is comparable to that of the opioids (Editorial, 1980).

There have been few controlled studies of LAS for the relief of pain after surgery. LAS has been investigated when given i.m. (Kweekel-De Vries et al., 1974; Korttila, Pentti and Auvinen, 1980), and when given as a bolus i.v. (Blendinger and Eberlein, 1980; Tammiisto and Tigerstedt, 1980; McAteer and Dundee, 1981). The results of these studies have been inconclusive with regard to the relative merit of LAS compared with opioid analgesics. Furthermore, intraoperative opioids were used in some of these studies (Kweekel-De Vries et al., 1974; McAteer and Dundee, 1981), and in one study LAS was not administered until at least 16 h after surgery (Blendinger and Eberlein, 1980).

Intermittent injections of analgesics i.m., even when carried out at strictly regular intervals may be associated with poor control of pain after operation (Editorial, 1978; Austin, Stapleton and Mather, 1980a). This may be the result of variability in rates of absorption resulting in widely fluctuating and unpredictable blood concentrations of analgesic (Mather et al., 1975; Shih, Robinson and Au, 1976; Editorial, 1978). Indeed, it has been suggested that there is a minimum analgesic concentration necessary for effective pain relief (Shih, Robinson and Au, 1976; Austin, Stapleton and Mather, 1980b). The administration of an analgesic in small but frequent doses or as an infusion results in a more stable blood concentration and may be expected to provide superior analgesia (White, 1982).

The results of the present study suggest that, after inguinal herniorrhaphy, an i.v. infusion of LAS...
provides pain relief of a quality similar to that provided by morphine—a conclusion in broad agreement with that of a number of other workers (Kweekel-De Vries et al., 1974; Blendinger and Eberlein, 1980; kortila, Pentti and Auvinen, 1980; Tammisto and Tigerstedt, 1980; McAteer and Dundee, 1981). However, reservations have been expressed concerning the efficacy of LAS in the treatment of pain after surgery, and it has been suggested that its use be reserved until the later postoperative period (McAteer and Dundee, 1981) or alternatively that, if it is used in the period immediately after operation, it be supplemented with a small dose of opioid (Tammisto and Tigerstedt, 1980). In one study, LAS was found to have a significantly slower onset of action than oxycodone; this was felt to be consistent with its pharmacokinetic properties (Korttila, Pentti and Auvinen, 1980), since LAS must first be converted to acetyl salicylate, which is then metabolized in the liver to salicylic acid (the active form of the drug). It is salicylic acid which reduces the sensitivity of pain receptors to nociceptive stimuli by decreasing prostaglandin synthesis (Vane, 1971). Previous studies have tended to wait for the patients to complain of pain before administering any analgesic and this has been, on average, 60 min after the end of surgery. This may offer a partial explanation for some of the conflicting results. We decided to administer the trial drug as soon as the patients regained consciousness, rather than wait for the complaint of pain.

The lower incidence of side effects associated with LAS was confirmed. Although we did not measure bleeding times during the infusion period, nor make any comparison of blood loss between the two groups, results from a similar trial in patients undergoing thoracic surgery suggest that LAS is not associated with a significantly greater blood loss after surgery than is morphine (Jones et al., 1985). Indeed, although small doses (<1 g) of aspirin prolong bleeding time, the drug appears to have a paradoxical effect in that there is no significant prolongation if larger doses (≥1 g) are used (O’Grady and Moncada, 1978; Rajah, Penny and Kester, 1978).

In conclusion, following inguinal hernia repair, infusion of LAS i.v. can provide pain relief equivalent to that provided by the i.v. infusion of morphine and is associated with a significantly lower incidence of nausea, vomiting and drowsiness.

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REFERENCES


