COMPARISON OF I.M. LYSINE ACETYL SALICYLATE AND OXYCODONE IN THE TREATMENT OF PAIN AFTER OPERATION

K. KORTTILA, O. M. PENTTI AND J. AUVINEN

SUMMARY

Lysine acetylsalicylate (LAS) is a soluble salt of acetylsalicylic acid and can be given parenterally. LAS 12.5 mg kg\(^{-1}\) and 25 mg kg\(^{-1}\) were compared with oxycodone 0.15 mg kg\(^{-1}\) in the treatment of pain after operation in 60 patients undergoing varicose vein surgery. Both treatments almost completely relieved moderate to severe pain for the 3-h observation period. The time until the peak of action was longer after LAS (60-90 min) than after oxycodone (30-60 min). No significant differences were found between the smaller and larger doses of LAS, suggesting a plateau effect. Further clinical experiments with LAS using i.v. mode of administration and other pain models are warranted.

Advantages of antipyretic analgesics over narcotic analgesics in treatment of pain after operation include absence of depression of breathing (Woodbury and Fingl, 1975), and less harmful effects on psychomotor performance, which is important in outpatient practice (Korttila, 1976).

Since the absorption of orally administered drugs is often unpredictable immediately after anaesthesia, the use of antipyretic analgesics in treatment of pain after operation has been limited. Lysine acetylsalicylate is a soluble salt of acetylsalicylic acid and can be given parenterally. It has been reported to have less influence on haemostasis and to produce less intestinal microbleeding than comparable doses of acetylsalicylic acid (Aron, Delbarre and Besnard, 1975; Schöndorf, 1975).

Previous investigators have suggested that the efficacy of lysine acetylsalicylate (LAS) is comparable to that of narcotic analgesics. Kweekel-DeVries and others (1974) compared LAS 1.8 g administered i.m. with morphine 10 mg in treatment of pain after gynaecological laparotomy and found a similar degree of relief of pain. Cattaneo, Rivara and Launo (1975) gave LAS i.v. and pethidine i.m. to patients suffering pain after cholecystectomy and came to the conclusion that LAS 14.67 mg kg\(^{-1}\) given i.v. corresponds to pethidine 1 mg kg\(^{-1}\) given i.m. Papatheodossiou (1976) concluded that parenterally administered LAS was comparable to pentazocine when given for pain relief after orthopaedic and gynaecological operations.

This previous work prompted us to undertake a double-blind controlled comparison of LAS and oxycodone in the treatment of pain after operation.

MATERIALS AND METHODS

Patients and anaesthesia

We studied 60 patients undergoing varicose vein surgery (table I). All of the patients were ASA Class I-II in respect of their general health and informed consent was obtained from each one. Premedication was diazepam 7.5, 10 or 12.5 mg orally according to weight 60-90 min and atropine 0.01 mg kg\(^{-1}\) i.v. 5 min before induction of anaesthesia. Anaesthesia was induced with a sleep-dose (approximately 7 mg kg\(^{-1}\)) of propanidid and maintained with 1-2% halothane in 66% nitrous oxide in oxygen. Tracheal intubation was facilitated by suxamethonium 1.0 mg kg\(^{-1}\) i.v., but no other drug was given during anaesthesia. The average duration of anaesthesia was 60-90 min (table I).

Administration of analgesics

At an average of 60-90 min after operation patients complained of moderate to severe pain. Then they received, in double-blind random fashion from coded ampoules, lysine acetylsalicylate (ONR-297, Orion, Helsinki) (LAS) 12.5 mg kg\(^{-1}\) or 25 mg kg\(^{-1}\) or oxycodone chloride (Oxanest, Leiras, Turku) 0.15 mg kg\(^{-1}\) i.m. into the lateral vastus muscle of thigh.
Table I. Characteristics of test groups and injected drug doses (means ± SD)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of patients (male/female)</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>Duration of anaesthesia (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycodone 0.15 mg kg⁻¹</td>
<td>13  (2/11)</td>
<td>47 ± 10</td>
<td>69 ± 9</td>
<td>166 ± 4</td>
<td>67 ± 22</td>
</tr>
<tr>
<td>LAS 12.5 mg kg⁻¹</td>
<td>22 (2/20)</td>
<td>46 ± 10</td>
<td>72 ± 12</td>
<td>165 ± 7</td>
<td>63 ± 16</td>
</tr>
<tr>
<td>LAS 25 mg kg⁻¹</td>
<td>25 (1/24)</td>
<td>45 ± 10</td>
<td>65 ± 10</td>
<td>163 ± 7</td>
<td>73 ± 22</td>
</tr>
</tbody>
</table>

LAS was prepared by dissolving equivalent amounts of acetylsalicylic acid and lysine plus approximately 10% of glycine (aminoacetic acid) into water followed by lyophilization into vials as lysine acetylsalicylate powder. Before injection, 7 ml of sterile water was used as solvent to obtain solutions containing LAS 150 or 300 mg ml⁻¹ with the pH value of 5.5.

Assessment of analgesic efficacy and side-effects

Trained nurses asked the patients to score the intensity of pain and the pain relief before and at 15, 30, 45, 60, 90, 120, 150 and 180 min after administration of LAS or oxycodone as 0 = nil, 1 = slight, 2 = moderate, and 3 = severe pain or complete pain relief. Six patients given LAS 25 mg kg⁻¹, one given LAS 12.5 mg kg⁻¹ and one given oxycodone were given oxycodone 0.15 mg kg⁻¹ 90-120 min after anaesthesia in addition to the test dose because of persistent severe pain. In these patients pain was considered to be severe (3) and pain relief none (0) for each assessment after the additional dose of oxycodone as a known analgesic had been given.

Heart rate was counted from the e.c.g., systolic arterial pressure was measured by auscultation and sphygmomanometry and respiratory rate was noted. Other side-effects, especially drowsiness, nausea, vomiting, sweating and headache were rated by the nurses as 0 = nil, 1 = slight, 2 = moderate, and 3 = severe.

Statistics

Changes in heart rate, arterial pressure and respiratory rate were compared with Student’s t test. Pain intensity, pain relief, and the frequency of side-effects were compared with Chi-square test and Fisher exact probability test because of the non-parametric nature of these data.

Results

Pain intensity and pain relief

After oxycodone moderate to severe pain was alleviated to almost nil and pain relief was almost

![Fig. 1. Pain intensity as a function of time in different test groups (mean ± SEM). *P < 0.05, **P < 0.01 and ***P < 0.001 in comparison with oxycodone.](image)

![Fig. 2. Pain relief as a function of time in different test groups (mean ± SEM). *P < 0.05, **P < 0.01 and ***P < 0.001 in comparison with oxycodone.](image)
LYSINE ACETYLSALICYLATE AND POSTOPERATIVE PAIN

A OXYCODONE 0.15 mg kg\(^{-1}\)

LAS 12.5 mg kg\(^{-1}\)

LAS 25 mg kg\(^{-1}\)

FIG. 3. Changes in systolic arterial pressure and respiratory rate as a function of time in different test groups (mean ± SEM). *P < 0.05 and **P < 0.01 in comparison with oxycodone.

complete within 30 min. Its duration of action lasted for the whole observation period of (3 h) (figs 1, 2). Both doses of LAS also alleviated pain, but its speed of action was significantly (P < 0.05 to P < 0.001) slower than that of oxycodone. Pain intensity was greater and pain relief worse 30–60 min after both doses of LAS when compared with the scores after oxycodone, but no significant differences were noticed between the three treatments in either of these indices 90–180 min after drug administration (figs 1, 2).

No significant differences were noticed in the action of LAS 12.5 mg kg\(^{-1}\) or 25 mg kg\(^{-1}\). However, pain relief was worse after the greater dose of LAS than after the smaller one (figs 1, 2).

Side-effects

No clinically significant changes were noticed in arterial pressure, heart rate or respiratory rate. Heart rate remained almost unaltered after each treatment. Systolic arterial pressure averaged 120 mm Hg before the injection of analgesics and decreased by an average of 15 mm Hg after oxycodone but less after both doses of LAS (fig. 3). The respiratory rate of 20 b.p.m. was not decreased by more than a mean of 2 b.p.m. after each of the three treatments (fig. 3).

Headache, emetic symptoms and tiredness were the most common side-effects, but no significant differences were noticed in the frequency among the three groups (table II).

TABLE II. Side-effects (number of patients) after i.m. injection of oxycodone chloride or lysine acetylsalicylate (LAS), for pain relief after operation. No significant differences between groups (Chi-square and Fisher exact probability test)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Side-effect</th>
<th>Oxycodone 0.15 mg kg(^{-1}) (n = 13)</th>
<th>LAS 12.5 mg kg(^{-1}) (n = 22)</th>
<th>LAS 25 mg kg(^{-1}) (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiredness</td>
<td>slight</td>
<td>3</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>moderate</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>severe</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>slight</td>
<td>4</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>moderate</td>
<td>2</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>severe</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>severe</td>
<td>0</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>slight</td>
<td>3</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>moderate</td>
<td>2</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>severe</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Sweating</td>
<td>slight</td>
<td>2</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>moderate</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>severe</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>slight</td>
<td>4</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>moderate</td>
<td>3</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>severe</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>severe</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Others</td>
<td>vertigo</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>tremor</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

DISCUSSION

The principal result was that LAS relieved pain almost as effectively as oxycodone, but the speed of action of LAS was distinctly slower than that of oxycodone. No significant differences were noted between the effects of the smaller and larger doses of LAS.

Trial design

A comparison of the analgesic efficacy of the drugs studied is justified in this investigation, since type and duration of anaesthesia and type of operation were similar in each group. The groups differed only in
respect of the analgesics given. The doses of LAS were based on reports in the literature (Kweekel DeVries et al., 1974; Ventafridda and Spravevic, 1974; Cattaneo, Rivara and Launo, 1975; Papatheodossiou, 1976) on the analgesic efficacy of LAS in the treatment of pain. The dose of oxycodone used corresponds to the same dose (0.15 mg kg⁻¹) of morphine and both are generally known to have a good analgesic action (Jaffe and Martin, 1975).

A placebo was not included for ethical reasons because our previous clinical experience indicated that, after operations of the type undertaken in this study, moderate to severe pain lasts more than 3 h if not treated. The relief of pain after the analgesics were given can be considered to be a result of the drugs, and not of the spontaneous alleviation of the pain.

The type of anaesthesia used provides very rapid recovery and minimal residual effects (Korttila and Linnoila, 1975; Korttila et al., 1975; Korttila et al., 1977). The results of the present study best relate to treatment of moderate somatic pain in alert patients. Clinical situations which differ from this study, such as laparotomy or bone surgery, would have to be assessed separately.

**Effects of lysine acetylsalicylate**

The slow onset of action of lysine acetylsalicylate is consistent with its pharmacokinetics (Ventafridda and Martino, 1976). LAS is first converted to acetylsalicylic acid which is metabolized in the liver to salicylic acid, the active drug. The analgesic effect seems to occur after i.v. injection of LAS during high plasma concentrations of salicylic acid when the hydrolysis of acetylsalicylic acid has already occurred (Ventafridda and Martino, 1976). Even following i.v. injection of LAS, the maximum effect was not reached until 60 min after injection when enough salicylic acid had been produced (Ventafridda and Martino, 1976).

The finding that doubling the dose of LAS did not improve its analgesic efficacy, that is a plateau effect occurred, has not been suggested before for LAS. The greater dose was actually less efficient than the smaller dose. Recently, a paradoxical effect of aspirin on bleeding-time has been reported; small doses prolong the bleeding time but not larger doses (O'Grady and Moncada, 1978; Rajah, Penny and Kester, 1978). This has been explained by the different actions of small and large doses of acetylsalicylic acid on cyclooxygenase, the enzyme involved in the synthesis of one of the prostaglandins (P.G.I.) required in the blood clotting process (O'Grady and Moncada, 1978).

The mechanism of analgesic action of acetylsalicylic acid is also related to prostaglandin synthesis. Salicylic acid is believed to decrease the sensitivity of pain receptors to nociceptive stimuli by decreasing prostaglandin synthesis (Collier, 1971; Vane, 1971). If inhibition of the synthesis of prostaglandins related to mediating painful stimuli, like that of those involved in blood clotting, is dependent on the dose of acetylsalicylic acid, greater doses of LAS need not be as effective as smaller doses in pain relief.

Our results suggest that i.m. LAS is effective in treatment of moderate to severe somatic pain. Further clinical experiments with lysine acetylsalicylate using i.v. administration and other pain models are warranted.

**Acknowledgements**

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**References**


Lysine Acetylsalicylate and Postoperative Pain


**VERGLEICH ZWISCHEN I.M. LYSINAZETYLSALIZYLAT UND OXYCODON IN DER POSTOPERATIVEN SCHMERZBEKÄMPFUNG**

**ZUSAMMENFASSUNG**

Lysinazetylsalizylat (LAS) ist ein lösliches Salz der Azetylsalizyssäure und kann parenteral verabreicht werden. LAS 12,5 mg kg⁻¹ und 25 mg kg⁻¹ wurde mit Oxycodon 0,15 mg kg⁻¹ im Bezug auf Schmerzbekämpfung nach Krampfadernoperationen bei 60 Patienten verglichen. Beide Drogen beseitigten massige bis schwere Schmerzen fast völlig auf die Dauer der dreistündigen Beobachtungsperiode. Die Zeit bis zur Spitzenwirkung war bei LAS länger (60-90 min) als bei Oxycodon (30-60 min). Zwischen kleinerer und größerer Dosis von LAS zeigten sich keine signifikanten Unterschiede, was einen Kontinuierzeit effekt andeutet. Weitere klinische Experimente mit LAS in intravenöser Verabreichung und mit anderen Schmerzfallen sind angezeigt.

**COMPARAISON DE L’ACETYLSALICYLATE DE LYSINE ET DE L’OXICODONE ADMINISTRES PAR VOIE INTRAMUSCULAIRE POUR LE TRAITEMENT DE LA DOULEUR APRES LES INTERVENTIONS CHIRURGICALES**

**RESUME**

L’acetylsalicylate de Lysine (LAS) est un sel soluble d’acide acétylsalicylique que l’on peut administrer d’une manière parentérale. On a comparé des doses de 12,5 mg kg⁻¹ et de 25 mg kg⁻¹ de LAS à une dose de 0,15 mg kg⁻¹ d’oxycodone, pour le traitement de la douleur après les interventions chirurgicales, sur 60 patients souffrant de varices. Les deux traitements ont presque entièrement soulagé les douleurs allant de modérées à graves pendant la période d’observation qui a duré trois heures. Le temps qui a fallu pour atteindre le point culminant de l’action a été plus long après l’administration de LAS (60-90 min) qu’après l’administration d’oxycodone (30-60 min). On n’a trouvé aucune différence significative entre les doses les plus fortes et les doses les plus faibles de LAS, ce qui laisse penser à un effet plateau. D’autres expériences cliniques à l’aide de LAS administré par voie intraveineuse et d’autres modèles de douleurs sont justifiées.

**COMPARACION ENTRE EL ACETILOSALICILATO DE LISINA I.M. Y LA OXICODONA EN EL TRATAMIENTO DEL DOLOR DESPUES DE OPERACIONES**

**SUMARIO**

El acetilosalicilato de lisina (ASL) es una sal soluble de ácido acetilasalicilico y puede administrarse parenteralmente. Se llevó a cabo una comparación de 12,5 mg kg⁻¹ y de 25 mg kg⁻¹ de ASL con 0,15 mg kg⁻¹ de oxicodona en el tratamiento del dolor después de la operación en 60 pacientes sometidos a cirugía de las varices. Ambos tratamientos alivianaron casi totalmente el dolor moderado a severo durante el periodo de observación de 3 h. El tiempo transcurrido hasta el punto culminante de la acción fue más largo después de ASL (60-90 min) que después de la oxicodona (30-60 min). No hubo diferencias significativas entre las dosis mayores y menores de ASL, lo que hace pensar en un efecto de nivelación. Se responde de los experimentos clínicos adicionales con ASL, al usar el método de administración i.v. y otras estructuras del dolor.