VENOUS SEQUELAE FOLLOWING THE INJECTION OF ETOMIDATE OR THIOPENTONE I.V.

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SUMMARY

The frequency of local venous reactions after the injection i.v. of etomidate or thiopentone was studied in 61 patients undergoing surgery for prolapsed lumbar disc. Of the patients who received etomidate, 24% developed thrombophlebitis in the period after operation (up to 14 days). Of the patients who received thiopentone, 4% developed thrombophlebitis in the period after operation. Pain on injection occurred in 24% of the patients receiving etomidate, but there was no correlation between pain on injection and the subsequent thrombophlebitis.

Etomidate, a water-soluble derivative of imidazole, is used clinically as a short-acting i.v. anaesthetic agent. However, because of its instability in water, it is dissolved in propylene glycol, a solvent known to cause pain on injection and thrombophlebitis when used in combination with diazepam (Schou Olesen and Hüttel, 1980). Zacharias and colleagues (1979) found that 23% of patients had venous sequelae following the administration of etomidate in propylene glycol, while Korttila and Aromaa (1980) observed a frequency as high as 43% after a 14-day period of observation. Hewitt and co-workers (1966) have demonstrated previously that the frequency of venous sequelae following the injection of thiopentone i.v. was between 5% and 9%.

In the present study, the frequency of thrombophlebitis after operation in a group of patients receiving etomidate was compared with that in a similar group of patients receiving thiopentone.

PATIENTS AND METHODS

The programme of the investigation was approved by the regional Ethics Committee and after informed consent was obtained, 65 consecutive patients, undergoing surgery for prolapsed lumbar disc, were allocated to two groups.

On the day of operation the patients received diazepam 10–20 mg, by mouth as premedication. On arrival in the operation theatre each patient had a disposable Teflon cannula (Venflon 1.40, Viggo, Sweden) inserted to both the right and left cephalic veins, after which patients were randomized to receive the active medicament in either the left or the right arm. Once the “injection arm” was chosen, only etomidate or thiopentone was administered through that cannula. The dose of etomidate was 0.3 mg kg⁻¹ followed by 0.15 mg kg⁻¹ after 5 min and that of thiopentone 5 mg kg⁻¹ followed by 2.5 mg kg⁻¹ after 5 min. All other drugs administered during the operation (gallamine, fentanyl and suxamethonium) were given through the other cannula. Neither cannula was utilized for the infusion of fluids i.v. Following induction, anaesthesia was maintained with halothane and nitrous oxide in oxygen (2:1). On completion of the operation both cannulae were withdrawn. If leakage occurred outside the vein, if a haematoma developed or if the vein was used subsequently for the infusion of fluids, the patient was excluded from the study. One of the authors (P.H.) administered each anaesthetic and recorded any symptoms of discomfort or pain which were noted on injection, whether these were mentioned spontaneously by the patient or elicited after questioning. Each patient was seen daily during their stay in hospital by one of the other two authors, who were unaware of which medication had been given. The mean observation time was 5 days. Both arms were examined and the presence or absence of tenderness on palpation of the vein, venous thickening or erythema were recorded. Two weeks after the injection patients received a questionnaire which sought information on these same points. Thrombophlebitis was diagnosed when at least two of the three symptoms were recorded. This was necessary because some patients were discharged to their local hospital after 2 days.

For statistical evaluation the Mann–Whitney test and χ²-test were used.

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RESULTS
Three patients were excluded because the cannula was not removed at the end of the operation and was used subsequently for an i.v. infusion. One patient did not answer the questionnaire and, thus, the total number of patients completing the study was 61.

Thirty-three patients received etomidate (25 men, age range 33–69 yr, median 42 yr), and 28 patients received thiopentone (21 men, age range 19–64 yr, median 41.5 yr). The two groups were comparable in regard to age and sex. Of the patients receiving etomidate, one patient experienced pain on injection, while a further seven patients admitted to pain when asked—a total frequency of pain on injection of 24%. None of the patients who received thiopentone had pain on injection.

The frequency of venous sequelae in the two groups is presented in table I. The difference between etomidate and thiopentone regarding thrombophlebitis was significant ($\chi^2 = 5.146; P < 0.05$). Looking at the group of patients without pain or local reactions, a difference was found between the right and left arms for both etomidate and thiopentone. In the etomidate group 80% had no pain or local reactions when the right arm was used, compared with 56% when the left arm was used. This difference was not statistically significant ($\chi^2 = 2.2$). In the thiopentone group, 87% had no pain or local reactions when the right arm was used, compared with 69% when the left arm was used ($\chi^2 = 1.25; n.s.$).

DISCUSSION
The recorded frequency of pain on injection after etomidate is in accordance with the literature (Zacharias et al., 1979). No correlation was found between pain on injection and subsequent thrombophlebitis.

The frequency of thrombophlebitis following the injection of etomidate was 24%, a value too high to be accounted for by the Venflon catheter alone (Mikkelsen et al., 1980). In contrast, the frequency of thrombophlebitis in the thiopentone group was 4%.

In a previous study we demonstrated that the frequency of thrombophlebitis after the injection i.v. of Stesolid (diazepam) with propylene glycol as solvent was 48% (Schou Olesen and Hüttel, 1980) and expected a similar frequency in this study, since the design of both investigations was similar. One possible explanation could be the difference between the total amount of propylene glycol injected. In the present study a total dose of etomidate 0.45 mg kg$^{-1}$ (about 15 ml) was used to induce anaesthesia. Since each millilitre contained 350 mg of propylene glycol, 5500 mg of propylene glycol was injected in total. In the previous study (Schou Olesen and Hüttel, 1980) of diazepam, 4 ml (5 mg ml$^{-1}$) was used per patient. Since each millilitre contained 400 mg of propylene glycol, a total 1600 mg was injected. As a result, it is unlikely that the total amount of propylene glycol injected was of major importance. Since the pH values which were measured were similar for etomidate and diazepam (7.0 unit and 6.8 unit, respectively), this could not explain the marked difference. The higher frequency of thrombophlebitis following diazepam could be a result of the presence of other solvents, namely alcohol, benzoate and phenylcarbinol or, possibly, the concentration of propylene glycol could be of importance. If this is so, a concentration of 35% would seem to be critical, since the frequency of thrombophlebitis is doubled if the concentration is increased from 35% to 40%. In view of this we are studying the frequency of local venous reactions using etomidate in an 9% propylene glycol solution.

The difference between the frequency of venous sequelae in the right and left arms is interesting—although a statistically significant difference was not found (possibly as a result of the relatively small population studied). Obviously, if a difference could be found this would be of practical importance and, therefore, merits further study in relation to the right- or left-handedness of the patient, and the influence of use of the arterial pressure cuff.

### Table 1. The frequencies of local reactions and thrombophlebitis (defined as two of the three symptoms: redness, induration or tenderness). Figures in parentheses are percentages

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Etomidate (n = 33)</th>
<th>Thiopentone (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Redness</td>
<td>4 (12)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Induration</td>
<td>9 (27)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Tenderness</td>
<td>9 (27)</td>
<td>5 (18)</td>
</tr>
<tr>
<td>Thrombophlebitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In the first 5 days</td>
<td>6 (18)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>After 2 weeks</td>
<td>8 (24)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Without pain or local reaction</td>
<td>20 (61)</td>
<td>22 (79)</td>
</tr>
</tbody>
</table>
ETOMIDATE AND THIOPENTONE: VENOUS SEQUELAE

REFERENCES


VENÖSE FOLGEERScheinungen nach Injektionen i.v. von Etomidate und Thiopental

ZUSAMMENFASSUNG
Bei 61 Patienten, die wegen eines Diskusprolapps operiert wurden, wurde die Häufigkeit lokaler venöser Reaktionen nach der intravenösen Injektion von Etomidate und Thiopental untersucht. Von den Patienten, die Etomidate erhalten hatten, entwickelten 24% postoperativ (bis zu 14 Tage post-op.) eine Thrombophlebitis, von den Patienten, die Thiopental erhalten hatten, 4%. Vier und zwanzig Prozent der Patienten klagten über Schmerzen bei der Injektion von Etomidate, es fand sich jedoch keine Korrelation zwischen dem Injektionsschmerz und nachfolgender Thrombophlebitis.

SEQUELLES VEINEUSES APRES INJECTION D'ETOMIDATE ET DE THIOPENTAL I.V.

RESUME
Nous avons étudié la fréquence des réactions veineuses locales après injection i.v. d'etomidate et de thiopental chez 61 patients opérés de hernie discale lombaire. Parmi les patients qui ont reçu de l'etomidate, 24% ont développé une thrombophlébite dans la période post-opératoire (jusqu'au 14e jour). Parmi les patients qui ont reçu du thiopental, 4% ont développé une thrombophlébite post-opératoire. La douleur à l'injection était présente chez 24% des patients recevant de l'etomidate mais il n'y avait pas de corrélation entre cette douleur et la survenue secondairement d'une thrombophlébite.

SECUELAS VENOSAS DESPUES DE LA INYECCION I.V. DE ETOMIDATO Y DE TIOPENTONA

SUMARIO
Se estudió la frecuencia de reacciones venosas locales después de la inyección i.v. de etomidato y de tiopentona en 61 pacientes sometidos a cirugía por causa de discos lumbares en prolapso. Entre los pacientes que recibieron etomidato, un 24% desarrolló tromboflebitis en el periodo después de la operación (hasta 14 días). De los pacientes que recibieron tiopentona, un 4% desarrolló tromboflebitis en el periodo después de la operación. En un 24% de los pacientes que recibieron etomidato, ocurrió un dolor al momento de la inyección, pero no hubo correlación entre el dolor en la inyección y la tromboflebitis subsecuente.