Histamine release after injection of benzodiazepines and of etomidate. A problem associated with the solvent propylene glycol

Libération d'histamine après injection de benzodiazépines et d'étomidate. Rôle du solvant propylène-glycol

A. DOENICKE *, W. LORENZ **, R. HOERNECKE *, A.E. NEBAUER *, M. MAYER *
* Institut für Anaesthesiologie der LMU München, Innenstadtkliniken, Pettenkoferstraße 8a, 8000 München 2, Germany
** Theoretische Chirurgie, Philipps-Universität, Marburg, Germany

PATIENTS AND METHODS

After approval by the institutional ethics committee and after having obtained their informed consent, 10 healthy volunteers (age 20-30 years, weight 50-90 kg) were investigated in this single-blind, crossover study. The investigators were not blinded because, due to its solubility characteristics, it is not possible to dilute diazepam to a volume of 5 ml, as needed for the administration of lormetazepam. The subjects had a four day recovery interval after the first anaesthesia with etomidate and premedication with one of the two benzodiazepines. The sequence of injection of diazepam and lormetazepam in every volunteer was randomized.

Following amounts of drugs were injected into a distal forearm vein: diazepam 10 mg · 70 kg⁻¹ or lormetazepam 1 mg · 70 kg⁻¹; 30 min prior to etomidate 0.15 mg · kg⁻¹. The time table of trial procedure is schematically presented in figure 1.

Blood samples were drawn through a cannula placed in an antecubital vein and plasma histamine levels were measured according to the fluorometric method described by LORENZ et al. [10]. Responders were subjects which presented at least a 40 % increase in plasma histamine levels from the previous baseline value.

Heart rate was continuously monitored and blood pressure was measured in two min intervals.


Tirés à part : A. Doenicke.
RESULTS

Diazepam solved in benzyl-alcohol did not release substantial amounts of histamine (slight mean increase from 0.35 to 0.61 ng · ml⁻¹). Plasma levels were well below 1 ng · ml⁻¹. Mean plasma histamine values ± SD are presented in Table I.

Table I. — Plasma histamine levels (ng · ml⁻¹) after administration of diazepam 10 mg · 70 kg⁻¹ i.v. and lorometazepam 1 mg · 70 kg⁻¹ i.v., 30 min before etomidate 0.15 mg · kg⁻¹ i.v.

<table>
<thead>
<tr>
<th>Before</th>
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</tr>
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<tbody>
<tr>
<td>Diazepam</td>
<td>Etomidate</td>
<td>Diazepam</td>
<td>Etomidate</td>
</tr>
<tr>
<td>0.35 (0.16)</td>
<td>0.61 (0.17)</td>
<td>0.41 (0.12)</td>
<td>0.54 (0.22)</td>
</tr>
<tr>
<td>Lorometazepam</td>
<td>Etomidate</td>
<td>Lorometazepam</td>
<td>Etomidate</td>
</tr>
<tr>
<td>0.46 (0.22)</td>
<td>0.98 (0.82)</td>
<td>0.53 (0.33)</td>
<td>0.94 (0.95)</td>
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Mean ± SD; n = 10 volunteers; crossover study with two different i.v. premedications (diazepam and lorometazepam, respectively) 30 min before etomidate injection; 4 day interval between study sessions.

Lorometazepam solved in propylene glycol showed a distinct histamine release in two subjects (Fig. 1). According to the elimination kinetics of histamine the levels returned to baseline values within ten minutes. The subsequent injection of etomidate solved in propylene glycol (30 minutes later) caused a further liberation of histamine. Both volunteers did not show any cardiovascular reactions expected with these histamine concentrations. In both instances diazepam was given on the first trial day and lorometazepam on the second day, i.e. four days later. Histamine levels in a third volunteer rose from 0.75 to 1.15 ng · ml⁻¹, but did not present a true histamine release according to our definition.

DISCUSSION

A previous study on 10 volunteers revealed moderate histamine release after i.v. administration of flunitrazepam in 5 subjects with a maximal histamine level of 1 ng · ml⁻¹. These were associated with cutaneous symptoms indicating local histamine liberation [5]. Flunitrazepam was solved in 829 mg · ml⁻¹ propylene glycol. In 1978, we found elevated histamine levels associated with clinical symptoms (erythema) in volunteers receiving the muscle relaxants alloferin, pancuronium or suxamethonium in combination with etomidate [4]. At that time we would not find an explanation for histamine release after flunitrazepam or etomidate in combination with muscle relaxants.

In 1973, we had shown that etomidate did not release histamine [3]. Watkins (personal communication) suggested the possibility of histamine release after etomidate, in such small amounts, however, that due to its fast elimination from the circulation it could not cause haemodynamic effects. This was based on the observation of subclinical reactions like chemotaxis of leukocytes through the surrounding tissue. The production of anaphylatoxins following C3-activation reached its highest value 30-40 minutes after etomidate administration, whereas methohexital showed this effect already after 5 minutes.

Our own investigations on etomidate solved in various solvents may now help to resolve the problem on histamine release after etomidate. In 1973, we had studied histamine release with a formulation of etomidate sulphate solved in phosphate buffer. This etomidate preparation had a pH of 3.3 and an osmolality of 270 mosm · kg⁻¹ [9] and did not cause histamine release [3]. Since 1977 etomidate is formulated in 35 vol % propylene glycol. We now know that its osmolality of 4,900 mosm · kg⁻¹ is conveyed by the content of propylene glycol in the drug preparation [6]. It has been shown that replacement of propylene glycol with lipid emulsion prevented thrombophlebitis of diazepam [7] and significantly reduced the occurrence of pain on injection, thrombophlebitis [2] and haemolysis [12] after etomidate injection.

In the present study, the volunteers received etomidate in 35 vol % propylene glycol on two occasions and for premedication, once diazepam in benzylalcohol, and once lorometazepam in 50 vol %
propylene glycol, respectively. Lormetazepam in propylene glycol has an osmolality of 6,750 mosm · kg⁻¹ [6].

We believe that not only the first injection of etomidate after diazepam but also the injection of lormetazepam and etomidate four days later, may cause osmotic tissue damage. The unphysiologic osmolality of these drugs therefore can cause histamine release from damaged endothelium and/or mast cells. The occurrence of pain and thrombophlebitis reported in previous studies [2, 14] can be interpreted as symptoms of irritation of the vascular tissue.

Interestingly the high histamine levels after lormetazepam (2.05 and 2.7 ng · ml⁻¹) and etomidate (1.85 and 3.2 ng · ml⁻¹) observed in two volunteers were not associated with haemodynamic reactions or other side effects seen with similar histamine concentrations. This may be explained by the very short presence of histamine in the circulation suggested by Watkins and the limited histamine release from destroyed blood and tissue cells, not sustained by cascade mechanism of mediators [13].

Independently from this, we advocate the replacement of solvents that convey an unphysiologic osmolality to commercial drug preparations and therefore cause vascular and cellular sequelae. Studies comparing etomidate solved in propylene glycol and etomidate solved in lipid emulsion with medium chain triglycerides have clearly demonstrated the advantages — no pain on injection, no thrombophlebitis, no haemolysis — of the preparation containing the lipid solvent at a physiologic osmolality (400 mosm · kg⁻¹; pH = 7.6) [6] [2].

Since February 1992, etomidate is available in Germany in a medium chain triglycerides containing lipid emulsion (Etomidat-Lipuro®). A new solvent should also be found for other drugs, especially benzodiazepines like lormetazepam, lorazepam or flunitrazepam, yet solved in propylene glycol.

Promising results have been presented by Habazettl et al. in animal studies with propanidid formulated in liposomes. They reported a dramatic reduction of mortality due to anaphylactic reactions in rats from 86 % with propanidid solved in cremophor vs 0 % propanidid in the liposome formulation [8].

## REFERENCES


