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Basophil Histamine Release in Asthma Patients after *in Vitro* Provocation with Althesin and Etomidate

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Our aim was to compare the histamine-releasing effect of etomidate and Althesin® on basophil leukocytes from asthmatic patients and normal persons. Blood from eight asthmatic patients and six normal persons was tested for histamine release after *in vitro* provocation with etomidate and althesin. In the group of asthmatic patients there was a significantly higher histamine release after provocation with althesin than after provocation with etomidate at all concentrations ($P<0.05$, $P<0.01$, $P<0.02$). There was significantly higher histamine release for asthmatic patients than for normal persons after provocation with althesin at all concentrations ($P<0.05$, $P<0.01$, $P<0.02$). There was no difference between the asthma group and the normal group after provocation with etomidate. Data were analysed using Wilcoxon's and Mann-Whitney's rank sum tests. We conclude that asthmatic patients may risk bronchospasm during induction of anaesthesia with althesin, and that etomidate may be a suitable intravenous anaesthetic for asthmatic patients.

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Althesin® produces a marked histamine release in normal man whilst the effect of etomidate is insignificant (1). Asthma patients are more sensitive to histamine than normal persons and demonstrate greater leukocyte histamine release to some non-specific substances (2, 3). We are not aware of any controlled clinical trial dealing with the effect of etomidate and althesin during induction of anaesthesia in asthmatic patients. This paper describes the histamine-releasing effect of etomidate and althesin on basophil leukocytes of asthmatics and normal persons after *in vitro* provocation.

PATIENTS AND METHODS

Eight patients with severe asthma were included in the study. Six blood donors served as a comparison. We tested the histamine release from basophil leukocytes after provocation *in vitro* with the following concentrations of etomidate: 4 μg/ml, 2 μg/ml and 0.4 μg/ml. Althesin was used in the following concentrations: 0.7 μl/ml, 0.35 μl/ml and 0.07 μl/ml. The chosen concentrations are compatible with calculated plasma levels in the first minutes after intravenous induction of anaesthesia with a normal dose of these agents.

Etomidate and althesin were the commercially available drugs at the time of the experiment. Etomidate was dissolved in propylenglycol and althesin in chremophor EL.

Mononuclear cells were isolated by the Ficoll-Hypaque density gradient technique, and the cell suspension was incubated with the various concentrations of the anaesthetic to be tested (4). The release of histamine was expressed as a percentage of the total histamine content of the sample. Correction was made for spontaneous histamine release.

Data were analysed by Wilcoxon's and Mann-Whitney's rank-sum tests. P values less than 0.05 were considered as significant.

RESULTS

The results are shown in Tables 1 and 2. It can be seen from Table 1 that althesin produced a significantly higher histamine release in the group of asthma patients than in the control group. Table 2 shows that there was no significant difference in the two groups when etomidate was used. Althesin produced a higher histamine release than etomidate at all concentration levels in the group of asthma patients; the P-values were (in decreasing concentrations) < 0.05, 0.01 and 0.02. Likewise, in the normal group,

Table 1

Histamine release (per cent) from basophil leukocytes after *in vitro* provocation with althesin. Median values and ranges are indicated.

	Asthma patients n = 8	Normal persons n = 6
Althesin 0.7 μl/ml	*19.5 (2–53)	*15.5 (3–38)
Althesin 0.35 μl/ml	§59 (22–70)	§21 (7–38)
Althesin 0.07 μl/ml	†47.5 (5–69)	† 8 (5–19)

* $P<0.05$, § $P<0.01$, † $P<0.02$.

Althesin produced a significantly higher histamine release than etomidate; P in all cases < 0.05.

DISCUSSION

The role of histamine in anaphylactoid reactions is central. Clarke et al. (5) have analysed 100 anaphylactoid reactions to intravenous anaesthetics and concluded that 80% were histamine-induced. Histamine results in hypotension and cardiovascular collapse, flushing, urticaria and bronchospasm. Asthma patients in particular are at risk of bronchospasm from histamine release (6).

The present investigation agrees with earlier *in vivo* investigations on normal persons. Althesin increases the histamine concentration approx. 1 ng/ml. Etomidate produces no change in plasma histamine concentration (1). There are no reports of anaphylactoid reactions to etomidate, and etomidate is therefore recommended to atopic patients (7). The results of this investigation support this recommendation.

As far as we know, there are no *in vivo* investigations concerning the plasma histamine level in asthma patients after induction of anaesthesia with althesin or etomidate. We have used an *in vitro* method as this is without risk to the patients. The method is extremely reliable in the demonstration of allergy with a sensitivity of approx. 90% and a specificity of approx. 95% (4, 8). Histamine release above 25% is considered positive.

The strong histamine-releasing effect in response to althesin at low concentrations in asthma patients is surprising, since as far as we know they had not been exposed to althesin earlier. This might be because asthmatic patients have a deficiency of the granulocyte membrane. Our investigation did not attempt to differentiate the effect of althesin from the solvent chremophor EL. One of the eight asthmatic patients failed to give the same degree of histamine release with althesin. This might be because there may be two population types, but our numbers are too small to reveal this.

We conclude that asthmatic patients have a greater risk of bronchospasm during induction of anaesthesia with althesin. We suggest that etomidate is a suitable intravenous anaesthetic for asthmatic patients.

Table 2

Histamine release (per cent) from basophil leukocytes after *in vitro* provocation with etomidate. Median values and ranges are indicated.

	Asthma patients n = 8	Normal persons n = 6
Etomidate 4 μg/ml	2 (0–13)	1 (0–5)
Etomidate 2 μg/ml	4.5 (0–10)	1 (0–7)
Etomidate 0.4 μg/ml	3 (0–9)	1.5 (0–3)

The differences between the two groups are not significant.

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