

HISTAMINE RELEASE AFTER INTRAVENOUS APPLICATION OF SHORT-ACTING HYPNOTICS

*A Comparison of Etomidate, Althesin (CT1341) and Propanidid**

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SUMMARY

The subject of histamine release was investigated in 16 volunteers by means of plasma histamine determination after the administration of etomidate, Althesin, propanidid, and Cremophor EL. Althesin and propanidid caused release of histamine in various degrees of frequency. Blood pressure changes were rather pronounced with both anaesthetic agents; tachycardia reached its maximum in the first and second minute, which seems to be an argument against histamine release as the underlying cause of this reaction. Histamine was, indeed, only released to such an extent (with the exception of one borderline case) that no clinical symptoms other than secretion of gastric juice and erythema were to be expected. After the application of etomidate and Cremophor EL an increase in plasma histamine was not detectable. Changes in the differential blood picture in terms of a decrease in basophils only occurred after Althesin and propanidid; not, however, after etomidate and Cremophor EL. Etomidate is, therefore, the first hypnotic drug for intravenous application which is unlikely to cause chemical histamine release.

The increasing incidence of anaphylactic and anaphylactoid reactions after the administration of anaesthetic agents, muscle relaxants and plasma substitutes in recent years has enhanced the clinicians' interest in the question of drug-induced histamine release. After experiments in man and animals, certain circulatory reactions of unknown origin resulting from the administration of short-acting intravenous anaesthetics can now be explained by the release of pharmacologically highly potent histamine (Doenicke and Lorenz, 1970; Lorenz et al., 1969, 1970, 1971, 1972a,b,d; Seidel et al., 1973).

Our team (Lorenz et al., 1972b) has pointed out repeatedly that the circulatory effects of anaesthetic agents must be carefully analysed before physical or biochemical mechanisms can be held responsible for the clinical manifestations of certain signs and symptoms. Various studies (Kettler et al., 1970; Patschke et al., 1972; Soga and Beer, 1972; Sonntag et al., 1973) seem to indicate that the fall in arterial pressure frequently observed during the first 3 minutes after injection of the anaesthetic is caused by, among other mechanisms, reduced myocardial contractility. The delayed decrease in blood pressure after propanidid, however, often accompanied by allergic skin reactions, depends on a massive histamine

release into the circulatory system (max. about 5 minutes after the injection) (Lorenz et al., 1972b).

Two new short-acting anaesthetics (hypnotics) are under clinical investigation at present, i.e. etomidate and Althesin (CT1341) and the question arises as to whether they can release histamine under certain conditions. These studies with volunteers were preceded by clinical experiments carried out by various groups (Benke et al., 1972; Campbell, 1972; Campbell et al., 1971; Clarke et al., 1971; Hempelmann et al., 1973) with Althesin, and by our team (Doenicke and Kugler, 1973, unpublished; Doenicke et al., 1973a; Doenicke, Wagner and Beetz, 1973b) with etomidate. The experience thus acquired justifies a clinical-experimental study in man, since etomidate, in particular, proved to be a hypnotic devoid of adverse circulatory effects.

In the first study on etomidate, Janssen and associates (1971) reported on its hypnotic and toxic effects in rats when it was given in increasing concentra-

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tions. It was concluded from such comparative animal trials that etomidate, because of its relatively large safety margin, appeared to be excellent as compared with the other hypnotics, its LD_{50} being 30 times that of the hypnotic dose. We therefore considered it reasonable to assess the action of etomidate in man, whilst observing the necessary precautionary measures.

Etomidate is a carboxylate, such as is carbamoyl propylester (propanidid), and is injected intravenously. From the similarity of both substances one would expect a short narcotic action and rapid breakdown of etomidate since, as with propanidid, enzymatic hydrolysis in serum and liver is supposed to occur.

MATERIAL AND METHODS

Material

Drugs.

Etomidate (Janssen Pharmaceutica, Belgium) is R-1-ethyl-1-(α -methyl-benzyl) imidazole-5-carboxylate, available as an aqueous solution and neutralized with phosphate buffer (Janssen et al., 1971) (fig. 1).

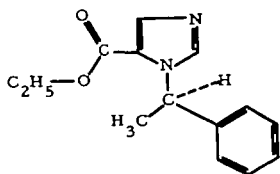


FIG. 1. Structural formula of etomidate.

Althesin (CT1341) (Glaxo, England) is composed of two steroids: 0.9% 3 α -hydroxy-5 α -pregnane-11, 20 dione, and 0.3% 21-acetoxy-3 α -hydroxy-5 α -pregnane-11, 20 dione. These two components, both slightly soluble in water, are dispersed with 20% Cremophor EL, 0.25% sodium chloride, and water, with the object of obtaining an injectable mixture (fig. 2).

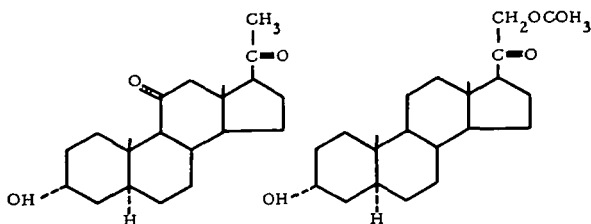


FIG. 2. Structural formula of the steroids contained in Althesin (CT1341).

Epontol (Bayer, Leverkusen) is a colloidal solution consisting of propanidid (3 - methoxy - 4(N, N - diethyl - carbamoylmethoxy) phenyl - acetic acid - n - propyl - ester, Micellophor (20%), various salts, and water (Scholtan and Sue Yung Lie, 1966).

Cremophor EL (BASF, Ludwigshafen) contains 84% of hydrophobic ORPE (oleum ricini polyoxyethylate Elbersfeld) and 16% of a hydrophilic mixture of polyglycols and glycerine-polyglycol-ethers—atropinum sulfuricum (medicinal).

Reagents.

Histamine dihydrochloride o-phthaldialdehyde (Fluka, Buchs), Dowex 50 W-X8, H⁺ (Serva, Heidelberg)—organic and inorganic solvents as Uvasol (Merck, Darmstadt). For purity and detailed specification of the reagents see Lorenz et al. (1972c).

Anaesthesia and Trial Scheme

Anaesthesia, trial scheme and measuring methods have already been described in detail in a previous publication (Lorenz et al., 1972a).

The trial group comprised 16 male, amnestically healthy volunteers, between 21 and 33 years of age and weighing 58–85 kg. They had been fasting for at least 6 hours.

Trial procedure.

Anaesthesia was carried out with spontaneous breathing between 8 a.m. and 4 p.m. over several days. Fifteen minutes before injecting the anaesthetic agent, a catheter (Braunula) was placed in a forearm vein, two blood samples were taken for plasma histamine determination and blood count purposes, and an intravenous injection of atropine 0.5 mg was given. The rates of injection were: 20 sec for etomidate 0.2 mg/kg bw and propanidid 5 mg/kg bw, 60 sec for Althesin 0.075 ml/kg bw, and 10 sec for Cremophor EL 0.15 ml/kg bw. The other arm was used for measurement of blood pressure.

Measuring Methods

Plasma histamine determination.

Plasma was obtained, using the method of Lorenz and associates (1972c); 19.5 ml whole blood was taken from each of the volunteers immediately before anaesthesia and 1, 5, 10, 20 and 30 min after injecting the anaesthetic agent. Histamine was isolated by ion exchange chromatography with Dowex 50 W-X8 and subsequent extraction into alkaline butanol and was determined fluorometrically after condensation with 0.05% σ -phthaldialdehyde.

The blood pressure was measured at 1-min intervals by auscultation using the Riva Rocci technique; the heart rate was continuously monitored by electrocardiogram (Hellige Multiscriptor EK22) up to 20 min after injecting the anaesthetic agent.

The differential blood count was determined from venous blood by counting 1,000 cells from each of two samples, using Pappenheim staining. Total white blood cells per mm³ were counted by means of a counting chamber. For details of the method of counting basophils and eosinophils, see Lorenz and associates (1972c).

Evaluation.

Results were statistically evaluated by means of the Student *t*-test.

RESULTS

Plasma histamine concentrations.

After intravenous injection of anaesthetic agents (hypnotics) and plasma substitutes in man and dog, release of histamine is not invariable, but occurs only in a certain number of test persons or animals. The occurrence of an increase in plasma histamine levels or even of serious anaphylactic incidents varies, and with high-molecular mixtures (Cremophor EL and Micellophor in our case) it even varies from batch to batch. It is, therefore, not surprising that

in comparison with previous investigations (Lorenz et al., 1972a,b) the release of histamine following the administration of Epontol (active substance propanidid+Micellophor) occurred comparatively infrequently (fig. 3c), which is probably attributable to the dosage reduction from 7 to 5 mg/kg body weight.

If, however, the same subjects who had received propanidid, were treated with etomidate (the sequence of administration of the two drugs being randomized with the aid of random tables), none of the 8 volunteers showed evidence of histamine release (fig. 3A). The plasma histamine level rose after Althesin in 4 of 8 volunteers (fig. 3B). The course of this reaction corresponds to that obtained with propanidid and thiopentone, as we had been able to demonstrate already (Doenicke and Lorenz 1970; Lorenz et al., 1972b). Since methohexitone also causes histamine release corresponding to that caused by the other anaesthetics mentioned (Seidel et al., 1973),

etomidate is the only short-acting anaesthetic (hypnotic) for intravenous application so far tested which is not associated with a detectable degree of histamine release.

The increase in plasma histamine levels found in the volunteers has no direct clinical significance (Doenicke and Lorenz, 1970; Lorenz et al., 1972b). It indicates, however, that massive histamine release might occur under unfavourable conditions with the possible risk of life-threatening anaphylactoid incidents (Doenicke and Lorenz, 1970; Lorenz et al., 1972b). Furthermore, the possibility of the anaesthetically-induced histamine release being at least partly responsible for the postoperative occurrence of stress ulcers cannot be excluded (Seidel et al., 1973).

The same volunteers, who were treated with Althesin, also received the solvent Cremophor EL in the same type of injection mixture as used in the

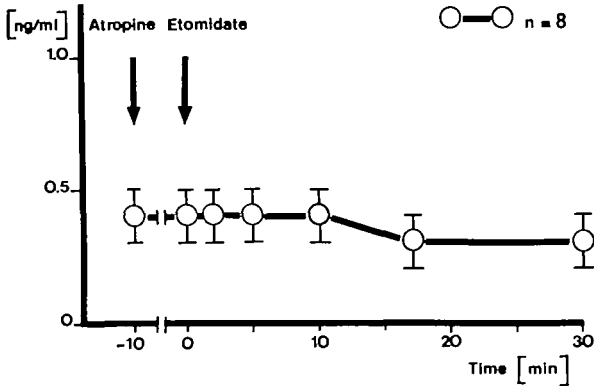


FIG. 3A

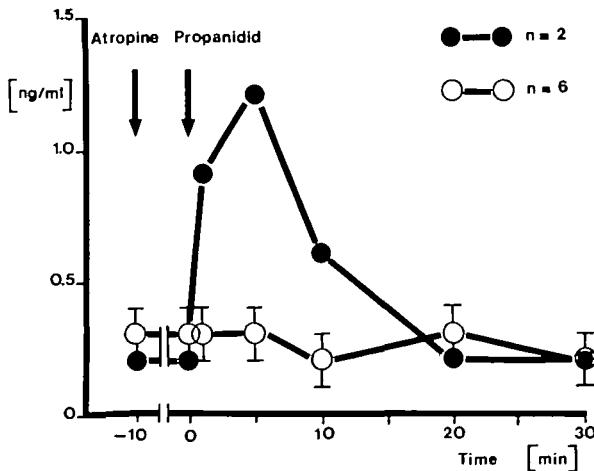


FIG. 3c

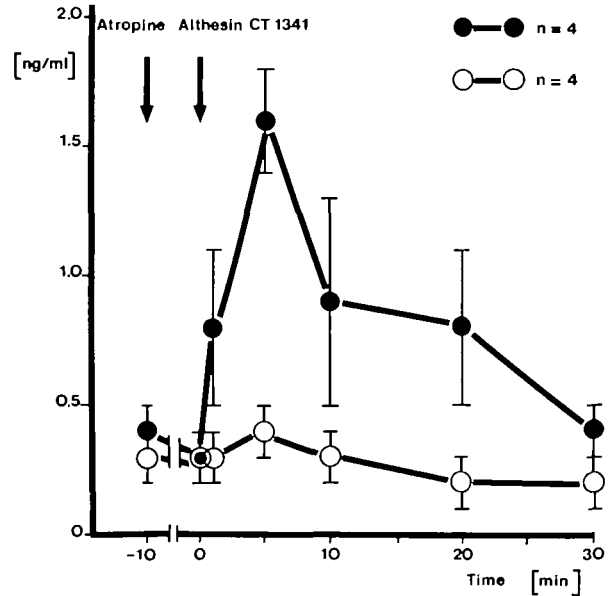


FIG. 3B

FIG. 3. Plasma histamine concentrations in volunteers after intravenous administration of etomidate, Althesin and propanidid. Mean values \pm SEM.

preparation of Althesin. In none was an increase in plasma histamine levels found; these had been within normal limits before the injection.

In one volunteer (Hal.) the plasma histamine concentration rose to 3.8 ng/ml, remained at the 3.5 ng/ml level for 10 min and fell to 0.8 ng/ml only at the 30th min, thereby approaching the initial value (fig. 4).

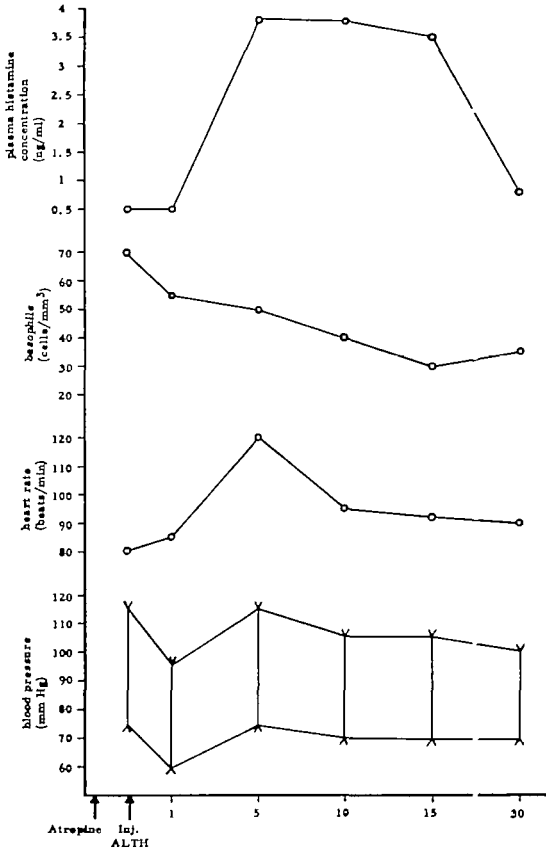


FIG. 4. Plasma histamine concentrations, basophilic content of venous blood, heart rate, and arterial blood pressure of volunteer Hal. after injecting Althesin.

The basophilic granulocytes decreased by 60%, which was not compensated after 30 min. Blood pressure values dropped temporarily by about 25 mm Hg, which cannot be attributed to histamine release. A prolonged mild tachycardia was observed, however, for which histamine as a partially causative factor may not be excluded. The same volunteer showed no significant changes in haemogram, blood pressure, and heart rate after Cremophor, which was administered 14 days after anaesthesia with Althesin. With regard to histamine release, the volunteer

(Hal.) is already to be considered a borderline case, who, after another dose of Althesin accompanied by unfavourable conditions (Lorenz et al., 1972b), might develop a more severe reaction with corresponding clinical symptoms and signs.

Blood pressure and heart rate.

After the administration of Althesin a significant hypotension occurred, averaging 15% compared with preanaesthetic values (fig. 5B) (see Patschke et al., 1972, and Benke et al., 1972). A mild degree of tachycardia was observed, reaching its maximum in the second minute and lasting distinctly longer than had been the case with thiopentone and propanidid (Lorenz et al., 1972b).

By comparison, the circulation after the administration of etomidate showed a marked stability in all volunteers. Systolic and diastolic blood pressures showed only very small changes and the heart rate only rose from 70 to 95 beats/min in the first minute following the injection (fig. 5A). This rise was of statistical significance.

The same volunteers exhibited a significant decrease in blood pressure ($P < 0.05$) at the first and second minutes after propanidid, the systolic pressure being more affected than the diastolic (fig. 5C). At the same time marked tachycardia was noted with the heart rate rising by an average of 60% during the first and second minutes ($P < 0.005$). After 5 min, however, these parameters had more or less regained initial values.

Injection of Cremophor EL alone had no significant effect on the blood pressures and heart rates of those volunteers who had already been given Althesin (fig. 5D), as has already been pointed out elsewhere (Lorenz et al., 1972a,b).

Total white blood cells, basophilic and eosinophilic granulocytes.

After the administration of Althesin the four volunteers in whom a pronounced increase in plasma histamine levels had occurred, showed a considerable decrease in basophils which fell from 56 to 32 cells/mm³ by the 15th minute, still remaining at this level after 30 min. The eosinophilic granulocyte counts also fell in these subjects (fig. 6A).

Four other volunteers, however, exhibited no change in the blood picture; even after the administration of Cremophor EL such a rapid shift of leucocytes was not observed (fig. 6B).

After injection of etomidate the blood picture remained unchanged. A fall in basophil count

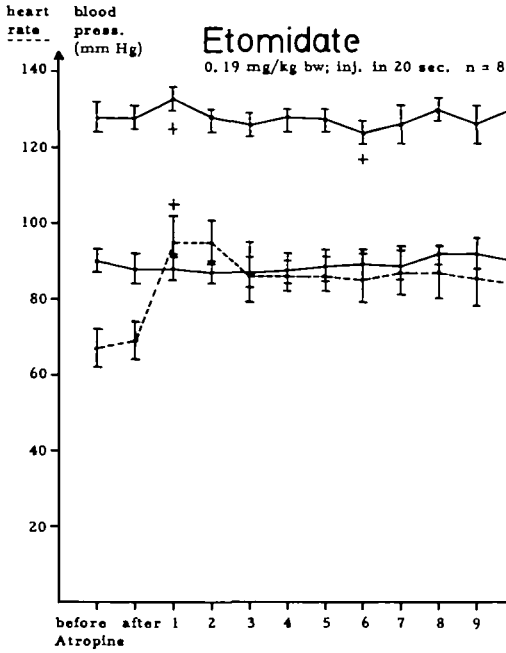


FIG. 5A

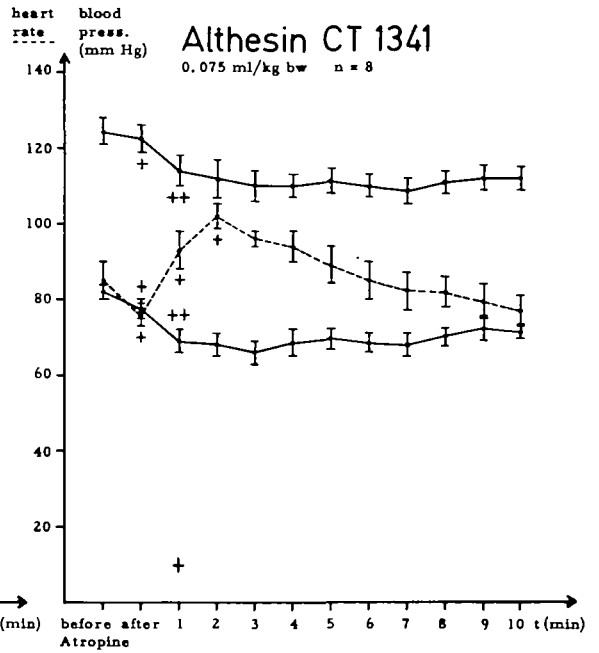


FIG. 5B

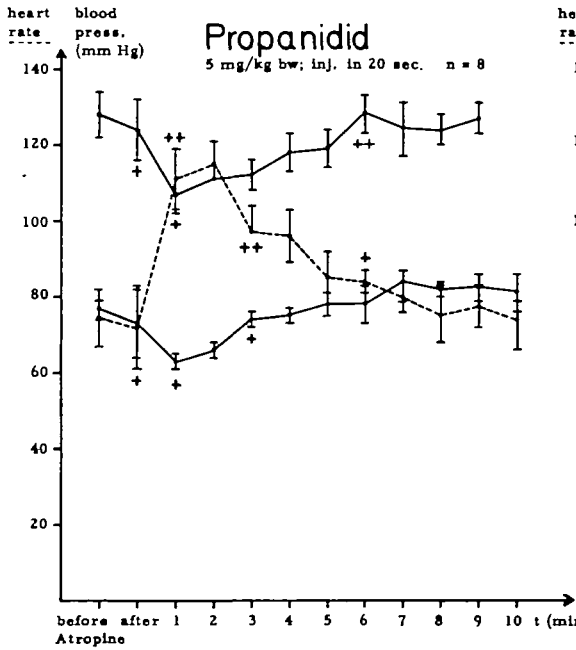


FIG. 5C

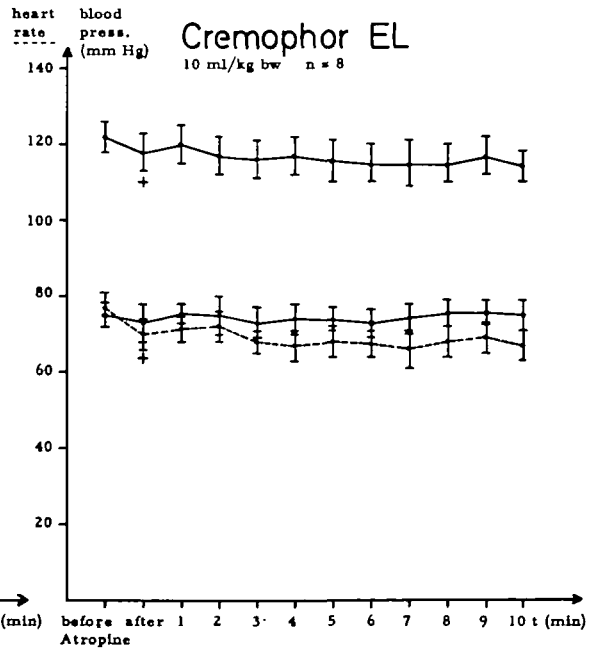


FIG. 5D

FIG. 5. Arterial blood pressure and heart rate after etomidate, Althesin, propanidid, and Cremophor EL. (Mean values \pm SEM.)

— blood pressure - - - - heart rate + P < 0.05 ++ P < 0.005

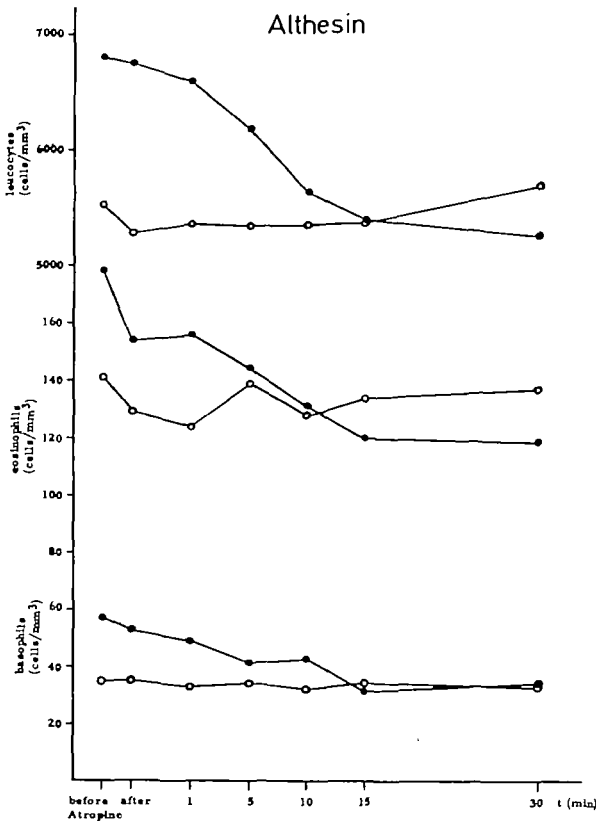


FIG. 6A

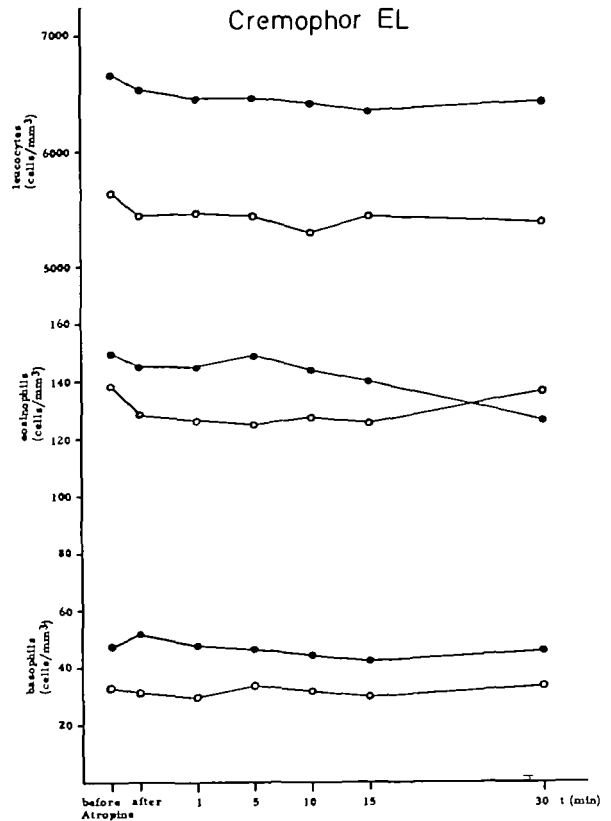


FIG. 6B

FIG. 6. Total white blood cells, basophilic and eosinophilic granulocytes in the venous blood of volunteers after intravenous injection of Althesin and Cremophor EL. (Mean values.)

- 4 subjects with an increase in plasma histamine levels.
- 4 subjects with no increase in plasma histamine levels.

could not be detected, whereas after propanidid injection the basophilic granulocyte count was reduced but not the eosinophilic. The latter even increased in number, as we have already reported (Lorenz et al., 1972b).

Whether there is a causal connection between the changes in the blood picture and the histamine release is not certain, but this possibility should not be excluded, however, considering the reaction of the basophilic granulocytes. In view of these changes, histamine determinations in whole blood cannot be used to demonstrate histamine release.

Clinical side-effects.

Apart from the circulatory changes described we noted the clinical side-effects listed in table I after administration of the drugs under review.

The muscular movements appearing after etomi-

date in 50% of all cases could be called "myocloni" and are reported in detail elsewhere (Doenicke et al., 1973a). We were able to largely eliminate these "myocloni" by injection of diazepam 1 mg/10 kg in clinico-pharmacological experiments with volunteers and also in hospital. Muscular movements were also observed after Althesin, but less frequently after propanidid.

The development of erythema in the upper half of the trunk was noted in particular after propanidid and Althesin, and in one case also after Cremophor EL. Erythema never occurred, however, after etomidate. Histamine release may be responsible for these erythemas.

Hyperventilation was always observed after propanidid injection, with or without the subsequent development of apnoea, and in 4 cases after Althesin. It did not occur, however, after etomidate. Regard-

TABLE I. Clinical side-effects after intravenous administration of etomidate, Althesin, propanidid and Cremophor EL.

Date (1972):	Etomidate May 9-13	Althesin July 3-5	Propanidid July 3-5	Cremophor EL July 10-18
Number of volunteers	8	8	8	8
Muscular movements	4	4	1	0
Reddening (neck, face, chest)	0	3	4	1
Hyperventilation	0	2	8	0
Hyperventilation + apnoea	0	2	1	0

ing the absence of clinical side-effects, etomidate, therefore, appears to be superior to the other substances examined. For a final and conclusive answer to this question, controlled studies with randomization will be required.

DISCUSSION

In the course of our investigations carried out during the past six years on histamine release after the administration of anaesthetic agents and plasma substitutes, we examined two new non-barbiturate anaesthetics (hypnotics) in 1972, which have not yet been marketed in Germany.

By determining three parameters (plasma histamine level, blood pressure and heart rate) we were able to demonstrate that propanidid, Althesin, as well as thiopentone and methohexitone, probably cause a chemical histamine release. This means that histamine may be released from mast cells directly by the drug and not via an immunological mechanism. Histamine release after Althesin has not been mentioned directly in the literature available so far (Campbell, 1972; Clarke et al., 1971), but Hempelmann and associates (1973), on the strength of clinical observations, recently suggested the possibility of "allergic reactions".

On the basis of existing experimental investigations and of our own clinical observations in 2,500 cases we may assume that etomidate is the first intravenous hypnotic that does not cause release of histamine. Such a statement should be accepted with caution, however, from a prognostic point of view, because sensitization after repeated application or the release of histamine under certain conditions (e.g. activation of the complement system) cannot yet be excluded.

We reported in detail on the clinical symptoms of histamine release some time ago (Doenicke and Lorenz, 1970; Lorenz et al., 1972b). In the case of propanidid we could again observe erythema and also signs of urticaria in the face, neck and chest in 60% of the volunteers, but also after Althesin these symptoms were noticed in 40% of the cases.

We also dealt in detail with the treatment of anaphylactic shock, should such an incident occur (Doenicke and Lorenz, 1970; Lorenz et al., 1972b). In the present study, however, there was no case of a serious or life-threatening anaphylactoid reaction.

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HISTAMINFREISETZUNG NACH
INTRAVENÖSER VERABREICHUNG
KURZWIRKENDER NARKOTIKA: EIN
VERGLEICH ZWISCHEN ETOMIDATE,
ALTHESIN CT1341 UND PROPANIDID

ZUSAMMENFASSUNG

An 16 freiwilligen Probanden wurde die Frage einer Histaminfreisetzung durch Plasma-Histaminbestimmung nach Etomidate, Althesin CT1341, Propanidid und Cremophor EL untersucht. Sowohl Althesin CT1341, als auch Propanidid setzten in verschiedener Häufigkeit Histamin frei. Blutdruckveränderungen waren bei beiden Narkotika stark ausgeprägt, die Tachykardie erreichte jeweils in der 1. und 2. Minute ihr Maximum, was gegen eine Histaminfreisetzung als Ursache dieser Reaktion spricht. Die Histaminfreisetzung war in der Tat nur so stark (mit Ausnahme eines Grenzfalles), daß keine klinischen Symptome mit Ausnahme von Magensaftsekretion und Erythem erwartet werden konnte. Nach Etomidate und Cremophor EL war ein Histaminanstieg im Plasma nicht nachweisbar. Veränderungen im Differentialblutbild im Sinne eines Abfalles der Basophilen waren nur nach Althesin CT1341 und Propanidid, nicht aber nach Etomidate und Cremophor vorhanden. Etomidate ist damit das erste i.v. Hypnotikum, bei dessen Anwendung eine chemische Histaminfreisetzung unwahrscheinlich ist.

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