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HISTAMINE RELEASE IN MAN BY PROPANIDID AND THIOPENTONE: PHARMACOLOGICAL EFFECTS AND CLINICAL CONSEQUENCES

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SUMMARY

Using a new, highly sensitive and specific method for the determination of histamine in human plasma, it was shown that release of histamine followed injection of propanidid and thiopentone. Observations of gastric secretion, arterial pressure and pulse rate supported these findings. In normal persons the release of histamine had no special clinical significance. On the other hand, when anaphylactoid reactions occurred following propanidid injection histamine release was so massive as to explain the severe clinical signs and symptoms observed. In this study no reactions occurred following thiopentone injection. Although it seems likely that massive histamine release can occur during anaphylactoid reactions with this anaesthetic, we have no observations to confirm this. In one case it was shown that premedication with glucocorticoids and anti-histaminics and therapy with plasma substitutes could prevent the development of a severe reaction.

It has been shown that drugs used before and during the administration of anaesthetics, in man and animals, may cause the release of histamine (for reviews see Paton, 1959; Murphy, 1962; Rothschild, 1966; Lorenz and Werle, 1971). Sometimes direct methods have been used when histamine itself was measured in body fluids or in tissues. More often, however, indirect methods have been employed, such as the measurement of gastric secretion, observation of the decrease in peripheral arterial pressure, tachycardia and increase in bronchial resistance. These reactions are, however, specific for histamine only in a limited sense.

We have developed an assay by which histamine can be measured specifically in human plasma (Lorenz et al., 1971c) and have studied the release of histamine in man caused by two commonly used anaesthetic drugs, namely propanidid and thiopentone. Recent reports of anaphylactoid reactions during anaesthesia with both substances led us to undertake this investigation. To demonstrate, however, that the increased concentration of plasma histamine was actually free, pharmacologically active histamine, we studied gastric acid secretion, heart or pulse rate, and peripheral arterial pressure in the subjects of the investigation.

MATERIALS AND METHODS

Materials.

Drugs. Propanidid; Micellophor (Bayer, Leverkusen); thiopentone (Pentothal, Abbott, Ingelheim); atropine sulphate (from University pharmacy); clemastine‡ (Tavegil, HS 592, Sandoz, Nürnberg); prednisolone (Prednisolon "Lentia", Lentia Munich); suxamethonium (Lystenon, Lentia, Munich); halothane (Fluothane, Rheinpharma, Heidelberg); antazoline (Antistin, Ciba, Basel); dextran (Longasteril-75, Fresenius, Bad Homburg).

Reagents. Histamine dihydrochloride puriss. (Fluka, Buchs); *o*-phthaldialdehyde puriss. p.a. (Fluka, Buchs) (recrystallized from petrol ether p.a., b.p. 40–60°); Methanol, n-heptane, inorganic acids and bases as Uvasol (Merck, Darmstadt); n-butanol (for chromatography, Riedel de Haën, Seelze near Hannover); Dowex 50 W–X8, H^+, mesh 200–400 (Serva, Heidelberg); unless otherwise stated, only twice distilled water was used.

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‡ Known also as neclastinum.

Heparin for biochemical research (180 i.u./mg) (Hoffmann-La Roche, Grenzach); 0.1N NaOH for titration of gastric juice (Titrisol, Merck, Darmstadt).

Subjects.

The investigations were carried out on 143 healthy volunteers and 1 patient. Consent was obtained. The volunteers, who had healthy medical histories consisted of 140 male and 2 female students and anaesthesists between the ages of 22 and 31 years, weighing between 54 and 100 kg. One subject (A.D.) was one of the investigators. The patient had a compound comminuted fracture of the left lower leg and a compound fracture of the right femur as a result of an industrial accident. He was an alcoholic, but was otherwise clinically healthy, having no special previous medical history. Before each study the test persons and the patient had fasted for at least 12 hours.

Sequence and arrangement of investigation.

Studies were conducted from 7 a.m. to 9 a.m. in a quiet well-lit room. The procedure was as follows (fig. 1). A nasogastric tube was introduced into the stomach under radiological control. After the tube was fixed to his nose, the subject lay down with the upper body slightly raised. Leads

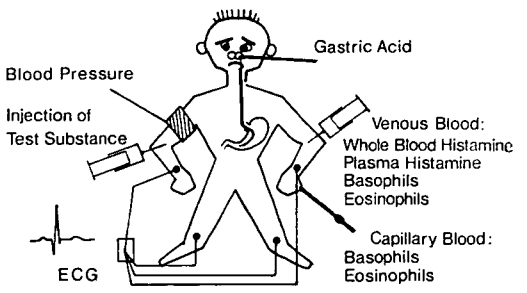

FIG. 1. Scheme of the arrangement of investigation in the test subjects. For explanations see text under Methods.

for the electrocardiogram were attached to the extremities and a sphygmomanometer (Riva-Rocci) was applied to the right upper arm. A polyethylene cannula (Braunüle, Braun, Melsungen) was inserted into a superficial vein in each arm, the right being used for the injection of the anaesthetic or solvent and of other drugs, and the left for withdrawal of blood for histamine assay in plasma and whole blood, and for leucocyte counts and blood smears. When in any one of the investigations, a solvent and agent, or an agent alone and together with atropine, was employed on one and the same subject, then the sequence of administration of the solutions was alternated. Thus, if Micellophor was used first and then propanidid, in the next subject propanidid was used first and then the solvent. Two to four weeks elapsed between the first and second investigation.

Histamine infusion.

The same order was adhered to in studies with histamine infusion. Gastric acid secretion was not determined because the dose-effect relationship between histamine infusion and gastric acid secretion in humans is well known from the literature (Lawrie, Smith and Forrest, 1964).

The histamine solution was prepared from a sterilized stock solution from the university pharmacy, diluted with physiological saline, and drawn up in a 50-ml polyethylene syringe.

The intravenous infusion was carried out in the right arm using the infusion apparatus Unita II (Braun, Melsungen), while, as in the other investigations, blood was withdrawn from the left median cubital vein. NaCl solution 0.9 per cent was first infused, followed by histamine from a separate syringe, and then physiological saline.

In order to avoid any side effects of histamine infusion (headache, flush, etc.), antazoline (2 mg/kg) was injected intravenously just before the highest dose of histamine was administered.

Determination of the Various Parameters.

Histamine assay in whole blood and plasma.

From the left arm, 5.0 ml of blood was drawn into a polyethylene syringe 15 min before and immediately before injection of anaesthetic or solvent, and at 1, 5, 10, 20 and 30 min after injection. The samples were put immediately into centrifuge tubes containing 5.0 ml of 1N $HClO_4$ and centrifuged for 5 min at 1800 *g*; 4.0 ml of the supernatant was stored for several days at −20°C and used later for histamine assay.

Immediately after withdrawal of samples for whole blood histamine determination, 19.5 ml of blood was withdrawn slowly and with care to avoid bubble formation, using a polyethylene syringe containing 2 mg heparin dissolved in 0.5 ml of 0.9 per cent NaCl solution. After gently mixing the contents in the syringe, it was transferred slowly and with minimum pressure into a 30-ml polyethylene centrifuge tube pre-cooled thoroughly in an ice-

cold water bath, and centrifuged immediately for 30 min at 1000 *g* and 1–2°C. 6.0 ml of plasma was withdrawn, immediately mixed with 3 ml of 2N $HClO_4$ and centrifuged for 10 min at 1800 *g*. The whole supernatant was filtered through a paper filter and used for histamine assay immediately or was stored in the freezer at −20°C, and histamine determined several days later.

The amine in whole blood was measured fluorometrically according to the method of Lorenz and associates (1970) after isolation by ion-exchange chromatography on Dowex 50 W–X8. Histamine in human plasma was determined according to the method of Lorenz and associates (1971c) after isolation by chromatography on Dowex 50 and subsequent extraction into alkaline *n*-butanol. The histamine content in whole blood and plasma is given in ng histamine base/ml of body fluid.

Determination of gastric acid secretion (Lorenz et al., 1969; Lorenz, 1971).

While the subject was sitting, a nasogastric tube with X-ray contrast strips (Levin No. 12–14) was inserted under radiological control. After complete emptying of the stomach by manual suction using a syringe the tube position was further tested by instillation of 20 ml of 0.9 per cent NaCl solution (37°C) and re-aspiration of the same. Basal secretion was then collected by suction at intervals of 2 min over a period of 30 min. When atropine had to be used, a dose of 0.01 mg/kg was administered intravenously 15 min after the beginning of the collection. At the end of the 30 min, the anaesthetic was injected and the gastric juice withdrawn by suction every minute and collected in portions corresponding to the blood withdrawals, i.e., in two 3-min portions, one 4-min portion and two 10-min portions. The volume of gastric juice was measured and the acid output determined for each portion by titration with 0.1 NaOH up to pH 7.0 using a glass electrode. The acid output was given in m.equiv HCl/min (Lorenz et al., 1969).

Determination of heart rate and arterial pressure.

The heart rate was determined by measuring the average internal length in lead II of the standard e.c.g. and given as beats/min (Heinecker, 1970). The arterial pressure (mm Hg) was determined by indirect sphygmomanometric measurement (Riva-Rocci) according to the method of Burton (1965). Because the subjects were all young people (very little or no arteriosclerosis), the arterial pressure values obtained by the indirect method probably differed little from those obtained by a direct method. Indeed, the values measured by indirect methods during anaesthesia agreed well with those which were measured by direct methods (Henschel and Buhr, 1965; Avrucki and Zinovjev, 1969; Soga and Beer, 1971, personal communication).

Determination of basophil granulocyte content in peripheral venous and capillary blood.

At the same time as the blood was withdrawn for histamine assays in whole blood and plasma, two blood smears and one leucocyte count were made using venous blood. The leucocyte count was performed according to Müller, Seifert and v. Kress (1962), while the blood differential was determined according to Pappenheim, whereby 1000 cells from each sample were counted. The content of basophils in venous and capillary blood was determined according to Hamerston and associates (1956) (number of leucocytes/mm^3 and per cent of basophils in the blood smear). The results of Moore and James (1953) and Hamerston and associates (1956) showed that the values from such an indirect method agree well with those obtained by direct methods. The content of basophils in the blood is given in number of cells/mm^3.

Cutaneous prick test for testing of allergens.

In order to test an antigen-antibody reaction as the cause of histamine release by propanidid, a prick test (for method, see Stüttgen and Ippen, 1969) was performed in co-operation with H. Bandmann* in all subjects who showed clinical symptoms of an anaphylactoid reaction to propanidid. The anaesthetic dissolved in Micellophor, and the solvent alone were applied separately on the upper arm. As controls, a 0.9 per cent NaCl solution and histamine dissolved in physiological saline (1 : 10,000) were employed. The reaction tests were made not sooner than 4 weeks after the clinical reaction.

RESULTS

Histamine Release by Propanidid and Thiopentone.

Concentrations of plasma histamine after propanidid, Micellophor and thiopentone.

After propanidid in doses which are commonly used for anaesthesia in man, the mean histamine

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level in plasma increased significantly to about 350 per cent of the norm (fig. 2). The highest value was found at 5 min after injection. The concentration remained elevated for some time after the end of anaesthesia. Up to 30 min was needed before initial levels were approached. The i.v. administration of atropine had no significant influence on plasma histamine concentration, although this agent has been shown to be a histamine liberator in humans, dogs and cats (Rothschild, 1966).

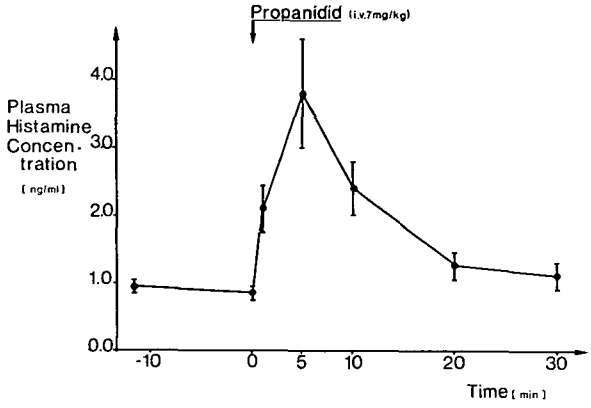

FIG. 2. Increase of plasma histamine concentration in man after intravenous injection of propanidid. Mean values with SEM. Twelve subjects were anaesthetized with propanidid 7 mg/kg, injection time 20 sec.

It has been said that the solvent of propanidid, Cremophor, or currently Micellophor, is a possible cause of histamine release in humans. As wetting agents, both liberate histamine in dogs and cats (Lorenz et al., 1971b), but have no effect on humans (Lorenz et al., 1969). In this study the same subjects who were treated with propanidid were also investigated using Cremophor and Micellophor alone. The increase of plasma histamine concentration of about 20 per cent, which was found in subjects, is not statistically significant.

In one subject (A.D.), however, there was a slight reaction to the injection of Micellophor.

One min after the administration of the solvent in a dose of 0.15 ml/kg in 20 sec there was slight reddening of the face. 2 min later, the redness became brighter, the face felt hot and he experienced itching behind the ears. 5 min after injection, the eyelids began to swell. 10 min later, he had pain in the stomach, and heartburn, and his nose and ears became bright red. 16 min after injection, prednisolone 50 mg was administered intravenously. 4 min thereafter, improvement of the complaints was observed, but during the next 15 min the face and eyes remained swollen and the subject exhibited marked lassitude. On the other hand, neither tachycardia nor change in blood pressure was observed and dyspnoea or headache did not occur.

The plasma histamine concentration in this subject before injection of Micellophor was 1.4 ng/ml. At 1, 3, 5, 10, 16, 20 and 30 min after injection, the plasma histamine level was 2.3, 1.8, 1.1, 2.5, 2.3, 2.2 and 1.7 ng/ml. The slight increase in plasma histamine concentration could hardly be responsible for the symptoms experienced (cf. the results with histamine infusion which are reported below). Another cause of these symptoms must therefore be assumed.

The Micellophor injection was repeated four weeks after this incident and resulted neither in clinical symptoms nor any increase of plasma histamine concentration. The prick-test with Micellophor was negative.

Further, after injection of Micellophor in all subjects, also in the one patient who reacted to propanidid with an incident, neither clinical symptoms nor increases of plasma histamine concentration were found. Thus, it can be concluded that propanidid (anaesthetic drug plus solvent), and not Cremophor or Micellophor alone, releases histamine in humans.

Thiopentone, in doses which are used in anaesthesia, also led to an elevation of plasma histamine concentration (fig. 3), the degree of elevation being similar to that following propanidid. The plasma concentration fell at approximately the same rate as after propanidid. The solvent used for thiopentone was 0.9 per cent NaCl solution. Rapid injection of this solvent did not lead to any increase in plasma histamine levels.

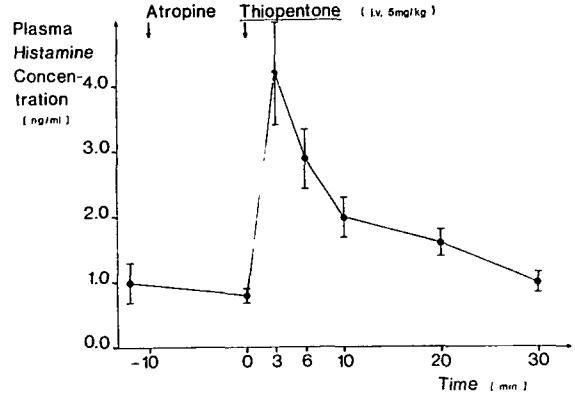

FIG. 3. Increase of plasma histamine concentration in man after intravenous injection of thiopentone. Mean values with SEM. Eight subjects were anaesthetized with thiopentone 5 mg/kg, injection time 20 sec. Atropine 0.01 mg/kg i.v. was given as premedication 10 min before thiopentone.

Plasma histamine levels during infusion of histamine and correlation with heart rate and blood pressure.

In three healthy students who were also included in the investigations with anaesthetics, the follow-

ing two questions were studied: (1) Does the dose of histamine needed to produce a moderate to medium stimulation of gastric acid secretion also increase the plasma histamine level? (2) Does a relationship exist between the dose of histamine infused and the elevation of plasma histamine level?

With the new histamine assay developed in our laboratory, it was now possible to show (1) that an increase of plasma histamine concentration can be measured after infusion of relatively low doses of histamine (18–90 ng/kg/min), and (2) that a relationship exists between the doses of histamine infused and the elevation of plasma histamine level (fig. 4). Therefore, by determination of plasma histamine concentration after administration of an anaesthetic, the amount of histamine that has been released during this treatment can be estimated.

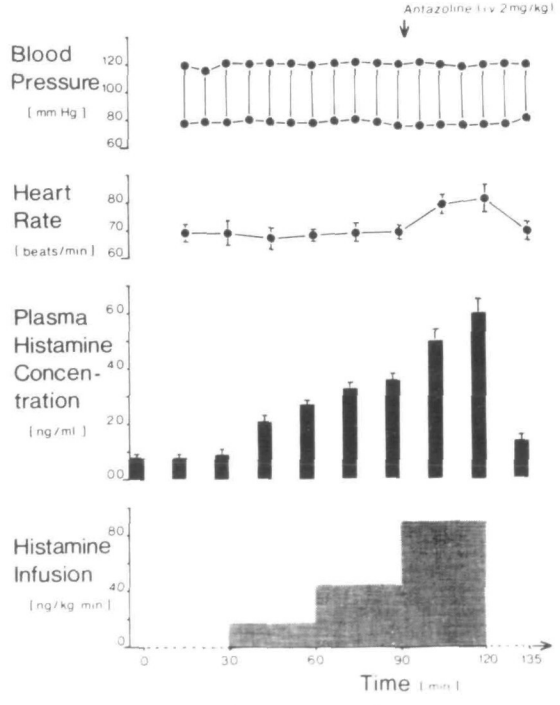

FIG. 4. Plasma histamine concentration, blood pressure and heart rate after intravenous infusion of increasing doses of histamine. Mean values with SEM. Three subjects were tested.

Histamine up to a dose of 45 ng/kg/min, which produces a half-maximum gastric secretion (Lawrie, Smith and Forrest, 1964), did not produce complaints or clinical symptoms in any of three subjects. No effect on blood pressure or heart rate was observed (relatively sensitive indicators of histamine release). Only with a dose of 90 ng/kg/min, and despite anti-histamine medication, was there any clinical reaction and that was confined to slight tachycardia in one volunteer only, accompanied by mild headache.

Gastric acid secretion after propanidid, Micellophor and thiopentone.

To study the problem whether the increase of histamine in plasma during anaesthesia actually is an increase of free, pharmacologically active histamine, we investigated one of the most sensitive reactions of the human organism to histamine, that is an increased gastric acid secretion.

Rapid injection of propanidid in five volunteers resulted in an approximately half-maximum gastric acid secretion. The increase of acid output ran parallel to the increase in plasma histamine concentration (fig. 5). After 30 min, the plateau of basal secretion was again reached. When Micellophor was injected, only a small and non-significant increase of gastric secretion was found.

After injection of thiopentone, stimulation of gastric acid secretion could also be demonstrated (fig. 6). The acid output and the secretion curve are in complete accord with those observed after propanidid injection. For safety purposes, thiopentone was not administered without atropine premedication. After intravenous injection of 10 ml physiological saline, the solvent of thiopentone, no stimulation of gastric acid secretion was observed.

Heart rate and blood pressure after propanidid, Micellophor and thiopentone.

During the first 5 min after propanidid injection, there was an increase in the heart rate (table I). This response has often been described in the literature (see Discussion). The systolic and diastolic pressures decreased significantly only during the first 2 min, that is before the maximum increase in plasma histamine concentration had been reached (fig. 5). Therefore, it is very improbable that the initial tachycardia and acute peripheral hypotension have a connection with the release of histamine into the plasma. The stimulation of gastric acid secretion and the decrease of basophils in the blood, on the other hand, ran almost parallel with the increase of plasma histamine concentration (fig. 5). In fact, the maximum mean plasma histamine level of 3.1 ng/ml was such that, from the results of histamine infusion studies (fig. 4), tachycardia or hypotension would not have been expected.

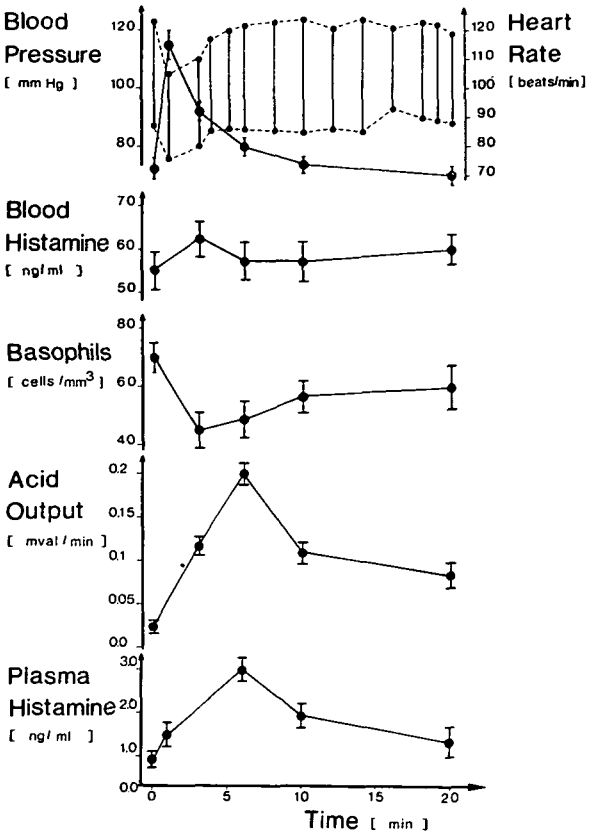

FIG. 5. Histamine concentration in whole blood and plasma, basophils, gastric acid secretion, blood pressure and heart rate after intravenous injection of propanidid. Mean values with SEM. Five subjects were tested after injection of propanidid 7 mg/kg, injection time 20 sec. In each subject all parameters were studied simultaneously. Values at zero time for heart rate (●——●) and blood pressure (● - - - - ●) are calculated according to table I. Blood pressure is given as systolic-diastolic pressure.

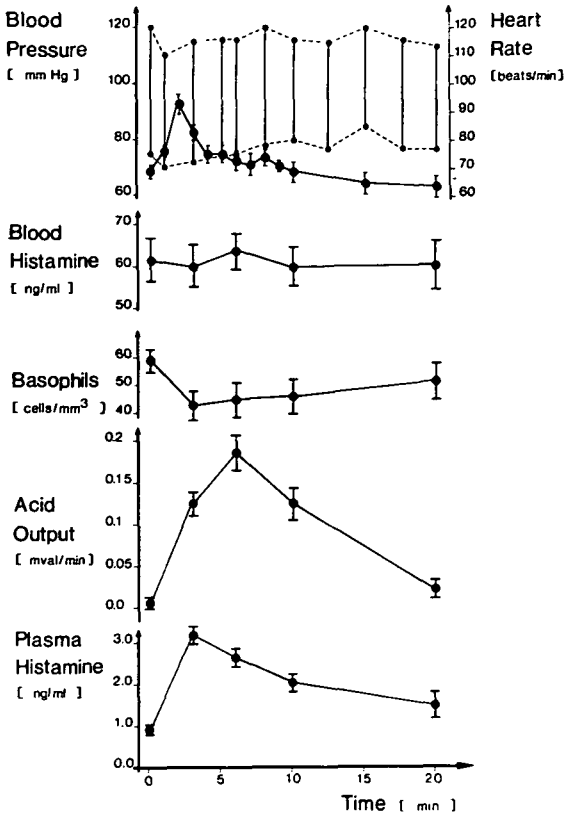

FIG. 6. Histamine concentration in whole blood and plasma, basophils, gastric acid secretion, blood pressure and heart rate after intravenous injection of thiopentone. Mean values with SEM. Five subjects were tested after the injection of thiopentone 5 mg/kg, injection time 20 sec. In each person all parameters were studied simultaneously. Values at zero time for heart rate (●——●) and blood pressure (● - - - - ●) are calculated according to table I.

TABLE I. *Heart rate and blood pressure in man after intravenous injection of propanidid, Micellophor and thiopentone.*

Time after injection (min)	Propanidid			Micellophor			Thiopentone		
	Heart rate (beats/min) $n=12$	Blood pressure (mm Hg)		Heart rate (beats/min) $n=12$	Blood pressure (mm Hg)		Heart rate (beats/min) $n=12$	Blood pressure (mm Hg)	
		Systolic	Diastolic		Systolic	Diastolic		Systolic	Diastolic
0	63±6	124±9	74±8	72±15	120±7	79±9	67±10	120±7	78±12
1	116±10 ($P<0.001$)	107±11 ($P<0.001$)	66±8 ($P<0.025$)	73±14	122±9	80±8	83±11 ($P<0.005$)	113±9 ($P<0.5$)	74±9
2	90±14 ($P<0.001$)	113±10 ($P<0.01$)	72±9 (—)	72±12	123±9	80±10	82±8 ($P<0.001$)	118±7	75±8
3	78±9 ($P<0.001$)	117±8 ($P<0.1$)	73±9 (—)	73±14	121±10	81±11	72±11 ($P<0.3$)	118±7	73±10
5	69±6 ($P<0.025$)	124±11 (—)	81±8 ($P<0.05$)	73±14	122±9	80±9	70±9 (—)	115±8	73±7 ($P<0.3$)
10	65±6 (—)	128±11 ($P<0.4$)	83±11 ($P<0.05$)	71±13	121±9	81±9	69±11 (—)	117±8	76±6
15	64±6 (—)	128±11 (—)	84±10 ($P<0.02$)	70±12	119±8	79±8	67±11 (—)	119±6	77±6
20	64±6 (—)	127±11 (—)	79±8 ($P<0.2$)	69±10	120±9	79±9	66±11 (—)	118±10	77±8

Mean values with SD. Propanidid 7 mg/kg, injection time 20 sec, without atropine premedication. Micellophor 0.15 ml/kg, injection time 20 sec, Thiopentone 5 mg/kg, injection time 20 sec, with premedication of atropine 0.01 mg/kg i.v. n=number of subjects tested. Statistical calculations according to the Student t-test, P-values in parentheses. For further conditions see Methods. The values at zero time were obtained by calculating the average values from 5 determinations during the last 5 min before the injection of the drugs.

After injection of Micellophor, there was neither a change of heart rate nor of arterial pressure (table I).

Following thiopentone injection, there was a slight and short-lived increase in heart rate and a slight but insignificant fall in arterial pressure (table I). As in the case of propanidid, the changes in circulation occurred earlier than the maximum increase of plasma histamine concentration. However, the stimulation of gastric secretion and the decrease of basophils in the blood ran parallel to the increase of plasma histamine (fig. 6). Therefore, as with propanidid, there was no correlation between the changes of heart rate and blood pressure and the release of histamine into the plasma. Because of a mean peak plasma histamine level of 3.2 ng/ml, this should also not have been expected.

From these results, as far as concerns histamine release by propanidid and thiopentone, the following conclusions may be drawn:

(1) In normal persons, the intravenous injection of both anaesthetics resulted in the release of histamine into the plasma, sufficient to stimulate gastric acid secretion, but insufficient to produce changes in the circulatory system.

(2) In persons with abnormalities relating to the histamine storage or catabolism as well as in those with an "allergic diathesis", the possibility cannot be excluded that release of large amounts of histamine can be elicited by propanidid or thiopentone sufficient to evoke severe circulatory reactions. Such incidents with propanidid are described later.

Release of large amounts of histamine during incidents with propanidid.

In four subjects (three males and the patient) allergic reactions or so-called anaesthetic incidents were observed after injection of propanidid (table II). The extent of the reaction to propanidid differed greatly from person to person and ranged from a clinical picture as severe as cardiac arrest, observed as a baseline in the e.c.g. on the oscilloscope, to relatively slight symptoms such as persistent tachycardia and erythema.

In all four persons, the plasma histamine levels before and after the injection of the anaesthetic were measured. The increase in plasma histamine concentration was in accordance with the degree of severity of the clinical symptoms (table II). An

TABLE II. *Anaphylactoid and allergic reactions after intravenous injection of propanidid.*

Case No.	Premedication (i.v.)	Exposure to propanidid: No. of injection, injection speed	Exposure to propanidid: Days after first injection	Clinical observations	Plasma histamine concentration (ng/ml): Before injection	Plasma histamine concentration (ng/ml): After injection (M)*
1	Atropine 0.01 mg/kg Clemastine 0.04 mg/kg	3rd; 70 sec	36	Cardiac arrest 7½ min after injection, severe hypotension (BP not measurable, pulse not palpable), tachycardia for about 90 min (160 beats/min), erythema of the face, neck and thorax, bronchospasm, cyanosis	8.0	100
2	Atropine 0.01 mg/kg	2nd; 20 sec	29	Severe hypotension (BP not measurable, pulse not palpable), tachycardia for about 30 min (140 beats/min), bronchospasm, cyanosis, oedema of the galea and eyelids, erythema of the face, neck and thorax	0.8	26
3	Atropine 0.01 mg/kg	2nd; 20 sec	17	Slight hypotension (30 mm Hg, tachycardia for 17 min (120 beats/min), bronchospasm, cyanosis, erythema of the face and neck, strong oedema of the face and galea	0.85	12
4	Atropine 0.01 mg/kg	1st; 5 sec	—	No significant hypotension, tachycardia for 10 min (84 beats/min), erythema of the face and neck, no bronchospasm	0.9	6.4

* M=point of time at the maximum decrease of blood pressure, at cardiac arrest or maximum tachycardia. For details see Methods.

increase of the plasma histamine level of more than 90 ng/ml, as in the case of one patient studied, caused a massive degree of hypotension. This is in agreement with results obtained from studies of histamine release in various animals, for instance in pig and dog (Lorenz et al., 1968; Messmer et al., 1970; Lorenz et al., 1971a, b).

CASE REPORTS

Case No. 1.

Numerous investigations were made on this patient with his consent. This patient is the first case in the world literature to show abnormally high plasma histamine concentrations (Lorenz et al., 1971c; see below). The course of investigations is here only briefly stated, but more details can be found elsewhere (Doenicke et al., 1972).

The patient received the first propanidid anaesthetic on August 4, 1969. An osteosynthesis was necessary for an open supracondylar compound fracture of the right femur and an open compound fracture of the left lower leg. In this instance anaesthesia was uncomplicated.

On August 27, a second anaesthetic was administered for an autoplastic graft. After a slow (40–50 sec) injection of propanidid 7 mg/kg, the patient suffered an anaesthetic incident with hypotension (60 mm Hg), tachycardia (110 beats/min) and moderate bronchospasm.

At this time we were convinced from the results obtained in case No. 2 (see below) and those obtained with Micellophor in dogs (Lorenz et al., 1971b), that antihistamine premedication would prevent this response to propanidid. With the patient's consent, which was given after extensive explanation of all side effects and reactions which might occur after propanidid injection, propanidid was likewise administered for further surgery.

On September 9, in addition to atropine 0.01 mg/kg i.v., the antihistamine clemastine 0.04 mg/kg i.v. was given as premedication. Parallel to the measurement of blood pressure and pulse rate, blood samples were withdrawn for plasma histamine determinations.

After slow administration of propanidid 7 mg/kg, over 1 min, bronchospasm occurred 2 min after injection; increasing tachycardia (120 beats/min) and a massive flush were noted 3 min after injection. After 7 min, the peripheral arterial pulse became impalpable and the blood pressure was not measurable. 7½ min after injection, cardiac arrest occurred. Immediately external cardiac massage and further resuscitation were applied (i.v. injection of 1 mg/kg of prednisolone, infusions etc.). 2 minutes later the peripheral pulse was again palpable (160 beats/min), but the blood pressure was still not measurable. 20 min after injection the pulse rate was 140 beats/min and the blood pressure 80/40 mm Hg. 45 min after injection, the pulse rate was 140 beats/min and the blood pressure had risen to 140/80 mm Hg.

Before atropine and clemastine were injected the plasma histamine concentration was 8.0 ng/ml.* 10 min after the injection of both and immediately before the injection of propanidid, the plasma histamine concentration was 9.2 ng/ml. It increased 2 min after propanidid administration to 26.0 ng/ml, and 7 min after the injection (immediately before cardiac arrest) to the very high value of 100 ng/ml. During the time following, no blood samples were withdrawn. However, this overwhelming increase of histamine concentration in plasma explains the severe clinical symptoms. The administration of the antihistamine clemastine was unable to prevent the reactions to such a massive release of histamine.

The ineffectiveness of a strong antihistaminic drug in a severe anaphylactoid reaction to propanidid raised the highly important question of a suitable premedication and therapy in such harmful events. Glucocorticoids have been shown to prevent largely the pharmacological effects of massive histamine release (Rocha e Silva, 1966). Prednisolone had been found very effective during the previous incident in this patient. We discussed this problem with him. The patient consented to another propanidid narcosis which should be performed after premedication with high doses of prednisolone and using a reduced dose of propanidid (for details of this ethical problem see Doenicke et al., 1972).

About 2 months later, on November 5, a further operation (spongiosa-graft) was necessary. As premedication, prednisolone 2 mg/kg, together with atropine and clemastine, was intravenously administered. 15 min later propanidid 5 mg/kg was injected over 40 sec. 4 min thereafter, the pulse rate began to rise (120 beats/min). The blood pressure increased insignificantly by about 20 mm Hg. Otherwise, the anaesthetic proceeded completely without complications, the circulation parameters returning after 10 min to the values obtained before anaesthesia.

Simultaneous determinations of histamine concentration in plasma showed an unexpected decrease of plasma histamine from 9.3 ng/ml immediately before to 2.8 ng/ml 5 min after the application of premedication. 4 min after the injection of propanidid, the plasma histamine concentration was still 2.8 ng/ml. After 8, 15 and 20 min plasma histamine levels of 17.7, 12.5, and 4.7 ng/ml respectively were measured. The increase from 2.8 to 17.7 ng histamine/ml should have led to clinical symptoms when comparing it with the circulatory reactions during histamine infusion and Case 3 in table II. Apparently, the prednisolone therapy prevented any reaction.

On January 22, 1970, under propanidid anaesthesia, the steel plate from osteosynthesis on the lower leg was removed. After the same premedication as on November 5, 1969, propanidid 7 mg/kg was administered in 35 sec. Within a half-hour, neither clinical symptoms of an anaphylactoid reaction nor an increase of histamine concentration in plasma was found.

The patient received the next and last propanidid anaesthetic on November 2, 1970, a little more than 9 months later. The removal of a scale from the osteosynthesis was necessary. After the same premedication as in the previous two operations, propanidid 7 mg/kg was administered in 40 sec. The patient suffered a slight hypotension lasting about 20 min (before propanidid, 120/80 mm Hg; after, 100/70 mm Hg), a tachycardia lasting about 35 min, the maximum being at 15 min after propanidid injection (before, 82 beats/min; 15 min after, 140 beats/min). After a pause of 40 min at normal pulse rate, a tachycardia again set in with a maximum of 150 beats/min. This disappeared in the course of an hour. The blood pressure remained constant during this time with a value of 110/80 mm Hg, after plasma substitutes (Longasteril, Laevulose) to a total volume of 1000 ml were infused. Moreover, at the time of maximum tachycardia, a relatively coarse tremor appeared which ceased after about 20 minutes (cf. Lorenz et al., 1971a). During and after the anaesthesia, no bronchospasm was observed.

The plasma histamine concentration before the premedication was 9.3 ng/ml. It increased to 16.5 ng/ml 1 min after propanidid injection, to 30 ng/ml 5 min after injection and to 45 ng/ml at 10 and 15 min after propanidid injection. Thereafter, no blood was withdrawn

* This value was more than 10 times higher than the normal plasma histamine concentration which was found to be 0.6 ng/ml (Lorenz et al., 1970, 1971c).

because the operation began. At the time of maximum tachycardia, the histamine level in plasma was also at its highest. The premedication, however, was apparently able to prevent almost completely the effects of such a considerable histamine release. One may compare the results of this last anaesthesia with those in figure 4 (histamine infusion) and in table II, as well as with the results of the third anaesthetic administration to the patient, to see that a severe hypotension and a severe clinical picture would have been expected to develop.

Further investigations were made on this patient as follows (described in detail by Doenicke et al., 1972). Histamine concentration in whole blood (59 and 63.5 ng/ml on two different days) and basophil content of the blood (52 cells/mm^3) were in the normal range. An anaesthesia with thiopentone (5 mg/kg i.v.) led only to an insignificant increase of plasma histamine concentration (about 1.4 ng/ml) and to no clinical symptoms relating to an anaphylactoid reaction. The injection of Micellophor, the solvent of propanidid, 3 months after the last propanidid anaesthesia, caused neither an anaphylactoid reaction nor an increase in plasma histamine concentration. The prick-tests with propanidid made a month after the third anaesthesia (September 9, 1969) and at 2 months after the last anaesthesia (November 2, 1970) were negative. Neither clemastine nor atropine, nor both together, in all applications, led to an increase of plasma histamine concentration.

Case No. 2.

This male volunteer who was one of the anaesthetists in our team was first anaesthetized with propanidid on March 26, 1969 (7 mg/kg in 7 sec). 10 min before the injection, he was given atropine 0.01 mg/kg i.v. During anaesthesia the usual reaction to propanidid was noted, i.e., brief tachycardia and hypotension; there were no signs or symptoms of an anaphylactoid reaction. The plasma histamine level before anaesthesia was 0.8 ng/ml. At 3, 6, 10 and 20 min after propanidid injection, concentrations were 1.6, 2.0, 1.5 and 1.5 ng/ml. The increase of plasma histamine level remained within the normal range.

On April 24, 1969, he received a second propanidid anaesthesia in order to study the effect of the injection speed on histamine release. After premedication with atropine as above, propanidid 7 mg/kg was injected in 35 sec. 1 min later severe facial erythema developed and extended over his neck and thorax. As he awoke, he began to cough and 3 min after injection bronchospasm developed. At the same time, tachycardia was still present (before propanidid, 70 beats/min; 4 min later, 110 beats/min). This intensified to 140 beats/min until at 6 min after propanidid injection the volunteer had neither a palpable pulse nor a measurable blood pressure. At the same time, cyanosis developed and severe oedema was observed in the face and scalp. Immediately, 500 ml dextran (Longasteril) and 500 ml glucose (Laevulose) were infused. The intubation was difficult because of oedema of the glottis. Oxygen was administered and prednisolone 1 mg/kg injected intravenously 8 min after the beginning of anaesthesia. The pulse and blood pressure were again measurable, and were 140 beats/min and 80/40 mm Hg. The tachycardia and hypotension lasted for 30 min. Nausea and headache were present, and the erythema disappeared first, 24 hours after narcosis.

The plasma histamine values before and 10 min after atropine injection were both 0.8 ng/ml. 1, 5, 10 and 20 min after propanidid the levels were 8.6, 26.0, 18.0 and 13.0 ng/ml respectively.

Since we and the volunteer who was, as previously mentioned, an anaesthetist, were still convinced at this time that the antihistaminic clemastine could nearly completely prevent an anaphylactoid reaction after propanidid injection so that a third anaesthetic was without danger to the volunteer, with the subject's explicit permission we gave him a third propanidid anaesthesia on May 29, 1969. This was expected to provide the sought-after proof that premedication with an antihistamine drug would prevent the occurrence of incidents during propanidid narcosis.

10 min before propanidid injection 7 mg/kg in 35 sec, clemastine 0.04 mg/kg and atropine 0.01 mg/kg were injected intravenously. After propanidid injection, the typical short-lived and moderate tachycardia and hypotension occurred (10 mm Hg; 3 min duration), but no signs or symptoms of an anaphylactoid or allergic reaction were observed.

The plasma histamine concentration before anaesthesia was 0.7 ng/ml, and 1, 5, 10 and 20 min after injection of propanidid 0.7, 1.2, 4.3 and 2.0 ng/ml respectively. The histamine release in this subject was therefore in accordance with that of the other subjects.

Prick-tests were performed 4 weeks after the incident following propanidid injection and 10 weeks after the last administration of anaesthesia and were found to be negative. The histamine level and basophil content in whole blood was 72 ng/ml and 78 cells/mm^3, which is in the normal range. On April 24, 1970, the subject was given thiopentone 5 mg/kg, in 20 sec, which was without complication. The histamine concentration in plasma rose from 0.9 ng/ml before thiopentone to 1.9, 2.1, 1.5 and 1.3 ng/ml, at 3, 6, 10 and 20 min respectively after the anaesthesia. After 30 min, it reached the base value again of 0.9 ng/ml. The basophil content of venous whole blood fell at 3, 6 and 10 min after thiopentone injection to 45, 58 and 58 per cent of the value before anaesthesia. This is in the normal range (cf. fig. 6). After injection of Micellophor in the same subject there were no significant changes in plasma histamine level.

Case No. 3.

As in the case of the previous volunteer the first propanidid anaesthesia, given on April 9, 1968, was uncomplicated.

After premedication with atropine 0.01 mg/kg, 1 min after injection of propanidid 7 mg/kg i.v., in 20 sec, the expected tachycardia resulted, which, however, lasted somewhat longer than usual (5 min; before narcosis 93 beats/min; thereafter to a maximum of 111 beats/min). Furthermore, the typical decrease in blood pressure was noted, having a maximum of 30 mm Hg, and persisting until the third minute. The plasma histamine concentration before anaesthesia was 1.0 ng/ml and at 1, 5, 10, 20 and 30 min after injection, 2.4, 2.6, 3.2, 1.0 and 1.0 ng/ml respectively. The increase remained, therefore, within the normal range.

On April 26 a second propanidid injection, after the same premedication, was administered. 2 min after injection, 7 mg/kg, in 20 sec, the subject began to cough and hiccup. Immediately thereafter, erythema of the face and neck developed which soon proceeded to cyanosis, since a moderate bronchospasm and a swelling of the nasal mucosa caused difficulties in breathing. At this time also, a fine tremor was observed. The tachycardia lasted 17 min (before narcosis, 96 beats/min; 5 min after as the maximum, 135 beats/min). A blood pressure decrease of 30 mm Hg was measured during the first 5 min after injection. Approximately 10 min after injection, oedema of the face and scalp appeared. The subject complained of headache and dizziness. The persistent cyanosis, resulting from the breathing difficulties, made it necessary to administer oxygen. After approximately 1 hour and without further therapy, the clinical symptoms subsided to the point where the subject could be transported home.

The plasma histamine level in this subject before anaesthesia was 0.85 ng/ml and at 1, 5, 10, 20 and 30 min after injection of propanidid 8.0, 11.0, 12.0, 3.4 and 1.0 ng/ml respectively. As in the other two cases here reported, the histamine release following propanidid far exceeded the normal range. The prick-test response was negative.

Case No. 4.

This subject received for the first time in his life a propanidid anaesthesia. This was administered on October 16, 1969, in the form of a so-called "one-shot injection" as part of our investigations on the rapid injection of propanidid. After premedication with atropine 0.01 mg/kg, propanidid 7 mg/kg i.v. in 5 sec was injected 10 min later. 2 min after injection, erythema of the face and neck was noted as well as a slight cramping of the arms and hands. There was no marked respiratory distress. The blood pressure was decreased only about 10 mm Hg for a period of 6 min. A tachycardia lasting 10 min was observed (before narcosis, 60 beats/min; 5 min after narcosis, still 84 beats/min). The subject complained of a slight headache and dizziness. No other symptoms of an allergic reaction were observed.

The plasma histamine level before propanidid injection was 0.9 ng/ml and 1, 5, 10 and 20 min after injection, 2.6, 6.4, 5.7, and 4.3 ng/ml respectively. Therefore, after injection of propanidid, the plasma histamine level of this subject was slightly above those levels of others who had no actual clinical symptoms and subjective complaints, as may be seen from the results of histamine infusion (fig. 4).

Relationship between the severity and the course of clinical symptoms, and the elevation of plasma histamine levels.

Table II shows a connection between the severity of the clinical symptoms and the increase of plasma histamine levels after injection of propanidid. Apparently, the first noticeable symptoms of histamine release in man are development of tachycardia and erythema, especially in the skin of the face in which the highest histamine content is found of all human skin (Johnson, 1957; Zachariae, 1964; for survey see Lorenz and Werle, 1971). Then follow bronchospasm, oedema formation and hypotension, the severity of which correlates largely with the increase of plasma histamine concentration.

The time relationships between the increase and decrease of the plasma-histamine levels and the development and disappearance of hypotension and tachycardia in the foregoing four cases are represented in figure 7. It shows largely a parallel development of the three parameters. Only in the first 3 min after the injection of the anaesthetic are there effects of propanidid which appear to have nothing to do with histamine release into the plasma (see Discussion).

DISCUSSION

By use of indirect methods, histamine release in man has been shown to follow the use of several drugs frequently administered during anaesthesia. These include:

Muscle relaxants such as tubocurarine (Comroe and Dripps, 1946; Grob, Lilienthal and Harvey, 1947; Collier and Macauley, 1952; Smith, 1957; Westgate, Schultz and Van Bergen, 1961; Salem, King and El Etr, 1968; McDowell and Clarke, 1969); gallamine (Sniper, 1952; Smith, 1957); suxamethonium (Bourne, Collier and Gomers, 1952; Smith, 1957; Jerums, Whittingham and Wilson, 1967).

Ganglionic blocking agents such as trimetaphan (Mitchell et al., 1951; Payne, 1955).

Anaesthetics such as thiopentone (Carrie and

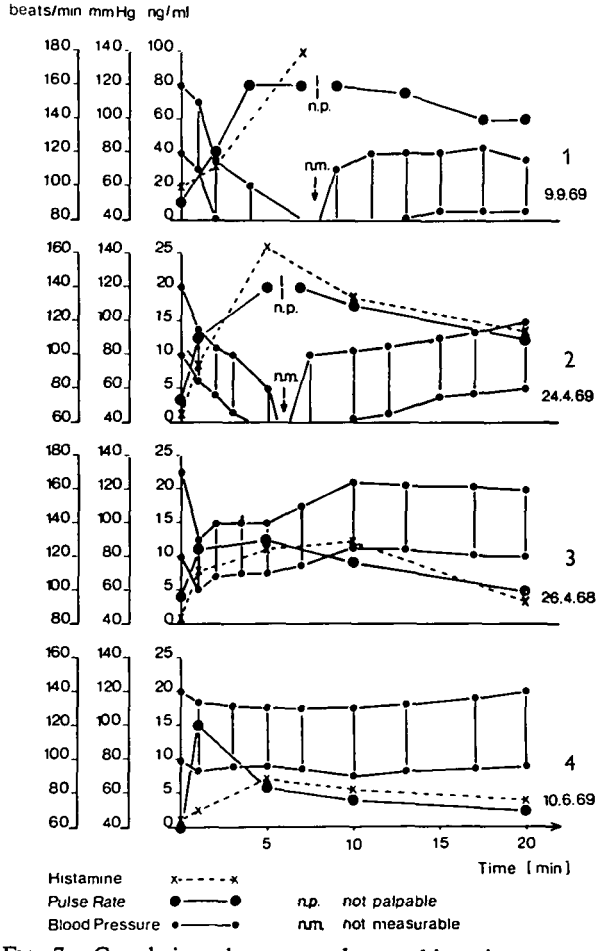

FIG. 7. Correlation between plasma histamine concentration, pulse rate and blood pressure in four cases of anaphylactoid and allergic reactions to propanidid. Values from single determinations. Plasma histamine concentration is given in ng/ml, blood pressure in mm Hg and pulse rate in beats/min.

Buchanan, 1967) and propanidid (Lorenz et al., 1969; Kay, 1969; Johns, 1970).

Analgesics such as morphine (Salter and White, 1949; Nasmyth and Stewart, 1950) and pethidine (Finer and Partington, 1953).

Parasympatholytic agents such as atropine (Sollman, 1948).

We chose propanidid and thiopentone for our investigation of histamine release using direct and indirect methods, because in recent times, and in regard to thiopentone also in earlier times, there have been several reports of anaphylactic and anaphylactoid incidents in response to administration of these drugs. The preceding survey shows, however, that these incidents are in no way specific for both anaesthetics, but are described for many drugs used during anaesthesia. With the use of propanidid, however, the following authors have reported incidents during narcosis with clinical symptoms of anaphylactoid or allergic reactions: Beck, 1965; Michel 1965; Radway, 1965; Manz and Frank, 1969; Kay, 1969; Doenicke and Lorenz, 1970; Johns, 1970; Dannemann and Lübke, 1970; Krüger, 1970.

Using thiopentone, the following case reports were published: Hunter, 1943; Moore, 1946; Hayward and Kiester, 1957; Strunk, 1962; Shinohara and Inamoto, 1965; Currie et al., 1966; Carrie and Buchanan, 1967; Anderton and Hopton, 1968.

As an explanation for these anaphylactoid and allergic reactions, different mechanism must be considered:

(1) Chemical histamine release by both anaesthetics as a direct effect on histamine stores (chemical liberators) (Paton, 1956, 1957).

(2) Histamine release by both anaesthetics indirectly from or in connection with hypoxia, hypercapnia and acidosis (co-liberators) (Mongar and Schild, 1955).

(3) Histamine release due to immunological processes, i.e., after sensitization with both anaesthetics or by cross-allergy.

(4) Release of kinins, serotonin, slow reacting substance (SRS), and prostaglandins in connection with release of histamine or with neural (e.g., parasympathetic) mechanisms.

From the present results there is no doubt that histamine in humans is released in considerable amounts during anaphylactoid reactions from propanidid. This direct evidence cannot be provided for thiopentone, because we have not as yet observed an incident in one of our subjects or patients. Furthermore, it must be likewise considered proven on the grounds of the present results that in normal subjects, propanidid and thiopentone both liberate histamine in small amounts. The clinical evaluation of these two facts, however, differs greatly from each other:

(1) In normal persons histamine release is relatively small. It leads to a pronounced gastric secretion, but to no actual reaction of the circulatory system. It is, therefore, clinically of little importance. During anaesthesia, regurgitation and aspiration of copious gastric juice could possibly occur. Atropine lessened the histamine-stimulated gastric secretion and is therefore recommended as premedication.

Histamine release in normal persons is dependent upon the injection speed (Lorenz et al., 1969). It is independent of sensitization because it also occurs after first injection. This supports the view that propanidid and thiopentone, under these circumstances, act as chemical histamine liberators or as co-liberators. Histamine release in animal experiments using both anaesthetics has not yet been proved. In the case of propanidid, only the solvent Micellophor was shown to be a histamine releaser in dog (see below).

(2) The histamine release occurring during the investigated incidents was considerable. Sometimes it led to severe, even to life-threatening, reactions of the circulatory system and is therefore of critical clinical importance.

This severe histamine-release reaction occurred in three of four cases after the second injection of propanidid. The point in time of the second injection supports the view of a sensitization in the person. The decrease of the histamine liberation with an increasing number of anaesthetics, as in the case of patient No. 1, supports the view of desensitization. In spite of negative cutaneous tests, histamine release is most probably due to immunological reactions.

In the fourth case, however an "allergic" reaction occurred at the first injection. In the literature it has been reported that incidents occurred not only at the second injection, but also at the first injection. Moreover, the patient showed also abnormally high plasma histamine levels. Therefore from the present state of knowledge, it is in no way justifiable to explain incidents with propanidid exclusively on the basis of immunological reactions (for example, as hapten or hapten-inducer). Although it is unsatisfactory at present to postulate an elevated sensitivity to histamine liberators or histamine release in some of the incidents, because for this a bio-

chemical or morphological substrate has not yet been identified, this hypothesis appears more necessary than ever for the moment (cf. Schachter, 1952). The frequency of incidents in patients who have been exposed to radiation or in patients with suppurating processes which became obvious in the case reports (see above) may result from primary diseases which produce increased sensitivity to histamine liberators. Exact investigations in this respect have been hitherto unavailable.

With thiopentone, all case reports known to us refer to a sensitization. Histamine release as a result of immunological reactions appears to stand in the foreground.

The question of a release of other vasoactive substances in adverse reaction to propanidid and thiopentone raises at the same time another question about the pathophysiological and clinical importance of histamine release. When histamine is released from mast cells as a direct effect of the anaesthetic or mediated by immune reactions, depending upon species and body region, also many other substances are liberated, such as serotonin, catecholamines, and heparin, as well as proteolytic enzymes, which form vasoactive polypeptides such as bradykinin and kallidin.

Calculations on the basis of recent investigations on pig and dog (Messmer et al., 1970; Lorenz et al., 1971a, b), which can here be employed, help to provide an answer. When histamine is released in these two species by the classical histamine liberator 48/80, or in dogs by macromolecular substances such as gelatine, Cremophor or Micellophor, then a highly significant correlation exists between the extent of the peripheral arterial hypotension and the increase of histamine concentration in plasma. Since it was shown that the fall in arterial pressure, but not the histamine release, was largely prevented by antihistaminics in animal experiments, there exists not only an accidental parallelism, but a causal connection between histamine release and the fall in blood pressure.

Because of the proportionality between the fall in pressure and the increase in plasma histamine concentration, it can be determined in what range of histamine concentrations a severe hypotension (over 60 mm Hg) or even a life-threatening incident occurs in test animals. In pigs, the range of plasma histamine concentrations is about 50–100 ng/ml (Lorenz et al., 1971a), in dogs about 35–90 ng/ml (Messmer et al., 1970). Dogs and pigs exhibit nearly the same sensitivity to histamine, taking into consideration the blood pressure response of these animals. Humans react, however, with at least twice the sensitivity of these species. In man, therefore, on this basis an elevation of the plasma histamine concentration of about 20–50 ng/ml would be enough to cause severe hypotension progressing to cardiovascular arrest. This degree of increase in histamine concentration was in fact measured in cases 1 and 2.

Our calculations make it highly probable, therefore, that histamine release represents the real cause of the incidents observed after propanidid injection. This view is further supported by the observation that the severity of the clinical symptoms paralleled the extent of histamine release (table II), and the development and cessation of clinical symptoms corresponded with the increase and decrease of the plasma histamine concentration (fig. 7).

The release of other tissue hormones may increase or reduce the histamine effect on the circulation but lack of experimental data concerning the quantities of these substances released during anaesthesia renders discussion of the role of these substances largely speculative.

The demonstration of the presence of a vasoactive substance in severe hypotensive reactions caused by anaesthetics allows too easily the convenience of attributing all circulatory reactions after injection of propanidid and thiopentone to histamine release into the blood stream. This is in no way true. Neither for reason of the quantity of histamine released (cf. histamine infusion, fig. 4) nor for reasons of the time-course of histamine release (cf. fig. 7) can tachycardia and hypotension after propanidid narcosis and after thiopentone narcosis be attributed to histamine release into the blood stream in the first 1–3 min after injection of the anaesthetics. According to investigations previously reported, hypotension during propanidid narcosis was (1) explained by myocardial depression (Bernhoff, 1968; Aström, Bernhoff and Persson, 1970; Lennartz, Zindler and Hepfer, 1970; Soga and Beer, 1971, personal communication) and (2) by peripheral vasodilatation on the basis of a direct action of propanidid on smooth muscle (Langrehr, 1965, 1968). As noted, the hypotension induced by histamine release shows itself as a "delayed blood pressure response" and in general reaches its maximum 5–7 min after the administration of the histamine releaser.

The best way to demonstrate the two different causes of hypotension after propanidid injection is by administration of this anaesthetic to dogs. In this species, Cremophor or Micellophor, the solvent of

propanidid, acts as a macromolecular histamine releaser (Wirth and Hoffmeister, 1965; Lorenz et al., 1971b). After the typical initial hypotension and tachycardia, and after a short, more or less complete return to normal, there follows a second, much more severe, hypotension of longer duration (Conway, Ellis and King, 1967; Lorenz et al., unpublished).

This second episode of hypotension is caused by histamine (Lorenz et al., 1971b). One can demonstrate the same reaction only in cat, but not in rabbit, pig and man, in which species, Cremophor is not a histamine liberator (Lorenz et al., 1969, 1971a, b; Doenicke and Lorenz, 1970).

Our investigations during the described incidents give indications for therapy as follows. Glucocorticoids, antihistaminics and plasma substitutes (see Doenicke and Lorenz, 1970), should prevent the reactions to a massive histamine release. Antihistaminics, in the usual doses as premedication, attain only a mitigating effect, but in severe incidents they do not suffice to block completely the action of histamine on the receptors. Therefore, it is recommended that antihistaminics should be included in preanaesthetic medication, in order to prevent slight allergic reactions and, if severe reactions occur, to inject a high dose of prednisolone immediately as a functional antagonist to histamine.

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LIBERATION D'HISTAMINE CHEZ L'HOMME CONSECUTIVE A L'ADMINISTRATION DE PROPANIDIDE ET DE THIOPENTONE: EFFETS PHARMACOLOGIQUES ET CONSEQUENCES CLINIQUES

SOMMAIRE

En recourant à un nouveau procédé spécifique et extrêmement sensible, en vue du dosage de l'histamine présente dans le plasma humain, on a montré que l'injection de propanidide et de thiopentone était suivie d'une libération histaminique. L'étude de la secrétion gastrique, de la pression artérielle et de la fréquence cardiaque a confirmé cette découverte. Chez des sujets normaux, la libération d'histamine ne présente aucune signification clinique particulière. D'autre part, lorsque des réactions de type anaphylactique sont survenues à la suite d'une injection de propanidide, la libération d'histamine était suffisamment massive pour expliquer la sévérité des symptômes et signes cliniques observés. Au cours de cette étude, aucune réaction n'a été notée à la suite de l'injection de thiopentone. Bien qu'il semble vraisemblable qu'une libération massive d'histamine puisse survenir au cours de réactions

de type anaphylactique engendrées par cet agent anesthésique, nous ne disposons d'aucune observation pour le confirmer. Dans un cas, on a montré qu'une prémédication comportant l'administration de glucocorticoïdes et de substances antihistaminiques et un traitement à base de substituts du plasma, pouvaient s'opposer à l'apparition d'une réaction grave.

HISTAMINFREISETZUNG DURCH PROPANIDID UND THIOPENTONE AM MENSCHEN: PHARMAKOLOGISCHE WIRKUNGEN UND KLINISCHE FOLGERUNGEN

ZUSAMMENFASSUNG

Mit einer neuen, hoch empfindlichen und spezifischen Methode zur Bestimmung von Histamin in menschlichem Plasma konnte gezeigt werden, daß die Injektion von Propanidid und Thiopentone eine Histaminfreisetzung hervorruft. Beobachtungen der Magensaftsekretion, des arteriellen Blutdrucks und der Pulsfrequenz unterstützten diese Befunde. Bei Normalpersonen führte die Histaminfreisetzung nicht zu klinischen Erscheinungen. Wenn jedoch nach Propandidid-Injektion anaphylaktoide Reaktionen auftraten, war die Histaminfreisetzung jeweils so massiv, daß man aus ihr die schweren klinischen Zeichen und Symptome ableiten konnte. Bei dieser Untersuchung war die Injektion von Thiopentone von keinen Reaktionen gefolgt. Obwohl es wahrscheinlich scheint, baß bei Verwendung von diesem Anaesthetikum massive Histaminfreisetzungen unter anaphylaktoiden Reaktionen auftreten, konnten wir mit unseren Beobachtungen dies nicht bestätigen. In einem Fall konnte gezweigt werden, daß Prämedikation mit Glucocoricoiden und Antihistaminika sowie Therapie mit Plasma-Substitution die Entwicklung einer schweren Reaktion verhindern konnte.

LIBERACION DE HISTAMINA EN EL HOMBRE POR PROPANIDID Y TIOPENTONA: EFECTOS FARMACOLOGICOS Y CONSECUENCIAS CLINICAS

RESUMEN

Utilizando un nuevo método, muy sensible y específico, para la determinación de histamina en el plasma humano, se demostró que después de la inyección de propanidid y tiopentona hay liberación de histamina. La observación de la secreción gástrica, presión arterial y frecuencia del pulso apoyó este hallazgo. La liberación de histamina no tiene ninguna importancia clínica especial en personas normales. Por otra parte, cuando ocurrieron reacciones anafilactoides después de la inyección de propanidid, la liberación de histamina fue tan masiva que podía explicar diversos signos y síntomas clínicos observados. En este estudio no ocurrieron reacciones después de la inyección de tiopentona. Aunque parece probable que puede haber un desprendimiento masivo de histamina durante reacciones anafilactoides con este anestésico, no poseemos observaciones que puedan confirmarlo. En un caso fue demostrado que la premedicación con glucocorticoides e histamínicos y la terapia con sustitutos de plasma pueden impedir el desarrollo de una reacción intensa.