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6. Prophylaxis and Treatment of Adverse Reactions and Histamine Release in Anaesthesia and Surgery – H_1- and H_2-Receptor Antagonists

Histamine Release in Anaesthesia and Surgery. Premedication with H_1- and H_2-Receptor Antagonists: Indications, Benefits and Possible Problems* **

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Summary. Our clinical and experimental studies have so far demonstrated, that the drugs used in anaesthesia; such as hypnotics, sedatives, narcotics or muscle relaxants, release histamine.

The intravenous short acting anaesthetic etomidat has not shown either in experimental studies or in clinical use for 10 years any anaphylactoid reaction. The benzodiazepines are another group of drugs which appear not to release high amounts of histamine.

Accurate studies on volunteers as well as on patients on the application of H_1- and H_2-receptor antagonists have demonstrated an effective inhibition of the anaphylactoid reaction. We suggest that in case of a history of allergy H_1- and H_2-receptor antagonists should be administered as a prophylactic premedication.

Key words: Histamine release – Anaesthesia – Surgery – Antihistamines

Histamin-Freisetzung in der Anästhesie und Chirurgie. Prämedikation mit H_1- und H_2-Rezeptor-Antagonisten: Indikationen, Vorteile und mögliche Probleme

Zusammenfassung. Die in der Anaesthesie verwendeten i.v. Hypnotika, Anaesthetika und Muskelrelaxantien sind in der Lage Histamin freizusetzen. Dies ist das Ergebnis einer 12jährigen klinisch-experimentellen Forschung.

Das i.v. zu applizierende Hypnotikum Etomidat hat sowohl im Experiment als auch nach 10jähriger klinischer Erfahrung noch keine anaphylaktoide Reaktion verursacht. Aber auch die Benzodiazepine sind keine potenten Histaminfreisetzer.

Die Applikation von H_1- und H_2-Rezeptor-Antagonisten erscheint nach sorgfältiger Prüfung sowohl im klinischen Experiment als auch in der Klinik in der Lage zu sein, anaphylaktoide Reaktionen zu verhindern. Es wird daher bei entsprechender Anamnese eine prophylaktische Praemedikation mit H_1- und H_2-Rezeptor-Antagonisten empfohlen.

Schlüsselwörter: Histamin-Freisetzung – Anästhesie – Chirurgie – Antihistaminika

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1 Modern Anaesthesia and Histamine Release in Man

Although modern anaesthesia using combined narcotics offers a pleasant, mentally less disturbing, experience at operation for the patient, it also involves dangers. Cardiovascular disturbances (apart from unexpected side-effects) mostly during induction, have been recognized more and more in recent years [2, 9, 11, 12].

The identification of certain symptoms due to histamine is very important for the anaesthesist.

1.1 Evidence for Histamine Release in Man as an Important Pathophysiological Event

Histamine release in man following i.v. injection of anaesthetic and hypnotic agents under clinical conditions was first demonstrated in 1969 in volunteers and patients suffering from severe reactions to the anaesthetic druc propanidid (Epontol) [6, 17].

In all 10 volunteers of one experimental series an increase of plasma histamine levels up to 3 ng/ml was determined (Fig. 1). In 3 other volunteers and in 1 patient with high basal histamine very high plasma levels were observed (Fig. 2) (patient Gr. AL, No. 1). The kinetics of the plasma histamine levels in all cases corresponded largely to a Bateman function which should be expected in the case of histamine release [9, 14].

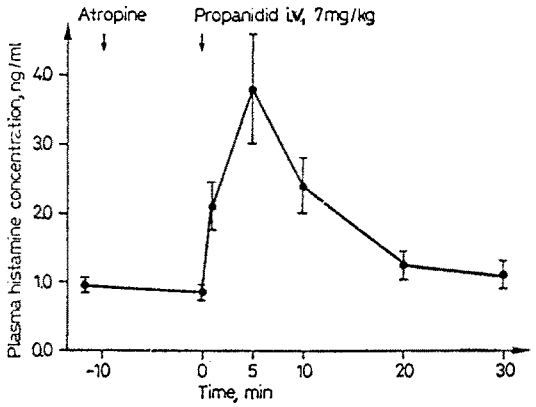

Fig. 1. Plasma histamine concentrations in human subjects after intravenous injection of propanidid (Epontol). Mean values ± SEM from 12 patients [19]

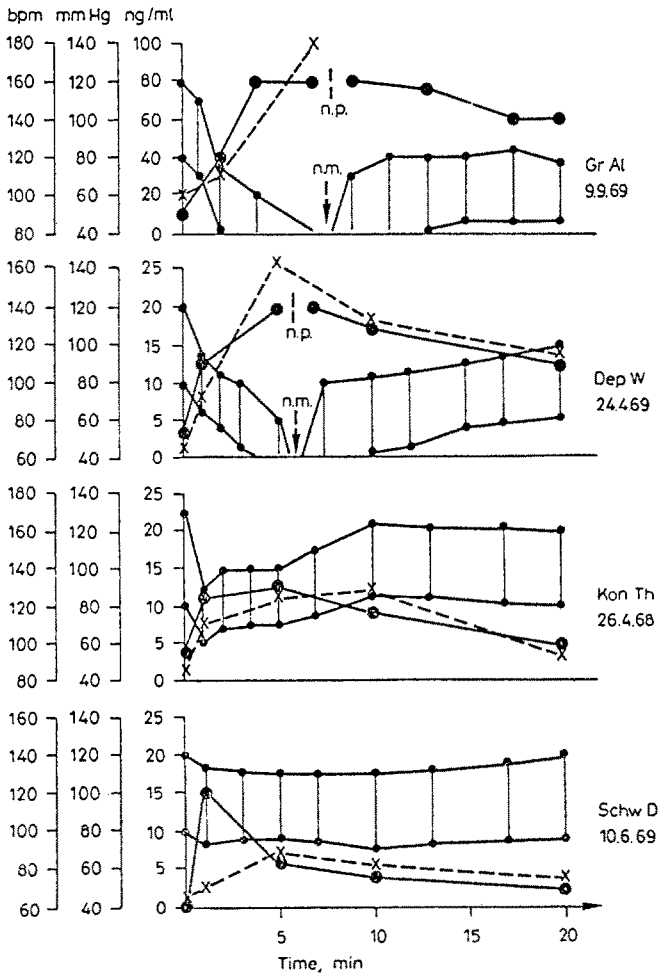

Fig. 2. Correlation between plasma histamine concentration, pulse rate and blood pressure in 4 cases of pseudo-allergic reactions to propanidid (Epontol). Values from single determinations [19]. – – – = Histamine; —— = pulse rate; ⊡ = blood pressure; n.p. = not palpable; n.m. = not measurable

Changes in plasma histamine levels after injection of propanidid were accompanied by clinical symptoms and biological reactions which in intensity and time course corresponded to the alterations in plasma histamine concentration (Fig. 3).

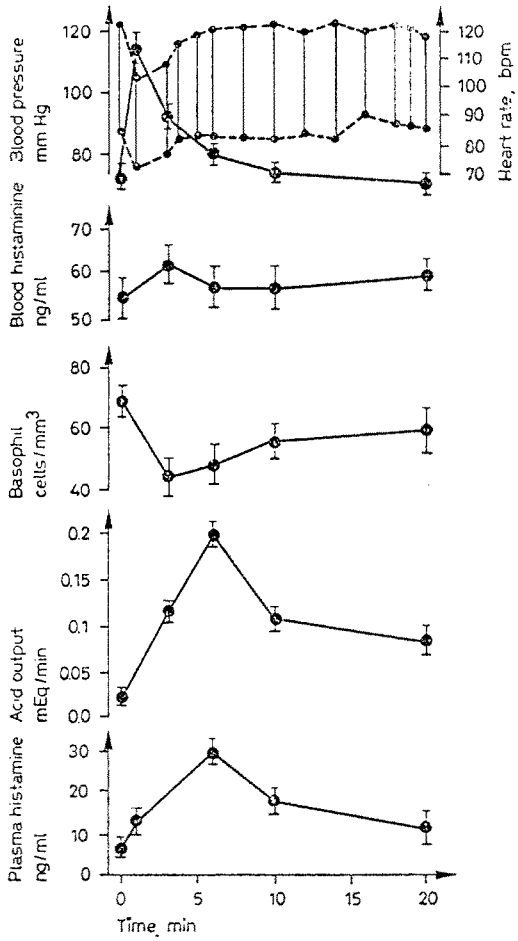

Fig. 3. Histamine concentration in plasma and whole blood, gastric acid secretion, blood pressure and heart rate after intravenous injection of propanidid (Epontol). Mean values ± SEM from 5 patients. —— = Heart rate; – – – = blood pressure [19]

Since our first investigation in 1969 [17] we investigated eight anaesthetic and hypnotic agents in man. Our studies on thiopentone in volunteers were made in 1970 (Fig. 4), on methohexitone in 1971, for propanidid, althesin and etomidat a controlled double cross-over randomized study (propanidid versus etomidat) was performed in 1972 [19, 20] flunitrazepam (Rohypnol, Roche) was tested in 1976 and diazepam and lormetazepam together with etomidat in 1977 [6–11]. In 1979, we finished the study investigating the protective effect of H_1- and H_2-receptor antagonists with propanidid [4, 14, 15].

Following flunitrazepam 50% of the test subjects showed elevated plasma histamine levels, but after etomidat there was no increase in the plasma histamine concentration during the time of investigation in any of the 9 volunteers. Thus, etomidat was the only intravenous hypnotic drug which did not cause histamine release in these experiments [8, 9].

The changes in heart rate and blood pressure after injection of the anaesthetics have already been reported in other publications for all the drugs. The stimulation of gastric acid secretion (Figs. 3, 4) [19] has been tested after propanidid and thiopentone. From their limited histamine release, it would not be expected that any of the drugs studied will normally cause serious circulatory disturbances following their administration. Using flunitrazepam there was no

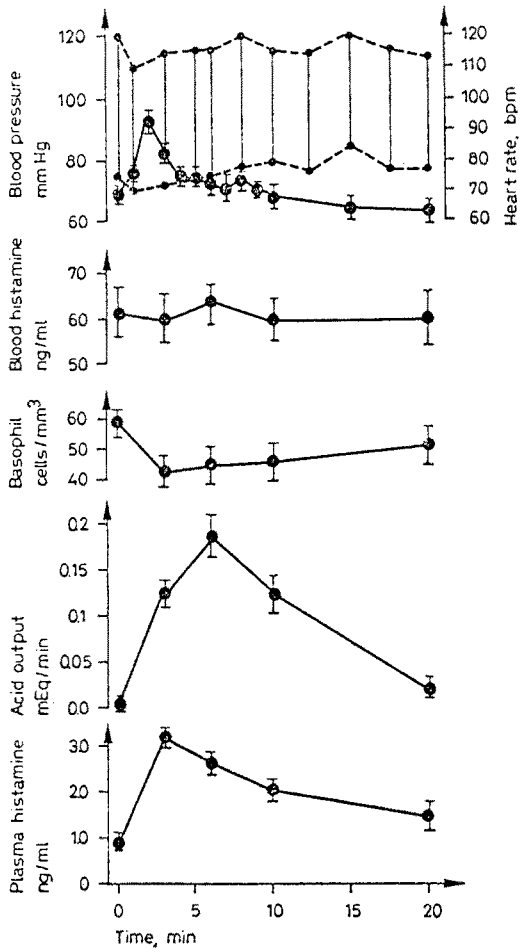

Fig. 4. Histamine concentration in whole blood and plasma, basophils, gastric acid secretion, blood pressure and heart rate after intravenous injection of thiopentone. Mean values with SEM. 5 subjects were tested after the injection of thiopentone 5 mg/kg, injection time 20 sec. All parameters were studied simultaneously in each person. Values at zero time for heart rate (——) and blood pressure (– – –)

change in blood pressure in any of the volunteers within the whole period of investigation. However, two of the volunteers showed a slight tachycardia (increase in heart rate, 17 and 20 bpm) starting 1 min after drug injection and lasting for 10 min in both cases. These two individuals showed the highest plasma histamine levels after flunitrazepam injection.

Administration of diazepam cannot be claimed to liberate histamine despite a slight increase in the plasma histamine value from 0.35 to 0.6 ng/ml on average, since in no circumstance was 1 ng/ml attained. We have demonstrated [15] that 1 ng/ml is the cut-off point between pathological and physiological plasma histamine levels.

1.2 Histamine Release in Man Following Intravenous Injection of Muscle Relaxants in Combination with Etomidat

The muscle relaxants (suxamethonium, pancuronium and alloferin) [11, 15] have been investigated for their histamine-releasing activity in man. Using the experimental design described in previous communications [9, 13, 19, 25], a combination of drugs was administered to each of the test individuals, since for clinical and ethical reasons it was impossible to administer muscle relaxants to human subjects without also administering atropine and hynotics.

All three muscle relaxants released histamine. The highest incidence was found following suxamethonium, the lowest after pancuronium. Prostigmine was without effect in this series of 15 individuals. The combination of the different drugs apparently had little effect on histamine release since etomidat injected repeatedly did not alter plasma histamine levels and did not change them when given alone. Furthermore, the kinetics of histamine release after injection of the muscle relaxants corresponded well with those which were expected for a histamine release when given alone, especially regarding the time of onset and the velocity of increase of the elevated plasma histamine levels. But clinical observations (occurrence of erythema etc.) strongly suggest that there may be a slight histamine releasing effect of etomidat when administered repeatedly during the time of muscle relaxation [5, 15].

Clinical symptoms of pseudo-allergic reactions were observed in many subjects during the whole series of experiments. Tachycardia occurred in all subjects receiving etomidat and pancuronium and in most of the individuals being treated with etomidat and alloferin. The skin reactions corresponded partly with the occurrence of elevated plasma histamine concentrations. But 2 persons with increased plasma histamine levels after injection of suxamethonium and 1 person after alloferin did not show any skin reaction. Local histamine release may cause single wheals but histamine may be diluted during diffusion into the vessels to such an extent that it does not significantly increase plasma histamine levels and does not produce the systemic effects of a pseudo-allergic reaction.

A certain combination of drugs used for muscle relaxation under clinical conditions releases histamine in man and the muscle relaxants are themselves mainly responsible for this. Before the investigation presented here, no histamine release or pseudo-allergic reactions after etomidat had been

Table 1. Plasma histamine values in healthy subjects after intravenous injections of lormetazepam

Test subject No.	Plasma histamine value, ng/ml	
	before	after[a]
Responsive subjects		
1	0.35	2.7 (5)
2	0.4	2.05 (5)
3	0.75	1.15 (5)
Mean	0.50	2.00
Non-responsive subjects		
1	0.1	0.1 (1)
2	0.5	0.8 (5)
3	0.15	0.3 (5)
4	0.45	0.4 (1)
5	0.75	0.95 (10)
6	0.5	0.4 (1)
7	0.65	0.9 (5)
Mean	0.45±0.25	0.55±0.35

[a] Highest value measured; time (min) in parentheses

Table 2. Comparison of 2 clinically symptomless subjects who showed an increase in plasma histamine value after lormetazepam and etomidat

Subject No.	Pharmacological data	Plasma histamine value, ng/ml		Notes	Etomidat		Notes
		before	after		before	after	
1. K.H.	diazepam 12.12.77	0.2	0.4 (5)	–	0.25	0.45 (1)	thrombosis
3. S.H.	diazepam 12.12.77	0.5	0.75 (5)	–	0.4	0.7 (1)	myoclonus
1. K.H.	lormetazepam 15.12.77	0.35	2.7 (5)	HF const. AP const.	0.55	3.2 (5)	HF const. AP const. 'goose pimples'
3. S.H.	lormetazepam 16.12.77	0.4	2.05 (5)	HF const. AP const.	0.35	1.85 (5)	HF const. AP const. 'pins and needles'

HF = heart rate, AP = arterial blood pressure. For further conditions see Table 1

recognized [9]. On the other hand, in some subjects we found elevated plasma histamine values after giving alloferin, pancuronium and suxamethonium with etomidat. In these subjects, clinical symptoms (erythema) were noted which at the second injection at least indicated a local histamine liberation [11, 15].

1.3 Histamine Release After Combination of two Hypnotics

In recent years it has become apparent that some drugs after some time develop increasing incompatibility [11, 17, 19]. Thus, in the case of etomidat, and particularly in combination with a further drug, the possibility of a release of histamine cannot be excluded. Two instances of histamine release were observed, but which drug in the combination or whether the combination itself releases histamie is difficult to decide [11].

In contrast to diazepam, lormetazepam in 2 subjects showed a significant release of histamine (Table 1).

In the 2 responsive subjects, who earlier had increases in histamine after lormetazepam, a subsequent etomidat injection again caused a further histamine release. Since an elimination kinetic for histamine was evident both before etomidat and also after injection of this short-acting hypnotic, this histamine release was unequivocably shown.

Since the 10 subjects received two hypnotics – i.e. etomidat and lormetazepam – within a few days (Table 2) both responsive subjects, No. 1 and 3, according to the chronological order of the hypnotics are specified separately. In both instances diazepam/etomidat was given first, and 3 to 4 days later the combination lormetazepam/etomidat.

At the elevated histamine concentration of 2.7 ng/ml after lormetazepam and 3.2 ng/ml after etomidat in subject No. 1 (K.H.), cardio-circulatory disturbances were expected but an increased heart rate did not occur. The mean arterial pressure after diazepam decreased in the first 5 to 10 min while the heart rate remained constant, whereas after lormetazepam no changes occurred. Since no cardiovascular side effects occurred with the combination lormetazepam/etomidat at a plasma histamine value of 2.7 to 3.2 ng/ml, lormetazepam may also have acted as an antihistaminic. Based on in vitro and in vivo findings from animal experiments using the guinea-pig asthma model, it can be claimed that lormetazepam and lorazepam have histamine antagonistic effects (H_1-type). So far in the clinic, no pseudo-allergic side-effects have been ascertained in about 1,200 lormetazepam administrations, nor after repeated injections of up to 80 mg over several days.

Watkins [26] also suggested the possibility of histamine release after etomidat, but in such small amounts that it disappears from the circulation as fast as it is liberated, so that a circulatory reaction does not occur. Subclinical reactions after etomidat such as chemotaxis of blood leucocytes through the surrounding tissue were observed. This is probably due to the production of anaphylatoxins after C3 and C5 activation, which was measured by the decrease of complement factors and immunoelectrophoresis. 60% of all patients treated with propanidid, althesin, methohexitone [27] or etomidat showed this effect. Whereas the production of anaphylatoxins reached its highest value only 30 to 40 min after the administration of etomidat, they appeared after the other drugs as early as 5 min after injection.

2 Prophylaxis of Anaphylactoid Reactions in Man by H_1-Receptor Antagonists and Glucocorticoids

15 years ago we started systematically premedication with antihistaminics for every anaesthesic performed with propanidid.

In a retrospective study of the cases in whom we used H_1-receptor antagonists for premedication, we could not see a decrease in either frequency or potency of the anaphylactoid reactions due to propanidid.

In the retrospective evaluation of 1,700 anaesthesia with an H_1-receptor antagonist (clemastine) as premedication 29 allergic reactions were seen [3]. 10 patients showed a severe reaction with decrease in blood pressure.

A very important example, the fact that premedication with H_1-receptor antagonist does not help was the case of the patient G.R., 1969, who sulffered cardiac arrest because of a histamine release up to 100 ng/ml plasma [19].

The administration of clemastine was unable to prevent the reaction to such a massive release of histamine. Prednisolone had been found very effective during a previous incident in this patient. We discussed this problem with him. The patient consented to another propanidid anaesthesia after premedication with high doses of prednisolone and using a reduced dose of propanidid. About two months

No. of subject	Plasma histamine levels [ng/ml] Sodium + propanidid		Symptoms
18	1,7 ng/ml		Flush, Headache
11	1,8 ng/ml		Flush, HF ↑
			Pharyngeal narrowness
	$H_1 + H_2$ + propanidid	Sodium + propanidid	
30	1,7 ng/ml	1,6 ng/ml	HF unchanged

Fig. 5. Premedication with H_1- and H_2-receptor-antagonists before Propanidid anaesthesia
HF = heart rate, sodium = NaCl

later a further operation was necessary. As premedication, prednisolone (2 mg/kg) together with clemastine was injected intravenously. After that propanidid anaesthesia proceeded without any complication. Later on, two more operations were necessary. We premedicated always with clematine and prednisolone. No complication was observed during and after the anaesthesia. The plasma histamine concentration before the premedication was 9.3 ng/ml. It increased to 16.5 ng/ml 1 min after propanidid, to 30 ng/ml 5 min after injection and to 45 ng/ml at 10 and 15 min after injection [19].

3 The Introduction of H_2-Receptor Antagonists: The H_1- and H_2-Blockade as Premedication in Anaesthesia and Surgery

Although a glucocorticoid has shown this positive function first [7, 19] Lorenz recommended in 1973 in London (H_2-Meeting) as an ideal premedication a combination of H_1- and H_2-receptor antagonists in order to block the histamine release effect after infusion of plasma substitutes. With the successful synthesis of a specific H_2-receptor antagonist by Black et al. [1] new possibilities for the investigation of the role of histamine during anaphylactoid reactions were introduced.

The best technique for demonstrating free histamine in adverse responses to intravenous agents is when a randomized controlled clinical trial is performed in which concommittantly altered histamine contents are measured, and histamine induced biological reactions as well as clinical symptoms are recorded and these reactions are prevented in a treatment group by application of H_1- and H_2-receptor antagonists.

In this way we studied, from 1977, adverse reactions to the plasma substitute Haemaccel in two groups, 25 human volunteers, each, in which saline or the combination of an H_1- and H_2-blocker was given [16].

Elevated plasma histamine levels were shown in both groups of test persons with a high incidence.

Clinical symptoms and biological reactions corresponding quantitatively to the histamine levels were observed only in the control group, not in the subjects being treated by the H_1- and H_2-blocker.

Especially interesting was that there was no increase in heart rate in the treatment group, whereas the histamine plasma levels were significantly increased [16].

In a controlled randomized single-blind trial in 32 volunteers it was determined whether an i.v. premedication (consisting of dimethpyrindene 0.1 mg/kg and cimetidine 5 mg/kg i.v.) prevented the effects of histamine release after administration of propanidid. The study was designed as cross-over versus NaCl. The H_1-blocking dimethpyrindene was injected within 30 s, the H_2-receptor antagonist cimetidine consecutively within 2 min [4, 24].

Elevated plasma histamine levels were shown in both groups. But their extent was relatively small. It was, however, interesting to note, that the "propanidid flush" was to a large extent prevented in the H_1- and H_2-group, and the headache – resembling "a hangover" – was more frequently observed in the saline group than in the treatment group. Myoclonia, however, occurred more in the treated group than in the control group. Except for preventing a flush however, these differences, were not significant in the small sample of 32 subjects.

The considerable increase in heart rate in the first minute after propanidid was also significantly reduced by premedication with H_1- and H_2-blockers, whereas the hypotensive response remained the same in the two groups. The influence of the H_1- and H_2-blockers on the propanidid-induced tachycardia is a remarkable finding since at this time the plasma histamine levels have still not reached the highest value. Like wheals in the skin this may be another example the fact that local histamine release is not or not yet associated with an increase in plasma histamine levels and therefore not or not yet with a systemic reaction to the histamine release.

Some interesting aspects from this cross-over study should be taken into account. Histamine release in the second injection of propanidid is less pronounced than in the first injection. It is important that after the second injection of propanidid a great number of volunteers did not show a significant increase of histamine plasma levels. It is suggested that this phaenomenon is due to tachyphylaxis.

The symptoms following the increase of histamine plasma levels are demonstrated in Fig. 5. Volunteer No. 18: flush, headache; No. 11: flush, increase of heart rate of 54 bpm. In Case of volunteer No. 30 the histamine plasma levels were increased but neither tachyphylaxis nor headache was found. As we demonstrated even when an increase of histamine plasma levels up to 1.7 ng/ml was measured, no anaphylactoid symptoms were found. From this we conclude that the combination of H_1- and H_2-receptor antagonist for premedication significantly decreases the incidence of side effects.

In general the side effects of the premedication with a combination of H_1- and H_2-receptor antagonists may be considered as weak, and it seems that they depend mainly on the speed of injection. The administration of

dimethpyrindene and cimetidine in less than one minute causes more often side effects whereas the slow injection of dimethpyridene (2 min) and cimetidine (2 min) did not cause any side effect in 300 orthopaedic patients [21, 23, 24].

4 Considerations About the Premedication with H_1- and H_2-Blockers: Alternatives, Questions to be Solved and Possible Indications

4.1. Considerations

– In every evaluation of a newly synthetized drug the question whether the drug releases histamine should be answered.
– The pharmaceutical companies should produce drugs which do not release histamine. So we accepted in 1972 with pleasure the development of etomidat, a barbiturate free hypnotic, because propanidid would no longer be required [3, 9].

We accepted it in spite of disadvantages such as myoclonia and vein pain.

We considered as a great advantage that the drug did not release histamine [9].
– If one substance does release histamine the producer should try to improve the drug; for example, the classical Haemaccel was replaced as plasma substitutes by the purified Haemaccel [18, 22].
– Drugs which release histamine should be injected slowly [20]
– In certain situations we should replace some drugs with others in order to avoid some hazards; for instance in long lasting operations we should use pancuronium instead of suxamathonium.
– In high risk patients we should take a good case history to determine the likelihood of allergy.

4.2 Alternatives

In several experiences (since 1969) we noticed that application of glucocorticoids 10 minutes before the start of anaesthesia completely inhibited the incidence of allergic reactions. This would allow us to consider glucocorticoids as an alternative way of premedication in allergic patients, taking in account the side effect of the drug.

4.3 Questions to be Clarified

– It is planned to determine if premedication with H_1- and H_2-receptor antagonists is ideal by testing the drugs in 5 to 10 anaesthesia departments with a prospective controlled study and to clarify which reactions are caused by histamine release during different kinds of operations
– Do anxious patients have a higher incidence of anaphylactoid reactions?
– Do poor-risk patients (polytrauma, septicaemia, etc.) have a higher incidence of these reactions?

4.4 Indications for the Use of H_1- and H_2-Receptor Antagonists for Premedication

– Hypersensitivity reactions during previous anaesthesia or during in previous administration of substances used in X-ray procedure or after plasma substitutes.
– Second drug exposure within few days (Watkins theory of short-term-memory-effect).
– Clear-cut history of allergy, such as asthma, hay-fever.
– Expectation of a heavy blood loss because it is possible that during transfusion exogenous histamine will be introduced into the patient.
– Use of pallacos in patients with an allergic history and cardiac insuffiency

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