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Anti H_1- and anti H_2-premedication

Prémédication aux anti H_1 et anti H_2

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Histamine-release responses in clinical conditions show a wide range of severity, from a single spot of erythema or a wheal up to a life-threatening reaction or the death of the patient.

To demonstrate the efficiency of H_1- and H_2-blockade in preventing histamine-induced anaphylactic and anaphylactoid reactions, a series of controlled trials was carried out in patients, volunteers and dogs presenting histamine-release responses of all three grades of severity (table I). Both the histamine-releasing drugs and the histamine H_1- and H_2-receptor antagonists had to be chosen for these trials according to a series of well-conceived and strict criteria.

For the histamine H_1- and H_2-receptor antagonists, the criteria for selection included potency, selectivity, duration of action, clinical experience with the drug and the availability both for the oral and the intravenous routes. For the H_2-receptor antagonist, selection was not difficult since, at the time of the first trials, cimetidine was the only available drug on the market. However, the choice of the H_1-receptor antagonist was very difficult.

Dimethindene (Forhistal® in the USA, Fenistil® in Europe) was chosen since it is very potent [12, 14], highly selective [11, 14], its duration of action was long enough for 2-3 h of operation, but not too long-lasting to interfere with postoperative recovery, and the drug did not release histamine in man [6].

Five controlled clinical and experimental trials were conceived and carried out in the last six years, a synopsis of which has been compiled in table II. Materials and methods of all these trials have been described in previous communications [4, 9, 10, 13]. In

Table I. — Classification of histamine-release responses by severity as a special form of anaphylactoid reactions to drugs or physical injury

Severity grade	Clinical symptoms and groups of symptoms	Operational criteria	Plasma histamine
I. Cutaneous	— Erythema, urticaria and/or dermal pruritus *only*	— Not considered as threatening — No intensified observation, no treatment	≤ 1 ng · ml^{-1}
II. Systemic	— Generalized skin reactions plus discomfort — Tachycardia, arrhythmias, medium hypotension — Respiratory distress	— Considered as threatening by patient and doctor — Intensified observation and/or treatment	>1 ng · ml^{-1}
III. Life-threatening	— Severe hypotension (pulse and RR not measurable) — Ventricular fibrillations, cardiac arrest — Bronchospasm, respiratory arrest	— Considered as life-threatening by doctor — Emergency treatment	>12 ng · ml^{-1}

From LORENZ *et al.* [7].

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Table II. — Synopsis of five randomized controlled trials on prevention of anaphylactoid reactions to several histamine releasers with histamine H_1- + H_2-receptor antagonists

N°	Severity grade	Histamine releaser (ml and mg · kg^{-1} i.v. respectively)	H_1- + H_2-antagonists (mg · kg^{-1} i.v.)		Frame of the trial (Individuals, location and time)
1	Cutaneous	Polygeline-35 7 ml · kg^{-1}, 10-15 min infusion	H_1 : Fenistil Piriton H_2 : Tagamet	0.1 0.1 5.0	Randomized controlled, single and double-blind, 450 patients, Heidelberg 1979/80
2	Systemic	Classical polygeline 7 ml · kg^{-1}, 3 min, after bleeding	H_1 : Fenistil H_2 : Tagamet	0.1 10.0	Randomized controlled, single and double-blind, 50 volunteers, Munich 1977
3	Systemic	Propanidid (Epontol®) in Micellophor (2x) 7 mg · kg^{-1}, 60 s	H_1 : Fenistil H_2 : Tagamet	0.1 5.0	Randomized, cross-over, single and double-blind, 32 volunteers, Munich 1979
4	Life-threatening	Classical polygeline 20 ml · kg^{-1}, 3 min, after bleeding	H_1 : Fenistil H_2 : Tagamet	1.0 5.0	Randomized, controlled, single and double-blind, 40 dogs, Marburg 1977
5	Life-threatening	48/80 in Ringer 20 ml · kg^{-1}, 3 min, after bleeding	H_1 : Fenistil H_2 : Tagamet	0.1 0.5 5.0	Randomized controlled, single and double-blind, 84 dogs, Marburg 1982

Fenistil® = dimethindene maleate; Piriton® = chlorpheniramine; Tagamet® = cimetidine. For details and further conditions, see [1, 7, 10].

this paper, we only report the main results of the four trials, excluding that with propanidid.

1. Cutaneous anaphylactoid reactions to polygeline 35 in patients

In contrast to the now outdated formulation of polygeline (« classical » Haemaccel®), « purified » polygeline (Haemaccel 35) did not elicit any systemic anaphylactoid reactions in patients (table III). There still were, however, cutaneous anaphylactoid reactions. They only consisted of wheals of 2-3 mm diameter and caused, if nothing else was detectable, itching and burning which was usually neglected by the patients expecting surgery. The incidence of this banal histamine-release response to polygeline was less than in studies with « classical » Haemaccel [7], but still 18% ! However, by premedicating with H_1- and H_2-receptor antagonists, it was drastically reduced, not only in the overall number of reactions (table III), but also in the « severity » of those remaining. Dimethindene was superior to chlorpheniramine. Since the premedication was administered slowly (2 min for each drug), there were no side-effects of the H_1- and H_2-blockade in such

Table III. — Cutaneous anaphylactoid reactions in patients receiving three kinds of premedication and subsequent infusion of « purified » polygeline (Haemaccel 35)

Premedication	Patients with anaphylactoid reaction		No reaction	Total
	systemic	cutaneous		
Saline	0	27	123	150
Fenistil plus Tagamet (H_1+H_2)	0	4	146	150
Piriton plus Tagamet (H_1+H_2)	0	9	141	150
Total	0	40	410	450

Total (H_1 + H_2) *versus* saline : χ^2 = 24.11 ($p < 0.005$). Fenistil® = dimethindene maleate; Piriton® = chlorpheniramine; Tagamet® = cimetidine. For further conditions, see SCHÖNING *et al.* [13].

Table IV. — Anaphylactoid reactions and other clinical symptoms in volunteers following H_1+H_2-blockade and isovolaemic haemodilution with classical polygeline

Reactions and symptoms	Incidence	
	H_1 + H_2 blockade	Saline premedication
Cutaneous reaction	0/25	3/25
Systemic reaction	0/25	6/25 *
Severity grade I + II	0/25	9/25 **
Flush	1/25	6/25
Feeling of heat	12/25	17/25
Metallic taste	2/25	5/25
Other qualities of taste	15/25	14/25

χ^2-test : * $p < 0.05$; ** $p < 0.01$. For further conditions, see [4, 9, 13].

a relatively large sample of 300 patients. Basal plasma histamine concentrations were in the normal range and did not rise to a pathological level (>1 ng · ml^{-1}) in any of the subjects [13]. In addition, no difference in plasma histamine levels could be detected between subjects with « no reaction » and those with a « cutaneous reaction ».

The most remarkable result of this trial in patients was the suppression of urticaria by H_1- and H_2-receptor antagonists.

2. Systemic anaphylactoid reactions to outdated polygeline (« classical » Haemaccel) in human volunteers

This clinical trial was the first study in human subjects with H_1- and H_2-receptor antagonists at a time when purified polygeline (Haemaccel 35) has not yet been developed. In those test subjects who received saline as « premedication » followed by a rapid infusion of classical polygeline, three cutaneous and six systemic reactions were observed. The overall incidence of adverse reactions was 9/25, *i.e.* 36 % ! In those volunteers who received the H_1- and H_2-blockade, no reactions occurred, not even a single spot of erythema or a single wheal and flare-response (table IV). Two of the six systemic reactions were quite severe : mild bronchospasm, generalized urticaria with great discomfort (blepharoedema, cough, sneezing, stuffy nose) and subjective fear for life in combination with tachycardia and mild hypertension.

The maximum plasma histamine levels in these two subjects were only about 2 ng · ml^{-1} (table V). However, they were pathological as well as all of the values in the four other subjects suffering from a systemic response. In the test group receiving the H_1- and H_2-blockade, seven volunteers released histamine to greater levels than in the control group, including two subjects with plasma histamine concentrations of 5 ng · ml^{-1}, at the top of the Bateman curve. Since in all previous studies (see especially [5, 7]), increasing plasma histamine levels to this order of magnitude always caused anaphylactoid reactions of a considerable severity, the complete prevention of any clinical signs and cardiovascular reactions in these subjects was very remarkable. The result of this trial justified the definition of histamine release as predominant in the adverse reaction to polygeline [2].

3. Life-threatening anaphylactoid reactions to outdated polygeline (« classical » Haemaccel)

For ethical reasons, this trial could be conducted only in experimental animals. All dogs except one reacted to « classical » Haemaccel by systemic histamine-release responses (table VI). More than half of them were life-threatening with falls in blood pressure of more than 100 mmHg.

H_1- and H_2-receptor antagonist premedication did not significantly change the extent of histamine release elicited by polygeline, but the hypotensive response was drastically reduced (table VI). On the average, the fall in blood pressure was completely prevented. In the least successful pretreatment, the blood pressure fall by 50 mmHg —a reaction which was well tolerated without any treatment and which disappeared after 20 min.

This was the first controlled trial which showed that life-threatening histamine-release is prevented by H_1- and H_2-blockade. Apparently, this type of prophylaxis could be successfully used in patients at risk of presenting a severe anaphylactoid and anaphylactic reaction.

Table V. — Tachycardia and hypertension following rapid infusion of classical polygeline in volunteers with systemic anaphylactoid reactions, but pretreated with placebo (saline) or H_1- + H_2-blockers

	Saline					H_1 + H_2-receptor antagonists			
N°	Plasma histamine level (ng · ml^{-1}) before	after	Hypertension (mmHg)	Tachycardia (c · min^{-1})	N°	Plasma histamine level (ng · ml^{-1}) before	after	Hypertension (mmHg)	Tachycardia (c · min^{-1})
3	0.1	1.25	10/5	12	2	0.3	1.8	0	0
16	0.2	1.8 *	20/10	26	17	0.3	5.1	0	0
41	0.3	1.2 *	0	23	21	0.25	1.5	0	0
44	0.6	1.0	0	22	22	0.2	4.95	0	0
47	0.25	1.05	0	0	25	0.1	3.05	0	0
48	0.1	1.0	0	16	28	0.5	1.05	5/5	0
					34	0.75	1.3	0	0
Total	0.25 (0.1-0.6)	1.15 (1.0-1.8)	2/6	5/6	Total	0.3 (0.1-0.75)	1.8 (1.05-5.1)	1/7	0/7

Numbers according to the course of the controlled trial. $\bar{x}$ (range) or incidences. Hypertension as systolic/diastolic pressure. * subjects suffering from a considerable, but in the doctor's opinion not life-threatening reaction. Significance in Fisher's exact test : $p < 0.05$ for tachycardia. Values given as maximum responses in plasma histamine, hypertension and tachycardia (1 min after the end of the polygeline infusion). For further conditions, see SCHÖNING *et al.* [13].

Table VI. — Prevention of severe, life-threatening anaphylactoid reactions in dogs following rapid infusion of classical polygeline by premedication with H_1- + H_2-receptor antagonists

Rank	Increase in histamine (ng/ml)		Hypotension (mmHg)	
	Saline	$H_1 + H_2$	Saline	$H_1 + H_2$
1	5.3	0	0	0
2	10.1	1.2	30	0
3	21.3	2.9	35	0
4	37.5	8.4	60	0
5	42.5	19.6	110	0
6	55.2	22.7	120	0
7	69.4	48.7	140	0
8	72.0	52.2	150	30
9	107.5	62.2	170	30
10	—	91.3	—	40
11	—	113.7	—	50
Median	42.5	22.7 *	110	0 **
(Range)	(5.3-107.5)	(0-113.7)	(0-170)	(0-50)

Investigators measuring blood histamine levels were not aware of the blood pressure responses. Investigators injecting the premedication did not know the composition of the fluid used in the syringes. Increase in blood histamine levels and hypotension (decrease in systolic blood pressure) are given for the time of maximum response (about 1-5 min after the end of the infusion). Statistical analysis using the Mann-Whitney test : saline *versus* $H_1 + H_2$; * Increase in histamine (not significant); ** Hypotension ($p < 0.01$). Note that the median is 0, which is different from the mean, but the frequency distribution of the values does not resemble a normal distribution.

4. Life-threatening anaphylactoid reactions to a reduced dose of compound 48/80 dissolved in Ringer's solution

To imitate life-threatening anaphylactoid reactions in surgical patients in the perioperative period with an experimental design in animals, a dog model was developed. In adult mongrel dogs of both sexes, barbiturate anaesthesia was maintained for two and a half hours; after an interval of 20 min for achieving homeostasis, 1/3 of the blood volume was taken by arterial bleeding and, after one minute, restored within 3 min by the same volume of Ringer solution. Compound 48/80 was dissolved in this solution at a concentration which in prior experiments had been shown to increase plasma histamine levels to the same extent as in life-threatening anaphylactoid reactions in man [10].

Dimethindene was given i.v. in the two doses of 0.1 and 0.5 mg · kg^{-1} together with cimetidine (5 mg · kg^{-1}). The time intervals between prophylaxis and the histamine-releasing event were 5 min (induction of anaesthesia), 60 min (minor surgery) and 120 min (major surgery). The time of application was 2 min for cimetidine (first) and 2 min for dimethindene (second).

Using saline as « premedication », a mid fall in blood pressure of 75 mmHg was obtained in the 12 dogs of the control group (fig. 1). This severe response was considered as life-threatening when compared to the clinical situation. Quite remarkably, however, the dose of compound 48/80 used in these experiments caused very variable histamine releases as measured by the plasma histamine levels (fig. 2). This was exactly what happens in clinical conditions when a drug is safe in most individuals, whilst causing severe side-effects in a minority of other subjects. For this reason, the reactions to 48/80 in the control group were considered as proof of the clinical relevance of the animal model.

The hypotensive reactions in all groups of the clinical trial were compiled in table VII. The premedication with H_1- and H_2-blockers did not prevent the fall in arterial blood pressure, but the severity of the reactions was so much reduced that H_1- and H_2-blockade was considered as sufficiently successful. On average, the hypotensive response to 48/80 was inhibited in the 5 min-interval group by 70 %, this being the same for the low and high doses of H_1-receptor antagonist. However, in the 60 min-interval group, the effect of H_1- and H_2-

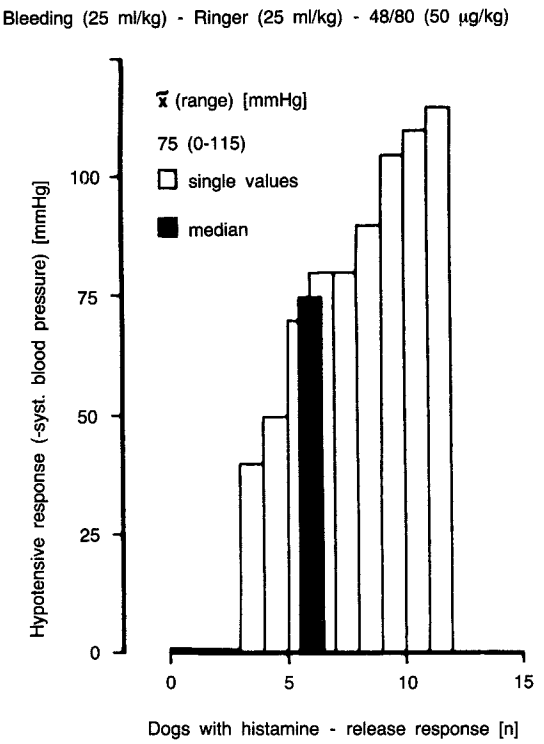

Fig. 1. — Hypotensive reactions in dogs during life-threatening anaphylactoid reactions following bleeding and rapid infusion of Ringer solution containing 50 µg · kg^{-1} 48/80. Single values from 12 dogs in the control group (saline as premedication, 5 min interval between placebo medication and bleeding of 1/3 of the blood volume, followed 1 min later by infusion of the same volume of Ringer solution within 3 min. For further conditions, see LORENZ *et al.* [10].

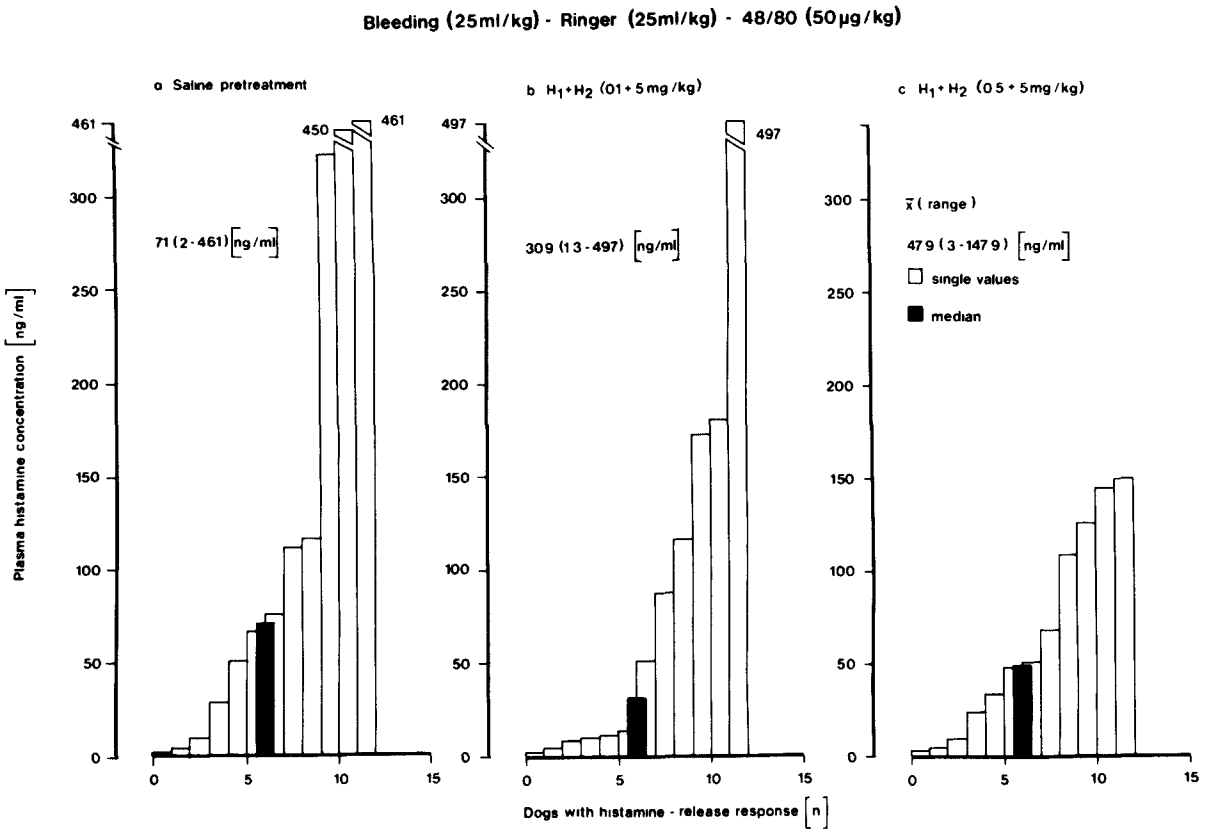

Fig. 2. — Plasma histamine levels in the first three groups of dogs in the controlled trial on life-threatening anaphylactoid reactions following bleeding and rapid infusion of Ringer solution containing 50 µg · kg^{-1} 48/80. Single values from 12 dogs in the control group and in two treatment groups. The differences in the plasma histamine levels in the three groups were statistically *not* significant using an analysis of variance for the whole study design. For further conditions, see figure 1 and LORENZ *et al.* [10].

Table VII. — Hypotension in dogs following H_1 + H_2-blockade and isovolaemic haemodilution with 25 ml · kg^{-1} Ringer solution containing 48/80 (50 µg · kg^{-1})

Time after premedication (min)	Hypotension (mmHg)		
	Saline	H_1 + H_2	H_1 + H_2
5	75 (0-115)	23 * (0-65)	28 * (0-70)
60	—	33 * (0-65)	15 * (0-90)
120	—	20 * (0-80)	8 ** (0-60)

Median values and range in 12 animals of each group. H_1 : dimethindene (0.1 or 0.5 mg · kg^{-1} i.v.), H_2 : cimetidine (5 mg · kg^{-1} i.v.). Statistical testing by analysis of variance : * $p < 0.05$ and ** $p < 0.01$. For further conditions, see LORENZ *et al.* [10].

Table VIII. — Plasma histamine levels in dogs following H_1 + H_2-blockade and isovolaemic haemodilution with Ringer solution containing 48/80

Time after premedication (min)	Plasma histamine level (ng · ml^{-1})		
	Saline	H_1 + H_2	H_1 + H_2
5	71 (2-461)	31 (1-497)	48 (3-148)
60	—	18 * (0.3-155)	14 * (3-94)
120	—	20 * (0.2-80)	9 ** (1-37)

Mean values and range in 12 animals of each group. H_1 : dimethindene (0.1 or 0.5 mg · kg^{-1} i.v.), H_2 : cimetidine (5 mg · kg^{-1} i.v.). Statistical testing by analysis of variance : * $p < 0.05$; ** $p < 0.01$. For further conditions, see LORENZ *et al.* [10].

blockade was not diminished —as expected from the data on the pharmacokinetics of the two drugs— but enhanced in the group with the higher dose of H_1-antagonist. This unexpected reaction was more pronounced in the 120 min-interval group and led to an inhibition of the hypotensive response to 48/80 by 90 % !

This tremendous attenuation of the life-threatening histamine-release response was explained by the data on plasma histamine levels which were obtained in the same controlled trial (table VIII). The histamine release due to 48/80 was reduced in all groups of the 60 min- and 120 min-intervals by H_1- and H_2-blockade. Thus, the H_1- and H_2-blockade showed a dual mechanism of action : blocking histamine at the receptors, and increasing with time the blocking of histamine release from mast cells.

In the 5 min-interval group, the hypotension elicited by 48/80 was diminished to such an extent that the blood pressure did not fall below 80 mmHg in any of the dogs. In one of the 60 min-interval and 120 min-interval groups, one of the dogs suffered from a fall in blood pressure below this critical value. Thus, reasonable protection against life-threatening reactions to 48/80 was achieved in 70 of 72 dogs, corresponding to 97 % of the animals.

Thus, premedication with dimethindene and cimetidine was shown to be effective enough to protect the individual against histamine-release responses of any degree of severity.

5. Analysis of the clinical relevance of the anti-H_1 + anti-H_2 trials (Discussion)

The question as to whether our patients need H_1- and H_2-blockade in the perioperative period as a new and additional premedication is a matter for clinical decision-making. Twenty-three trials in patients and volunteers showed an overall incidence of 30 % of anaphylactoid reactions of all grades of severity (table I) and about 1-5 % systemic and 0.1-0.5 % life-threatening reactions [10].

Anaphylactoid reactions and histamine-release responses are never considered as beneficial but are judged as unwanted effects, however to a different degree :

Skin rashes, flush and wheal or flare responses, even clinically classified as banal, are usually unpleasant, inconvenient and, because of itching, sometimes really tormenting. Thus, also, grade I severity reactions cannot be completely neglected, especially in the immediate postoperative period during which patients very often suffer considerably from itching.

Systemic anaphylactoid reactions are unwanted effects of drugs and treatments in the perioperative period, but the extent to which they are unwanted effects varies considerably from anaesthetist to anaesthetist, and the surgeon usually does not take care of them in any case. Discarding all histamine-releasing drugs and surgical manoeuvres at present is impossible, considering the tremendous number of different drugs and manipulations in surgery which elicit histamine release in the perioperative period. However, in the patient whit cardiovascular and respiratory risk any systemic reaction can be life-threatening, as shown in a case with Palacos implantation [10].

Prophylaxis with histamine H_1- and H_2-receptor antagonists was shown to be effective and safe and can therefore fill the gap between the present status of perioperative risks due to histamine release and the final aim of « histamine-free anaesthesia and surgery ».

6. Conclusion and recommendations

We think it is time to use the premedication to avoid unnecessary cases of death in surgical patients who have a higher risk of histamine-release responses than normal subjects or who suffer more than normal individuals from the effects of released histamine because they are old or poor-risk patients. For this reason, we do not longer hesitate in recommending H_1- and H_2-blockade for surgical patients who :

— have a case history of hypersensitivity reactions to intravenous agents (anaesthetics, analgesics, contrast media, plasma substitutes, etc.);

— have a history of atopy (hay fever, asthma, allergic food reactions), cardiac and/or pulmonary disease;

— will undergo a second drug exposure within a few days, even if there was no reaction the first time they received the drug;

— undergo surgery with a high risk of histamine release (transplantation, implantation of bone cement, extracorporeal circulation);

— are older than 70 years;

— are poor-risk patients with preoperative cardiac, respiratory or liver insufficiency and shock.

In a general hospital, these patients will comprise about 30 % of all patients admitted for surgery [9].

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