

# Prophylaxis of Anaphylactoid Reactions to a Polypeptidal Plasma Substitute by H<sub>1</sub>- plus H<sub>2</sub>-Receptor Antagonists: Synopsis of Three Randomized Controlled Trials\*

B. Schöning,<sup>1</sup> W. Lorenz,<sup>2</sup> and A. Doenicke<sup>3</sup>

<sup>1</sup> Department of Anaesthesia, Orthopedic Clinic, University of Heidelberg Schlierbacher Landstr. 200a, D-6900 Heidelberg, Federal Republic of Germany

<sup>2</sup> Department of Theoretical Surgery, Centre of Operative Medicine I, University of Marburg (Lahn)

<sup>3</sup> Department of Anaesthesia, Surgical OPC Clinic, University of Munich

**Summary.** To demonstrate the efficacy of a premedication with H<sub>1</sub>- + H<sub>2</sub>-receptor antagonists against histamine-release responses in anaesthesia and surgery 3 randomized controlled trials were conducted in patients, volunteers and experimental animals (dogs). Cutaneous anaphylactoid reactions following infusion of polygeline (Haemacel®) in orthopedic patients were successfully abolished by premedication with 0.1 mg/kg dimethpyrindene (Fenistil) and 5 mg/kg cimetidine (Tagamet). Chlorpheniramine (Piriton) was also useful, but dimethpyrindene was more effective in the doses recommended and used. Side-effects of the premedication were not observed when the 2 drugs were slowly administered (2 min each).

Systemic anaphylactoid reactions following infusion of polygeline were completely prevented in volunteers by the same premedication (0.1 mg/kg dimethpyrindene and 10 mg/kg cimetidine). Life-threatening reactions could not be tested in human subjects, but were elicited in experimental animals (dogs). In this species which resembles man in its sensitivity against histamine, in plasma histamine levels and in response to polygeline life-threatening reactions were prevented or in especially severe cases diminished to such an extent by the premedication with H<sub>1</sub>- + H<sub>2</sub>-blockers that this premedication was finally judged to be very effective against histamine-release responses of any grade of severity.

To confirm this clinically very important hypothesis more clinical trials in patients at risk for anaphylactoid reactions to drugs are urgently needed.

**Key words:** Premedication – Dimethpyrindene – cimetidine – Polygeline – Anaphylactoid reaction

**Prophylaxe von anaphylaktoiden Reaktionen durch ein Plasmasubstitut auf Polypeptidbasis mit Hilfe von H<sub>1</sub>- plus H<sub>2</sub>-Rezeptorantagonisten: Synopse von drei randomisierten kontrollierten Studien**

**Zusammenfassung.** Um die Wirksamkeit einer Prämedikation mit H<sub>1</sub>- + H<sub>2</sub>-Rezeptorantagonisten gegen Histaminfreisetzungssreaktionen während Narkose und Operation

nachzuweisen, wurden drei randomisierte kontrollierte Studien bei Patienten, Probanden und Versuchstieren (Hunden) durchgeführt. Cutane anaphylaktoide Reaktionen nach Infusion von Polygeline (Haemacel) wurden bei orthopädischen Patienten durch Prämedikation mit 0.1 mg/kg Dimethpyrinden (Fenistil) und 5 mg/kg Cimetidin (Tagamet) nahezu vollständig verhindert. Der H<sub>1</sub>-Blocker Chlorpheniramin (Piriton) war ebenfalls wirksam, aber es war dem Dimethpyrinden in der empfohlenen Dosis an Wirksamkeit unterlegen. Nebenwirkungen der Prämedikation wurden bei langsamer Applikation (2 min) nicht beobachtet.

Systemische anaphylaktoide Reaktionen nach Infusion von Polygeline wurden bei Versuchspersonen durch dieselbe Prämedikation (0.1 mg/kg Dimethpyrinden und 10 mg/kg Cimetidin) vollständig verhindert. Lebensbedrohliche Reaktionen konnten am Menschen nicht geprüft werden, wohl aber beim Hund. Dieselbe Prämedikation wie in den beiden vorangehenden Studien (1 mg/kg Dimethpyrinden und 5 mg/kg Cimetidin) war außerordentlich erfolgreich und verhinderte in jedem Falle eine lebensbedrohliche Situation. Im Mittel wurden die klinischen Symptome der Histaminfreisetzungssreaktion sogar vollständig unterdrückt.

Es wird geschlossen, daß eine Prämedikation mit H<sub>1</sub>- plus H<sub>2</sub>-Rezeptorantagonisten wirksam genug ist, um auch beim Patienten Histaminfreisetzungssreaktionen aller Schweregrade zu verhindern oder soweit zu verringern, daß sie für den Patienten keine Gefährdung mehr darstellen. Zur Erhärtung dieser Schlußfolgerung sind weitere klinische Studien an Risikopatienten erforderlich.

**Schlüsselwörter:** Prämedikation – Dimethpyrinden – Cimetidin – Polygeline – anaphylaktoide Reaktion

## Rationale of Testing a Premedication with H<sub>1</sub>- plus H<sub>2</sub>-Receptor Antagonists

To prove the effectiveness of a H<sub>1</sub>- and H<sub>2</sub>-receptor antagonist premedication in reducing or eliminating histamine-induced adverse reactions, a controlled clinical trial [3, 4, 9, 13, 14, 20] must fulfil some very important conditions (Table 1). These include the patient's safety since severe side-effects are likely to occur [2, 14, 15] and the elucidation of the problem as quickly as possible with a minimum of

\* Supported by Grant of Deutsche Forschungsgemeinschaft (Lo 199/10 and Lo 199/13-6)

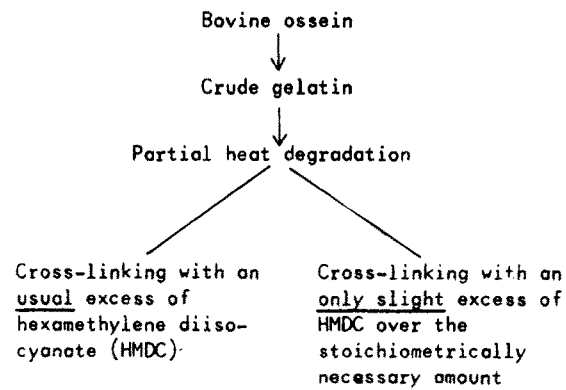
Offprint requests to: Dr. B. Schöning (address see above)

**Table 1.** Requirements for a histamine releaser to study the efficacy of H<sub>1</sub>- and H<sub>2</sub>-receptor antagonists in clinical trials

Clinically important and widely used
No alternative drug available
Utmost safety provided
Reasonably pure and chemically defined
No other drug, solvent or treatment interfering
Release of histamine predominant, no other mediator interfering
Incidence reasonably high in clinical situations
Mechanisms of release sufficiently investigated and rather uniform

subjects to be exposed to risk in an extremely complex situation which is typical for most clinical conditions.

Considering these criteria the best known groups of histamine releasers selected for trial purposes all possess advantages and disadvantages (Table 2). Of the muscle relaxants, anaesthetics and colloidal plasma substitutes polygeline (Haemaccel, Behringwerke Marburg, FRG) comes in for closer consideration as it is, compared to 48/80, a relatively weak histamine releaser, can be administered before anaesthesia and independent of other drugs [12]. Dextran, hydroxyethyl starch and human albumin should be excluded. Dextran elicits no unequivocal histamine release in man under clinical conditions, but induces a rather complex immunological event [2b]. For hydroxyethyl starch and human albumin the pathomechanisms are not known [17]. Polygeline was most intensely studied [6, 11]. Histamine release was shown to be the *predominant* cause of its adverse reactions, and the mechanism of this seems not to involve immunological processes and appears to be very uniform [1, 10, 17]. As Fig. 1 shows contained "classical" polygeline a defined, but according to our present knowledge a too great excess of cross-linking material which is converted into hexamethylene diamine. This compound releases histamine [10, 17]. When this was established in animals and in man, the product has been improved by reducing the amount of cross-linking material so that in a con-

**Fig. 1.** Procedure for preparation of "classical" and "purified" polygeline (Haemaccel). For details see Lorenz et al. [10]

trolled trial of the currently marketed "purified" polygeline in 450 patients, severe (i.e. systemic) anaphylactoid reactions could no longer be observed [16]. By this way the mechanism of histamine release by polygeline in man was further confirmed.

Using both "classical" and "purified" polygeline in human subjects and in animals we were able to test the efficacy of H<sub>1</sub>- and H<sub>2</sub>-receptor antagonists in anaphylactoid reactions (histamine-release responses) to polygeline in all three grades of severity (Table 3). Only controlled clinical trials (randomized, prospective, cohort and single or doubleblind depending on the data used) were conceived and conducted [20]. For ethical reasons this was only possible because the trials with "classical" polygeline were carried out first – at a time when "purified" polygeline was not yet available. With the latter formulation which has been developed in the course of our studies with this plasma substitute in cooperation with the company [10] only a clinical trial on cutaneous anaphylactoid reactions was carried out. For purposes of illustration, however, the time sequence of the three trials is converted: We start with the last one dealing with cutaneous reactions, proceed to the second dealing with systemic responses and describe finally the animal study which was conducted several years before, but includes really very severe reactions which have been found in patients only on rare occasions (see Lorenz et al. [12]

**Table 2.** Advantages and disadvantages of histamine releasers to be used in clinical trials on the efficacy of H<sub>1</sub>- and H<sub>2</sub>-receptor antagonists

Compounds	Advantages	Disadvantages
48/80	Classical liberator, mechanism investigated	No clinical indication
Dextran	Classical liberator, mechanism investigated in animals and cells	No effective releaser in clinical conditions, mechanisms not uniform
Muscle relaxants	Clinically important and widely used	Applied in combination with other drugs
Anaesthetics	Clinically important and widely used	Mechanism not uniform, solvents interfering
Contrast media	Clinically important, high incidence	Histamine release not predominant, mechanisms not clear
Aspirin	Clinically important and widely used	Histamine release not predominant, mechanisms not clear
Polygeline (Haemaccel)	Clinically important and widely used, not interfering with other drugs, histamine release predominant	Classical polygeline no longer applicable, purified polygeline no longer effective

**Table 3.** Classification of histamine-release responses by severity as a special form of anaphylactoid reaction to drugs (for details of definition and classification see Lorenz et al. [12])

Severity grade	Clinical symptoms and groups of symptoms	Operational criteria	Plasma histamine [ng/ml]
I. <i>Cutaneous</i> anaphylactoid	Erythema, urticaria and/or dermal pruritus <i>only</i>	Not considered as threatening No intensified observation, no treatment	≤ 1 ng/ml
II. <i>Systemic</i> anaphylactoid	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
III. <i>Life-threatening</i> anaphylactoid	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

**Table 4.** Synopsis of randomized controlled trials on prevention of anaphylactoid reactions to polygeline by premedication with histamine H<sub>1</sub>- and H<sub>2</sub>-receptor antagonists

Trial No.	Severity of reaction	Histamine releaser (Polygeline)	H <sub>1</sub> - + H <sub>2</sub> -receptor antagonists [mg/kg i.v.]	Frame of the trial
1	Cutaneous anaphylactoid	Purified 7 ml/kg, 10–15 min	H <sub>1</sub> : Fenistil 0.1 Piriton 0.3 H <sub>2</sub> : Tagament 5.0	Randomized controlled single and double-blind 450 patients, Heidelberg 1979/80
2	Systemic anaphylactoid	Classical 7 ml/kg, 3 min	H <sub>1</sub> : Fenistil 0.1 H <sub>2</sub> : Tagamet 10.0	Randomized controlled single and double-blind 50 volunteers, Munich 1977
3	Life-threatening anaphylactoid	Classical and purified 20 ml/kg, 3 min	H <sub>1</sub> : Fenistil 1.0 H <sub>2</sub> : Tagamet 5.0	Randomized controlled 40 dogs, Marburg 1977

in this issue). We will be able to show that even these very severe reactions can be successfully prevented by a premedication with H<sub>1</sub>- and H<sub>2</sub>-receptor antagonists.

## Materials and Methods

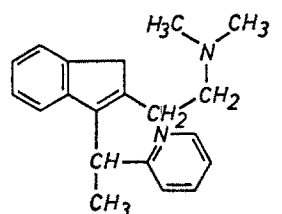
The synopsis of the three randomized controlled trials is compiled in Table 4, the details will be given in the following sections. The structural formulae of the H<sub>1</sub>- and H<sub>2</sub>-receptor antagonists mostly used in this communication are shown in Fig. 2.

### Trial 1: Cutaneous Anaphylactoid Reactions [16]

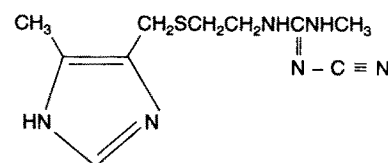
A protective, cohort, randomized, partly single-blind (clinical symptoms), partly double-blind (plasma histamine) placebo-controlled clinical trial was performed in 450 orthopaedic patients in Heidelberg in 1979/80. The aims of the study were to test whether cutaneous and systemic anaphylactoid reactions to polygeline could be prevented by premedication with H<sub>1</sub>- and H<sub>2</sub>-receptor antagonists. However, only one of the two questions could be answered at the end of the study since due to "purification" of polygeline only cutaneous anaphylactoid reactions occurred in the control group and plasma histamine levels never exceeded 1 ng/ml plasma indicating that also in the H<sub>1</sub>- and H<sub>2</sub>-receptor antagonist pre-treated groups no pathological plasma histamine levels [12] were produced by polygeline.

Premedication and polygeline were administered before general anaesthesia and operation. No further premedication was applied at the day of operation 2 h before the specific premedication and polygeline were administered.

The 450 patients comprised both sexes, divided into 5 classes of age (20–≥ 60 years, 30 patients in each class) according to Schönig and Koch [13]. The patients were without exception due to



H<sub>1</sub>-receptor antagonist  
dimethpyrindene (Fenistil)



H<sub>2</sub>-receptor antagonist  
cimetidine (Tagamet)

**Fig. 2.** Structural formulae of dimethpyrindene and cimetidine, the two mostly used H<sub>1</sub>- and H<sub>2</sub>-blocker in this communication

undergo elective surgery during the morning or early afternoon. Casualty and outpatients as well as emergency cases were excluded. The study had 2 test groups and 1 control group. Test group 1 received the H<sub>1</sub>-blocker dimethpyrindene (Fenistil, Zyma-Blaes GmbH Munich, FRG) and the H<sub>2</sub>-blocker cimetidine (Tagamet, SK&F Dauelsberg, Munich-Göttingen, FRG). Test group 2 re-

ER Auswirkung einer H<sub>1</sub>+H<sub>2</sub>-Rezeptorenblockade auf Nebenwirkungen prä-  
narkotischer Haemacel-Infusion bei orthop. Pat. Schöning/Lorenz. Or-  
thon.-Univ.-Klinik Heidelberg, VP79/HG, F92:29.3.79.

Kartenart ☐ 1  
Name..... ☐ 3  
Alter (Jahre) ☐ 4  
Geschlecht (1=M, 2=F) ☐ 7  
Gewicht (kg) ☐ 8  
Narkoserisiko ☐ 18

Gehirn ☐ 9 Allergie ☐ 18  
Querschn. ☐ 10 Endokri ☐ 19  
Resp. ☐ 11 PCP ☐ 20  
Herz ☐ 12 Anämie ☐ 21  
Hyperton ☐ 13 Wasser ☐ 22  
Leber ☐ 14 Elektrol ☐ 23  
Niere ☐ 15 Septisch ☐ 24  
Diabet ☐ 16 Tumor ☐ 25  
Adeps ☐ 17 Sonstg. ☐ 26

Prämedikationsgruppe 1=C15+CP0,3; ☐ 27  
2=NaCl (5ml)x2; 3=C15+Fe0,1;  
Charge (1-10) ☐ 29  
Zufallszahl ☐ 34  
Op Datum ☐ 40  
Krankenbl. Nr. ☐ 46

Uhrzeit VB ☐ 50  
Puls VB ☐ 53  
RR VB ☐ 59  
Reaktion H1 ☐ 60  
Reaktion H2 ☐ 61  
Flush H1/H2 ☐ 62  
Uhrzeit IB ☐ 66  
Puls IB ± 0 ☐ 69  
Puls IB ± 5 ☐ 72  
Puls (\*) IB ± 10 ☐ 75  
RR (\*) IB ± 10 ☐ 81  
Uhrzeit IE ☐ 85

Pathergie auf H<sub>6</sub> (0=nein; ☐ 86  
1=ja; 2=bis 4=VA)  
Pathergie auf H<sub>6</sub> Ausmaß ☐ 87  
(0=keine; 1=nur Haut;  
2=systemisch; 3=1+2)  
Pathergie auf H<sub>6</sub> Richtung ☐ 88  
(0=keine; 1=nur Haut;  
2=Puls > 20AW; 3=Puls > 20  
AW+Klin. Sympt.; 4=Puls >  
20AW+Hypotension; 5=KS  
Schock, Brochospasmus; 6=  
Sonstiges)

Pathergie auf H<sub>6</sub> :Haut-  
Symptome ☐ 89  
Solitärquaddel ☐ 91  
Quaddel-Anzahl ☐ 93  
Regionen-Anzahl ☐ 94  
Quaddel-Nester ☐ 95  
Erytheme-1/Fush=2 ☐ 96  
Urticaria ☐ 97  
Generalisation ☐ 98  
Jucken/Brennen ☐ 99  
Geschmacksirritation ☐ 100

Pathergie auf H<sub>6</sub>: systemisch ☐ 101  
Tachycardie > 20 AW ☐ 103  
Herz (\*) = 1, WDT (\*) = 2 ☐ 104  
Hypotonie < 40 mmHg ☐ 105  
Resp-Trakt (\*) ☐ 106  
Bronchospasmus ☐ 107  
Schmerzen (\*) = 1, ZNS (\*) = 2 ☐ 108  
Schock ☐ 109  
Sonstiges ☐ 110

Laboraten Schlüssel-Nr/ng-nl ☐ 111  
VB ± (bis 10) ☐ 112  
VB ± 0 ☐ 113  
IB ± 5 ☐ 114  
IB ± 10 ☐ 115

Fig. 3. Photograph of the original EDA protocol used in trial 1 on cutaneous anaphylactoid reactions. For development of this questionnaire see Lorenz et al. [12]

ceived the H<sub>1</sub>-blocker chlorpheniramine (Piriton, Allen & Hanburys, London, UK) and the H<sub>2</sub>-blocker cimetidine. The control group received the same volume of saline as used for the two drug applications in the test groups before the infusion of polygeline. Dimethpyrindene (0.1 mg/kg) was given i.v. in a volume of 20 ml within exactly 2 min, chlorpheniramine (0.3 mg/kg) and cimetidine (5 mg/kg) were administered i.v. in the same volume and in exactly the same time. Cimetidine was always applied *before* the H<sub>1</sub>-blocker as described in a previous communication [9].

Fifteen min after starting the premedication polygeline (Haemacel) was infused in a dose of 500 ml/patient over 10 min. 10 batches produced in January 1979 were randomly applied. Anaesthesia started 30 min after beginning the infusion. The clinical symptoms or physical alterations caused by the reactions were recorded or measured using a fixed EDA protocol (Fig. 3). Furthermore pulse rate, blood pressure and plasma histamine concentrations (in the saline and in the cimetidine-dimethpyrindene group) were measured. For plasma histamine 3 blood samples were taken at fixed intervals – before premedication as well as 5 and 10 min after the beginning of the infusion. Plasma was prepared already in the operation theatre in a Christ Minifuge according to Lorenz et al. [5] and histamine was measured fluorometrically as described in [5]. Quality control samples were included in every run and control charts were used as mentioned in [12].

#### Trial 2: Systemic Anaphylactoid Reactions [9]

A prolective, cohort, randomized, single-blind (clinical symptoms) and double-blind (plasma histamine) placebo-controlled trial was performed in 50 male, healthy volunteers (Table 5) in Munich (July 1977). The aim of the study was to test whether the combined i.v. administration of dimethpyrindene and cimetidine could prevent systemic anaphylactoid reactions following i.v. infusion of classical polygeline (Table 4).

Table 5. Attributes of the 50 volunteers in trial: Systemic anaphylactoid reactions

Attributes of the volunteers	Groups for pretreatment	
	Saline (n = 25)	H <sub>1</sub> + H <sub>2</sub> - blocker (n = 25)
Age (years, $\bar{x}$ (1st–3rd quartile))	25 (22–28)	24 (22–26)
Weight (kg, $\bar{x}$ (1st–3rd quartile))	74 (70–82)	72 (67–75)
Profession (S–NM, S–M, others)	12/11/2	13/8/4
Allergy – now (yes/no)	8/17	15/10
Allergy – more than 9 months ago (yes/no)	7/18	9/16

Professions: S–NM = student, non-medical, S–M = medical students, others = other professions (see [7])

Dimethpyrindene (0.1 mg/kg) and cimetidine (10 mg/kg) or saline as placebo solution were randomly applied to the volunteers (first cimetidine in 20 s, 10 s later dimethpyrindene in 2 min).

10 min later the plasma substitute was applied without any other medication following blood donation of 440 ml. The dose was 500 ml/volunteer corresponding to about 7 ml/kg on the average, the infusion time was 3 min. Two batches of Haemacel were randomly applied including the product numbers Op 3939 and Op 3946. Random assignment of the volunteers to the premedication and polygeline groups was performed always by using random digits. The clinical symptoms of the reactions were recorded by a specified questionnaire [7] which has been published as an original protocol in Lorenz et al. [12]. Heart rate (lead II in ECG), blood pressure (sphygmomanometric) and plasma histamine (fluorometric) were determined as described in detail in three previous communications [7, 9, 12]. Blood was taken for plasma histamine assays twice before injecting the antagonists, 3 min after their application and again 1, 5, 10 and 20 min after the end of the polygeline infusion. Top plasma histamine levels were chosen to define the extent of the histamine release [12].

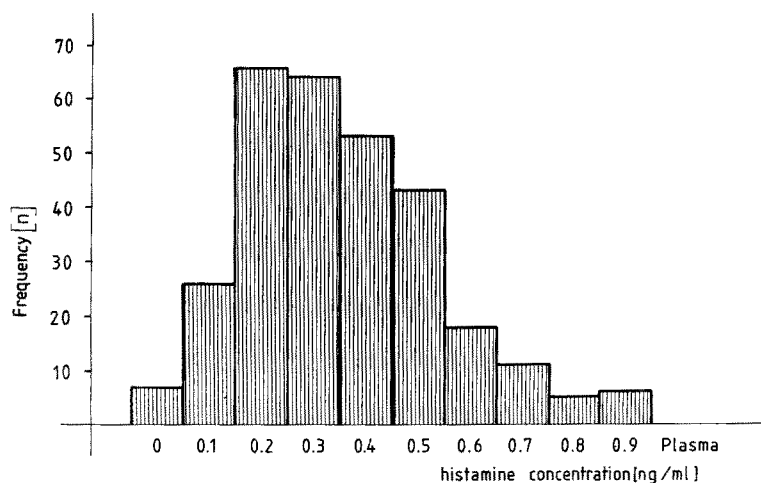
The observation period was confined to 60 min. In cases of systemic anaphylactoid reactions to polygeline stop of infusion was mandatory. Treatment included oxygen, sympathicomimetics, prednisolone, H<sub>1</sub>-receptor antagonists and orciprenaline. For further conditions and ethical considerations see in detail Lorenz et al. [12].

#### Trial 3: Life-threatening Anaphylactoid Reactions [8]

A prolective, cohort, randomized trial was conducted in 40 adult mongrel dogs of both sexes weighing 22–32 kg. The animals were kept separately in cages for a few days, were vaccinated against distemper, leptospirosis and canine hepatitis by Candur SHL (Behringwerke Marburg) and fed by standard food (Nagut-Vibromix, Dr. Müller, Lage, FRG) and tap water ad libitum.

The aim of the study was to test whether the combined application of dimethpyrindene and cimetidine could prevent life-threatening anaphylactoid reactions following rapid infusion of classical polygeline. Since “purified” polygeline was expected not to cause histamine release neither anaphylactoid reactions nor any histamine release or any other side-effects of the premedication and the polygeline infusion should have been observed (additional control groups in the trial!) (Table 4).

The dogs were anaesthetized with 15–25 mg/kg pentobarbitone i.v. and breathed room air spontaneously after intubation. Three



**Fig. 4.** Plasma histamine levels in orthopedic patients before premedication. 300 patients were investigated, (1 plasma was lost),  $n=299$ .  $\bar{x}=0.35$  ng/ml, range=0–0.9 ng/ml

polyethylene catheters were inserted, one into the v. cava inferior (infrahepatic) via the right femoral vein for infusing the plasma substitute and collecting the blood for *whole blood* histamine determination. Whole blood histamine assay is easier than plasma histamine assay, and in dogs whole blood histamine determinations can replace plasma histamine determinations since dogs have a very low whole blood histamine level due to a very small number of basophils [8, 11]. The other two catheters were inserted both into the aorta, one for measuring the arterial blood pressure by a Statham pressure transducer and Hellige compensograph, the other for a rapid bleeding (for details see Vars et al. [19] and Messmer et al. [12a]. After these manipulations the animals were allowed to recover for 20 min [18].

Dimethpyrindene (1 mg/kg) and cimetidine (5 mg/kg) or saline as a placebo solution were administered i.v. (first cimetidine in 20 s, 10 s later dimethpyrindene in 2 min!). After 10 min 20 ml/kg blood were removed and 1 min later replaced by the same volume of polygeline within 3 min. 2 batches of classical polygeline (Op 3939, Op 3946) and 2 batches of purified polygeline (V-244 and V-265) were administered. Again the animals were assigned to any of the pretreatment or polygeline groups by random digits.

Clinical symptoms were assessed by 2 observers, the blood pressure (systolic, diastolic) was continuously monitored and blood histamine levels were determined by the combined fluorometric assay of Lorenz and Doenicke [8]. 5 ml blood were taken twice before premedication, 3 min after premedication and 1, 5, 10, 20 and 30 min after polygeline infusion. Histamine levels were always expressed as top levels according to Lorenz et al. [12, 18].

## Results

### *Trial 1: Cutaneous Anaphylactoid Reactions [16]*

It was not intended in this trial to study *only* cutaneous anaphylactoid reactions. In contrast, however, to the now outdated formulations of Haemaccel [9, 12, 13] “purified” polygeline [10] did not elicit any systemic anaphylactoid reaction in the patients, neither in the test groups nor in the control groups receiving only saline as a “premedication” (Table 6). This considerable improvement of the drug could be demonstrated by calculating the confidence intervals for the incidences of systemic reactions in the 3 samples hitherto investigated (0(0–2.4%)/150 patients (this paper), 30(3.4–7.1%)/600 patients [9, 12] and 9(2.7–11.2%)/150 patients [13].

There were, however, still cutaneous anaphylactoid reactions. They did not have a detectable clinical significance since they consisted only of wheals of 2–3 mm diameter

**Table 6.** Cutaneous anaphylactoid reactions in patients receiving 3 kinds of premedication and subsequent infusion of “purified polygeline”

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 Tagmet ( $H_1 + H_2$ )	0	9	141	150
Total	0	40	410	450

Total ( $H_1 + H_2$ ) versus saline:  $\chi^2=24,11$  ( $p<0.005$ )

**Table 7.** Quantification of cutaneous anaphylactoid reactions in patients receiving 3 kinds of premedication and subsequent infusion of “purified polygeline”

Premedication	Number of wheals/Patient reacting with a cutaneous anaphylactoid reaction		
	$\leq 5$	$> 5$	Total
Saline	12	15	27
Fenistil plus Tagamet	4	0	4
Piriton plus Tagmet	7	2	9
Total	23	17	40

(Table 7). The incidence of this banale histamine-release response [12] to polygeline was less than in previous studies [9, 12], but still 18%. However, by premedication with  $H_1$ -plus  $H_2$ -receptor antagonists it was drastically reduced, not only in the overall number of reactions (Table 6), but also in the “severity” of the residual ones (Table 7). Fenistil in the dose used was superior to Piriton in the dose used both of them being recommended by the corresponding companies.

**Table 8.** Medians of plasma histamine levels before premedication and after infusion of "purified polygeline" (plasma samples of one patient were lost)

Response to polygeline	N	Plasma histamine level (ng/ml)		
		Before premedication	After start of infusion	
			5 min	10 min
No reaction	259	0.35	0.3	0.4
Cutaneous reaction	40	0.3	0.35	0.4

**Table 9.** Systemic anaphylactoid reactions in volunteers receiving 2 kinds of premedication and subsequent rapid infusion of "classical" polygeline

$H_1 + H_2$ versus saline: $\chi^2 = 4.76$ ( $p < 0.05$ )			
Premedication	Reactions systemic anaphylactoid		
	yes	no	Total
Saline	6	19	25
Fenistil plus Tagamet	0	25	25
Total	6	44	50

In agreement with previous extended studies [6, 8, 11, 12] the basal plasma histamine levels in all patients were within the normal range (Fig. 4). In the literature never a sample size of about 300 subjects was investigated. Thus this was the first study which showed in a statistically convincing manner that the basal plasma histamine level was *not* normally distributed, that the range was  $< 0.1$  ng–0.9 ng/ml and the median was about 0.3 ng/ml. Again in agreement with a previous study [12] the plasma histamine

concentration did not attain a pathological level of  $> 1$  ng/ml. On the average it was not different from the pre-infusion level (Table 8). In addition, no difference in plasma histamine levels could be detected between subjects with "no reaction" and those with "cutaneous reaction" (Table 8).

#### *Trial 2: Systemic Anaphylactoid Reaction [9]*

In volunteers receiving saline as a "premedication" followed by a rapid infusion of classical polygeline 6 systemic and 9 cutaneous anaphylactoid reactions were observed. None of them occurred in subjects of the test group pretreated by dimethpyrindene and cimetidine (Table 9). Two of the 6 systemic histamine-release responses had a considerable severity [7]: mild bronchospasm, generalized urticaria with great discomfort (blepharodema, cough, sneezing, stuffy nose) and subjective fear for life occurred along with tachycardia and mild hypertension.

It was remarkable that the maximum plasma histamine levels in these two subjects were only about 2 ng/ml (Table 10). However, also in the 4 other volunteers developing systemic reactions following polygeline pathological plasma histamine concentrations ( $> 1$  ng/ml) were detected supporting the definition and classification of histamine-release responses described by Lorenz et al. [12]. In the test group receiving  $H_1$ - and  $H_2$ -receptor antagonists 7 volunteers reacted by histamine release following polygeline infusion. The extent of release was even greater than in the control group including 2 subjects with plasma histamine values of 5 ng/ml. Since in a series of previous studies [6, 11, 12] increases of plasma histamine levels in this order of magnitude always caused considerable systemic anaphylactoid reactions to polygeline the *complete prevention of any clinical signs and circulatory reactions* in these volunteers seemed very remarkable.

Tachycardia as the most sensitive parameter of systemic histamine-release response [12] was present in 5 of the 6 volunteers with placebo premedication and histamine release by polygeline (Table 10). However, none of the subjects receiving  $H_1 + H_2$ -receptor antagonists showed any increase in heart rate ( $> 5$  beats/min).

**Table 10.** Tachycardia and hypertension following rapid infusion of "classical" polygeline in volunteers with systemic anaphylactoid reactions, but pretreated with placebo (saline) or dimethpyrindene and cimetidine

No name	Saline				No. name	H <sub>1</sub> + H <sub>2</sub> -receptor antagonists				
	Plasma histamine level (ng/ml)		Hyper- tension (mm Hg)	Tachy- cardia (beats/min)		Plasma histamine level (ng/ml)		Hyper- tension (mm Hg)	Tachy- cardia (beats/min)	
	before	after				before	after			
3 M.S.	0.1	1.25	10/5	12	2 W.J.	0.3	1.8	0	0	
16 D.P.	0.2	1.8 <sup>a</sup>	20/10	26	17 D.H.	0.3	5.1	0	0	
41 M.W.	0.3	2.2 <sup>a</sup>	0	23	21 B.K.	0.25	1.5	0	0	
44 V.M.	0.6	1.1	0	22	22 R.C.	0.2	5.0	0	0	
47 S.R.	0.25	1.2	0	0	25 K.J.	0.1	3.1	0	0	
48 P.K.	0.1	1.1	0	16	28 D.M.	0.5	1.1	5/5	0	
—	—	—	—	—	34 T.A.	0.75	1.3	0	0	
Total	0.25 (0.1–0.6)	1.25 (1.1–2.8)	2/6	5/6	Total	0.3 (0.1–0.75)	1.8 (1.1–5.1)	1/7	0/7	

Numbers according to the course of the controlled clinical trial.  $\bar{x}$  (range) or incidences Hypertension as systolic/diastolic pressure

<sup>a</sup> Subjects suffering from a considerable, but not life-threatening reaction

Significance in Fisher's exact test  $p < 0.05$  for tachycardia

**Table 11.** Prevention of severe, life-threatening anaphylactoid reactions in dogs following rapid infusion of "classical" polygeline by premedication with H<sub>1</sub>- and H<sub>2</sub>-receptor antagonists

Rank	Increase in histamine [ng/ml]		Hypotension [mm Hg]	
	Saline	H <sub>1</sub> + H <sub>2</sub>	Saline	H <sub>1</sub> + H <sub>2</sub>
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 <sup>a</sup>	110	0 <sup>b</sup>
(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<sub>1</sub> + H<sub>2</sub>

<sup>a</sup> Increase in histamine not significant

<sup>b</sup> Hypotension  $p < 0.01$

### Trial 3: Life-threatening Anaphylactoid Reactions [8]

All dogs except one reacted to "classical" polygeline by a systemic histamine-release response (Table 11). More than half of them were life-threatening, with hypotensive reactions of more than 100 mm Hg. The time course of such Haemaccel shocks both with regard to blood pressure and whole blood histamine changes had been illustrated by Messmer et al. [12a], demonstration of curves was therefore omitted in this communication.

Instead of plasma histamine levels whole blood concentrations were measured in dogs (for reasons see Materials and Methods). An increase by about 40 ng/ml whole blood corresponded to about 10 ng/ml plasma (Fig. 6 in Lorenz et al. [22]) which in human subjects caused life-threatening anaphylactoid reactions, too [12]. The premedication by H<sub>1</sub> + H<sub>2</sub>-receptor antagonists did not change significantly the extent of histamine release elicited by "classical" polygeline (Table 11). About half of the blood histamine concentrations were higher than 40 ng/ml in the saline and the H<sub>1</sub> + H<sub>2</sub>-group.

In contrast to that, however, was the hypotensive response to polygeline drastically reduced by premedication with H<sub>1</sub> + H<sub>2</sub>-receptor antagonists (Table 11). *On the average, the blood pressure decrease was completely prevented.* In the least successful pretreatment it was diminished to 50 mm Hg (Table 11) – a hypotension which was well tolerated by the animal and which disappeared after 20 min.

Infusion of "purified" polygeline did not elicit any life-threatening anaphylactoid reaction in dogs – either pretreated by saline or by H<sub>1</sub> + H<sub>2</sub>-receptor antagonists. There was only a slight hypotension of 40 mm Hg in one animal

in the saline group and no hypotension at all in the H<sub>1</sub> + H<sub>2</sub>-group. In each group only one animal showed an increase in blood histamine levels, 1.9 ng/ml in the saline group and 1.1 ng/ml in the H<sub>1</sub> + H<sub>2</sub>-group. Thus there was no indication that pretreatment with dimethpyridine and cimetidine either altered the histamine release [2a] nor had an influence on the catabolism of the released histamine [18].

### Discussion

Histamine liberation by drugs used in anaesthesia and surgery was demonstrated now in patients, volunteers and experimental animals in *clinical conditions* [6–12]. There is a tremendous variety of substances which elicit histamine-release responses as adverse reactions. Hitherto we do not know how dangerous an *average* reaction [12] is for the intra- and postoperative period of an individual patient. There is, however, no doubt that some of the reactions are life threatening [12] and some of them also end with the immediate death of the patient [2].

Three questions arise from these clinical observations: (1) Is the incidence of histamine release *high* in patients during routine anaesthesia and surgery? The 3 controlled trials in this communication give only a limited answer to this very urgent question. (2) Can the clinical effects of histamine release be prevented by a premedication with H<sub>1</sub> + H<sub>2</sub>-receptor antagonists? We suggest that this problem has been solved very convincingly with polygeline (Haemaccel) as a prototype substance. (3) Are there any side-effects of such a premedication? We suggest that from the data accumulated in the three trials and in a previous study [9] it became apparent that with dimethpyridine as an H<sub>1</sub>-receptor antagonist and cimetidine as an H<sub>2</sub>-receptor antagonist in the doses and the *speed of administration* used in man this question also can be answered in favour of the H<sub>1</sub> + H<sub>2</sub>-blockade. In the first trial in 450 patients 300 were pretreated by H<sub>1</sub>- and H<sub>2</sub>-receptor antagonists. No cardiac arrhythmia, no other side-effects were observed when the H<sub>1</sub>- and H<sub>2</sub>-receptor antagonists were injected *slowly* each in 2 min [9, 10, 16]. Chlorpheniramine (Piriton) and cimetidine, but not dimethpyridine (Fenistil) released histamine in volunteers when the drugs were administered as a bolus injection [9]. Dimethpyridine can replace chlorpheniramine, but for cimetidine (one of the best investigated drugs in our time) hitherto there is no better alternative. Ranitidine also elicits histamine release when applied as a bolus injection in human volunteers [11].

The premedication with H<sub>1</sub>- and H<sub>2</sub>-receptors antagonists was effective against cutaneous anaphylactoid reactions elicited by histamine release. It was, however, necessary to use the antihistaminic drugs for prophylaxis. Treatment of the reactions by H<sub>1</sub> + H<sub>2</sub>-blockade proved to be unsuccessful [7]. Systemic anaphylactoid reactions by polygeline in human volunteers also could be prevented completely by premedication with H<sub>1</sub>- and H<sub>2</sub>-receptor antagonists. There is, however, no evidence that patients in general and especially patients at risk (advanced age, tumors or septic complications, respiratory and cardiac insufficiency) can be protected from the effects of released histamine with the same efficacy as healthy volunteers. The results of trial 2 seemed to be very promising, but *more* clinical trials are needed to establish the high efficacy of an H<sub>1</sub> + H<sub>2</sub>-blockade against histamine mediated adverse reactions.

Life-threatening reactions could not be produced in volunteers or patients to test the efficacy of a premedication. Thus the animal species was chosen which with regard to histamine sensitivity, plasma histamine levels and response to polypeptidal plasma substitutes was shown to be the most similar to human subjects: the dog [8, 10, 11, 12a, 18, 22]. In this species life-threatening histamine-release responses were caused by polygeline, but could be prevented by the premedication with  $H_1$ - and  $H_2$ -receptor antagonists. This result seemed to be very promising for testing this premedication also in patients at risk: subjects who already suffered from a histamine-release response of any grade of severity, patients with an allergic constitution (hay fever, asthma, allergic exanthema etc.), patients with diseases in whom immunological reactions are considered to be very common (tumor patients or those with suppurative processes).

There are other ways to protect patients from anaphylactoid reactions in general and more specifically from histamine-release responses. They have been successfully pursued in the past decade – the discarding of some histamine-releasing drugs [23], development of better drugs [2a] and solvents [11], limitation of prescribing indications, and avoidance of unduly rapid administration. Polygeline is a prototype drug for such a development: instead of producing consistently new substances the effects and side-effects of which are not well known for many years of clinical experience it is much more preferable to improve “old” drugs by a systematic research: “Purified” polygeline no longer elicited systemic anaphylactoid reactions in patients. Other approaches such as premedication with low-molecular dextran, to prevent dextran induced anaphylactoid reactions, are very appreciated, too [2b].

**Acknowledgements.** The authors are very grateful to P.J. Conry, Frankfurt, for helping with the English and to the surgeons of the operating theatre of the Orthopaedic Clinic, University of Heidelberg, for their cooperation with the clinical trials.

## References

- Adelmann B, Schöning B (1980) Binding of native and denatured collagen to immunoglobulins and cold insoluble globulin (CIG) in serum of patients undergoing orthopedic surgery. *Klin Wochenschrift* 58:625–629
- Ahnefeld FW, Fischer F, Frey R, Kilian J, Schöning B (1979) Der Infusionszwischenfall nach künstlichen Plasmasubstituten im Meldekollektiv der Arzneimittelkommission. – *Medizinistische Problematik, Prophylaxe und Soforttherapie. Anaesthesist* 28:207–220
- Doenicke A (1980) Pseudoallergic reactions due to histamine release during intravenous anaesthesia. In: Dukor P, Kallos P, Schlumberger HD, West GB (eds) *Pseudoallergic reactions: Genetic aspects and anaphylactoid reactions*. S Karger, Basel, pp 224–250
- Hedin H, Richter W, Messmer K, Renck H, Ljungstöm K-G, Laubenthal H (1981) Incidence, pathomechanism and prevention of dextran-induced anaphylactoid-anaphylactic reactions in man. In: Hennesen W (ed), *Joint WHO-IABS Symposium on the Standardization of Albumin, Plasma Substitutes and Plasmapheresis*, Geneva 1980. *Dev Biol Stand* 48:179–189
- Immich H (1974) *Medizinische Statistik*. Schattauer, Stuttgart New York
- Koller S (1977) Angriff auf den Fortschritt der Medizin. *Behauptung der Strafbarkeit kontrollierter Klinischer Therapieversuche. Fortschr Med* 95:2570–2573
- Lorenz W, Reimann H-J, Barth H, Kusche J, Meyer R, Doenicke A, Hutzel M (1972) A sensitive and specific method for the determination of histamine in human whole blood and plasma. *Hoppe-Seyler's Z. Physiol Chem* 353:911–920
- Lorenz W (1975) Histamine release in man. *Agents Actions* 5:402–416
- Lorenz W, Doenicke A, Dittmann I, Hug P, Schwarz B (1977) Anaphylaktoide Reaktionen nach Applikation von Blutersatzmitteln beim Menschen: Verhinderung dieser Nebenwirkung von Haemacel® durch Prämedikation mit  $H_1$ - und  $H_2$ -Rezeptorantagonisten. *Anaesthesist* 26:644–648
- Lorenz W, Doenicke A (1978) Histamine release in clinical conditions. *Mount Sinai J Med* 45:357–386
- Lorenz W, Doenicke A, Schöning B, Mamorski J, Weber D, Hinterlang E, Schwarz B, Neugebauer E (1980)  $H_1$ - +  $H_2$ -receptor antagonists for premedication in anaesthesia and surgery: A critical view based on randomized clinical trials with Haemacel® and various antiallergic drugs. *Agents Actions* 10:114–124
- Lorenz W, Doenicke A, Schöning B, Karges H, Schmal A (1981) Incidence and mechanisms of adverse reactions to polypeptides in man and dog. *Dev Biol Stand* 48:207–234
- Lorenz W, Doenicke A, Schöning B, Neugebauer E (1980) The role of histamine in adverse reactions to intravenous agents. In: Thornton A (ed) *Adverse reactions of anaesthetic drugs*, pp 169–238. Biomedical Press, Elsevier/North Holland
- Lorenz W, Doenicke A (1982) Histamine release by drugs used in anaesthesia and surgery. *Klin Wochenschrift*
- Messmer K, Lorenz W, Sunder-Plassmann L, Klövekorn W, Hutzel M (1970) Histamine release as cause of acute hypotension following rapid colloid infusion. *Naunyn Schmiedeberg's Arch Pharmacol* 267:433–445
- Schöning B, Koch H (1975) Pathergiequote verschiedener Plasmasubstitute an Haut und Respirationstrakt orthopädischer Patienten. *Anaesthesist* 24:507–516
- Schöning B (1980) Inzidenz pathergischer Nebenwirkungen von Hydroxyäthylstärke (HES 450/0,7): Kritik einer Studie. *Allergologie* 3:369–375
- Schöning B, Koch H (1981) Suppression der Nebenwirkungsquote von Neo-Plasmagel durch Promethazin. *Anaesthesist* 30:34–43
- Schöning B, Lorenz W (1981) Prevention of allergoid (cutaneous anaphylactoid) reactions to polygeline (Haemacel) in orthopaedic patients by premedication with  $H_1$ - and  $H_2$ -receptor antagonists. *Dev Biol Stand* 48:241–249
- Schöning B, Lorenz W (1981) Anaphylaktoide Reaktionen. *Klinikarzt* 10:621–631
- Lorenz W, Thermann M, Messmer K, Schmal A, Dorman P, Kusche J, Barth H, Tauber R, Hutzel M, Mann G, Uhlig R (1974) Evaluation of histamine elimination curves in plasma and whole blood of several circulatory regions: A method for studying kinetics of histamine release in the whole animal. *Agents Actions* 4:336–356
- Vars HM, Parkins WM, Perlmutter JP (1952) Various plasma expanders in animals. *Ann New York Acad Sciences* 55:46–530
- Feinstein AR (1978) Epidemiologic studies. In: Masberg F (ed) *Epidemiologie und Arzneimittelsicherheit. Med Wiss Buchreihe Schering AG, Berlin Bergkamen*, pp 23–33
- Watkins J, Clarke RSJ (1978) Report of a symposium: Adverse responses to intravenous agents. *Br J Anaesth* 50:1159–1164
- Lorenz W, Barth H, Thermann M, Schmal A, Dormann P, Niemeyer I (1974) Fluorometric histamine determination in canine plasma under normal conditions, following application of exogenous histamine and during histamine release by Haemacel. *Hoppe Seyler's Z Physiol Chem* 355:1097–1111
- Clarke RSJ, Dundee JW (1981) Adverse reactions to intravenous induction agents. In: Thornton A (ed) *Adverse Reactions to Anaesthetic Drugs*. Elsevier/North Holland Biomedical Press, Amsterdam, pp 29–46