Br. J. Anaesth. (1976), **48**, 151

HISTAMINE RELEASE IN HUMAN SUBJECTS BY MODIFIED GELATIN (HAEMACCEL) AND DEXTRAN: AN EXPLANATION FOR ANAPHYLACTOID REACTIONS OBSERVED UNDER CLINICAL CONDITIONS?

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SUMMARY

Histamine release by modified gelatin (Haemaccel) and dextran (Macrodex) has been demonstrated in volunteers by direct and indirect methods. In a pilot study of Haemaccel, histamine release was observed in six of seven volunteers. The highest plasma histamine concentration was 4.8 ng/ml, the lowest 1.7 ng/ml: two of the subjects showed slight allergic reactions. Using Haemaccel batch 2551, 10 out of 12 subjects reacted to the rapid infusion of Haemaccel with increased plasma histamine concentrations, whereas none reacted to Ringer's solution. None of the 10 subjects had an allergic reaction, but an increase in gastric secretion was observed in eight. Changes in the venous basophil granulocyte count were found in both those who reacted and those who did not react to Haemaccel. After the rapid infusion of dextran the highest plasma histamine concentration was 5.0 ng/ml, the lowest 1.3 ng/ml. The withdrawal of blood had no influence on plasma histamine concentration. The incidences of histamine release produced by Haemaccel varied with different batches. Thus, it seems unlikely that immunological mechanisms are principally responsible. Nine instances of allergic and anaphylactoid reactions to plasma substitutes have been reported, seven after Haemaccel infusion, and two after dextran administration. One of the patients who received dextran died. Histamine release was always associated with Haemaccel infusion and corresponded in extent to the clinical symptoms observed, but there was no significant histamine release associated with the reactions to dextran.

Solutions containing dextran and gelatin have been used in a wide variety of clinical situations (Bauer and Östling, 1970). These drugs may cause anaphylactoid and allergic reactions the explanation of which is not clear. Adverse reactions to dextran (Brisman, Parks and Haller, 1968; Strebel and Siegler, 1968; Maddi, Wyso and Zinner, 1969; Carlsson et al., 1972) and to gelatin (Eberlein and Dobberstein, 1962; Meisel and Zöckler, 1971; Schmidt and Pflüger, 1971; Müller and Dietzel, 1972) have been reported.

It has been shown that plasma substitutes release histamine in animals (Giertz and Hahn, 1966; Messmer et al., 1970; Goth, 1972; Lorenz, Barth, Karges et al., 1974; Lorenz, Barth, Thermann et al., 1974; Lorenz, Thermann et al., 1974). However, there are differences between species. Dextran liberates histamine in rats (Hahn and Wellmann, 1952) and rabbits (Haining, 1956), but not in dogs (Messmer et al., 1970) and pigs (Lorenz, Barth et al., 1971). Gelatin preparations increase whole-blood histamine concentrations in dogs (Messmer et al., 1970), but do not release histamine in guineapigs, rats and rabbits (Keller, 1969; Schwick and Heide, 1969; Lorenz, W., unpublished data). Thus it is uncertain whether the anaphylactoid reaction to plasma substitutes in man is a result of histamine release. We have reported previously on histamine release in man by dextran and gelatin (Lorenz et al., 1970; Lorenz, Doenicke et al., 1971; Lorenz, Schmal et al., 1972; Seidel et al., 1973a), but it was not known whether this was a result of chemical histamine release from mast cells (Paton, 1956) or a result of anaphylaxis (Bauer and Östling, 1970; Lorenz, Seidel et al., 1974).

The frequency of histamine release associated with plasma substitutes in animals and man varies from batch to batch, from species to species and even from strain to strain (Giertz and Hahn, 1966; Messmer et al., 1970; Seidel et al., 1973b; Lorenz, Seidel et al.,

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1974). In this report evidence for histamine release in man by plasma substitutes has been obtained using both chemical and biological techniques. The incidence of histamine release was found to vary with the batch used. Thus hypersensitivity is probably not the main cause of these reactions.

MATERIALS AND METHODS

Materials

Volunteers and patient. Seventy-eight volunteers and one patient were tested in 1969–73. There were 72 males and six females (69 medical students, three technicians and six anaesthetists). The weight range was 54–94 kg and the age range was 19–36 yr. None of the volunteers had a history of allergy (asthma, hay fever, or intolerance of medicaments or foodstuffs (Mendez and Hughes, 1952)), pneumonia, salmonellosis (Gropper, Raisz and Amspacher, 1952; Kabat et al., 1957), collagen disease or gout (Maurer, 1954a, 1960). None had received dextran or gelatin previously (Kabat and Bezer, 1958; Schwick and Heide, 1969). The presence of pre-formed antibodies to gelatin (Maurer, 1954b) and dextran, however, was not tested. None of the subjects in whom gastric secretion was to be measured had any history of gastric disease.

Blood for plasma histamine determinations was withdrawn and processed according to Lorenz, Reimann and colleagues (1972).

Plasma substitutes. Dextran-60 (Macrodex, Knoll, Ludwigshafen) and gelatin (Haemaccel, Behringwerke, Marburg) were studied (table I). Gelatin contained neither preservative agents (Schöne, 1969) nor antihistaminic drugs (Lorenz, Barth, Karges et al., 1974). Dextran, several batches of gelatin and Ringer's solution (pH 6.0) were obtained from Munich University pharmacy, and gelatin batches Nos. 2549, 2551, 2559, 3000, and V 183/I directly from the manufacturer. Batches 1786 (manufactured in June 1967), 2019 (July 1968), 2406 (November 1969), 2549 (April 1970), 2559 (May 1970) and 3000 (May 1972) were on the market. Batches 2551 and V 183/I, available for clinical trials only, were obtained from the commercially available batches Nos. 2498 and 3214 by adsorption on charcoals (Supra Norit and Carbopuron 4n, Degussa) at pH 9.0 and 7.0, respectively. Batches 1786 and 2019 were prepared from crude gelatin which contained fractions from various stages of the extraction procedure; later batches consisted of only the first fraction of crude gelatin (Lorenz, Barth, Karges et al., 1974). The patient received dextran-60 (Medac, Hamburg), batch R 614 which showed the same properties as dextran-60 (Macrodex) (table I).

Reagents and drugs. For the assay of plasma histamine, reagents were used according to Lorenz and colleagues (Lorenz, Reimann et al., 1972; Lorenz, Barth, Thermann et al., 1974). Dextran did not contain fluorescence-producing or -quenching material whereas the interfering substances in all the gelatin batches had to be eliminated by modified reaction conditions (Lorenz, Reimann et al., 1972; Lorenz, Barth, Karges et al., 1974; Lorenz, Barth, Schmal et al., 1974; Lorenz, Barth, Thermann et al., 1974; Lorenz, Thermann et al., 1974). The volunteers received no drugs other than the plasma substitutes, whereas the patient was treated with prednisolone (Lentia, Munich) and clemastine (Sandoz, Basle). These drugs did not interfere with plasma histamine assay.

Infusion of plasma substitutes ("normovolaemic" haemodilution) and methods

The experimental protocol guaranteed an approximately isovolaemic haemodilution, notwithstanding Schmier's (1969) reservations. The subjects fasted for at least 6 hr and the experiments were carried out from 3 a.m. to 5 p.m. No medication was allowed within the 36 hr immediately preceding the study. A nasogastric tube was inserted under x-ray control to permit aspiration of gastric secretion (Lorenz, Doenicke et al., 1972a, b). E.c.g. leads and a sphygmomanometer cuff were applied. The subjects were studied supine. A polyethylene cannula was inserted into a superficial vein in the left arm for blood sampling. Blood was withdrawn from the right arm and plasma substitutes were infused by the same route.

Fifteen minutes after the preparations had been completed, blood for baseline plasma histamine assay and, thereafter, 500 ml of blood were withdrawn (approx. 2 ml/kg/min). Thirty seconds later a sample for histamine determination was taken and 500 ml of the plasma substitute was infused under pressure (approx. 2 ml/kg/min, 37 °C). At 1, 5, 10, 20 and 30 min after the end of the infusion further samples for histamine assay were taken.

Histamine in human plasma was determined fluorimetrically using the method of Lorenz, Reimann and colleagues (1972). For each series of reaction mixtures, two reagent blanks and one revised blank were used. Two determinations of recovery after the addition of authentic histamine 6 ng were performed daily and were found to be

TABLE I. *Origin, preparation and some physico-chemical properties of the clinical dextran and gelatin used in this communication*

Properties of the substances	Dextran*	Gelatin†
Origin	Saccharose	Bovine ossein
Preparation	Bacterial biosynthesis using *Streptococcus leuconostoc mesenteroides* NRRL B 512 F, precipitation by alcohols, partial acid hydrolysis, fractionation by ethanol	Partial heat degradation of the native gelatin, crosslinking of peptides (mol. wt. ≈12 000) by hexamethylene diisocyanate
Linkages	>93% α-1,6-glycosidic	Reaction of α-amino, imidazole and ε-amino groups with hexamethylene diisocyanate
Weight average of molecular weight ($\overline{M}_w$)	60 000	35 000
Number average‡ of molecular weight ($\overline{M}_n$)	32 000	24 500
Range of molecular weight	20 000–95 000 (80%)	5000–50 000 (90%)
Viscosity	0.23 (intrinsic viscosity η)	1.7–1.8 (relative viscosity, $H_2O = 1$)
Concentration	60 g/litre	35 g/litre
Solvent	0.9% saline‡	Ringer's solution
pH (units)	7.0–7.1	7.2–7.3
Clinical batches used in this communication	K 169, 3262 A 3	1786, 2019, 2406, 2549, 2551, 2559, 3000, V 183/I

The data were obtained from: *Gruber, 1968; Appel, 1972; †Schöne, 1969; ‡Stoll and Nitschmann, 1969.

between 60 and 70%. Plasma histamine was expressed as histamine base ng/ml plasma.

Gastric secretion, heart rate, arterial pressure and the number of leucocytes, eosinophils and basophil granulocytes in venous blood were determined by methods described previously (Lorenz, Doenicke et al., 1972a, b). In subjects who showed allergic and anaphylactoid reactions after gelatin or dextran infusion, a cutaneous prick test was performed (Lorenz, Doenicke et al., 1972b). The test included Haemaccel together with the gelatin hydrolysate before cross-linking with hexamethylene diisocyanate.

Evaluation of histamine release and statistical methods

In contrast to dextran-60, the various gelatin batches were administered in a random sequence according to Goldstein, Aronow and Summer (1969). Haemaccel batch 2551 was tested against Ringer's solution, batch 1786 against batch 2019, and 2549 and batch 3000 against V 183/I in a double-blind pilot study.

The criteria for histamine release under clinical conditions have been defined previously (Lorenz, Thermann et al., 1974). They include the demonstration of a histamine clearance curve in plasma, determination of histamine concentrations of more than 1 ng/ml in plasma and confirmation by bio-assay of the fluorimetric measurements such as gastric secretion, heart rate or arterial pressure. By these criteria reacting and non-reacting individuals were identified. The incidence of histamine release by the plasma substitutes was determined for each batch of these solutions. It was defined as the number of reacting subjects per number of subjects receiving the substance.

In comparing groups both the t test and the Wilcoxon test for paired samples were used. The χ^2 test was used for testing the incidences of histamine

TABLE II. *Histamine release by Haemaccel in human subjects (pilot study)*

Test subject	Plasma histamine concentration (ng/ml)				
	Before bleeding	Before infusion	After infusion of Haemaccel		
			1 min	5 min	10 min
Non-reacting:					
1	0.5	0.2	0.3	0.4	0
Reacting:					
2	0.6	0.6	1.7	1.1	0.6
3	0.5	0.4	1.8	1.4	1.0
4	0.9	0.7	2.2	2.2	1.1
5	0.6	0.8	3.2	3.3	1.8
6	1.0	1.2	3.3	4.3	2.0
7	0.9	0.6	4.0	4.8	2.1
Mean ±SD	0.75 ±0.2	0.7[a] ±0.3	2.7[b] ±0.9	2.85 ±1.5	1.4 ±0.6

Single values obtained from seven test subjects. Mean ±SD was calculated for the reacting subjects. Statistical significance in the *t* test for paired data: a/b, $P < 0.02$; in the Wilcoxon test a/b, $P < 0.05$.

release after the infusion of different batches of the plasma substitutes (Snedecor and Cochran, 1967).

RESULTS

Plasma histamine concentrations in test subjects following rapid infusion of Haemaccel (pilot study)

In a pilot study (August 1969) Haemaccel obtained from the University Pharmacy, Munich, was infused into seven test subjects. Since we did not know at this time that the histamine-releasing activity of this plasma substitute probably depended on the batches used, the batch numbers were not noted, but would be less than 2406, which was produced in November 1969 (see Materials). Histamine release was observed in six of the seven test subjects (table II). The plasma histamine concentrations in this series were in the range 1.7–4.8 ng/ml. No changes in heart rate or in arterial pressure occurred, whereas skin reactions were observed in two test subjects (Nos. 6 and 7, table IV).

Plasma histamine concentrations following rapid infusion of Haemaccel, dextran and Ringer's solution (known batches)

Haemaccel (batch 2551) which was obtained from the manufacturer for clinical trials caused a high frequency of histamine release (fig. 1). Ten out of 12 individuals had an increase in plasma histamine concentration although they did not show any significant histamine release following the infusion of Ringer's solution. The rapid loss of 500 ml of blood

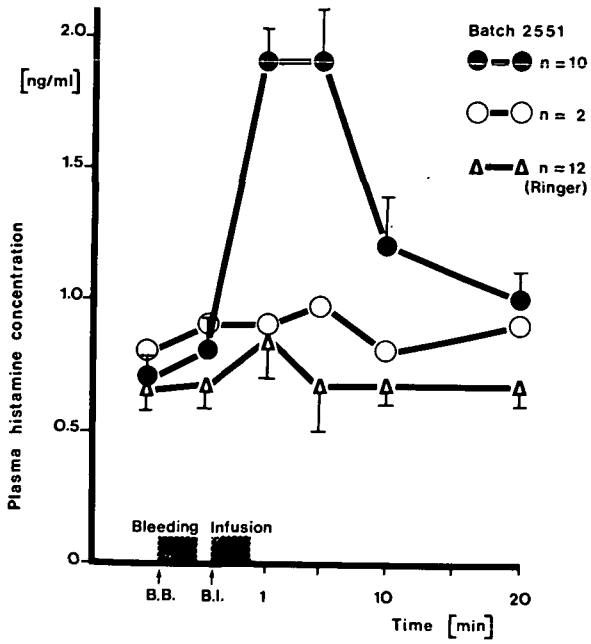

FIG. 1. Histamine release in human subjects by rapid intravenous infusion of gelatin (Haemaccel). Mean values ±SEM. ●——● subjects reacting to Haemaccel by elevated plasma histamine concentrations according to the criteria described in Materials and Methods. ○——○ non-reacting subjects. B.B. and B.I.: values from samples taken before bleeding and before infusion, respectively. For further conditions see Materials and Methods. Statistical significance in the *t* test for paired data. B.I./1 min, $P < 0.001$; B.I./5 min, $P < 0.001$. Wilcoxon test in both cases $P < 0.01$. All these values refer to the reacting subjects.

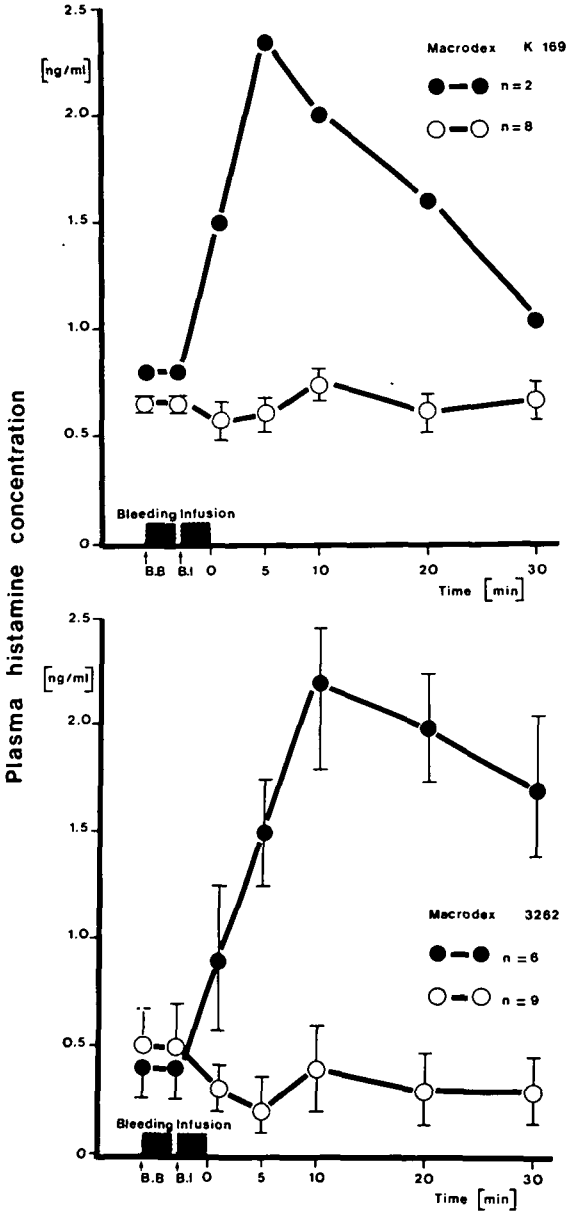

FIG. 2. Histamine release in human subjects by rapid intravenous infusion of dextran. Mean values ± SEM. ●——● subjects reacting to dextran by elevated plasma histamine concentrations. ○——○ non-reacting subjects. For further comments and conditions see figure 1 and Materials and Methods. Statistical significance in the *t* test for paired data (batch 3262/A 3): B.I./10 min, $P < 0.025$; B.I./15 min, $P < 0.01$. Wilcoxon test in both cases $P < 0.01$. All these values refer to the reacting subjects.

did not alter the plasma histamine concentration. The histamine release did not cause clinically detectable effects in any subject. The plasma histamine concentrations were in the range 1.6–3.0 ng/ml.

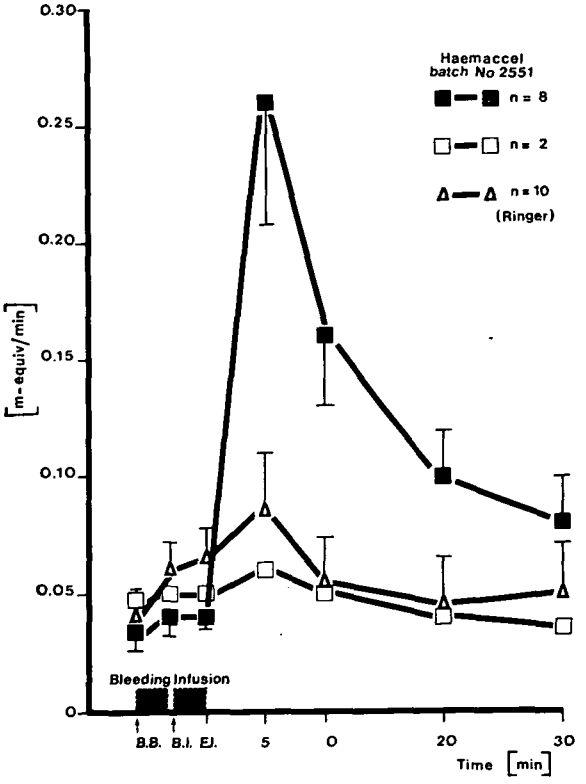

FIG. 3. Gastric acid secretion in human subjects following rapid infusion of Haemaccel and of Ringer's solution. Mean values ± SEM. ■——■ subjects reacting to Haemaccel by an elevation of the plasma histamine concentrations. □——□ non-reacting subjects. △——△ subjects receiving Ringer's solution (the same test persons, who were also treated by Haemaccel). B.B. = before bleeding, B.I. = before infusion, E.I. = end of infusion. For further comments and conditions see figure 1 and Materials and Methods. Statistical significance in the *t* test for paired data. E.I./5 min, $P < 0.005$; E.I./30 min, $P < 0.02$. Wilcoxon test in both cases $P < 0.01$. All these values refer to the reacting subjects.

After a rapid infusion of dextran there was an increase in the plasma histamine concentration also (fig. 2). Different incidences were obtained with the two batches used. The histamine release was not clinically significant; the range in subjects who reacted was 1.3–5.0 ng/ml. Blood loss had no influence on the plasma histamine concentration. The increase and decrease of the plasma histamine concentrations

after the administration of dextran differed, however, from those after gelatin. The maximum histamine release was observed 10 min after the dextran infusion, and the increase in plasma histamine lasted more than 30 min. Following gelatin infusion, the maximum histamine liberation occurred after 1–5 min and normal plasma histamine concentrations occurred as early as 20 min later. The effect of gelatin corresponded more closely to that of other histamine liberators such as compound 48/80.

Biological reactions in human subjects to histamine release by gelatin and dextran

For technical reasons only 10 of the 12 test subjects who received Haemaccel, batch 2551, underwent measurements of gastric secretion (fig. 3), blood leucocyte count, heart rate and arterial pressure (fig. 4).

No stimulation of *gastric secretion* occurred in these two subjects, who showed no increased histamine concentrations after gelatin administration (fig. 3). Neither the withdrawal of blood nor the rapid infusion of Ringer's solution affected gastric secretion to any great extent. In the test subjects who reacted to Haemaccel with increased plasma histamine concentrations, however, the acid output increased by more than 600% (fig. 3). At the time of maximum stimulation the acid output corresponded to nearly half of the maximum gastric secretion which in turn corresponded to plasma histamine concentrations of 3–4 ng/ml in histamine infusion experiments (Lorenz, Doenicke et al., 1972a, b).

The *venous leucocyte count* showed characteristic changes after Haemaccel infusion (fig. 4), but was similar in reacting and non-reacting subjects. Thus it may be independent of histamine release. Therefore the determination of histamine liberation by whole-blood histamine assay, which depends on the basophil count, is not justified (Lorenz, Doenicke et al., 1972a; Lorenz, Reimann et al., 1972). Bleeding alone and Ringer's solution did not alter the leucocyte count (fig. 4).

Gastric secretion and leucocyte concentrations were not determined in subjects who received dextran.

Heart rate and arterial pressure were not altered significantly by the infusion of Haemaccel, Ringer's solution (fig. 4) or dextran with the exception of one subject who reacted to Macrodex with an anaphylactoid reaction without histamine release (see below). These results are in agreement with findings obtained during histamine infusion in man (Lorenz, Doenicke et al., 1972a, b).

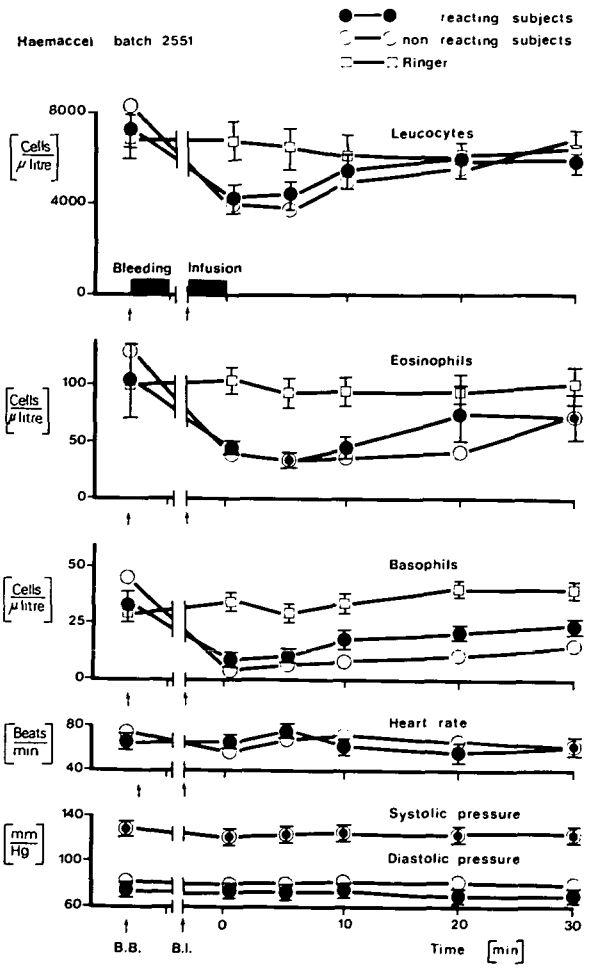

FIG. 4. Effect of Haemaccel and Ringer's solution on leucocyte concentration, heart rate and arterial pressure in human subjects. Mean values ± SEM. ●——● subjects reacting to Haemaccel by an elevation of the plasma histamine concentrations. ○——○ non-reacting subjects. □——□ subjects receiving Ringer's solution. For heart rate and arterial pressure the values obtained after infusion of Ringer's solution were not shown, because they were situated just within the range of those obtained after infusion of Haemaccel. B.B. = before bleeding, B.I. = before infusion. For further comments and conditions see figure 1 and Materials and Methods. Statistical significance in the Wilcoxon test: B.B./1 min, $P < 0.01$ for leucocytes, eosinophilic and basophilic granulocytes of the subjects receiving Haemaccel.

Incidence of histamine release in human subjects following infusion of various batches of plasma substitutes

The incidence of the reactions to Haemaccel (increase in acid output following administration of

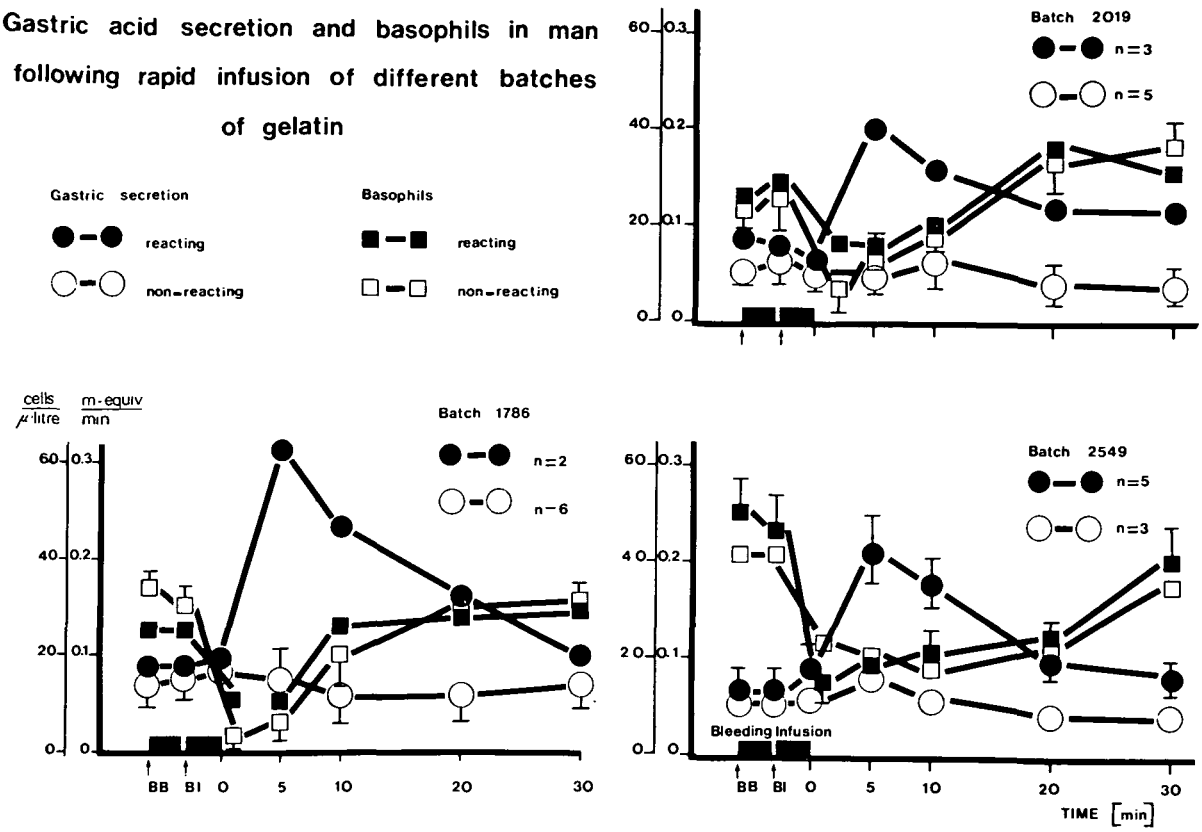

FIG. 5. Gastric acid secretion and basophilic granulocyte concentrations in the venous blood of human subjects following rapid infusion of different batches of Haemaccel. Mean values ± SEM. ●——● (■——■) subjects reacting to Haemaccel by an increased acid output; ○——○ (□——□) non-reacting subjects. B.B. = before bleeding, B.I. = before infusion. For further conditions see figure 1 and Materials and Methods.

the plasma substitute) varied from batch to batch (fig. 5). Because of the limited number of subjects, the differences were not statistically significant in this series of experiments (table III). The two subjects reacting to Haemaccel batch 1786 by an increased acid secretion showed also symptoms of an "allergic" reaction which are described in table IV.

In a double-blind pilot study in which five subjects received Haemaccel batch 3000 and five received Haemaccel batch V 183/I, none who received the first batch showed any reaction, whereas two showed considerable anaphylactoid reactions with the second batch. Because of these two reactions (table IV) the pilot study was discontinued. Since both Haemaccel batches 2551 and V 183/I, which were treated with charcoal, were associated with high incidences of histamine release (table III) charcoal adsorption is not recommended for clinical use.

The findings following infusion of Haemaccel and dextran are presented in table III. The varying, and in some cases high, incidences of histamine release, depending on the batches used, would suggest that the histamine response to Haemaccel is not the result of an immunological process, but a chemical action on mast cells or basophils, or both.

Anaphylactoid and allergic reactions to Haemaccel and dextran in human subjects

In eight out of 78 subjects, anaphylactoid and allergic reactions occurred following the rapid infusion of 500 ml of plasma substitutes. Table IV shows the responses to Haemaccel. In four volunteers, plasma histamine concentrations were measured, but in three subjects histamine release could be demonstrated only indirectly by measuring gastric secretion, and by observing tachycardia and hypotension. The

TABLE III. *Incidence of histamine release in man by different batches of gelatin and dextran, measured by an increase of gastric acid secretion or by increased plasma histamine concentrations*

Macromolecular substance	Batch no.	Incidence of histamine release: Gastric secretion n_1/n_2	Gastric secretion: Maximum value observed (m-equiv/min)	Plasma histamine concentration n_1/n_2	Plasma histamine concentration: Maximum value observed (ng/ml)
Gelatin					
Haemaccel	1786	2/7	0.32	—	—
	2019	3/8	0.20 ± 0.2	—	—
	2549	5/8	0.21 ± 0.8	—	—
	2551	8/10	0.26 ± 0.12	10/12	1.9 ± 0.3
	3000	—	—	0/5	0.2
	V 183/I	—	—	2/5	6.2
Dextran					
Macrodex	K 169	—	—	2/10	2.3
	3262/A3	—	—	6/15	2.2 ± 0.9

Mean values ± SD; n_1 = number of subjects reacting to Haemaccel by histamine release: n_2 = number of subjects investigated. The maximum values are the maximum response. Statistical significance (χ^2 test) Batch 1786/2551 $\chi^2 = 2.53$, $P < 0.2$; 2551/3000 $\chi^2 = 7.5$, $P < 0.01$. The last two batches were assessed in different trials, but the experiments were performed in the same room under the same experimental conditions by the same observers.

increase in acid output, especially in subject No. 5, was considerable and corresponded to plasma histamine concentrations of about 6–10 ng/ml (Lorenz, Doenicke et al., 1972a, b). In all who had plasma histamine concentrations of 5 ng/ml or more after the infusion of Haemaccel (or the corresponding increase in acid secretion), an increase in heart rate accompanied the increase of histamine concentration (fig. 6). The arterial pressure was a less sensitive index than heart rate: hypotension did not occur in subject No. 1 (table IV), but was just measurable in subjects Nos. 2 and 5 (table IV).

In contrast to Haemaccel, the two anaphylactoid reactions to dextran described in this communication seemed not to be mediated by a release of histamine (table V). One of the reactions occurred in a volunteer and one in a patient.

The patient who died following dextran was a 69-year-old man who was undergoing surgery for occlusion of the right common iliac artery. Premedication was atropine 0.01 mg/kg and dimenhydrinate 1.5 mg/kg. At least 15 min later, dextran-60 was infused slowly. About 3 min later (when only 20 ml had been given) a severe anaphylactoid reaction occurred (table V). The patient died, and the post-mortem findings were normal (no pulmonary embolism or myocardial infarction). The bottle containing the residue of the plasma substitute was sent to the University's pharmacy and was found to be free from bacteria and pyrogens.

Two samples of heparinized venous blood were obtained 5 min after cardiac arrest, while external cardiac massage was being performed. One minute later the blood specimens were centrifuged at 0–4 °C, and plasma was prepared. Plasma histamine concentrations were determined simultaneously in one of the patient's samples and in those of two normal individuals, while histamine was added to the other sample from the patient in order to test its recovery and to detect any interference in the assay from fluorescing or fluorescence-quenching material. The venous plasma histamine concentrations in the normal subjects were 0.2 and 0 ng/ml, the recovery of authentic histamine 6 ng added to the patient's plasma was 60%, which is usual with the method. No increase in the plasma histamine concentration, exceeding normal values, could be detected in the plasma of the patient.

Also, in the one volunteer who reacted to dextran, no significant increase in plasma histamine concentration could be measured (table V, fig. 6), although significant tachycardia was observed.

In the eight volunteers with anaphylactoid and allergic reactions to Haemaccel and Macrodex, the cutaneous prick test was found to be negative in all but one. This subject, K. B., reacted both to

TABLE IV. *Anaphylactoid and allergic reactions in human subjects following rapid infusion of gelatin (Haemaccel)*

Patient no.	Batch no.	Clinical observations	Plasma histamine concentration (ng/ml) Before infusion	After infusion
1 (K. B.)	V 183/I	*At the end of infusion* hot red ears, pressure in the middle ear, continuous sneezing. Small weals behind the ears. *3 min later*: bronchospasm, cyanosis and weals in the face, thorax and extremities. Oxygen was administered together with prednisolone 2 mg/kg and clemastine 0.025 mg/kg i.v. *20 min thereafter*: normal respiration, disappearance of erythema; weals remained for about 2 hr. Mild tachycardia; no significant changes in arterial pressure	0	7.3
2 (K. F.)	V 183/I	*1 min after beginning of infusion*: erythema of face, "crawling" in mouth. *At the end of infusion*: increasing, generalized sensation of warmth, itching on the right arm. *2 min later*: weals on the face. *4 min later*: weals on neck and thorax. *7 min later*: nausea, coughing and mild respiratory distress. *20 min later*: erythema disappearing and bronchospasm easing. Significant changes in heart rate, but not in arterial pressure. No drugs were administered	0	5.0
3 (A. B.)	<2406	*3 min after infusion*: slight oedema of upper eyelids and behind ears; erythema on face, disappeared spontaneously *1 hr later*. No tachycardia, hypotension, or bronchospasm	0.9	4.8
4 (U. H.)	<2406	*At the end of infusion*: slight erythema on face and neck, disappeared *30 min later*. No tachycardia, hypotension, or bronchospasm	1.0	4.3
			Gastric acid secretion [m-equiv/min]	
5 (H. G.)	2551	Hot flushed sensation immediately *after infusion*. *5 min later*: weals, beginning on the face, then appearing on the extremities and the body; burning of skin; respiratory distress. Tachycardia (before infusion 80, 5 min after infusion 96 beats/min, lasting for 20 min). Mean arterial pressure decreased 20 mm Hg.	0.05	0.57
6 (H. K.)	1786	General feeling of heat immediately *after infusion*; few weals on the face and forearm, no tachycardia or hypotension	0.12	0.36
7 (H. F.)	1786	Itching and feeling of heat on the head and neck immediately after the *end of infusion*. *3 min later*: weals on these areas, no tachycardia, or hypotension	0.08	0.28

Single values from each of the test subjects. The highest plasma histamine values showed in this table were obtained 1 min or 5 min after the end of infusion. Values for acid output increased within the first 5 min after the end of infusion.

Haemaccel (batch V 183/I) and to gelatin hydrolysate (before cross-linking of the peptides) by an erythema of the immediate type. This response, however, could be caused also by a chemical action of gelatin on mast cells (Sicuteri, Michelacci and Franchi, 1963; Lorenz, Thermann et al., 1974), and not only by an immunological mechanism.

DISCUSSION

Histamine release by plasma substitutes in man in relatively small amounts (2–3 ng/ml plasma) stimulates acid secretion in the stomach. If regurgitation occurs in unconscious patients or during operations this may lead to the aspiration of copious amounts of gastric juice. Furthermore, postoperative stress ulcers may be provoked (Seidel et al., 1973a, b; Lorenz, Seidel et al., 1974).

Allergic and anaphylactoid reactions following the infusion of Haemaccel were observed in seven out of 53 subjects investigated. Histamine release was demonstrated in all of these volunteers both by direct and indirect methods.

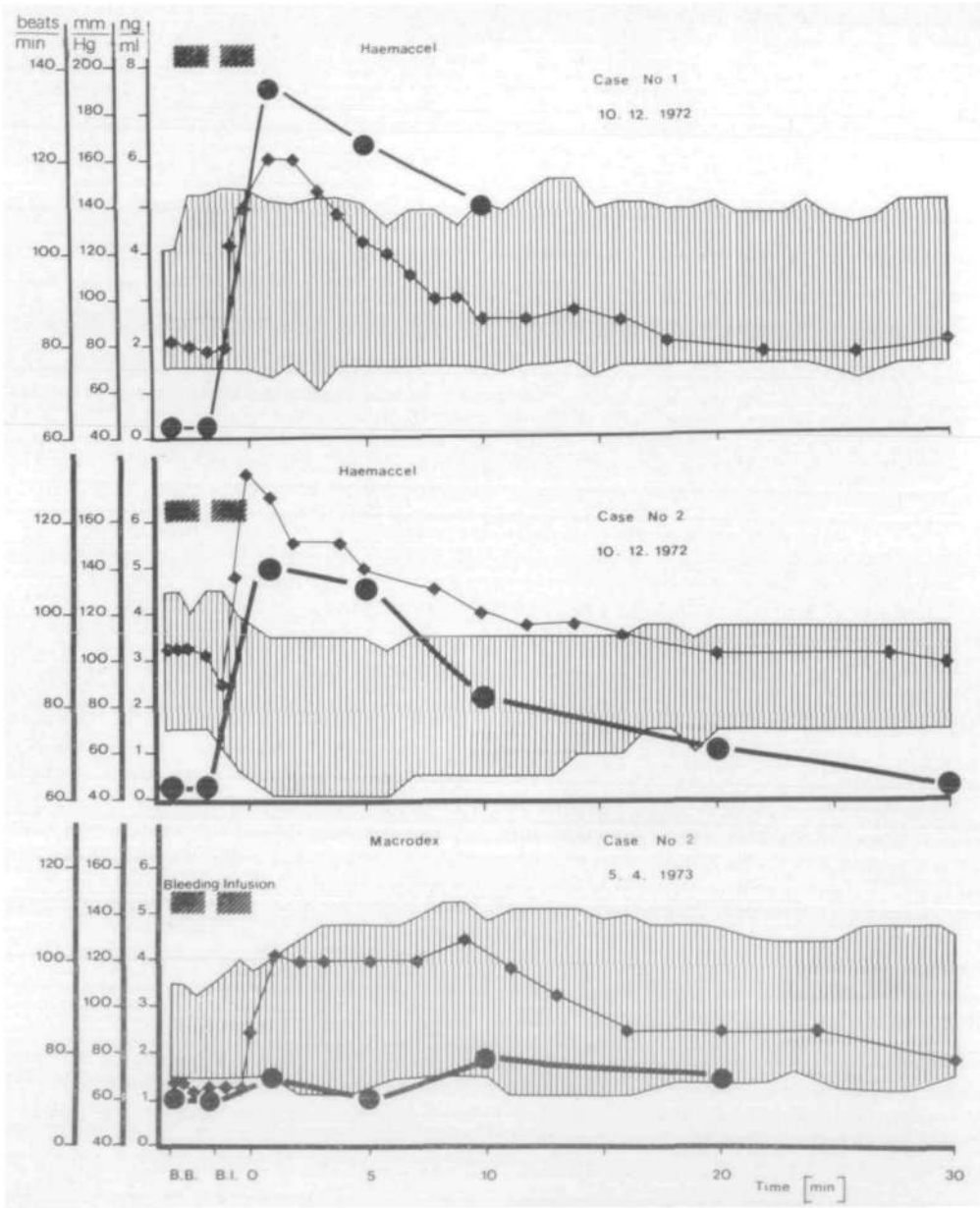

FIG. 6. Correlation between plasma histamine concentration, heart rate and arterial pressure in three cases of an anaphylactoid and allergic reaction to Haemaccel and Macrodex. Single values from each of the test subjects. ●——● plasma histamine concentration (ng/ml), ▥ systolic and diastolic arterial pressure (mm Hg) and ◆——◆ heart rate (beats/min). B.B. = before bleeding, B.I. = before infusion. For further conditions see Materials and Methods.

No severe or life-threatening anaphylactoid reaction was observed in the test subjects. Some clinical symptoms (in cases 1 and 5, table IV) were found to be less pronounced than expected from the relatively high plasma histamine concentrations and the strong gastric acid secretion. An intrinsic antihistaminic activity against H_1-receptors (Black et al., 1972) and both activating and inhibiting effects on histamine methyltransferase, the enzyme which inactivates mainly histamine in human subjects, was demon-

TABLE V. *Anaphylactoid reactions in human subjects following infusion of dextran-60*

Patient no.	Dextran-60 batch no.	Clinical observations and symptoms	Plasma histamine concentration (ng/ml)	
			Before infusion	After infusion
1 (O. A.)	Dextran-60 Medac R 614	After slow infusion of about 20 ml of dextran (within approximately 3 min): dizziness, feeling of weakness, generalized erythema. *2 min later*: weals on the neck and thorax, cyanosis, bronchospasm. The infusion was stopped. Ringer and bicarbonate solution were administered together with oxygen, cortisone 2 mg/kg, calcium gluconate 10 mg/kg, clemastine 0.03 mg/kg and orciprenaline 0.06 mg/kg. *5 min later* pulse not palpable, arterial pressure not measurable, but e.c.g. normal. *2 min later* cardiac arrest. Despite external cardiac massage, electrical defibrillation, administration of bicarbonate, cortisone, orciprenaline, the patient died	Not tested	0.5
2 (J. D.)	Macrodex 3262/A 3	*3 min after the beginning of infusion* erythema on the face, hot feeling, swelling in the nose. *2 min after the end of infusion* weals on the neck and the thorax, bronchospasm. *5 min later*: oxygen given. *1 min thereafter* prednisolone 1 mg/kg and clemastine 0.025 mg/kg were injected i.v. and the bronchospasm disappeared within a few minutes. *30 min later*: the test subject still complained of pain in the chest and feeling cold. Mild tachycardia but no hypotension	1.2	1.8

Single values from each of the subjects. The sample for testing the plasma histamine concentration in the patient was obtained 5 min after cardiac arrest when external cardiac massage was already in progress. The sample from patient no. 2 (test subject) was obtained 1 min after the end of the rapid infusion of dextran. For further conditions see Materials and Methods.

strated in Haemaccel (Lorenz, Barth, Karges et al., 1974; Lorenz, Barth, Schmal et al., 1974). Thus this plasma substitute may modify considerably the effects of the histamine released by itself: the activation of the enzyme may increase the elimination velocity for high concentrations of histamine, as was shown for another H_1-receptor antagonist, dimethpyrindene (Lorenz, Thermann et al., 1974). It may, however, enhance the effects of released histamine at the H_2-receptors, that is those responsible for vasodilatation in the face (erythema) and for the increase of heart rate (Wyllie, Hesselbo and Black, 1972), as was the case with dimethpyrindene (Lorenz, Thermann et al., 1973). By its H_1-receptor antagonist activity, Haemaccel may diminish the effects of released histamine at the H_1-receptors, which are responsible mainly for arterial hypotension, bronchospasm and intestinal motility.

In animal experiments it was shown that Haemaccel released histamine in the dog mainly from the skin of the upper half of the body and from the liver (Lorenz, Doenicke et al., 1971; Lorenz, Thermann et al., 1974). In human subjects the liver was a poor source of histamine in all but a few of the 33 individuals tested (Lorenz, Matejka et al., 1973; Lorenz, Seidel et al., 1974). Thus the clinical symptoms following histamine release by Haemaccel at present may be explained by the specific biochemical and pharmacological actions of this plasma substitute on the histamine system. Allergic reactions were reported relatively frequently, but severe anaphylactoid incidents with marked hypotension and bronchospasm were rare (Eberlein and Dobberstein, 1962; Bark, 1964; Gasparetto, Giron and D'Amigo, 1965; Bortoluzzi et al., 1967; Meisel and Zöckler, 1971; Müller and Dietzel, 1972; Lorenz, Doenicke et al., 1973; Lund, 1973; Schöning, Krahl and Koch, 1973; Lorenz, Seidel et al., 1974).

In this report, histamine release by dextran has been demonstrated in human subjects for the first time, but the two anaphylactoid reactions, which were observed in one patient and in one test subject, were not accompanied by a significant histamine release. Thus, it would appear that anaphylactoid reactions to dextran do not have to be caused by histamine release, although this mechanism cannot be excluded in all of the cases reported in the literature, since dextran did indeed release histamine in some of our volunteers. The clinical symptoms, however, which have been described in reports on anaphylactoid reactions to dextran, differ from those observed after infusion of Haemaccel (Maycock, 1952; Tarrow and Pulaski,

1953; Wilkinson and Storey, 1953; Tarrow, 1955; Wilkinson, 1956; Henley, McPhaul and Albert, 1958; Thorsén, 1959; Thompson, 1960; Meissner, 1961; Shepherd and Vandam, 1964; Simone, 1965; Bailey et al., 1967; Brisman, Parks and Haller, 1968, 1971; Maltby, 1968; Michelson, 1968; Strebel and Siegler, 1968; Maddi, Wyso and Zinner, 1969; Kohen et al., 1970; Schobinger, 1970; Carlsson et al., 1972; Schöning, Krahl and Koch, 1973). An increased intestinal motility with defaecation, rapidly developing and often severe hypotension and bronchospasm are dominant in the clinical picture, whereas skin reactions are not reported very frequently. Thus it may be assumed that anaphylactoid reactions to dextran in man are not usually caused by histamine release, which is in contrast to the effect of Haemaccel. Other vasoactive substances, such as kinins, prostaglandins and the slow-reacting substance A, have to be investigated as possible causes of these clinical incidents. It should be emphasized that even in true anaphylactic reactions histamine is not necessarily released in significant amounts as one of the mediators of the second phase of the immune response. There are examples in rats (Austen and Humphrey, 1963) and sheep (Alexander et al., 1970), which would indicate the greater importance of serotonin, kinins and slow-reacting substance A in such pathophysiological reactions.

ACKNOWLEDGEMENTS

This study was supported by Deutsche Forschungsgemeinschaft (Lo 199/4 and SFB 37 "Restitution und Substitution innerer Organe", Munich) and by Behringwerke AG, Marburg/Lahn.

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LIBERATION DE L'HISTAMINE DANS DES SUJETS HUMAINS PAR LA GELATINE MODIFIEE (HAEMACCEL) & DEXTRAN: EST-CE UNE EXPLICATION DES REACTIONS ANAPHYLACTOIDES OBSERVEES DANS DES CONDITIONS CLINIQUES?

RESUME

Il a été démontré sur des volontaires, par des méthodes directes et indirectes, que la gélatine modifiée (Haemaccel) et le dextran (Macrodex), libèrent de l'histamine. Au cours d'une étude pilote de l'Haemaccel, la libération d'histamine a été observée dans le cas de six volontaires sur sept. La forte concentration d'histamine dans le plasma a été de 4,8 ng/ml, la plus faible de 1,7 ng/ml et deux sujets ont accusé de légères réactions allergiques. Lorsqu'on a utilisé de l'Haemaccel—lot 2551—10 sujets sur 12 ont réagi à l'infusion rapide d'Haemaccel par des concentrations plus importantes d'histamine dans le plasma, alors qu'aucun d'entre eux n'a réagi à la solution de Ringer. Aucun de ces dix sujets n'a eu réaction allergique, mais on a observé sur huit d'entre eux une augmentation de la sécrétion gastrique. On a trouvé des changements dans la numération des granulocytes basophiles veineux aussi bien chez les personnes qui ont eu des réactions que chez celles qui n'ont pas réagi à l'Haemaccel. Après une infusion rapide de dextran, la concentration la plus forte d'histamine dans le plasma a été de 5,0 ng/ml, et la plus faible: 1,3 ng/ml. Le prélèvement de sang n'a eu aucune influence sur les concentrations d'histamine dans le plasma. L'incidence des libérations d'histamine produites par l'Haemaccel a varié suivant les lots utilisés. Il semble donc improbable que les mécanismes d'immunologie soient les principaux responsables de cet état de choses. On a signalé neuf cas de réactions allergiques et anaphylactoïdes aux substituts du plasma: sept après une infusion d'Haemaccel et deux après l'administration de dextran. L'un des patients auquel on avait administré du dextran est mort. La libération d'histamine a toujours été associée aux infusions d'Haemaccel et a correspondu, en importance, aux symptômes cliniques observés, mais il n'y a eu aucune libération significative d'histamine associée aux réactions au dextran.

FREIGABE VON HISTAMIN IM MENSCHEN, DURCH MODIFIZIERTE GELATINE (HAEMACCEL) UND DEXTRAN: EINE ERKLÄRUNG FÜR ANAPHYLAKTOIDE REAKTOINEN, BEOBACHTET UNTER KLINISCHEN BEDINGUNGEN?

ZUSAMMENFASSUNG

Freigabe von Histamin durch modifizierte Gelatine (Haemaccel) und Dextran (Macrodex) wurde bei freiwilligen Versuchspersonen durch direkte und indirekte Methoden demonstriert. In einer richtungweisenden Untersuchung des Haemaccel wurde die Freigabe von Histamin bei sechs der sieben Freiwilligen beobachtet. Die höchste Plasma-Histaminkonzentration war 4,8 ng/ml, die niedrigste 1,7 ng/ml: zwei der Versuchspersonen zeigten leichte allergische Reaktionen. Bei Verwendung von Haemaccel-Satz 2551 reagierten 10 der 12 Versuchspersonen auf die rapide Verabreichung von Haemaccel mit erhöhten Plasma-Histaminkonzentrationen, wogegen niemand auf Ringers Lösung reagierte. Keine dieser 10 Versuchspersonen zeigte allergische Reaktionen, aber bei acht kam es zu einer verstärkten gastrischen Sekretion. Veränderungen in der Anzahl venöser basophiler Granulozythen ergaben sich bei allen Versuchspersonen. Nach rapider Verabreichung von Dextran betrug die höchste Plasma-Histaminkonzentration 5,0 ng/ml, die niedrigste 1,3 ng/ml. Die Entnahme von Blut hatte keinen Einfluss auf diese Konzentrationen. Die Freigabe von Histamin variierte je nach den verschiedenen Sätzen von Haemaccel, die verwendet wurden. Es ist daher unwahrscheinlich, dass immunologische Mechanismen dafür verantwortlich sind. Neun Fälle von allergischen und anaphylaktoiden Reaktionen auf Plasmasubstitute, sieben nach Haemaccel-Verabreichung und zwei nach Dextran-Verabreichung wurden gemeldet. Einer der Patienten starb

nach der Verabreichung von Dextran. Die Freigabe von Histamin war stets mit der Verabreichung von Haemaccel verbunden, und entsprach dem Ausmass nach den beobachteten klinischen Symptomen, doch gab es keine signifikante Freigabe von Histamin im Zusammenhang mit den Reaktionen auf Dextran.

DESCARGA DE HISTAMINA POR GELATINA MODIFICADA (HAEMACCEL) Y DEXTRANO EN EL HOMBRE: UNA EXPLICACION DE LAS REACCIONES OBSERVADAS EN CONDICIONES CLINICAS

SUMARIO

La descarga de histamina por gelatina modificada (Haemaccel) y dextrano (Macrodex) ha quedado demostrada en voluntarios por métodos directos e indirectos. En un estudio piloto del Haemaccel, se advirtió una descarga de histamina en seis o siete voluntarios. La mayor concentración histamínica de plasma fue de 4,8 ng/ml, la menor de 1,7 ng/ml: dos de los pacientes mostraron reacciones alérgicas ligeras. Con el uso de Haemaccel lote 2551, 10 de los 12 pacientes reaccionaron a la rápida infusión de Haemaccel con un incremento de concentraciones histamínicas de plasma mientras que ninguno reaccionó a la solución de Ringer. Ninguno de los 10 pacientes sufrió una reacción alérgica, pero se observó en ocho de ellos un aumento en la secreción gástrica. Se hallaron cambios en la medida de los granulocitos basofílicos en las venas, tanto en los que reaccionaron como en los que no reaccionaron al Haemaccel. Después de la rápida infusión de dextrano la mayor concentración histamínica de plasma fue de 5,0 ng/ml; la menor fue de 1,3 ng/ml. La extracción de sangre no tuvo influencia en la concentración histamínica de plasma. Las incidencias de descarga de histamina producida por el Haemaccel variaron según los diferentes lotes. Así pues, no parece probable que los mecanismos inmunológicós sean mayormente los responsables. Se han reseñado nueve casos de reacciones alérgicas y anafilactoides a sustitutos del plasma, siete después de una infusión de Haemaccel y dos después de la administración de dextrano. Uno de los pacientes que recibió dextrano murió. La descarga de histamina estuvo siempre relacionada con la infusión de Haemaccel y correspondió en extensión a los síntomas clínicos que se advirtieron, pero no hubo una descarga de histamina significante relacionada con las reacciones al dextrano.