

Letters to the Editor

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Reactions to gelatin plasma expanders

SIR—Lorenz and colleagues (April 16, p 933) seem to create a circular argument. They define histamine-related reactions as perturbations accompanied by an increase in plasma histamine. They then note a number of these episodes and claim that histamine release is an important perioperative event. However, they also comment that "histamine-related cardiorespiratory disturbances occurred with remarkably low plasma histamine levels". Further, patient 147 had a blood pressure that was falling long before histamine rose. This was classed as a histamine event because hypotension and an increase in histamine level did coexist. However, a fall in systemic pressure resulting from the major inhalation anaesthetic agent used seems a more probable explanation.

A second problem is clinical relevance. Lorenz et al exposed patients in whom cardiovascular perturbations were undesirable to medications known to release histamine. Some patients received no prophylaxis against the histamine release. Would not prudent clinicians simply avoid agents that release histamine in such patients? How was informed consent obtained when it was known that half the patients would probably have reactions which they would not be expected to tolerate well?

Lorenz et al indicate that their study is one of the few where a rigorous protocol has been applied to the question of the relevance of histamine release during anaesthesia. However, "Blindness was not uniformly achieved". Why not?

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SIR—As Dahl hints in his commentary (p 929), accompanying the striking finding of Lorenz' study is that there is an unacceptably high incidence of adverse reactions when Haemacel-35 is used in combination with a "typical general anaesthetic". Some anaesthetic agents are more likely to release histamine than others, and the anaesthetic regimen used in this study (thiopentone, suxamethonium, and alcuronium) is a cocktail renowned for adverse reactions. Neuromuscular blockers are the anaesthetic drugs with the highest incidence of anaphylaxis; the most commonly implicated is suxamethonium, followed by alcuronium.¹ Indeed, the need to include suxamethonium for routine non-emergency surgery is puzzling. The study was approved by an ethics committee but should patients have been exposed to a combination of drugs, known individually to cause adverse reactions, for the purposes of assessing whether antihistamines abolish this effect? The addition of Haemacel-35 to this combination led to a three-fold increase (8% *vs* 26%) of relevant or life-threatening cardiorespiratory disturbances associated with histamine release. The data sheet states that "rapid administration of Haemacel-35, especially to normovolaemic patients, may cause the release of vasoactive substances".² 3 patients had to be admitted to intensive care because of life-threatening events. The death of a fourth patient may have been related

to his illness and the surgery but he too had a high concentration of histamine after the induction. Four critical events during induction in 57 patients is an unacceptably high rate, especially since the manufacturers in the UK have received only 13 reports of severe anaphylactic/anaphylactoid reactions related to Haemacel-35 since 1981 (personal communication, Hoechst UK).

Lorenz et al designate a change in heart rate of more than 10 beats per min or a change in blood pressure of more than 10 mm Hg as being "detectable" changes, either histamine-related or histamine-unrelated. In a group of patients of median age 52 an induction technique of thiopentone (in fairly high dose), suxamethonium, alcuronium, and enflurane is likely to result in hypotension by a variety of means other than histamine release. Thiopentone and enflurane are potent myocardial depressants and suxamethonium produces bradycardia or even asystole.³ Lorenz et al note that although haemodynamic instabilities were the most consistent markers of untoward events there was no characteristic direction of change, bradycardia being more common than tachycardia and hypotension more common than hypertension. To support their argument that bradycardias are histamine-induced, they state that bradycardia often accompanies the use of atracurium, which can cause histamine release. Bradycardia even more commonly accompanies the use of vecuronium, which only very exceptionally causes release of histamine. As an example of very low plasma histamine release leading to cardiorespiratory disturbances 2 patients are highlighted, both of whom become hypotensive despite attempts to remedy this. One had no histamine detected until 20 min after the start of the Haemacel-35 infusion, and the possibility that the hypotension was a direct effect of the anaesthetic agents was not considered.

Lorenz et al conclude that we should "consider the benefits of routine antihistamine prophylaxis". It would seem far more sensible to avoid combinations of anaesthetic drugs well known to produce histamine release, especially (as implied by this study) if Haemacel-35 is to be used.

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- 1 Fisher MMCD, Baldo BA. Anaphylactoid reactions during anaesthesia. In: Atkinson RS, Adams AP, eds. *Recent advances in anaesthesia and analgesia*; vol 18. Edinburgh: Churchill Livingstone, 1994: 161.
- 2 Inoue K, Reichelt W. Asystole and bradycardia in adult patients after a single dose of suxamethonium. *Acta Anaesthesiol Scand* 1986; 30: 571-73.

SIR—The excellent article by Lorenz and colleagues prompted us to consider the incidence and mechanism of adverse reactions to gelatin plasma substitutes. This laboratory operates a service for anaesthetists faced with life-threatening anaphylactoid reactions to drugs and plasma substitutes. Reactions are graded clinically as minor histaminoid presentations (grade I) with grades II, III, and IV progressively more life-threatening cardiovascular and pulmonary events requiring active intervention. Our

Product	Reaction grade			
Haemacel	1	12	3	3*
Gelofusine	1	3	1	1

*1 death.

Table: Adverse reactions to gelatins reported to Sheffield

investigation protocol¹ requires a sequence of blood samples and a concise clinical history of the event. We measure tryptase activity: the concentration of this enzyme, released from mast cells, parallels histamine release, provides a measure of mast-cell degranulation relating to reaction severity, and a pointer to the mechanism. Peak concentrations well above 20 ng/mL indicate true anaphylaxis.²

Our records contain 43 clinically significant reactions reported over the 5 years 1989-93 for which the laboratory and case history clearly implicated gelatin administration. Half the cases were life-threatening (grades III/IV, table). There were no obvious common features in respect of surgical risk, age, or sex; and there was no evidence of underlying allergy or atopy traits. Nor did a real difference in numbers (usage denominator unknown) emerge between the two chemically distinct proprietary gelatins Haemacel and Gelofusine. Over the same period, only 4 minor reactions implicating dextrans and 2 to polystarch were recorded. However, adverse reactions to all colloid plasma substitutes are probably under-reported.³

Histamine release is a feature of gelatin reactions but there is very little evidence for an IgE-mediated mechanism. Peak tryptase release was between 5 and 20 ng/mL so true anaphylaxis is unlikely. Previous studies⁴ indicate that such tryptase release arises as a result of non-immune complement C3 activation, triggered by colloid particles (complexes) in the gelatin formulations themselves or formed by combination with components in the patient's blood. Low concentrations of complexes may simply lead to low levels of plasma histamine and moderate clinical risk, readily controlled by antihistamines. However, higher concentrations may give rise to "aggregate anaphylaxis" as complexes become sequestered by the pulmonary microvasculature. Aggregate anaphylaxis is manifest primarily in pulmonary vascular resistance and bronchospasm rather than cardiovascular response, and antihistamine premedication has little effect on this essentially physicochemical manifestation.⁵ The severe gelatin reactions have close parallels with reactions to the early dextran formulations.³

Far from being inert substances, gelatins can readily initiate a life-threatening anaphylactoid response. Their formulations carry the risk of haemorrhagic complications too. Gelatins are not ideal as plasma expanders and should not be chosen routinely on the basis of cost alone.

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- 1 Watkins J. Markers and mechanisms of anaphylactoid reactions. In: Assem E-SK, ed. *Allergic reactions to anaesthetics: clinical and basic aspects (Monogr Allergy, vol 30)*. Basel: Karger, 1992: 108-29.
- 2 Watkins J. Allergic and pseudoallergic reactions to colloid plasma substitutes: which colloid? *Care Crit Ill* 1991; 7: 213-17.
- 3 Watkins J, Wild G, Appleyard TN, Hardy G. Complement activation by polystarch and gelatin volume expanders. *Lancet* 1990; 335: 233.
- 4 Smedegård G, Revenas B, Saldeen T. Aggregate anaphylaxis in the monkey: haematological and histological findings. *Int Arch Allergy Appl Immunol* 1980; 61: 117-24.
- 5 Ljungström KG. Safety of dextran in relation to other colloids: ten years experience with hapten inhibition. *Infusionsher Transfusionsmed* 1993; 20: 206-10.

SIR—Lorenz and colleagues randomly assigned patients to receive preoperatively either Ringer's solution or a modified gelatin plasma volume expander (Haemacel-35). Haemacel is not indicated for the routine preoperative "volume loading of the circulation" (1994 data sheet, Behringwerke); it is not an alternative to Ringer's solution for this purpose. Furthermore, the gelatin solution was infused rapidly (20 min) to patients with little or no volume depletion (elective surgery), and anaesthetics and muscle relaxants were given concomitantly—three determinants of the frequency and severity of histamine-related anaphylactoid reactions to this gelatin expander. Does not the trial design therefore violate the Declaration of Helsinki, which states that "concern for the interests of the subject must always prevail over the interests of science and society"? This seems to have been the perception of the surgeons who excluded their 548 private patients from the trial.

No serious reactions occurred (as expected) after Ringer's solution (with or without antihistamines). The trial merely confirms that modified gelatin can cause severe histamine-related cardiovascular reactions during anaesthesia¹ and that antihistamines can prevent them.² The study offers no evidence for routine antihistamine prophylaxis in general anaesthesia, which typically does not (and should not) include gelatin plasma volume expanders.

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- 1 Lorenz W, Doenicke A, Messmer K, et al. Histamine release in human subjects by modified gelatin (Haemacel) and dextran: an explanation for anaphylactoid reactions observed under clinical conditions. *Br J Anaesth* 1976; 48: 151-65.
- 2 Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet* 1977; 1: 466-69.
- 3 Lorenz W, Doenicke A, Dittmann T, Hug P, Schwartz B. Anaphylactoid Reaktionen nach Applikation von Blutersatzmitteln beim Menschen: Verhinderung dieser Nebenwirkung von Haemacel durch Prämedikation mit H1- und H2-Rezeptorantagonisten. *Anaesthesist* 1977; 26: 644-48.

Authors reply

SIR—Perhaps our critics have not read our study protocol and the discussion of it by a forum of international experts (*Theor Surg* 1988; 3: 55-77 and 132-51) and our interim report in *Agents Actions* (1992; 36: C149-241). Our protocol stated (p 65) that the cut-off points chosen for changes in haemodynamics were obtained from a prospective validation study in patients "which included a separate test group" (so much for Gorsky's "circular argument" and O'Connor and Edwards' doubts). Not all details of the trial could be squeezed into a single paper, and publication of protocol, discussion forum, interim report, and *Lancet* article should be considered as a whole.

O'Connor and Edwards, referring to our "typical general anaesthetic", find suxamethonium "puzzling for routine non-emergency surgery" and question the approval of the two institutional review boards. We are surprised by this response, which is not shared by other anaesthetists who have written to us privately. In 1988, when we started the trial in Mainz, the combination of substances used was routine for anaesthesia in the hospital. The 59 anaesthetists who took part in the study over 3 years cannot have been willing to expose their patients to known risks for the purpose of the trial. One of us (JM) (Chicago) believes that "suxamethonium is the most frequently used drug for routine intubation in the United States . . . It is, in fact, the gold standard upon which all other drugs are compared". In

the 1988 international discussion forum. Dr Richard Clarke (Belfast) was concerned that: "if the extent of histamine liberation is very low, the study will have no statistical validity" while Dr Malcolm Fisher (Sydney) stated that: "the practice of warning patients who undergo life-threatening clinical anaphylaxis of all histamine-releasing drugs is both unscientific and hazardous". French anaesthetists, in a multicentre epidemiological inquiry, found that 70% of 813 cases of anaphylaxis in France in 1990-91 were due to muscle relaxants: 43% were caused by suxamethonium and 37% by vecuronium (claimed by O'Connor and Edwards to cause histamine release "only exceptionally").

Thiopentone, suxamethonium, and Haemacel are World Health Organization "essential drugs". Our anaesthetist critics seem to overlook our surprising finding that histamine release was not more frequent after suxamethonium and vecuronium than after fentanyl (which is assumed to be clean). The suppression of this matter for over 20 years has indeed prohibited "constructive discussion among clinicians about the rationale for antihistamine prophylaxis" (Dahl's commentary). We too were surprised by the "unacceptably high incidence" of critical events, not only in the Haemacel but also in the Ringer group. O'Connor and Edwards also raise the differentiation between histamine-related and histamine-unrelated cardiorespiratory disturbances. This point, surely, is answered by the efficacy of the H₁ blockers. Their final challenge, to our proposal about histamine prophylaxis, seems to require from them the naming of a combination of drugs that would be a "typical general anaesthetic" shown to be safe.

Gorsky questions our interpretation of the haemodynamic instability in patient 147 and the blindness of this study. In animal studies of the serial application of vasoactive substances² it was recognised that hypotensive responses to one agent could be distinguished from those of the preceding one only if an immediate fall after even a short steady state was recorded. Sudden change was the criterion in the trial, and in patient 147 the sudden change fell into the plasma substitute phase and was classified as hypotension in that period. Confirmation of blindness is usually not reported in randomised trials and our protocol was more rigorous than others in this respect. We wrote that "blood pressure responded less promptly to Ringer than to Haemacel": One of the senior observer anaesthetists (DD) was very successful in predicting allocation because of this difference, but the other's guesses were no better than chance. This concern should not be overplayed.

Haemacel-35 was not the old formulation of polygeline to which Simini refers, but the newer one with much less excess of cross-linking material, which seems to be the reason for its non-immunological histamine release.³ In the absence of anaesthetic, Haemacel-35 has proved to be safe: clinically important reactions were seen in none of 450 patients before induction³ and in only 0.3% of 600 patients during plasmapheresis (unpublished).

Dahl, in his commentary, suggested that without Haemacel-35 "no statistically significant effects of antihistamines might have been detected and no life-threatening disturbances observed". With access to more information than he had, we are not so sure. If, hypothetically, we extend the incidence of reactions in the Ringer group to that of the sample size including the patients given Haemacel, 10/118 reactions in the placebo group and 2/118 in the antihistamine would be significant ($p < 0.02$). One patient in the Ringer group had a plasma histamine of 11.3 ng/mL which might have caused a more serious reaction in the post-induction phase had he not been on Betathiazid (propranolol, triamterene, hydrochlorothiazide)

for hypertension, a combination with strong antihistaminic activity.⁴

Watkins knows very well how drug combinations impede the work of his "detective agency" when he tries to find out the guilty party and elucidate the pathomechanism. We have some newer information from a trial comparing Haemacel-35, human albumin, and hetastarch in patients on plasmapheresis. There was no complement activation when Haemacel-35 was given alone. The life-threatening reactions seen in the study reported in *The Lancet* were associated with very high plasma histamine levels and no serious respiratory symptoms: this fits in with non-immunological histamine release. In addition, aggregate anaphylaxis after dextran formulations develops within a few minutes or after only a few millilitres of these infusions.

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3. Schöning B, Lorenz W, Doenicke A. Prophylaxis of anaphylactoid reactions to a polypeptid plasma substitute by H₁- and H₂-receptor antagonists: synopsis of three randomized controlled trials. *Klin Wochenschr* 1982; 60: 1048-55.
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Harbour-acquired *Plasmodium falciparum* malaria

SIR—During the past 15 years about 50 cases of airport-acquired malaria have been reported in Europe.^{1,2} It has been suggested that the transmission of malaria either resulted from the introduction of infected mosquitoes by an aircraft or occurred with local mosquitoes contaminated by feeding on an infected person returning from an endemic area.³ To our knowledge no cases of malaria contracted in a port have been reported. During the summer of 1993 acute *Plasmodium falciparum* malaria occurred in two inhabitants living close to Marseille harbour in France.

A 64-year-old retired woman, who lived on the harbour pier, presented with a 7-day history of fever (40°C) resistant to co-amoxiclav. She was jaundiced, confused, and had a blood pressure of 100/70 mm Hg. Laboratory data included haemoglobin 105 g/L, white cell count 3000×10⁹/L, raised direct bilirubin (57 µmol/L), and alanine aminotransferase (88 U/L). She had acute renal failure (serum creatinine 241 µmol/L). Severe thrombocytopenia was noted on the automatic blood-cell counter (6×10⁹/L), and the blood smear revealed numerous *P. falciparum* trophozoites (400 000 parasites per mL). She was transferred to an intensive care unit and was treated successfully with intravenous quinine 500 mg three times a day.

1 week later a 67-year-old alcoholic man with a history of psychiatric illness, who occasionally worked as a labourer at the harbour docks, presented with fever (38°C), confusion, hepatomegaly, and splenomegaly. Laboratory data included anaemia, leucopenia, raised bilirubin, and thrombocytopenia