ANAPHYLACTIC REACTION INDUCED BY INFUSION OF HAEMACCEL.

Sir,—Two types of substances are used today as plasma substitutes: the dextrans and the gelatins. The antigenic properties of the dextrans are well known (Kabat and Berg, 1953; Maurer, 1953). The gelatin preparation Haemaccel (Behringwerke) has been thought to have no antigenic effects, and no cases of anaphylactic reactions have been described.

Case history.

The patient was a 30-year-old woman who had no previous history of allergic reactions, eczema or joint diseases. She had had three previous operations: a diagnostic laparoscopy, an exeresis and a laparotomy because of a right tubal pregnancy. The actual operation was done for a left tubal pregnancy. All drugs given at this operation, except Haemaccel, had been given at the earlier operations without difficulty. Twenty minutes before the end of the operation an infusion of Haemaccel was begun because of blood loss. After beginning this infusion only atropine 0.5 mg and neostigmine 1 mg were given to antagonize the neuromuscular blocking drug. Forty-five minutes later the patient suddenly developed urticaria, breathing difficulties and oedema of the face. The infusion was stopped but the patient had received 450 ml of Haemaccel. The blood pressure was not affected. As immediate treatment 10 ml of a 10% solution of calcium was given intravenously, and hydrocortisone 100 mg was given intramuscularly. After 30 minutes the urticaria and breathing difficulties had gone, but facial oedema persisted for about 20 hours during which she was given a total of 40 ml of a 10% solution of calcium.

An intradermal test on the patient with Haemaccel diluted 1:10,000 produced a positive skin reaction. Six days after the operation a venous blood-sample was taken and the plasma analysed for complement factors. The amounts of C1 esterase inhibitor, C1q, C1s, C3 and C4 were normal. C3 proactivator was 175% of normal.

Haemaccel has been claimed to have no antigenic effects. It is known that infusion of untreated gelatin produces antibodies in man, especially in patients with degenerative joint diseases (Maurer, 1960). However, Haemaccel is a modified gelatin where the polypeptides obtained by hydrolysis of gelatin are cross-linked with hexamethylene diisocyanate (Maurer and Lebowitz, 1956). Piccinino and di Stasio (1963) have studied patients with various pathological conditions who were given 10 ml of Haemaccel intravenously daily for 20 days followed by a final dose of 500 ml. Antibodies against Haemaccel could not be obtained in any of these patients (Schwick and Heide, 1969).

One of the reasons for the absence of immunogenicity in Haemaccel is that gelatin contains little tyrosine. The introduction of 2% tyrosine is sufficient to produce good immunogenic activity (Arnon and Sela, 1966). Another reason is the absence of a rigid structure in the gelatin molecule. From investigations into other gelatin derivatives the conclusion has been drawn that a rigid structure in a sufficiently large spatially accessible area is essential for immunogenicity. The stabilization of the molecule and the prevention of possible rearrangement to form a structure resembling collagen is prevented by the cross-links in Haemaccel (Sela and Arnon, 1960; Sela, 1962).

Recent investigations of the complement system have shown that the normal chain of reaction mechanisms (Müller-Eberhard, 1968) can begin directly at the C3-level, starting with the C3 proactivator (Müller-Eberhard, 1971; Cooper, 1971). The significance of this patient’s high level of C3 proactivator, however, is unknown today, but may perhaps one day give an explanation to her reaction to Haemaccel.

I offer my sincere thanks to Dr Nils Eriksson of the Allergologic Clinic, Sahlgren’s University Hospital, Gothenburg, for help with the skin test, and to Professor Anna-Brita Laurell of the Microbiological Laboratory of the University of Lund for her help with the plasma analysis.

References


THE EFFECTS OF KETAMINE ON GUINEAPIG HEART.

Sir,—Anaesthetic doses of ketamine cause a rise in cardiac output, heart rate, and systemic blood pressure (Corssen and Domino, 1966; Virtue et al., 1967; Dowdy and Kaya, 1968). These cardiovascular effects of ketamine in man have been associated with an increase in plasma noradrenaline, presumably released from storage sites (Bovill et al., 1971). Similar conclusions have been reached with animal studies carried out in our laboratory (Chang, Chan and Gaken, 1969). We have now extended our investigation into the action of ketamine on the isolated, perfused guineapig heart, studying the changes in heart rate and force of contraction, and in noradrenaline content following the administration of the anaesthetic agent.

Methods. The classical Langendorff’s heart preparation was perfused with Tyrode solution aerated with 5% carbon dioxide in oxygen, and maintained at 37°C. The contraction force and rate were measured by a force-displacement transducer and a tachograph respectively, and were recorded on a Grass Polygraph. Ketamine HCl (Parke-Davis) diluted in Tyrode solution was administered by means of a polyethylene tubing connected close to the aorta. A constant volume of 0.3 ml was injected and the—

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dilutions were adjusted to provide the required dose. Five minutes after each injection, and when the cardiac effects of ketamine had worn off, the heart was removed, weighed and its noradrenaline content was extracted and estimated by the method of von Euler and Lishajko (1961), using an Aminco-Bowman spectro-photofluorometer.

### Table 1. Effects of ketamine on heart rate and force of contraction of guineapig heart.

<table>
<thead>
<tr>
<th>Dose of ketamine (µg)</th>
<th>Percentage change (mean ± SEM) in</th>
<th>Force of contraction</th>
<th>Heart rate</th>
<th>Number of hearts</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13.2 ± 3.5</td>
<td>29.9 ± 3.8</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>78.5 ± 2.3</td>
<td>78.5 ± 2.3</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>20.4 ± 5.5</td>
<td>82.9 ± 3.5</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>17.1 ± 2.6</td>
<td>91.2 ± 1.8</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

**Results and Discussion.** Administrations of 1, 5, 10 and 20 µg of ketamine decreased the heart rate and the force of contraction of the perfused guineapig heart (table I). With a dose of 20 µg, the myocardial force was reduced by 91.2% and the heart rate by 17.1% of the controls.

Furthermore, at this dose level the duration of cardiac depression was more than twice that observed with a dose of 1 µg (fig. 1). Although there was a marked cardiac depression, the effect of ketamine on the heart was completely reversible, and the force of contraction always returned to its previous levels within 3-5 min (fig. 1). The noradrenaline content of the heart was not altered by doses of ketamine which depress the heart. The mean (± SEM; n=5) amine content following the injections of 10 and 20 µg of ketamine was 1.9 ± 0.2 and 1.6 ± 0.2 respectively compared with the control value of 2.0 ± 0.3 µg per g tissue. Similar results were obtained with the lower doses of ketamine. Thus, the results observed in the present study do not seem to suggest that there is a sympathomimetic action of ketamine as reported from clinical studies (Corssen and Domino, 1966; Virtue et al., 1967; Dowdy and Kaya, 1968; Bovill et al., 1971) and from in-vivo animal studies (Chang, Chan and Ganendran, 1969). There is no simple way to fully account for the present findings particularly when the doses used were within the clinical anaesthetic range. However, the unaltered noradrenaline content seems to support, at least in part, the cardiac depressant effects of ketamine observed.

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**REFERENCES**


