ANAPHYLAXIS TO SUXAMETHONIUM*

A Case Report

BY

GEORGE JERUMS, SENGA WHITTINGHAM AND PATRICIA WILSON

The Clinical Research Unit of The Walter and Eliza Hall Institute of Medical Research and the Department of Anaesthesia, The Royal Melbourne Hospital, Victoria, Australia

SUMMARY

Two severe reactions to suxamethonium occurred in a 26-year-old woman with an "allergic diathesis" but who had no previous exposure to suxamethonium. The diagnosis of anaphylaxis was supported clinically by the immediate onset of tachycardia, hypotension, bronchospasm, pharyngeal and facial oedema, and immunologically by the demonstration of immediate reagin-type cutaneous hypersensitivity reactions to suxamethonium, and a positive passive transfer (Prausnitz-Küstner) reaction. Suxamethonium can cause histamine release: this could explain previously reported cases of "sensitivity" to suxamethonium. Our case was considered to be true anaphylaxis.

Anaphylaxis (unusual sensitivity) to anaesthetic agents is an unrecognized hazard of anaesthesia. We recently reported the case of a woman aged 58 years who became sensitized to thiopentone after successive thiopentone anaesthetics over several years (Currie et al., 1966). The present case is a further probable example of anaphylaxis to a drug used in anaesthesia, suxamethonium. The clinical manifestations were classical, and immunological tests supported the diagnosis of anaphylaxis. The condition is in contrast with the more frequent idiosyncrasy with prolonged apnoea due to low serum pseudocholinesterase (Lehmann and Liddell, 1964).

CASE REPORT

Clinical features.

A female school teacher, aged 26 years, presented for tooth extraction. She was healthy but six years previously developed severe urticaria after intramuscular penicillin. She gave no history of asthma, hay fever, or allergy to food, plants or insect bites, but there was a strong family history of allergy to penicillin in that her father, brother and sister had developed hives after injections of penicillin.

The first attempt at tooth extraction in May 1965, under local anaesthesia, was abandoned because over-breathing and carpal spasm occurred during injection of procaine.

The second attempt, again unsuccessful, was in September 1965, in her dentist's surgery. Atropine 0.6 mg was given intramuscularly before anaesthesia. When given methohexitone 0.25 ml, she became frightened and complained of pain at the site of injection. Satisfactory anaesthesia was induced with nitrous oxide, oxygen and halothane. She was given suxamethonium chloride (Scoline—Allen and Hanbury) 40 mg intravenously and an endotracheal tube was inserted, but after 1 minute she developed tachycardia, pallor and cyanosis. After 1 hour she was admitted semiconscious to the Royal Melbourne Hospital: the skin although flushed was like gooseflesh, the systolic blood pressure was 50 mm Hg, and the heart rate was 180 beats/min; an electrocardiogram showed sinus rhythm, later changing to supraventricular tachycardia. She was given metaraminol 9 mg (1 mg/min), and digoxin 0.75 mg intravenously: the heart rate slowed to 100 beats/min and the arterial pressure rose to 120/100 mm Hg. After 12 hours she had recovered.

Anaphylaxis to suxamethonium

The third attempt at tooth extraction was made in October 1965, in the Royal Melbourne Hospital. Premedication consisted of papaveretum 20 mg and hyoscine 0.4 mg. Anaesthesia was induced under electrocardiographic control with thiopentone 200 mg, during which there was sinus rhythm at 90 beats/min. Four minutes later suxamethonium 75 mg was given intravenously. After 30 seconds she developed the usual muscle twitching followed by apnoea. Simultaneously there was sinus tachycardia at 150 beats/min. An endotracheal tube was inserted. After 1 minute transient severe bronchospasm occurred, the arterial pressure became unrecordable, a pink flush

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appeared over the chest and abdomen and the skin of the limbs showed gooseflesh; spontaneous respiration reappeared after the usual interval but "faded" as the circulation deteriorated. Supraventricular tachycardia replaced sinus rhythm. Metaraminol 2 mg intravenously was given immediately but was ineffective. Cardiac arrest did not occur but external cardiac massage was started, and she was given 120 mg of sodium bicarbonate, 1 mg of digoxin, 100 mg of hydrocortisone intravenously, and an infusion of 20 mg of metaraminol in 5 per cent dextrose. Because she had tetanic spasms of the hands, estimations of blood pH (7.42), and serum calcium (9.1 mg/100 ml), were made. After 10 minutes the arterial pressure became recordable. She showed gross oedema of the tongue, lips and face which persisted for several hours but there was no laryngeal oedema. Because the systolic pressure remained below 70 mm Hg 2 ml of 1 in 10,000 adrenaline was given intravenously; this produced temporary slowing of the pulse and a change from supraventricular to sinus rhythm. After 24 hours the heart rate and arterial pressure were normal, but she remained confused and restless and had ataxia and gross tremors for several days. After two weeks she had regained her ability to write, count and remember past events. Electroencephalograms on the fifth and thirteenth days showed bilateral slow wave formation maximal in the frontal region, suggesting ischaemic changes, but psychometric tests after four weeks showed no evidence of brain damage.

**Serum pseudocholinesterase.**

The level of serum pseudocholinesterase was measured by the method of Warburg: the level was 150 μ mole/ml/hour, the normal being 80–220 μ mole/ml/hour.

**Immunological Investigations.**

**Methods.**

*Patch tests* were performed by impregnating gauze with 0.5 ml of the drugs to be tested. The gauze patches, five layers thick and 1 cm square, were centred on adhesive plaster 2 cm square.

<table>
<thead>
<tr>
<th>Test drug</th>
<th>Patch test</th>
<th>Intradermal test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suxamethonium chloride (Anectine)</td>
<td>0.5 and 5</td>
<td>Positive*</td>
</tr>
<tr>
<td>Suxamethonium chloride (Scoline)</td>
<td>5</td>
<td>Positive</td>
</tr>
<tr>
<td>Suxamethonium bromide (Brevidil)</td>
<td>5</td>
<td>Positive</td>
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<tr>
<td>Acetylcholine</td>
<td>5</td>
<td>Positive</td>
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<tr>
<td>Choline theophyllinate</td>
<td>10</td>
<td>Negative</td>
</tr>
<tr>
<td>Choline chloride</td>
<td>10</td>
<td>Negative</td>
</tr>
<tr>
<td>Thiopentone</td>
<td>10</td>
<td>Negative</td>
</tr>
<tr>
<td>Lignocaine</td>
<td>1</td>
<td>Negative</td>
</tr>
<tr>
<td>Procaine hydrochloride</td>
<td>2</td>
<td>Negative</td>
</tr>
<tr>
<td>Gallamine</td>
<td>4</td>
<td>Negative</td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>1</td>
<td>Negative</td>
</tr>
<tr>
<td>Prostigmine</td>
<td>0.25</td>
<td>Negative</td>
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<tr>
<td>Lignocaine with noradrenaline 0.0015%, and adrenaline 0.005%</td>
<td>2</td>
<td>Negative</td>
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<tr>
<td>Prilocaine</td>
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<tr>
<td>Prilocaine with adrenaline 0.000003%</td>
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</tr>
<tr>
<td>Crystalline penicillin</td>
<td>10⁴ i.u./ml</td>
<td>Negative</td>
</tr>
</tbody>
</table>

* Twenty-two control subjects gave negative reactions to patch tests when tested with 5 per cent suxamethonium. n.t.=not tested. Six control subjects gave positive reactions to intradermal tests when tested with 10 per cent suxamethonium.
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Each patch was placed on the skin of the back and observed after 5 minutes and then at intervals of 10, 15 and 20 minutes and 1, 4, 12 and 24 hours. Each drug was first tested in high dilution and if no skin reaction occurred the concentration was progressively increased.

_Intradermal tests_ were performed by injecting 0.1 ml of the test drug into the forearm, starting with high dilutions. Suxamethonium was not tested intradermally because it was feared that this could precipitate a reaction. With drugs injurious to skin—thiopentone, gallamine, tubocurarine and neostigmine—the test was read as negative if the reaction in the patient was comparable with that of at least three control subjects matched for age and sex.

_Passive transfer_ (Prausnitz-Küstner) tests were performed by injecting 0.1 ml of the patient's serum intradermally into three sites on the left side of the back of two male subjects; after 24 hours 0.1 ml of 5 per cent suxamethonium in distilled water (5 g/100 ml), 0.4 per cent gallamine and 0.1 per cent tubocurarine were injected into these sites and into three sites at the same level on the right side of the back. The person reading the test did not know which drugs were being tested.

_Precipitating antibody_ was tested for by gel-diffusion in an Ouchterlony plate and by a tube test.

**Results (see table I).**

_Patch tests_. 0.5 per cent suxamethonium (Anectine—Burroughs Wellcome) produced a faint immediate flare confined to the skin under the patch; after 1 hour the patch was removed because the skin was intensely itchy. Five per cent suxamethonium produced a more intense reaction in that the immediate flare spread beyond the patch and reached a maximum diameter of 5 cm at 10 minutes, the skin again becoming intensely itchy; the patch was removed after 20 minutes and the flare faded gradually over the next 2 hours. Another preparation of suxamethonium chloride (Scoline) and a preparation of suxamethonium bromide (Brevidil—May and Baker) gave similar reactions. Five per cent acetylcholine (Roche) produced a flare at 10 minutes which was maximum at 20 minutes and of 4 cm diameter; when the patch was removed the flare faded after 2 hours.

_Passive transfer_ (Prausnitz-Küstner) test. Five per cent suxamethonium injected into the test site produced at 20 minutes a weal of 2 cm and a flare of 7 cm in one subject, and a weal of 2 cm and a flare of 9 cm in the other; on injection into the control sites erythema of 2 and 4 cm respectively was produced. Tubocurarine and gallamine gave similar weal and flare reactions when injected into both the test site and the control site.

_Precipitating antibody_. The gel diffusion test with the patient's serum and control sera against the drugs listed in table I showed no precipitin lines and there was no immune precipitate formation when the serum of the patient was tested against serial dilutions of these drugs.

_Controls_. Eighteen female and four male control subjects were patch-tested with suxamethonium but none gave a positive reaction, although one reacted to adhesive plaster. Smith (1957) reported that weal and flare reactions occurred after intradermal injection of 0.2 ml of 10 per cent suxamethonium. We tested six hospital patients similarly and all reacted; five gave flare reactions of 1 to 3 cm maximum at 5 minutes and one gave a weal and 5 cm flare reaction of maximum size at 5 minutes.

**DISCUSSION**

We believe that our patient experienced anaphylactic reactions to suxamethonium. The clinical features were tachycardia, hypotension, bronchospasm and oedema. There had been a hypersensitivity reaction to penicillin previously and there was a strong family history of allergy. She reacted immediately to skin contact with suxamethonium in the patch test, which produced a flare and intense itching. Further, when her serum was injected intradermally into two normal subjects and the skin site was challenged with suxamethonium 24 hours later (Prausnitz-Küstner reaction), a positive reaction was obtained: this indicated that her serum contained reagin-type antibody which had become bound to, i.e. sensitized, the skin of the normal subject.

A search of the medical literature revealed three examples of a reaction to suxamethonium comparable with that of our case.

Smith (1957) described a 72-year-old asthmatic man with acute intestinal obstruction. He
had dyspnoea, slight cyanosis and moderate bronchospasm. He received atropine 0.65 mg and ephedrine hydrochloride 48 mg 30 minutes pre-operatively. Anaesthesia was induced with thiopentone 250 mg and suxamethonium 50 mg. After intubation it was impossible to inflate his lungs and he became cyanosed although spontaneous respiration returned after a few minutes. A further dose of suxamethonium 50 mg was given and the same reaction occurred. Gallamine was given without difficulty. An intradermal test with 0.2 ml of 10 per cent suxamethonium gave a weal of 2.1 cm and a flare of 5.8 cm.

Kepes and Haimovici (1959) described a 61-year-old man with an abdominal aortic aneurysm. Eight minutes after a continuous intravenous administration of suxamethonium he had an urticarial rash, facial oedema and hypotension. The blood pressure rose after intravenous injection of diphenhydramine hydrochloride and hydrocortisone but urticaria remained for several hours and facial oedema for 24 hours. He had no previous allergy, and patch and intradermal tests with suxamethonium were negative. One week later he was again anaesthetized, suxamethonium 40 mg was given, and he had the same reaction. Three days later he was tested by intravenous injection of all the drugs used during his anaesthetic. When he received 30 mg of suxamethonium he had a generalized urticaria which disappeared after 1 hour.

Fellini, Bernstein and Zauder (1963) described an 11-year-old girl with acute appendicitis. When suxamethonium was administered intravenously she had bronchospasm, tachycardia and a rise in blood pressure. She rapidly recovered but repeated administrations of suxamethonium caused “wheezing”. Intradermal testing with 2 mg of suxamethonium produced a weal and flare. There had been no previous administration of suxamethonium and she had no history of hay fever, asthma or allergy to foods.

The adverse reactions to suxamethonium in these three cases could be explained by either of two mechanisms, allergy or release of histamine. Smith (1957) showed that suxamethonium can cause in man manifestations of histamine release, weal and flare reactions, independently of any allergic mechanism, and we confirmed this finding. Thompson and Walton (1964), moreover, showed that suxamethonium and other “muscle relaxants” produced in dogs a rise in the level of plasma histamine. Thus hyper-reactivity, e.g. bronchospasm, urticaria and hypotension, associated with administration of suxamethonium, rather than allergy, could represent a drug idiosyncrasy associated in some way with liberation of histamine.

We appreciate that the demonstration of immediate type hypersensitivity to suxamethonium is made difficult by its histamine liberating effects, and that our patient had no previous “sensitizing” exposure to suxamethonium before her first reaction: nevertheless we feel that anaphylaxis rather than idiosyncrasy was the more likely event in our case.

Our patient also gave an immediate cutaneous reaction to acetylcholine. This suggested that the molecular configuration associated with the reactions was not exclusively associated with that of suxamethonium. Moreover, this is possibly an example of immediate reagin-type hypersensitivity to a normal constituent of the body.

ACKNOWLEDGEMENTS

We are grateful to Dr. J. L. Frew, Honorary Physician to the Royal Melbourne Hospital, for kindly allowing us to study this case, and Dr. I. R. Mackay, Clinical Research Unit of the Royal Melbourne Hospital and The Walter and Eliza Hall Institute of Medical Research, for his help and advice. Dr. W. J. Lang, Department of Pharmacology, University of Melbourne, and Mr. C. B. Macgibbon, Pharmacologist to the Royal Melbourne Hospital, kindly prepared the choline chloride solutions.

REFERENCES

ANAPHYLAXIS TO SUXAMETHONIUM

ANAPHYLAXIE AU SUXAMETHONIUM:
RAPPORT D'UN CAS

SOMMAIRE

Deux graves réactions au suxaméthonium se sont produites chez une femme de 26 ans présentant une "diathèse allergique" mais qui n'avait pas été précédemment exposée au suxaméthonium. Le diagnostic d'anaphylaxie a été confirmé cliniquement par l'installation immédiate de tachycardie, hypotension, bronchospasme, œdème pharyngé et facial, et immunologiquement par des réactions cutanées immédiates d'hypersensibilité du type réagin au suxaméthonium, et une réaction positive de transfert passif (Prausnitz-Küstner). Le suxaméthonium peut libérer de l'histamine: ceci pourrait expliquer des cas déjà rapportés d'"allergie" au suxaméthonium. Notre cas a été considéré comme une anaphylaxie véritable.

ANAPHYLAXIE NACH SUXAMETHONIUM:
BERICHT EINES FALLES

ZUSAMMENFASSUNG


BOOK REVIEWS


This volume of Progress in Surgery consists of four parts of which only one will be of immediate interest to anaesthetists. The chapters by Dr. L. Schlicht on the "Hydraulic repair of arteriosclerosis and arterial repair" and by Dr. G. Segmuller on "Bone repair and internal fixation" are outside the scope of anaesthesia. The chapter by Drs. Eckmann, Girardin, Hochuli, Montigel and Allgöwer on "Experience with pre-operative and early postoperative application of hydroxy-coumarins in surgical patients" describes an important attempt to reduce the incidence of pulmonary embolism which is the second most frequent cause of postoperative mortality. This is a bold series and further evaluations of their technique are obviously required before the pre-operative administration of anticoagulants can be recommended routinely.

The chapter by Drs. Laver and Bendixen on "Atelectasis in the surgical patient; recent conceptual advances" sets out in a very competent manner to present modern views on the aetiology, diagnosis and prevention of pulmonary atelectasis. The concepts advanced should be familiar to most anaesthetists and it is to be hoped that they will soon be equally understood by our surgical colleagues since they dispel many traditional beliefs and advance important new parameters for the detection of pulmonary atelectasis. The only criticism would be that the phrasing tends to be continental but this does not mar what is otherwise an excellent chapter.

The important subjects dealt with in these two chapters fully justify the view that this book should be of value to all anaesthetists. Gordon H. Bush


This book is a translation of the section on Respiration in Physiologie, edited by Charles Kayser and published in 1963. Only a few references are later than 1961. We may well be at the end of the era when students are able to buy one book which contains all the physiology that they need to know. Apart from the weight of such a book, its sections are frequently unbalanced in quality and quantity, and there is much to recommend a series of soft-bound monographs such as Dejours's Respiration. This book is intended for the undergraduate and the author declines to be drawn into the physiopathology of disease or the applied respiratory physiology which specially concerns the anaesthetist. What remains is a terse but reasonably up-to-date account of "pure" respiratory physiology. It serves to emphasize how applied is the respiratory physiology seen by the anaesthetist. Excellent though this book may be for the purpose for which it was intended, it will be of limited value for supplying the answers to clinical problems. It may prove useful in preparation for the primary FFARCS and will certainly be a valuable source of Gallic contributions to the field, from Lavoisier to Dejours himself.

J. F. Nunn