ANAPHYLAXIS INDUCED BY PROPANIDID AND ATROPINE

Case Report

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SUMMARY

Propanidid followed by intravenous atropine and suxamethonium induced anaphylaxis in a 29-year-old woman. The patient had previously been exposed to suxamethonium and atropine but the episode reported here occurred after initial exposure to propanidid. The patient’s leucocytes eight weeks after anaesthesia released histamine in vitro in the presence of both propanidid and atropine. Histamine release, however, could not be demonstrated at 17 and 22 weeks after anaesthesia, hence the adverse reaction in this context was transient in nature. The abnormal response to these drugs does not appear to be dependent upon immunological mechanisms, but is in all probability idiosyncratic.

Abnormal reactions to drugs used in general anaesthesia are an increasingly difficult problem. Anaesthetics and other substances used in anaesthesia are able to release histamine and may induce anaphylactoid responses which can be severe and may have a fatal outcome. Abnormal reactions such as exanthema, facial oedema, urticaria, inspiratory stridor, respiratory arrest, fall of arterial blood pressure and absence of pulsation have been observed following propanidid (Epontol) anaesthesia but such reactions are rare (Eichler, 1969).* Depressor response, stimulation of gastric secretion and increase of histamine concentration in the blood strongly support the view that propanidid releases histamine (Lorenz et al., 1969; Doenicke, 1969; Eichler, 1969; Dudziak and Zindler, 1969). Among 70 cases of reported side effects with propanidid, 52 were considered to be hypersensitivity of varying severity but histories of these patients showed that only 7 were considered to be allergic cases (Dudziak and Zindler, 1969). Lorenz and colleagues (1969) suggest that many of these adverse side effects can be eliminated by the use of antihistaminic drugs in premedication before propanidid injection and that the rapid injection of propanidid should be avoided, particularly in the case of patients with an allergic diathesis.

The following report describes investigations undertaken to define the nature of an anaphylactoid reaction demonstrated by a healthy female patient with no history of allergic diathesis who was given propanidid, atropine sulphate and suxamethonium. The injection was completed in less than 27 sec but no adverse reactions had been demonstrated with the identical regime in 225 patients.

METHODS

Allergic histamine release from peripheral blood leucocytes was performed using the method of May and associates (1970). Passive sensitization of leucocytes with serum in preparation for allergic histamine release was done according to the method of Levy and Osier (1966). The histamine released was quantitated with the use of an Aminco-Bowman fluorescence spectrophotometer and a release of greater than 30 per cent of cellular histamine upon presentation of allergen was taken as significant (Melam, Pruzansky and Patterson, 1970).

Direct skin tests on the patient were carried out in a standard manner using graduated concentrations of propanidid and atropine. Serum collected 8 weeks after anaesthesia was injected intradermally into the patient’s forearm in an attempt to demonstrate skin-sensitizing reaginic antibodies to atropine and propanidid. Sites thus sensitized with 0.1 ml of serum were challenged with several concentrations of both atropine and propanidid 24 hours later.

Passive cutaneous anaphylaxis (PCA) was performed in a rhesus monkey. Following tranquilization by intramuscular injection of Sernylan (phencyclidine hydrochloride) shaved areas of skin on the abdomen were sensitized by the intradermal injection of 0.10 ml of the patient’s serum taken 8

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* In one series using 1,600 patients, 14 of whom suffered from bronchitis or asthma and 2 from pneumonia, no incidence of postoperative trauma could be attributed to propanidid.
weeks after anaesthesia. Twenty-four hours later 4 ml of a 5 per cent solution of Evans Blue dye in physiological saline was injected into a femoral vein; the sensitized sites were then challenged with intradermal inoculation of several concentrations of both atropine and propanidid. All skin reactions were then recorded 20 minutes after challenge with these drugs.

**CASE REPORT**

A 29-year-old married woman and trained nurse with two children was seen prior to an operation for a lower dental clearance under outpatient general anaesthesia. She was found to be healthy and had no relevant history of allergic manifestations. She had had dental extractions performed under endotracheal anaesthesia on two occasions, 5 years and 4 years previously. On both occasions the technique was similar and preoperative medication consisted of morphine sulphate 15 mg and atropine sulphate 1.2 mg given intramuscularly, 30 minutes prior to operation. Induction of anaesthesia was achieved with thiopentone 250 mg, immediately followed by suxamethonium 50 mg (25 mg in the second anaesthetic). Nasal intubation and pharyngeal packing with glycerine-soaked gauze followed and anaesthesia was maintained with nitrous oxide 8 l/min, oxygen 2 l/min and 1 per cent halothane, respiration remaining spontaneous. These two anaesthetics were uneventful.

On the recent occasion, May 7, 1970, the anaesthetic technique differed in that no preoperative drugs were given and anaesthesia was induced with propanidid 500 mg. This injection was immediately followed by intravenous administration of atropine sulphate 1.2 mg and suxamethonium 20 mg, mixed in a disposable plastic syringe.

Within a few seconds of completion of the injection of these three drugs, the patient lost consciousness and became very plethoric. Before an endotracheal tube could be passed, her lips, eyelids and ears began to swell rapidly. Fearing laryngeal oedema, the patient was intubated with all possible speed and the lungs ventilated with oxygen, followed by nitrous oxide, oxygen and halothane. The oedematous reaction continued to progress until her features were unrecognizable. Since there was no evidence of bronchospasm and the patient's airway was protected by the endotracheal tube, it was decided to withhold any further drugs to see if the condition would settle. After several minutes the oedema began to subside so the dental treatment was carried out, although not without difficulty because of the size of the lips. This was completed in 15 minutes. On recovering consciousness a few minutes later, the oedema was considerably reduced although the patient awoke complaining of a pounding frontal headache. Mebhydrolin napadisylate (Fabbistin) 150 mg was given and repeated after 1 hour. Four hours following recovery the patient was transferred home to bed and mebhydrolin 150 mg was given 4-hourly until the next day when the swelling was still evident but not disabling. The mebhydrolin dosage was reduced to 50 mg q.d.s. and 150 mg nocte, for a further 2 days following which the patient was completely recovered.

**RESULTS**

The results of in vitro histamine release studies performed on the patient's leucocytes at 8, 17 and 22 weeks after anaesthesia on May 7 are reported in table I. Leucocytes collected 8 weeks after anaesthesia released histamine when exposed to both propanidid and atropine in 10 per cent autologous serum. Thirty per cent* of the histamine in $2 \times 10^6$ leucocytes was released following addition of propanidid 13 \( \mu \text{g} \) or atropine 1.5 \( \mu \text{g} \), indicating that on a weight basis the hypersensitivity was more pronounced to atropine than to propanidid. Trace amounts of histamine were released on exposure of the leucocytes to suxamethonium. Leucocytes collected from the patient 17 weeks after anaesthesia released only trace amounts of histamine upon incubation with propanidid and atropine. This analysis was performed in 10 per cent autologous serum. In an attempt to eliminate any potential effect of "blocking antibody" inhibiting allergic histamine release (Osler, Lichtenstein and Levy, 1968) a further experiment was performed 5 weeks later utilizing 10 per cent homologous, instead of autologous, serum in the incubation mixture. Under these conditions the patient's leucocytes failed to release histamine with several concentrations of both drugs. Serum collected from the first bleed of the patient failed to sensitize leucocytes from four separate normal donors, each of a different blood group specificity.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Concentration</th>
<th>Percentage Histamine Release (%)</th>
<th>Weeks after Anaesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propanid</td>
<td>500 ( \mu \text{g} )</td>
<td>45%</td>
<td>8*</td>
</tr>
<tr>
<td></td>
<td>50 ( \mu \text{g} )</td>
<td>42%</td>
<td>17*</td>
</tr>
<tr>
<td></td>
<td>5 ( \mu \text{g} )</td>
<td>2.8%</td>
<td>22†</td>
</tr>
<tr>
<td>Atropine</td>
<td>12.5 ( \mu \text{g} )</td>
<td>49%</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>1.25 ( \mu \text{g} )</td>
<td>4.2%</td>
<td>0</td>
</tr>
<tr>
<td>Suxamethonium</td>
<td>20.0 ( \mu \text{g} )</td>
<td>8%</td>
<td>—</td>
</tr>
</tbody>
</table>

* Reaction mixture contained 10 per cent autologous serum. † Reaction mixture contained 10 per cent homologous serum.

![BRITISH JOURNAL OF ANAESTHESIA](https://example.com/bja.png)

* The 30 per cent figure was obtained by extrapolation of the results in table I.
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5 μg/ml to 5 mg/ml and with atropine at concentrations of 0.6 μg/ml to 60 μg/ml were all negative; these tests were carried out 30 weeks after anaesthesia. Negative skin reactions were also obtained when sites which had been sensitized with serum taken shortly after anaesthesia were challenged 24 hours later with both atropine and propanidid.

The results of passive cutaneous anaphylaxis testing in a monkey were negative, suggesting the absence of reaginic antibodies to propanidid and atropine in serum collected 8 weeks after anaesthesia.

DISCUSSION

Following anaesthesia induced with propanidid, immediately followed by intravenous atropine and suxamethonium, a 29-year-old woman lost consciousness and became very plethoric. The oedematous reaction progressed until her features were unrecognizable but the oedema began to subside after several minutes. This swelling subsided still further under the influence of antihistamines. The time course of anaphylaxis and the response to antihistamines indicated that anaphylaxis was mediated through the release of histamine. The patient had previously been exposed to both suxamethonium and atropine but the episode reported here occurred after initial exposure to propanidid. Propanidid is a eugenol derivative and although the patient had not been exposed to this drug on a previous occasion she had, some years previously, used clove oil for toothache and may in fact have been sensitized to the eugenol derivative at this time. She had also used atropine eyedrops up to two years prior to the anaphylactic reaction.

In-vitro studies with the patient's leucocytes supported the concept that anaphylaxis resulted from the release of histamine as 45-49 per cent of the histamine was released upon exposure to propanidid 500 μg and atropine 12.5 μg. It is interesting that this in vitro release of histamine did not occur with leucocytes taken after a further 9 weeks. Since both of these sets of results were obtained by incubation of the leucocytes in autologous serum it could be argued that the patient had produced "blocking" (IgG) antibody, following exposure to the drugs, which inhibited histamine release in vitro (Osler, Lichtenstein and Levy, 1968). A further experiment was performed 5 weeks later in homologous serum but again no in-vitro histamine release occurred. This suggests that the adverse reaction demonstrated by the patient towards propanidid and atropine was, in the context of these experimental procedures, transient in nature.

Scratch testing of the patient with propanidid and atropine 30 weeks after the anaphylactic reaction was negative. Furthermore, the patient's serum, taken at a stage when histamine release could be demonstrated in vitro, failed to (1) sensitize leucocytes from normal patients for histamine release, (2) sensitize the patient's own skin for histamine release, and (3) sensitize monkey skin for PCA reactions. These results clearly support the transient nature of the adverse reaction and also exclude the involvement of humoral antibody, particularly reagin (IgE). This adverse reaction is clearly not a classical immediate type hypersensitivity reaction, notwithstanding the time factor and the association with histamine. Similar adverse reactions involving non-immunologic mechanisms have been reported for aspirin (Yurchak, Wicker and Arbesman, 1970) and dextran (Kohen et al., 1970; Shephard and Vandam, 1964; Bailey et al., 1967; Voorhees, Baker and Pulaski, 1951). Patients showing adverse reactions to aspirin and dextran also yielded negative skin reactions upon challenge, but contrast with the case reported in this publication in that in-vitro histamine release assays to dextran (Kohen et al., 1970) were also negative.

The anaphylactoid reaction reported here was therefore in all probability idiosyncratic. In accordance with the definition of idiosyncrasy proposed by Ackroyd and Rook (1962) such reactions resemble hypersensitivity in that they are quantitatively abnormal responses to drugs but do not depend upon immunological mechanisms. There is no evidence to suggest that the speed of injection of the drugs was a contributing factor in the induction of anaphylaxis in our patient. We are unable to explain why this idiosyncratic reaction is transient, insofar as the in-vitro studies are concerned, and can therefore only speculate upon the possible outcome of further in-vivo exposure to these drugs.

ACKNOWLEDGEMENTS

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REFERENCES


**ANAPHYLAXIE NACH PROPANIDID UND ATROPIN: KASUISTISCHER BERICHT**

**ZUSAMMENFASSUNG**


**ANAFLAXIS INDUCIDA POR PROPANIDID Y ATROPINA: COMUNICACION DE UN CASO**

**RESUMEN**

El propanidid seguido por atropina y suxametionio intravenosos indujo anafilaxis en una mujer de 29 años de edad. La paciente había sido expuesta previamente a suxametionio y atropina, pero el episodio referido aquí ocurrió después de una exposición inicial a propanidid. Los leucocitos de la paciente liberaban in vitro histamina en presencia de propanidid o atropina 8 semanas después de la anestesia. Sin embargo, no se pudo demostrar liberación de histamina a las 17 y 22 semanas después de la anestesia, así que la reacción adversa era de naturaleza transitoria en este aspecto. La respuesta anormal a estos medicamentos no parece depender de mecanismos inmunológicos, pero es muy probablemente idiosincrásica.

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**THE SOCIETY OF ANAESTHETISTS OF HONG KONG**

The Society wishes to remind all colleagues that it is intended to hold the Post World Congress Meeting in Hong Kong on September 24, 1972. The registration fee for the meeting and the social part, which includes Chinese Dinner and show, is £5 per person. Applications, together with remittance, should be sent to Dr M. L. Yeung, Hon. Secretary, The Society of Anaesthetists of Hong Kong, c/o Queen Mary Hospital, Hong Kong, to arrive not later than April 30, 1972.