

Anaphylaxis due to succinylcholine

Immunoallergological study of thirteen cases

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Summary

The antigen non-specific release of histamine by synthetic neuromuscular blocking agents is well known, though our review of thirty-two cases reported in the literature of anaphylactoid reactions to succinylcholine, shows that there is insufficient evidence to determine whether the signs are due to anaphylactic or to anaphylactoid reactions.

We have examined thirteen cases in whom evidence of anaphylactic sensitization was examined by direct skin tests (in eleven cases) Prausnitz–Küstner tests (in five), rabbit basophil degranulation, Shelley test (in twelve) and human basophil degranulation (in seven). These tests were done on two to four occasions, and the optimal period for the first test ascertained to be 6 to 12 weeks after the episode. All eleven patients examined by direct skin tests showed evidence of anaphylactic sensitivity, and in three of five cases the sensitivity could be transferred by the Prausnitz–Küstner procedure. In one of these P–K tests there was evidence of both IgE and of IgG S-TS antibodies (heat-stable antibody conferring sensitivity for 2 hr).

Particular susceptibilities to adverse reactions to this drug appear to be prior drug allergy (in 50% of cases), several previous anaesthetics, and atopy.

Introduction

The histamine-releasing property of synthetic neuro-muscular blocking agents has been known for a long time (Paton, 1957; Smith, 1957). Of three blocking drugs, D-tubocurarine is the most active in releasing histamine, gallamine less active, and succinylcholine the least active. Clinical observations indicate that severe reactions due to antigen-non specific histamine release depend upon individual susceptibility. Recent studies have shown that reactions may be anaphylactic due to previous treatments sensitizing the patients. Certain conditions predispose persons to these anaesthetic risks, e.g. atopy, previous drug allergy, anomalies in histamine release and reactivity to histamine, anxiety and the frequency of anaesthesia during short periods and type of general anaesthetic.

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We report on thirteen cases occurring between 1973 and 1978 diagnosed as true anaphylaxis due to sensitization to succinylcholine. Tests for allergy were made *in vivo* and *in vitro* at intervals during 3 years following each episode.

Methods

The first immunological tests were usually made 4–6 weeks after the anaphylactic episode.

Examination for susceptibility to histamine

Cutaneous reactivity was examined by intradermal injections of histamine, and the response to histamine release was observed by injecting 48/80, in a volume of 0.1 ml containing 0.01 μg and 0.1 μg , using 48/80, or histamine dihydrochloride. The test is read after 15 min by measuring the diameter of the weal and tracing it on paper. Controls showed no reactions, the threshold concentration being 1 μg (Pupil & Berna, 1976).

An electromyogram (EMG) of the first and second interossei is recorded during 10 min ischemia with a brachial tourniquet in place and 2 min hyperventilation. After removal of the tourniquet, a repetitive activity is observed. Less frequently, an intermediate spontaneous activity may be seen with the tourniquet in place. This phenomenon indicates the existence of latent spasmophilia, an important diagnostic sign since only 10% of healthy persons have a positive EMG compared to 90% in spasmophilia subjects (Duc & Duc, 1976).

The plasma histamine concentrations were determined by fluorometry (Shore, Burkhalter & Cohn, 1959). The normal concentration being $60 \pm 20 \mu\text{g/ml}$. Serum IgE concentrations were determined by RIST, the normal amount being 125 to 300 u/ml.

Specific immunological tests

Cutaneous tests with succinylcholine. At volume of 0.1 ml of increasing doses of 0.01, 0.1, 1.0 and 10 μg were injected intradermally. The results were read after 15 min by measuring the diameter of the weal and erythema. In controls, doses of up to 10 μg never provoked a reaction, though 100 μg sometimes induced a reaction of less than 20 mm.

Prausnitz-Küstner test. The P-K test for IgE was made by injecting serum into the skin of a recipient and challenging with antigen 48 hr later. The test was also carried out by the modification of Parish (1973) to detect IgG short-term sensitizing antibody in which the serum is heated for 2 hr at 56°C before transfer, and challenge with antigen is made 2 hr later. Recipients who showed responsiveness to Prausnitz-Küstner tests for pollen sensitivity were chosen (Vervloët *et al.*, 1977). Two series of tests were made. In the first the sera were diluted from 1/2 to 1/16 and the sites challenged with a constant concentration of antigen (0.1 μg); in the second the serum was diluted 1/2 and the antigen injected in different concentrations of 0.01 μg to 100 μg .

Rabbit basophil degranulation test. The rabbit basophil degranulation test (RBDT) of Shelley & Juhlin (1961) was carried out by the modification of Moneret-Vautrin, Grilliat & Pupil (1971) using a range of concentrations of antigen from 0.1 μg , 1.0 μg and 100 μg .

Test on human basophils. The test on human basophils for degranulation was carried out according to Benveniste *et al.* (1977) using concentrations of antigen from 0.1 μg to 100 μg .

Lymphocyte transformation test. The lymphocyte transformation test (LTT) was carried out with two concentrations of antigen, 25 and 50 μg and the result determined by microscopical examination and counts, or by assay of the incorporation of tritiated thymidine.

Results

Clinical study of thirteen cases

Ten females and three males aged from 17 to 54 years (mean 33 years) were examined. There was a history of atopic disorders in seven, previous exposure to the suspected allergen in six, and a history of an 'incident or accident' of unknown aetiology in four.

The adverse reaction to anaesthetics in all occurred during induction of anaesthesia with penthiobarbitone followed by Succirurarium. In most cases, the synthetic curare used was succinylcholine iodine (Celocurine), but in some cases, succinylchloride was used (Succirurarium).

The clinical signs were severe in all cases. Bronchospasm occurred in eight cases, within 2 min of injection of the synthetic curare, before intubation was attempted. The bronchospasm was severe, and in two cases the obstruction was complete and no insufflation was possible. Cyanosis quickly followed the bronchospasm.

Cardio-vascular collapse was reported in ten cases, occurring with, or preceding the bronchospasm. Secondary cardiac arrest occurred in three cases as a complication of the bronchospasm. The collapse was always associated with sinus tachycardia with a rate of about 160. The tachycardia subsided only a few hours after blood pressure had returned to normal. Primary cardiac arrest was the first sign of anaphylaxis in two cases.

Cutaneous and mucosal manifestations occurred frequently appearing as a secondary change after treatment of the collapse. In seven cases the changes were erythema, either generalized or confined to the upper part of the body. Facial oedema was seen in two cases. These changes indicated that the bronchospasm and cardiovascular collapse were anaphylactic.

In the follow-up study, the treatment led to a favourable outcome in twelve cases. Anaesthesia was stopped in all cases and surgery postponed.

In three of the 12 cases there were transient sequelae, in one case there was intense abdominal pain and bloody faeces, in another melena or haematemesis, and the third case remained in coma for 12 hr with mild signs of disturbed liver and kidney function, which subsided after 8 days.

The thirteenth patient died from the secondary cardiac arrest and anoxia resulting from irreversible bronchospasm and collapse. The results of the clinical and laboratory tests are summarized in Table 1.

Reactivity to histamine, and spasmophilia

Examination of ten of the cases showed that histamine was released far more readily in three, and there was hypersusceptibility to the activity of histamine in four. The threshold of reactivity to histamine was lowered by from ten- to a hundredfold.

The amount of plasma histamine was increased above normal in four of the five patients examined. Assays of IgE in six patients showed variable amounts not considered to be of significance.

Table 1. Summary of investigations on thirteen patients reacting to Succinylcholine (The figures refer to the number of patients)

EMG spasmophilia	Skin Tests				RBDT (Shelley)	Lymphocyte transformation
	48/80 histamine	Succinylcholine	P-K†	HBDT		
+9	*48/80 ($\times 10$)+3	+11	2 hr heated	+4	+10	Doubtful 2
-3	*Hist. ($\times 10$)+4	n.d. 2	+1	-3	-2	-8
n.d. 1	Normal 5		-3	n.d. 6	n.d. 1	n.d. 3
	n.d. 3		48 hr unheated			
			+3			
			-1			
			n.d. 9			

EMG, Electromyogram; P-K, Prausnitz-Küstner test; HBDT, human basophil degranulation test; RBDT, rabbit basophil degranulation test—the Shelley technique.

+, positive; -, negative; n.d. not done.

* Response to tenfold more sensitive.

† Donor sera tested: heated and challenged 2 hr after transfer; unheated and challenged 48 hr after transfer.

The electromyogram tests on twelve patients showed spasmophilia in nine. The spasmophilia was associated with atopy in five cases.

Immunological investigations

The intradermal skin test with succinylcholine was positive in eleven cases, in four of which hypotension was also induced by the test and the patients treated with intravenous steroids. In one case, the positive intradermal test was not apparent until several months after the anaesthetic incident. The skin test susceptibility to this antigen could persist for several years.

The Prausnitz-Küstner test with the sera of five cases was positive in three after an interval between sensitization and challenge of 48 hr. If the sera were heated and challenged 48 hr the sensitization potential was abolished, indicating that the 48-hr response was due to IgE.

Specific IgE antibody to succinylcholine persisted for up to 6 years (in one case). In one case the test was positive for 2 hr heated serum and 48 hr unheated, indicating the presence of two populations of antibody, IgG, S-TS and IgE, which persisted for 2 years after the accident.

The rabbit basophil degranulation test (Shelley test) was positive in ten of twelve cases either within a few weeks of the incident (eight cases) or some months later (two cases). On follow-up this test could become negative within 6 months, or the serum remain positive 3 years later.

The human basophil degranulation test was positive in four of seven cases, and like the rabbit basophil test, the test remained positive for 3 years (the same case that gave a positive Shelley test for this duration), or became negative within 6 years.

The lymphocyte transformation (to lymphoblasts) test carried out ten times, in some instances repeatedly on cells from the same patient, was negative in eight cases, and gave inconclusive results twice.

Discussion

In twelve of thirteen cases of adverse reactions to succinylcholine, evidence of anaphylactic sensitivity to the drug was detected by intracutaneous injection, supported in some cases, by Prausnitz-Küstner passive transfer, and rabbit and human basophil degranulation tests.

Anaphylactic sensitivity is unlikely to be detected by doing the tests once only, especially if the samples are obtained soon after the incident. Tests on several occasions may be necessary to detect the sensitivity. We believe that the optimal time to do the tests is from 6 weeks to 3 months after the incident. We do not believe that we sensitized patients by the skin tests.

In the literature, thirty-seven cases of allergy are reported between 1957 and 1978 (Bela-Binda & Valeri, 1971; Cardan & Deacu, 1972; Dumas *et al.*, 1975; Dohi & Ogawa, 1973; Edward & Thomas, 1969; Eustace, 1967; Fellini, Bernstein & Zauder, 1963; Fujita, 1970; Gambarelli *et al.*, 1974; Gschaedler & Loeb, 1976; Hainsworth & Bingham, 1970; Jerume, Whittingham & Wilson, 1967; Jonecko, 1960; Katz & Mulligan, 1972; Kepes & Haimonici, 1959; Mandappa, Chandrasekhara & Nelvigi, 1975; Paton, 1957; Pavsek, 1977; Poirier, 1975; Pupil & Berna, 1976; Redderson *et al.*, 1971; Royston & Wilkes, 1978; Shelley & Juhlin, 1961; Smith, 1957). The differential

Table 2. Comparison of cases reported in literature with thirteen personal cases

	Cases in literature, 1957-1978 (n=32)		Personal cases, 1973-1978 (n=13)	
Past allergy		30%		60%
Previous expositions to succinylcholine	(1/3 with the same incident noted during a previous anaesthetic)	70%	(1/3 with the same incident noted during a previous anaesthetic)	50%
Collapse		70%		70%
Cutaneous and mucosal symptoms (erythema, urticaria, facial oedema)		60%		70%
Bronchospasm		50%		60%
Cardiac arrest	1 case		5 cases (2 primary CA, 3 secondary CA)	
Ventricular tachycardia	1 case			
Diarrhoea	1 case			
Vomiting	1 case			
Melena, haematemesis				2 cases
Shock lung-shock liver				1 case
Death	1 case (irreversible coma)		1 case (irreversible coma)	

Specific tests	Carried out (cases)	Positive (cases)	Carried out (cases)	Positive (cases)
Not done	4			
i.d.-R.	24	20 (70%)	11	11 (100%)
i.v. test	2	2 (100%)	—	—
P-K	6	1	5	3
RBDT (Shelley)	4	1	12	10
HBDT	—	—	7	4
LTT	6	1	10	0

diagnosis between non-specific histamine release and true anaphylaxis remains in most cases extremely controversial. Clinical changes alone do not allow the diagnosis to be made and immunological tests are essential. Apart from cutaneous tests, the cases reported hitherto have rarely been submitted to other investigations. In four cases, the diagnosis was made without any tests (Table 2).

In 70% of the cases reported in the literature, there had been previous exposure to muscle releasing drugs, and one third of these patients had shown the same pattern of response. The percentages of previous exposure, and the frequency of bronchospasm, collapse, cutaneous and mucosal signs reported in the literature are very similar to those observed in our series of cases. However, in our cases, cardiac arrest was seen in five, in two of which there was primary cardiac arrest interpreted to be the first sign of the impending anaphylaxis. Due to adequate treatment there have been only two deaths, consequent upon the prolonged anoxia, one reported in the literature and one in our series.

The diagnosis of anaphylaxis can only be made on the evidence of allergic sensitivity. Skin tests provide good evidence provided that low doses (0.01 μ g, 0.1 μ g, 1 μ g and 10 μ g) of succinylcholine are used. In twenty-four of the cases reported in the literature skin tests were positive in 70%. Hapten dilution was seldom used, though in our eleven cases this procedure was positive in all.

In previous investigations there were four reports of Prausnitz-Küstner tests being made to confirm the presence of anaphylactic antibodies; one positive test being reported by Jerume *et al.* (1967) and one reported by Vervloët *et al.* (1977). Positive P-K tests were observed in three of five cases examined in our series. We also detected one case (No. 5) in which IgG S-TS antibody also appeared to be present. This antibody is heat-stable and sensitizes human skin for only 2-4 hr (Parish, 1973, 1979) and may occur in the same sera containing IgE (Pepys *et al.*, 1979). The P-K test affords incontrovertible evidence of anaphylactic antibodies.

The rabbit basophil degranulation test was positive in one case examined by Vervloët *et al.* (1977) and in 80% of our cases, provided repeated examinations were made. The human basophil degranulation test is considered diagnostic of IgE-mediated hypersensitivity (Ishizaka, Ishizaka & Tomeoka, 1971; Bela-Binda & Valeri, 1971). The technique developed by Benveniste *et al.* (1977) is easy to carry out, is very sensitive, and antibody is detectable by this method several years after the anaphylactic episode.

The results of the lymphocyte (lymphoblastic) transformation tests are of little value. In previous reports it was positive in one of six cases, and in our series negative in eight of ten with doubtful results in the other two. Furthermore, this test does not provide evidence of anaphylactic reaginic allergy.

In our opinion, the most useful tests to detect anaphylactic allergy to this drug are the direct skin test, Prausnitz-Küstner test and human basophil degranulation test.

The same pharmacological substance, e.g. histamine, mediates the changes in anaphylactic reactions as in true anaphylaxis. In the susceptible persons there is an increased susceptibility to release histamine, and a hyperreactivity to the effects of histamine frequently associated with spasmophilia as demonstrated by the positive electromyogram tests (Laxenaire *et al.*, 1976).

It is an interesting observation that injection of steroids prior to the use of the muscle relaxant does not prevent anaphylaxis, as evident in one case of Mandappa *et al.* (1975) and one of our patients.

With the extensive use of synthetic muscle relaxants, the number of cases of anaphylactic or anaphylactoid accident is increasing: fifteen cases were reported in the 15 years from 1957 to 1971, and 30 more in the following 5 years 1972–1977. The true nature of the reactions observed can only be determined by careful tests such as those used in our study. The examination should be made within an optimal period of from 6 weeks to 3 months after the incident, and repeated a few months later if negative.

The patient should be informed of every anomaly occurring as a result of anaesthesia, and after a follow-up examination he should be provided with a chart on which all drugs and anaesthetics, to which he is believed to have adverse reactivity, should be noted. All patients having had anaphylactic reactions to anaesthetics, particularly with cardiac arrest as in one third of our patients, should be examined in detail before discharge.

We consider that it is important that anaesthesiologists and immunologists should be aware of the risks of reactions to synthetic muscle relaxants.

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