EARLY DIAGNOSIS OF ANAPHYLACTIC REACTIONS TO NEUROMUSCULAR BLOCKING DRUGS


SUMMARY

Neuromuscular blocking drugs (NMB) are involved in most of the anaphylactic reactions occurring during anaesthesia. Patients are evaluated usually 6 weeks after the reaction, by skin testing. In order to obtain an earlier diagnosis, we have measured plasma concentrations of histamine, tryptase and NMB-specific IgE antibodies in 14 patients after an anaphylactoid reaction. We have compared the results with those of skin tests and specific IgE obtained 8 weeks later. Good agreement was observed in all subjects between the results of skin tests and the values for histamine and tryptase, provided that both markers were measured simultaneously. Furthermore, there was no significant difference between the concentrations of NMB-specific IgE antibodies observed at the time of the reaction and 8 weeks later. Thus anaphylaxis to neuromuscular blocking drugs can be demonstrated at the time of the reaction by measuring plasma concentrations of histamine, tryptase and specific IgE. In the event of the patient’s death, such measurements may be useful in identifying the likely cause. (Br. J. Anaesth. 1992; 69: 611-614)

KEY WORDS

The frequency of anaphylactic reactions during anaesthesia has been estimated at 1 in 6000 operations, with neuromuscular blocking drugs involved in 80% of cases [1]. The mechanism is mediated usually via IgE antibodies related to substituted ammonium ions [2]. The diagnosis can only be made at a later date, as skin testing must not be performed earlier than 6 weeks after the reaction [3]. However, in some cases, earlier diagnosis is important: first when surgery has been stopped but is still urgent and second for legal reasons, if the patient dies.

However, most adverse reactions occurring during anaesthesia are not anaphylactoid events [4, 5]. Thus it is important to prove in vivo histamine release. This can be achieved by measurement of histamine or tryptase during the reaction [6-8].

Usually, several drugs are administered during induction of anaesthesia. The role of neuromuscular blocking drugs (NMB) may be assessed by demonstrating either NMB-specific IgE antibodies or in vitro release of histamine [9, 10]. The latter cannot be performed soon after the reaction, because basophil histamine stores are depleted [11]. NMB-specific IgE antibodies may be detected 6 weeks after the reaction, in 87.9% of reactive subjects [12]. Recently, it has been suggested that anaphylaxis could be diagnosed in fatal cases by measuring drug-specific IgE antibodies [13]. However, to our knowledge, there has been no work to examine if such measurements are reliable at the time the reaction occurs.

Thus the goal of the study was to evaluate the accuracy of the diagnosis obtained at the time of the reaction, by measurements of plasma histamine, tryptase and NMB-specific IgE antibodies. The results were compared with those of skin tests and specific IgE antibodies measured at 8 weeks or later.

PATIENTS AND METHODS

We studied 14 patients (six male) who had adverse reactions at induction of anaesthesia. Their mean age was 46 (SD 18.3) yr (range 13-71 yr). All had received a neuromuscular blocking drug and other anaesthetic agents. The clinical signs were cutaneous, bronchopulmonary or cardiovascular. The severity of the reaction was classified according to the scale of Ring and Messmer [14] (table I).

For all the patients, NMB-specific IgE antibodies were measured immediately after the reaction and at least 8 weeks later when skin tests were performed. The mean time interval between the two sample collections was 3.9 (2.0) months (range 2-9 months). Plasma histamine concentrations were measured in all patients during the 30 min after the reaction, as recommended by Lorenz, Neugebauer and Schmal [15]. Plasma concentration of tryptase was measured in nine patients.
NMB-specific IgE antibodies [12]

A quaternary ammonium-reactive phase was obtained by linkage of choline hydrochloride to Sepharose. A first incubation step with the serum of the patient allowed binding of specific IgE to the solid phase. After washing, a second incubation step was performed with $^{125}$I-anti-human-IgE IgG, followed by washing. The results were expressed as percent bound radioactivity. The within-assay coefficients of variation were 10% for normal values and 3% for large values. The mean value obtained in 20 control subjects was 1.3 (0.5)%.

Plasma histamine

Blood was obtained from a peripheral vein in EDTA-containing tubes and transferred immediately in chilled water to the laboratory. After centrifugation (4°C, 800 g), plasma was aspirated gently without approaching the white cell layer, then frozen at −20°C. Histamine was measured in duplicate in plasma or serum by an immunoradiometric assay [17] (Tryptase RIACT kit, Pharmacia, Uppsala, Sweden). The lower limit of detection of the assay is 0.5 μl litre$^{-1}$ (1 μg = 1 μg of purified human lung tryptase). Eighteen of 19 anaesthetized control subjects had tryptase values < 2 μl litre$^{-1}$. In one the tryptase concentration was 2.2 μl litre$^{-1}$. The normal value was considered < 2 μl litre$^{-1}$ and the pathological range > 5 μl litre$^{-1}$, according to Schwartz [6].

Skin tests

Serial dilutions of all the administered drugs were made in human serum albumin, and intradermal injections were performed as recommended by Fisher [18], 6 weeks after the reaction or later.

Statistical analysis

Data were expressed as mean (SD). Means were compared by Wilcoxon's test and linear correlation was performed using the method of least-squares. $P < 0.05$ was considered statistically significant.

RESULTS

Seven patients (Nos 1–7) had pathological concentrations of plasma histamine during the reaction (table I). Six of these seven patients had tryptase measurements made: four had increased concentrations of tryptase and two had normal or intermediate values. The seven patients had positive skin tests, six for the administered neuromuscular blocker and one (patient No. 5) for a urea-linked gelatine (Haemacel). Five of the six patients who had reacted to the administered neuromuscular blocker had increased concentrations of specific IgE antibodies, the remaining one (No. 1) being in the intermediate range.

One patient had intermediate concentrations of plasma histamine and increased concentration of tryptase (No. 8). Specific IgE antibodies were not found. However, skin tests were positive for pancuronium.

The six remaining patients (Nos 9–14) had small concentrations of plasma histamine. Tryptase was measured in two: the concentration was normal or in the intermediate range. Specific IgE antibodies were
found in none. Skin tests were negative for five. For the last patient (No. 9) the skin tests were not reliable because he reacted to the control solution.

The concentrations of NMB-specific IgE antibodies were compared in the 14 patients. The mean percent binding measured during the reaction was 7.6 (9.9) %, not significantly different from the mean binding ratio measured at least 8 weeks later—7.2 (9.5) %. A linear correlation ($r^2 = 0.972; P < 0.0001$) was found with a slope of 0.95 (0.04) and an intercept of 0.05 (0.5) (fig. 1). The values of slope and intercept were not significantly different, respectively, from 1 and 0.

Another patient, who experienced acute bronchospasm after injection of pancuronium leading to death within 1 h, was investigated before resuscitation was stopped: plasma histamine concentration was 1120 nmol litre$^{-1}$ and tryptase 240 u litre$^{-1}$. NMB-specific IgE antibody concentration was 16 %.

**DISCUSSION**

It has been recommended that patients undergoing anaphylactoid reactions be investigated as soon as the incident occurs [3, 9]. Plasma histamine, a major mediator involved in anaphylactic shock can now be measured routinely by a commercial radioimmunoassay of high sensitivity and specificity [16]. The half-life of histamine in plasma is in the order of minutes [19] and so the sample must be obtained as soon as possible after the reaction. Furthermore, blood basophils contain large concentrations of histamine; thus spontaneous haemolysis of the sample during blood collection may lead to false positive results because of concurrent damage of basophils. Tryptase, a stable protease stored in mast cell granules, is liberated into blood if mast cell activation occurs [6] and stays at increased concentrations in plasma for 6 h [8]. Moreover, blood cells do not contain tryptase [20], which allows for reliable measurements from haemolysed samples. Increased concentrations of these markers measured after an adverse reaction during anaesthesia suggest in vivo release of histamine.

In these studies, there was no discrepancy between the results of skin tests and the values of histamine and tryptase measured during the reaction. In five patients (Nos 10–14), skin tests failed to identify a responsible drug; all had moderate reactions, two having bronchospasm alone. Furthermore, plasma histamine was not increased, which suggested that in vivo histamine release had either occurred in very small concentrations (anaphylactoid reaction), or had not occurred. All the patients with positive skin tests had increased concentrations of plasma histamine or tryptase, or both. In patient No. 2, the sample was slightly haemolysed, but in vivo histamine release was confirmed by increased tryptase concentrations. In patient No. 8, histamine had disappeared from plasma, but not tryptase. In Nos 5 and 6, tryptase concentrations were not increased, but histamine concentrations were clearly pathological. Thus it is advisable to measure both histamine and tryptase from the plasma samples obtained during the reaction: if the sample has been obtained within a few minutes of the reaction, plasma histamine should be increased, but tryptase may not have reached blood yet. If blood has been sampled later, tryptase should have increased concentrations, whereas histamine concentrations may have returned to normal [8].

Neuromuscular blockers are responsible for 80 % of anaphylactoid reactions during induction of anaesthesia [1], and NMB-directed IgE stay for years at increased concentrations in the serum of sensitized subjects [21]. Our results demonstrate that these IgE may be reliably measured at the time the reaction occurs, with no significant difference in the concentrations 8 weeks later. These findings suggest that increased concentrations of IgE were present before the anaphylactic event, and thus that the reaction could be anticipated, as shown for protamine [22]. The sensitivity observed in this study was 85.7 % (six patients with increased IgE of seven patients with skin tests positive to neuromuscular blockers). This value is close to the sensitivity reported previously (87.9 %) [12].

Although our results are obtained from a small number of patients, they indicate that the diagnosis of anaphylaxis to neuromuscular blockers may be obtained early, by measuring plasma concentrations of histamine and tryptase, and specific IgE antibodies during the reaction. Such measurements provide the opportunity to elucidate immediately the mechanism of the reaction: anaphylaxis, with which plasma concentrations of histamine or tryptase and of specific IgE are increased, may be differentiated from anaphylactoid response, with which specific IgE are absent, and from non-anaphylactoid reactions with which plasma histamine, tryptase and specific IgE concentrations are normal. When skin tests are not available, either because the patient cannot return to hospital or when skin reactivity is abnormal, early investigations, if performed, appear to be useful. Moreover, it is of value when forensic evidence is requested, especially if the patient dies.
ACKNOWLEDGEMENTS

The authors thank the Laboratory of Nuclear Medicine for excellent technical assistance and Pharmacia Diagnostics AB for providing tryptase kits.

REFERENCES

11. Larochelle D, Gallet E, Bricard H. Whole blood histamine levels in the early retrospective diagnosis of anaphylaxis.

*BRITISH JOURNAL OF ANAESTHESIA*