

## RESISTANCE TO ATRACURIUM IN A PATIENT WITH AN INCREASE IN PLASMA ALPHA<sub>1</sub> GLOBULINS†

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### SUMMARY

*We observed that a female patient with a poorly differentiated adenocarcinoma of the stomach undergoing gastrectomy was markedly resistant to the action of the neuromuscular blocking drug atracurium. There was no evidence of tumour metastasis and her liver function tests were normal. Electrophoresis of plasma proteins revealed a marked increase in alpha<sub>1</sub> globulin. Alpha<sub>1</sub> acid glycoprotein is an acute phase reactant that is increased in patients with cancer and is present in the alpha<sub>1</sub> globulin electrophoresis pattern. It is likely that the mechanism for the resistance to neuromuscular block in the patient was an increase in drug binding to alpha<sub>1</sub> acid glycoprotein.*

### KEY WORDS

*Neuromuscular relaxants: atracurium. Complications: drug resistance. Protein: alpha<sub>1</sub> globulins.*

Several factors are known to cause resistance to the action of non-depolarizing neuromuscular blocking drugs. These include a variety of neurological conditions such as upper motor neurone lesions [1, 2], multiple sclerosis [3] and disuse atrophy [4] in addition to non-neurological conditions such as thermal injury [5-7] and concomitant administration of anticonvulsant drugs [8-10]. It has also been known since 1953 that patients with liver disease may be resistant to the action of tubocurarine [11] and, since that time, several reports have appeared which indicate that this occurs also with other drugs such as pancuronium [12, 13] and atracurium [14]. It is likely that the underlying cause of resistance differs according to the specific condition and blocking agent in question, but there have been conflicting reports on the role of altered plasma proteins, especially in burns patients [7] and those

with liver disease [14-18]. We report the case history of a patient who was markedly resistant to the action of atracurium, in the absence of manifest hepatic disease, but who did have a documented increase in alpha<sub>1</sub> globulins.

### CASE REPORT

A 65-year-old woman presented to the surgical outpatient department with a 5-month history of weight loss and, more recently, dysphagia and abdominal pain. Before this episode, she had been well and the only relevant previous history was that she had undergone a total abdominal hysterectomy in 1975. She was not receiving any regular medication.

The patient underwent gastroscopy, and mucosal biopsy revealed a poorly differentiated adenocarcinoma. She was admitted to hospital for gastrectomy where preoperative investigations revealed a normochromic, normocytic anaemia (haemoglobin 10.3 g dl<sup>-1</sup>) and a neutrophil leucocytosis (white cell count 13.2 × 10<sup>9</sup> litre<sup>-1</sup>). Plasma electrolytes and corrected serum calcium concentrations were within the normal range. Her liver function tests also were normal: alkaline phosphatase 206 iu litre<sup>-1</sup> (normal value < 300 iu litre<sup>-1</sup>), total bilirubin 4 µmol litre<sup>-1</sup> (< 23 µmol litre<sup>-1</sup>), aspartate transaminase 11 iu litre<sup>-1</sup> (< 43 iu litre<sup>-1</sup>). Total globulins were 28 g litre<sup>-1</sup>, immunoglobulins were: IgG 12.8 g litre<sup>-1</sup> (9-18.5 g litre<sup>-1</sup>), IgA 2.3 g litre<sup>-1</sup> (0.8-4.6 g litre<sup>-1</sup>), IgM 1.1 g litre<sup>-1</sup> (0.4-3.0 g litre<sup>-1</sup>).

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Electrophoresis revealed a marked increase in alpha<sub>1</sub> globulins. Plasma concentration of albumin was 19 g litre<sup>-1</sup> (30–46 g litre<sup>-1</sup>). Abdominal ultrasound revealed normal liver, kidneys and spleen, with no evidence of metastases. The patient's preoperative weight was 70.5 kg and the body mass index 29.8.

The patient was premedicated with temazepam 20 mg and anaesthesia was induced using a rapid sequence technique with thiopentone 3.5 mg kg<sup>-1</sup> and suxamethonium 1.3 mg kg<sup>-1</sup>. Anaesthesia was maintained with 66% nitrous oxide and 0.5–1.0% isoflurane in oxygen with an initial dose of alfentanil 30 µg kg<sup>-1</sup> followed by increments of 15 µg kg<sup>-1</sup>. Following return of neuromuscular transmission (determined by train-of-four stimulation of the ulnar nerve), atracurium 25 mg (0.35 mg kg<sup>-1</sup>) was administered which had no influence on the train-of-four. An additional 20 mg was given, which had the effect of reducing the fourth twitch in the train, but the patient was still clinically not paralysed. A different batch of atracurium was obtained fresh from the refrigerator and an additional 25 mg was given, which resulted in the abolition of the second, third and fourth twitches but not the first. After 30 min the train-of-four ratio had returned to normal and an additional 40 mg of atracurium resulted in abolition of the third and fourth twitches only. The procedure took approximately 70 min, after which the administration of neostigmine 2.5 mg caused prompt antagonism of block, with full return of the train-of-four response. Subsequently, the patient made an uneventful recovery with no signs of recurarization. Peroperative drugs included alfentanil, cefuroxime and metronidazole; the patient remained haemodynamically stable throughout the procedure. At operation there was evidence of local lymph node and omental involvement, but the liver and spleen were clear of tumour. In the immediate post-operative period the patient's temperature was 36.5 °C.

#### DISCUSSION

Dundee and Gray first commented in 1953 on the resistance to tubocurarine that may occur in the presence of liver disease [11]. Subsequent reports came to conflicting conclusions on the role of increased binding to plasma proteins and whether or not the protein subfraction involved was albumin or gamma globulin [15–18]. Soon after the introduction of pancuronium into clinical

practice, reports appeared indicating that there was resistance also to this drug in patients with liver disease [12, 13]. The liver plays an important role in the disposition of pancuronium, and it was reported that the resistance was caused by an increase in distribution and elimination half-life and a decrease in clearance [19, 20]. In contrast to its involvement in the disposition of pancuronium, the liver does not play an important role in the disposition of atracurium. However, as Gyasi and Naguib have reported recently, severe liver disease may be associated also with resistance to atracurium [14]. An alteration in plasma binding can influence the pharmacological activity of a drug, and in general a decrease in volume of distribution and a shortening of half-life occur [21, 22]. This would result in an increase in drug requirement for any given effect. Unlike acidic drugs, which are bound largely to albumin, basic drugs—although binding to some extent to albumin—associate more avidly with other plasma proteins [23]. The principal proteins to which basic drugs are bound include lipoproteins and alpha<sub>1</sub> acid glycoprotein [24]. Both these are present in the alpha<sub>1</sub> globulin fraction determined by electrophoresis. The varying results reported for the binding of neuromuscular blockers to gamma globulin have been referred to previously but it appears that, in general, basic drugs are not bound significantly to this fraction [24]. Of the two fractions associated with alpha<sub>1</sub> globulin, alpha<sub>1</sub> acid glycoprotein appears to play the major role in increasing binding in disease states [23, 24]. This acute phase reactant is known to increase non-specifically in response to a large number of conditions characterized by physiological stress such as infection, inflammation, trauma and, as in our report, cancer [25]. Although electrophoresis in our laboratory is unable to distinguish between the subfractions of alpha<sub>1</sub> globulin, in view of the association between carcinoma and the acute phase reactant, alpha<sub>1</sub> acid glycoprotein, we suggest that increased binding of atracurium to this plasma protein is the most likely explanation for the marked increase in dose requirement observed in our patient. In these circumstances it is probable that the decrease in albumin concentration had little or no influence on the overall binding of atracurium and was therefore largely an incidental finding.

It is widely appreciated that there is great individual variation in response to neuromuscular blocking drugs, but we believe that the degree of

resistance exhibited by our patient was such that it is highly unlikely that her response was merely that of a normal but insensitive individual. Another observation reinforces our point of view. The notes of her previous operation were available and revealed that, during her previous anaesthetic (for hysterectomy), she was given a total of 160 mg of gallamine for the procedure, which lasted 60 min.

In conclusion, we suggest that increased binding of atracurium to  $\alpha_1$  globulin plasma proteins was the most likely cause of resistance in our patient.  $\alpha_1$  acid glycoprotein is an acute phase reactant that is increased in patients with cancer and is present in the  $\alpha_1$  globulin electrophoretic fraction. An increase in this fraction is known to cause an increase in binding of basic drugs, which in turn leads to an increase in dose requirement for any given effect. It seems possible that this was the specific mechanism for resistance in our patient and, because of the variety of conditions, including thermal injury, that can lead to an increase in concentrations of  $\alpha_1$  acid glycoprotein, this may be the underlying cause in several circumstances.

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