Clinical Reports

Use of atracurium in a patient with plasma cholinesterase deficiency

Neil Donen MD

The use of atracurium during anaesthesia for abdominal hysterectomy in a 37-year-old patient with homozygous plasma cholinesterase [E³E³] deficiency is described. Intubation was achieved utilizing 0.47 mg·kg⁻¹ of atracurium. Subsequent doses of 0.08 mg·kg⁻¹, 0.12 mg·kg⁻¹ and 0.12 mg·kg⁻¹ were given 34, 57 and 78 minutes respectively after the initial dose. At the time of reversal of the residual effects of neuromuscular blockade, 26 minutes after the last dose, spontaneous respiration had resumed. The duration of action of the drug was not different from that described in normal patients. Atracurium would appear to be a safe drug to provide neuromuscular relaxation in patients with plasma cholinesterase deficiency, where surgical procedures of intermediate duration are being undertaken.

Atracurium is one of the newer non-depolarizing neuromuscular blocking agents. It is classified as an intermediate duration drug.¹ Inactivation occurs by ester hydrolysis and Hoffman elimination.² Atracurium is not dependent on plasma cholinesterase for its breakdown.³ Thus the drug would appear to be the preferred agent of choice for surgical procedures of intermediate duration, i.e., 30–60 minutes, in patients with plasma cholinesterase deficiency. The following case report details its use in a patient with a homozygous plasma cholinesterase deficiency.

Case report

A 37-year-old woman was admitted to hospital for a total abdominal hysterectomy and salpingo-oophorectomy for menorrhagia. Eight years previously she had required an

emergency Caesarean section for gestational diabetes complicated by pre-eclampsia. She had received 140 mg succinylcholine (1.75 mg·kg⁻¹) as the intubating dose. There was no response to nerve stimulation throughout the procedure. Postoperatively she required ventilatory support for another four hours before neuromuscular activity was judged adequate to allow spontaneous respiration. Investigation apparently indicated absent plasma cholinesterase activity. Unfortunately the actual results were not recorded on her chart. The patient was subsequently lost to follow-up until three years later when she presented with an unrelated medical problem.

The plasma cholinesterase level (first admission) was 400 u·L⁻¹ (normal 4900–8800 u·L⁻¹), measured by the colorimetric method of Dietz.⁴ The dibucaine and fluoride numbers were considered unreliable because of the low plasma cholinesterase level. These results are compatible with the E³E³ phenotype of plasma cholinesterase variants. The patient has a complex family history. She has eight siblings, each with a different father. No other member of the family have experienced any problems with general anaesthesia.

Pertinent physical examination during the present admission revealed a moderately obese 75 kg woman. Relevant laboratory investigations included normal liver function tests and a haemoglobin of 99 g·L⁻¹. Bone marrow examination revealed findings compatible with an iron deficiency anaemia. The patient was given two units of packed red blood cells. Blood for plasma cholinesterase was drawn 24 hours after completion of the blood transfusion. The results again confirmed plasma cholinesterase activity less than five per cent of normal (370 u·L⁻¹).

Anaesthetic management included omission of premedication. A nerve stimulator assessing ulnar nerve activity and evoked motor response was used. Following pre-oxygenation anaesthesia was induced with fentanyl 100 µg and thiopentone 350 mg. Once airway maintenance was assured atracurium 35 mg (0.47 mg·kg⁻¹) and an additional 250 mg thiopentone were given. The trachea was easily intubated two minutes later. Anaesthesia was

Key words

NEUROMUSCULAR RELAXANTS: atracurium;
ENZYMES: plasma cholinesterase.

From the Department of Anaesthesia, University of Manitoba, Winnipeg, Manitoba

Address correspondence to: Dr. Neil Donen, Department of Anaesthesia, St. Boniface General Hospital, 409 Tache Avenue, Winnipeg, Manitoba, R2H 2A6.

maintained using controlled ventilation with 50 per cent nitrous oxide and 1–1.25 per cent enflurane in oxygen. Diaphragmatic movement 34 minutes after the initial atracurium dose coincided with a 25 per cent twitch recovery using train of four nerve stimulation. Atracurium 6 mg ($0.08 \text{ mg} \cdot \text{kg}^{-1}$) was given. Twenty-three minutes later, atracurium 9 mg ($0.12 \text{ mg} \cdot \text{kg}^{-1}$) was given, followed by a final 9 mg dose 21 minutes later. At the time of reversal 26 minutes after the last dose the patient was breathing spontaneously with tidal volumes of 300–400 ml. The respiratory pattern was, however, very jerky and there was some fade of muscle contraction with tetanic stimulation. Reversal was accomplished with atropine 0.9 mg ($12 \mu\text{g} \cdot \text{kg}^{-1}$) and edrophonium 35 mg ($0.47 \text{ mg} \cdot \text{kg}^{-1}$). The patient was extubated and transferred to the recovery room. The postoperative recovery period and subsequent hospital course were uneventful.

Discussion

Plasma cholinesterase (butyrylcholinesterase or S-type cholinesterase) hydrolyses many esters but its main action is on butyrylcholine. Butyrylcholine is of laboratory interest only, with no apparent physiological significance. Although there is some experimental evidence to suggest plasma cholinesterase (ChE) has a useful physiological function, no unequivocal role has yet been assigned it. Its clinical importance is seen in its ability to rapidly hydrolyze esters, particularly succinylcholine. Prolonged paralysis occurs in those individuals unable to hydrolyze succinylcholine. A number of genetic variants have been described. The silent gene [E_1^s or E^sE^s] synthesizes ChE without the structure to hydrolyse the choline-ester bond. Thus there is no enzyme activity which can be measured against standard parameters. Biochemists are now able to recognize at least two different types of silent gene. One type of plasma cholinesterase deficiency is truly anenzymic with no ChE activity while a second type has two to eight per cent of the normal average level of ChE activity.⁵ The patient described fits into the latter group. Most clinical classifications, however, group the silent genes together as a single entity.

Atracurium offers the advantage of intermediate duration of action, 30–40 minutes to ten per cent recovery, compared to 90–150 minutes with pancuronium.⁶ This is particularly useful in cases where succinylcholine may be contraindicated. A particular advantage of atracurium is its essentially chemical or non-enzymatic degradation potential. Hoffman elimination is promoted by the combined electron-withdrawing properties of the ester carbonyl groups and positively charged nitrogens in its molecular structure. The net result is a breakdown of the bis-quaternary structure essential for its neuromuscular blocking activity, through molecular fragmentation. In-

creasing inhibition of this pathway occurs with falling pH and patient body temperature². Ester hydrolysis is also promoted by the electron-withdrawing effect of the positive charges on the quaternary ammonium groups. Chemically this would occur at acid pH, although at physiological pH it may be enzyme-catalyzed.⁷

Despite disagreement as to the major pathway of elimination,^{8,9} Merrett *et al.* demonstrated that *in vitro* there was no difference in the rate of degradation of atracurium in normal plasma versus plasma with low plasma cholinesterase activity.³ Two clinical cases support this observation. The first dealt with a case of organophosphate poisoning with low cholinesterase levels.¹⁰ The second occurred in a pregnant patient with heterozygous atypical cholinesterase deficiency.¹¹ The patient in this report had homozygous atypical plasma cholinesterase deficiency of the silent gene variety. In all cases the duration of action of atracurium did not appear to be different from that described in the literature.^{12,13}

Thus atracurium would appear to be a safe drug to provide neuromuscular relaxation in patients with plasma cholinesterase deficiency where surgical procedures of intermediate duration are being undertaken.

References

- 1 Basta SJ, Ali HH, Savarese JJ *et al.* Clinical pharmacology of atracurium besylate (BW33A): a new non-depolarizing muscle relaxant. *Anesth Analg* 1982; 61: 723–9.
- 2 Stenlake JB, Waigh RD, Urwin J *et al.* Atracurium: conception and inception. *Br J Anaesth* 1983; 55: 3S–10S.
- 3 Merrett RA, Thompson CW, Webb FW. *In vitro* degradation of atracurium in human plasma. *Br J Anaesth* 1983; 55: 61–6.
- 4 Dietz AA, Rubinstein HM, Lubrano T. Colorimetric determination of serum cholinesterase and its genetic variants by the propionylthiocholine-dithiobios (nitrobenzoic acid) procedure. *Clin Chem* 1973; 19: 1309–13.
- 5 Whittaker M. Plasma cholinesterase variants and the anaesthetist. *Anaesthesia* 1980; 35: 174–97.
- 6 Savarese JJ. A pharmacologic basis for choice of muscle relaxant. American Society of Anesthesiologists Annual Refresher Course Lectures 1985; 411.
- 7 Neill EAM, Chapple DJ, Thompson CW. Metabolism and kinetics of atracurium: an overview. *Br J Anaesth* 1983; 55: 23S–25S.
- 8 Stiller RL, Cook DR, Chakravorti S. *In vitro* degradation of atracurium in human plasma. *Anesth Analg* 1985; 64: 289.
- 9 Nigrovic V, Pandya JB, Auen M *et al.* Inactivation of atracurium in human and rat plasma. *Anesth Analg* 1985; 64: 1047–52.
- 10 Baraka A, Cava L, Jaude CA. Atracurium vs suxamethe-

nium in a case of organophosphorus poisoning. *Br J Anaesth* 1984; 56: 673.

- 11 Baraka A and Jaude CA. Atracurium in a parturient with atypical cholinesterase. *Br J Anaesth* 1984; 56: 930-1.
- 12 Foldes FF, Nagashima H, Boros M et al. Muscular relaxation with atracurium, vecuronium and Duador under balanced anaesthesia. *Br J Anaesth* 1983; 55: 97S-103S.
- 13 Hughes R. Atracurium - the first years. *Clinics in Anaesthesiology* 1985; 3: 331-45.

Résumé

L'utilisation de l'atracurium chez un patient âgé de 37 ans présentant une déficience en cholinestérase plasmatique homozygote (E⁺E⁺) se présentant pour chirurgie est rapportée. L'intubation a été accomplie avec 0.47 mg·kg⁻¹ d'atracurium. Des doses subséquentes de 0.08 mg·kg⁻¹, 0.12 mg·kg⁻¹ et 0.12 mg·kg⁻¹ ont été données à 34, 57 et 78 minutes respectivement après la dose initiale. Lors de l'antagonisme des effets résiduels du bloc neuromusculaire, 26 minutes après la dernière dose, la respiration spontanée était retenue. La durée d'action du médicament n'était pas différente de celle décrite dans la littérature chez les patients normaux. L'atracurium apparaîtrait sécuritaire pour les blocages neuromusculaires chez les patients atteints d'une déficience en cholinestérase plasmatique pour des procédures chirurgicales de durée intermédiaires.