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Atracurium during induced hyperthermia

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Abstract
During hyperthermic intraperitoneal chemotherapy (HIPEC), we observed a partial recovery from neuromuscular block in a hyperthermic patient after hours of monitored adequate surgical relaxation and continuous infusion of atracurium during normothermia. This recovery is indicative of the higher clearance of atracurium during hyperthermia. This case report emphasizes the clinical relevance of the well-known temperature dependence of the Hofmann elimination of atracurium. Moreover, this report illustrates the importance of monitoring muscle relaxation during HIPEC. Clinicians should be aware that the usual continuous infusion rate of atracurium at 0.3 $mg \cdot kg^{-1} \cdot h^{-1}$ may be inadequate in hyperthermic patients.

Key words Neuromuscular block · Atracurium · Monitoring · Neuromuscular function · Hyperthermia

Introduction

Atracurium is a widely used neuromuscular blocking drug. Clearance from the body is mainly through Hofmann elimination, a spontaneous nonenzymatic degradation process that is dependent on blood pH and body temperature. Hypothermia increases the duration of action of atracurium [1,2]. In a case report, a shorter than normal duration of action of a single shot of atracurium during hyperthermia has been described [3].

Hyperthermic intraperitoneal chemotherapy (HIPEC) in the treatment of peritoneal carcinomatosis of colorectal origin has been developed recently [4]. In short, during laparotomy all tumor foci are cleared from the abdomen and the abdominal cavity is subsequently perfused for 90 min with the chemotherapeutic agent mitomycin C at 40°C. This results in a 20 times higher peritoneal drug exposure compared to intravenous administration [5] and improves patient survival in comparison to palliative systemic chemotherapy [4].

We describe a patient who underwent HIPEC. We used a continuous and unaltered infusion of atracurium for muscle relaxation and monitored neuromuscular transmission (NMT) with train-of-four (TOF) responses [6]. We observed a partial recovery from atracurium-induced neuromuscular block during hyperthermia, after hours of adequate surgical relaxation during normothermia.

Case history

A 52-year old woman weighing 59 kg was diagnosed with peritoneal carcinomatosis following sigmoid resection for adenocarcinoma; she was scheduled for cytoreductive surgery and HIPEC.

After placement of a thoracic epidural catheter (Th 11–12), anesthesia was induced with propofol 2.5 $mg \cdot kg^{-1}$, midazolam 0.1 $mg \cdot kg^{-1}$, fentanyl 4 $\mu g \cdot kg^{-1}$, and atracurium 0.6 $mg \cdot kg^{-1}$ intravenously. After intubation the lungs were ventilated, maintaining normocapnia. Anesthesia was maintained with propofol (3.5–6 $mg \cdot kg^{-1} \cdot h^{-1}$) and relatively low-dose remifentanil (4–17 $\mu g \cdot kg^{-1} \cdot h^{-1}$) infusions. Analgesia was provided by epidural infusion of bupivacaine and sufentanil (0.17 $mg \cdot kg^{-1} \cdot h^{-1}$ and 0.14 $\mu g \cdot kg^{-1} \cdot h^{-1}$, respectively). Muscle relaxation was maintained with continuous and unaltered infusion of atracurium (0.3 $mg \cdot kg^{-1} \cdot h^{-1}$) and monitored with TOF responses at the adductor pollicis muscle. At constant pH and normothermia, no twitches were observed with TOF monitoring during 4 h of continuous infusion of atracurium, suggesting a steady state of adequate muscle relaxation. After extensive cytoreduction, HIPEC was started. Warmed dialysis fluid perfused the abdominal cavity for 30 min until a core temperature of 39°C was reached. The intraperitoneal temperature was measured to be 40°C at three sites.

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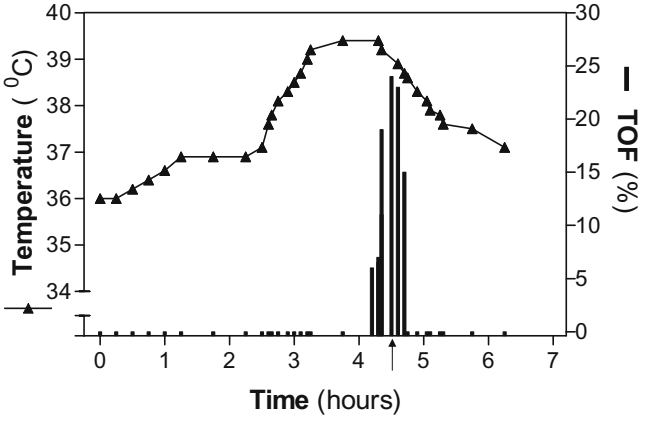

Fig. 1. Relaxation was adequate (train-of-four responses; *TOF* 0%) at normothermia (t = 0 to t = 2.5 h). At t = 2.5 h, intraperitoneal hyperthermia was started, increasing core temperature to 39°C at t = 3.2 h. TOF responses (24%) returned 1 h later. After the bolus of 10 mg of atracurium at t = 4.7 h (as indicated by the *arrow on the time axis*) TOF responses again returned to 0

Mitomycin C was added to the dialysis fluid and the abdominal cavity was perfused for another 90 min. Fifteen minutes after a core temperature of 39°C was reached, an increase in the number of twitches was observed with NMT monitoring (Fig. 1), despite continuing the infusion of atracurium (0.3 $mg \cdot kg^{-1} \cdot h^{-1}$). One hour after establishing a core temperature of 39°C, we observed four twitches, and the first twitch regained 25% of height at baseline, necessitating an extra bolus of 10 mg of atracurium. In this phase, adequate relaxation is of surgical importance to prevent spill of the perfusate containing the chemotherapeutic agent. After disconnection of the perfusion circuit, the core temperature decreased to 37.5°C and with an unaltered rate of atracurium infusion (0.3 $mg \cdot kg^{-1} \cdot h^{-1}$) muscle relaxation remained adequate. After completion of the surgery, the patient had an uncomplicated recovery in the intensive care unit.

Discussion

In the present patient hyperthermia caused partial recovery from surgical neuromuscular block.

Temperature is known to influence the duration of action of neuromuscular blocking drugs. Carrier-mediated active transport processes in the liver are temperature-dependent and are inhibited by hypothermia and enhanced by hyperthermia [7]. Therefore, without influence on the neuromuscular junction, hypothermia prolongs the duration of action of vecuronium, which is cleared solely by the liver and kidneys [7]. Hypothermia also prolongs the duration of action of atracurium. Dose requirements to maintain constant relaxation are reduced by 35% during cardiopulmonary bypass at 30°C [1]. The mechanism of prolongation of the duration of action of atracurium by hypothermia is probably multifactorial. Hofmann elimination is a temperature- and pH-dependent process of decomposition of quaternary amino compounds that is independent of enzyme or organ function and accounts for 40% of the clearance of atracurium [8]. The remaining 60% of clearance is by metabolism or hepatic and renal excretion. Liver clearance of atracurium occurs by the same carrier-mediated transport processes as with other neuromuscular blocking drugs (see above), and is thus influenced by temperature.

A model to predict the duration of action of vecuronium showed no linear relation between temperature and duration of action, i.e., a decrease in temperature had a larger influence per °C change than an increase from 37°C to 38°C [7]. In patients undergoing HIPEC, boluses of vecuronium during hyperthermia had a 40% shorter duration of action compared with that during normothermia [9]. However, for atracurium, both Hofmann elimination and clearance by the liver are augmented by hyperthermia; hyperthermic dogs required a 37% higher infusion rate of atracurium at 42°C than at normal temperature for the same degree of neuromuscular block [10]. A reduction of nearly 40% for a continuous infusion is presumed to be larger than 40% reduction of a single dose, as continuous infusions allow lower total dosing. A linear relationship was shown between temperature and dose needed [10]; dogs needed a 9.25% higher infusion rate per °C increase in body temperature. If one were to extrapolate this result to humans, which has not been verified in clinical studies, one would need 18.5% extra (or 55 $\mu g \cdot kg^{-1} \cdot h^{-1}$ extra) at 39°C, resulting in an infusion rate of 0.36 $mg \cdot kg^{-1} \cdot h^{-1}$ instead of 0.3 $mg \cdot kg^{-1} \cdot h^{-1}$.

We used the adductor pollicis muscle for TOF monitoring. A peripheral muscle like this is among the last to recover from muscle relaxants. At that point respiratory and laryngeal muscles would already have recovered. If we had measured TOF responses at the orbicularis oculi muscle it is possible that the observed time lag between rise in temperature and return of twitches would have been reduced and that we would have observed an earlier return of twitches.

In our patient, hemodynamics remained unchanged and ventilator settings were not altered. Arterial pH, P_{CO_2} and end-tidal CO_2 did not change during hyperthermia, which changes would have indicated an increase in metabolic rate. Hyperthermia could also have shortened the duration of action of atracurium by increasing muscle perfusion and increasing the relatively small volume of distribution. Moreover, ester hydrolysis may be enhanced in hyperthermia. Further, the possibility of

a yet unknown side effect of mitomycin on neuromuscular function during hyperthermia cannot be excluded.

Hofmann elimination accounts for 77% of the clearance of the newer neuromuscular blocking drug cisatracurium, one of the ten stereoisomers of atracurium [11]. Considering the above-mentioned data, one might expect a more pronounced influence of temperature on the duration of action of cisatracurium. However, there are no clinical data to support this assumption.

In conclusion, we observed a partial recovery from neuromuscular block in a hyperthermic patient during continuous infusion of atracurium. This recovery is indicative of the higher clearance of atracurium during hyperthermia than during normothermia. Augmented Hofmann elimination during hyperthermia may be the most likely mechanism. Therefore, clinicians should be aware that the usual continuous infusion rate of atracurium at $0.3\ mg \cdot kg^{-1} \cdot h^{-1}$ may be inadequate in hyperthermic patients. Moreover, this report illustrates the importance of monitoring muscle relaxation during HIPEC.

References

1. Flynn PJ, Hughes R, Walton B, Jothilingam S. Use of atracurium infusions for general surgical procedures including cardiac surgery with induced hypothermia. Br J Anaesth. 1983;55:135–8S.
2. Leslie K, Sessler DI, Bjorksten AR, Moayeri A. Mild hypothermia alters propofol pharmacokinetics and increases the duration of action of atracurium. Anesth Analg. 1995;80:1007–14.
3. Benzer A, Mitterschiffthaler G, Pomaroli A, Müller L. Atracurium in whole body hyperthermia. Anaesthesia. 1990;45:991.
4. Verwaal VJ, van Ruth S, de Bree E, van Slooten GW, van Tinteren H, Boot H, Zoetmulder FA. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol. 2003;21:3737–43.
5. Fernandez-Trigo V, Stuart OA, Stephens AD, Hoover LD, Sugarbaker PH. Surgically directed chemotherapy: heated intraperitoneal lavage with mitomycin C. Cancer Treat Res. 1996; 81:51–61.
6. Viby-Mogensen J. Neuromuscular monitoring. In: Miller RD, editor. Miller's anesthesia. 6th ed. Philadelphia: Elsevier Churchill Livingstone; 2005. p. 1552–3.
7. Caldwell JE, Heier T, Wright PMC, Lin S, McCarthy G, Szenohradszky J, Sharma ML, Hing JP, Scroeder M, Sessler DI. Temperature-dependent pharmacokinetics and pharmacodynamics of vecuronium. Anesthesiology. 2000;92:84–93.
8. Fisher DM, Canfell PC, Fahey MR, Rosen JI, Rupp SM, Sheiner LB, Miller RD. Elimination of atracurium in humans: contribution of Hofmann elimination and ester hydrolysis versus organ-based elimination. Anesthesiology. 1986;65:6–12.
9. Adachi T, Shinomura T, Nomura R. Duration of vecuronium-induced neuromuscular blockade is shortened during hyperthermic intraoperative intraperitoneal chemotherapy. Br J Anaesth. 2003;91:160–1.
10. Meyer RE, Page RL, Thrall DE, Dewhirst MW, Vose DL. Determination of continuous atracurium infusion rate in dogs undergoing whole-body hyperthermia. Cancer Res. 1986;46: 5599–601.
11. Kisor DF, Schmith VD. Clinical pharmacokinetics of cisatracurium besilate. Clin Pharmacokinet. 1999;36:27–40.