Determination of Continuous Atracurium Infusion Rate in Dogs Undergoing Whole-Body Hyperthermia

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ABSTRACT

Infusion rates for atracurium were calculated from multiple bolus injection data for normothermic (38°C; n = 4) and hyperthermic (42°C; n = 14) dogs anesthetized with thiopental and oxymorphone while undergoing whole-body hyperthermia treatment. The calculated infusion rate for atracurium at 38°C was 6.2 ± 0.3 μg/kg/min and the calculated infusion rate at 42°C was 8.5 ± 0.4 μg/kg/min. Infusion of atracurium at the calculated infusion rate of 8.5 μg/kg/min produced an estimated 90-100% neuromuscular blockade during heating from 38-42°C and at 42°C. Following discontinuation of the infusion and cooling to 38°C, neuromuscular function returned to normal within 20 min with no evidence of reaccumulation. Atracurium infusion rates appear to be linear and related to body temperature from 26-42°C. Clinically useful neuromuscular blockade in dogs may be obtained during whole-body hyperthermia by utilizing the 42°C atracurium infusion rate throughout the 38-42°C heating phase.

INTRODUCTION

WBH, in which body temperature is raised to 42°C under controlled conditions, is presently under investigation in both animals and humans as a possible means to enhance the anti-neoplastic activity of radiation therapy and chemotherapy. Use of general anesthesia for WBH permits more aggressive control and support of patient reflexes, fluid requirements, and blood gases (1). Control of ventilation by means of neuromuscular blocking agents prevents heat-induced hyperventilation and respiratory alkalosis during WBH, and in dogs also prevents heat loss via an effective panting mechanism.

Atracurium (Tracrium; Burroughs Wellcome, Research Triangle Park, NC) is a nondepolarizing muscle relaxant with an onset of action of 0.5-1 min, a duration of action of 40-60 min, and a terminal half-life of 2.7-3.5 h. It provides 100% neuromuscular blockade during heating from 38-42°C and at 42°C. The duration of neuromuscular blocking effect of atracurium was defined as the time required for return of spontaneous ventilatory activity following administration of the drug. Additional i.v. boluses of atracurium (0.1 mg/kg) were given when spontaneous ventilatory movement occurred following the initial atracurium bolus. The time required for return of spontaneous ventilatory activity was recorded following each subsequent dose of atracurium for the remainder of the heating procedure. Atracurium infusion rates were then calculated for each dog based on the amount of drug administered as intermittent boluses during a known period of time at a specific temperature. In addition, atracurium-induced neuromuscular receptor blockade in heated dogs was monitored by train-of-four stimulation. Carpal twitch responses to indirect ulnar nerve stimulation were visually determined with a Professional Instruments NS-3A stimulator. One lead was attached to the skin caudal to the median humeral epicondyle over the ulnar nerve and the other lead was placed midway between the elbow and carpus. Four supramaximal stimuli, 0.5 sec apart, were given at 10-sec or greater intervals (train-of-four response test) (8-10). The presence or absence of gross carpal movement in response to each twitch of the train-of-four stimulation was noted. Neuromuscular receptor blockade was estimated by the method of Lee (11), where the disappearance and

MATERIALS AND METHODS

For studies at 38°C, 4 normal mixed-breed dogs were obtained from the North Carolina State University School of Veterinary Medicine Laboratory Animal Service. For hyperthermic studies, data from 7 additional normal mixed-breed dogs from the same source were combined with data from 7 privately owned dogs with cancer referred to the School of Veterinary Medicine for cancer therapy. These 7 dogs had disseminated solid tumors unsuitable for more conventional types of therapy. All 14 dogs had normal renal, hepatic, and cardiac function and were clinically normal, except for presence of tumors. Except for 2 of the tumor-bearing dogs, the 14 dogs were each heated once for a total of 17 WBH treatments; one dog was heated 3 times and another was heated twice. Repeat WBH procedures were at 14-day intervals.

Food was withheld for 12 h prior to heating. All dogs were premedicated 30 min prior to induction of anesthesia with i.m. atropine sulfate (0.04 mg/kg), diazepam (0.4 mg/kg), and oxymorphone (0.08 mg/kg). Thiopental (5 mg/kg) and atracurium (0.4 mg/kg) were given i.v. through an indwelling catheter to induce anesthesia and facilitate orotracheal intubation. Positive-pressure ventilation was started with a rate of 16 breaths/min and a measured tidal volume of 15 ml/kg (Wright's respirometer). This rate and tidal volume produces arterial pH and pCO₂ levels of 7.35 ± 0.06 and 36.5 ± 5.8 mm Hg at 38°C, 7.29 ± 0.04 and 36.6 ± 5.1 mm Hg at 42°C, and 7.28 ± 0.09 and 39.2 ± 2.8 mm Hg following 60 min at 42°C (n = 6). Additional increments of thiopental (2.5 mg/kg) and oxymorphone (0.08 mg/kg) were administered i.v. based on assessment of indirect blood pressure (Dinamap 1255), heart rate, and pupillary dilation. Total thiopental dose was limited to a maximum of 30 mg/kg during the course of the WBH procedure. Lactated Ringer's solution was administered i.v. at 10 ml/kg/h throughout the procedure.

WBH to a core temperature (rectal) of 42°C, was produced in a radiant heating device (Enthermics Inc., Menomonee Falls, WI) similar to that used for WBH in humans (6, 7). The device is an open-ended chamber that allows 360-degree radial heating about the long axis of the dog (Fig. 1). After clipping ventral body hair that would interfere with heat transfer, dogs were placed in the chamber in dorsal recumbency on a mesh stretcher and the ends of the chamber were closed with heat-reflective blankets. Rate of core temperature rise was adjusted by altering heating element thermostatic settings. Temperature rise was limited to approximately 0.05°C/min; the time required to raise core temperature from 38-42°C was approximately 90 min. The target core temperature of 42 ± 0.1°C was maintained for 60 min.

The duration of neuromuscular blocking effect of atracurium was defined as the time required for return of spontaneous ventilatory activity following administration of the drug. Additional i.v. boluses of atracurium (0.1 mg/kg) were given when spontaneous ventilatory movement occurred following the initial atracurium bolus. The time required for return of spontaneous ventilatory activity was recorded following each subsequent dose of atracurium for the remainder of the heating procedure. Atracurium infusion rates were then calculated for each dog based on the amount of drug administered as intermittent boluses during a known period of time at a specific temperature. In addition, atracurium-induced neuromuscular receptor blockade in heated dogs was monitored by train-of-four stimulation. Carpal twitch responses to indirect ulnar nerve stimulation were visually determined with a Professional Instruments NS-3A stimulator. One lead was attached to the skin caudal to the median humeral epicondyle over the ulnar nerve and the other lead was placed midway between the elbow and carpus. Four supramaximal stimuli, 0.5 sec apart, were given at 10-sec or greater intervals (train-of-four response test) (8-10). The presence or absence of gross carpal movement in response to each twitch of the train-of-four stimulation was noted. Neuromuscular receptor blockade was estimated by the method of Lee (11), where the disappearance and

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2. To whom requests for reprints should be addressed, at Department of Anatomy, North Carolina State University, School of Veterinary Medicine, 4700 Hillsborough Street, Raleigh, NC 27606.
3. The abbreviation used is: WBH, whole-body hyperthermia.
ATRACURIUM INFUSION DURING CANINE WBH

Table 1 Atracurium infusion rates for canines and humans

<table>
<thead>
<tr>
<th></th>
<th>Temperature (°C)</th>
<th>Atracurium infusion rate (µg/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>6</td>
<td>4.0 ± 0.3*</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>6.8 ± 0.6†</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>6.2 ± 0.3‡</td>
</tr>
<tr>
<td>Canines</td>
<td>17</td>
<td>8.5 ± 0.4¶</td>
</tr>
</tbody>
</table>

* Significance is as follows: † is greater than ‡ (P < 0.01, canines; P < 0.05, humans) and is greater than § (P < 0.001). Human data from Flynn et al. (12). Values shown are means ± SE.

Fig. 1. The Enthermics radiant heating device with a dog in position for WBH treatment.

Fig. 2. Regression line for atracurium infusion rates observed for dogs at 38°C (n = 4) and 42°C (n = 17) and for humans at 26°C (n = 6) and 36°C (n = 6). Atracurium infusion rate = 0.2720 (temp °C) - 3.1009, r = 0.792; P < 0.001. Human data from Flynn et al. (12). Values shown are means ± SE.

rate for dogs at 38°C was the same as the measured infusion rate reported to produce 90–100% neuromuscular blockade in humans at 36°C (12, 13). The calculated infusion rate for dogs at 42°C was greater than the measured infusion rates for humans at 36 and 26°C, respectively.

The regression line for combined atracurium infusion rates observed in humans at 26 and 36°C and dogs at 38 and 42°C is presented in Fig. 2. The correlation coefficient is statistically significant (P < 0.001).

The calculated 42°C atracurium infusion rate (8.5 µg/kg/min) was used to produce continuous neuromuscular blockade in 5 additional dogs undergoing WBH. Estimated neuromuscular blockade was 90–100% as determined by consistent train-of-four responses (0–1 twitch/4 stimuli) and lack of spontaneous ventilatory movement during heating from 38–42°C as well as during the subsequent 60 min at 42°C. Recovery of neuromuscular function, as determined by return of 4 equal carpal twitches and the ability to generate a tidal volume of >10 ml/kg, occurred within 20 min following discontinuation of the infusion. No signs of residual curarization were observed following the procedure.

DISCUSSION

Administration of an atracurium bolus dose followed by a continuous atracurium infusion is a practical technique for inducing and maintaining neuromuscular blockade for WBH procedures. A single atracurium infusion rate of 8.5 µg/kg/min following an atracurium bolus (0.4 mg/kg) can be used for maintenance of neuromuscular blockade in dogs receiving thiopental and oxymorphone anesthesia during the 38–42°C heating period, as well as for 60 min at the target core temperature of 42°C. Under ideal circumstances, overdosage is avoided by individually varying infusion rates to provide the desired degree of neuromuscular blockade, as determined by monitoring of neuromuscular transmission. However, atracurium appears to be uniquely suited to infusion at constant rate during WBH because of its temperature and pH-dependent Hoffmann degradation into by-products that have no intrinsic neuromuscular blocking activity.

Hoffmann degradation is a nonenzymatic physical breakdown process that occurs simultaneously within all body compartments (2). All available evidence points toward linear kinetics over the therapeutic dose range. The rate-limiting step, \( V_{\text{max}} \), has not been determined for atracurium but appears to be
in excess of 0.7 mg/kg in normothermic humans. The elimination $T_{1/2}$ for atracurium (for i.v. bolus ranging from 0.3 to 0.7 mg/kg) in normal humans (14), humans in hepatic failure (15), and humans in renal failure (16) has been reported to be between 16 and 24 min. In the present study, this value of 0.7 mg/kg was probably not approached by either the initial i.v. bolus (0.4 mg/kg) or the subsequent i.v. maintenance boluses of atracurium (0.1 mg/kg) from which infusion rates were calculated. The 42°C infusion rate can be safely utilized during the 38–42°C heating phase without prolongation of neuromuscular blockade because termination of action at the neuromuscular receptor site will be predominantly dependent on temperature and pH and not on metabolism or excretion. This unique mechanism of elimination of atracurium should also be useful when dealing with canine or human patients presenting for WBH who are receiving nephrotoxic agents (cisplatin) or possess marginal renal or hepatic function prior to treatment.

The relationship between atracurium infusion rate and core temperature appears to be linear (Fig. 2). The calculated infusion rate for dogs at 38°C (6.2 ± 0.3 μg/kg/min) and the measured infusion rates obtained by both Flynn and coworkers (6.8 ± 0.6 μg/kg/min) (12) and Eager and coworkers (6.1 ± 0.3 μg/kg/min) (13) for humans at 36°C are nearly identical. The infusion rate for atracurium in humans at hypothermic temperature (25–26°C) has been shown to be significantly less than for humans at normothermic temperature (35–37°C), presumably due to decreased atracurium inactivation and depression of neuromuscular function at low temperature (12). Likewise, the infusion rate for atracurium in 42°C dogs is significantly higher than for 38°C dogs, probably due to increased atracurium inactivation. Ideally, infusion rate should be determined for both dogs and humans at several temperatures in order to determine whether this relationship is linear. However, this information exists neither for dogs at lower temperatures nor for humans at higher temperatures. Based on the combination of canine data determined in this study and the previously reported human data, atracurium infusion rates appear to be linearly related to temperature, but confirmatory work in both species over a wider range of temperatures will be required to definitively establish linearity.

Commonly used anesthetic drugs depress respiratory function, such that using ventilatory signs to assess neuromuscular blockade can be potentially misleading. Atracurium is not cumulative; recovery of neuromuscular function is predictably consistent following multiple doses and occurs 2 to 5 times faster than with other competitive neuromuscular blocking agents regardless of previously administered doses (5). Once recovery from neuromuscular blockade has begun, the recovery phase develops rapidly and is linear throughout that phase when plotted logarithmically (17). The primary muscles of ventilation, the diaphragm and intercostal muscles, are the last skeletal muscles to be affected by neuromuscular blocking agents and the first to recover. In this study, return of spontaneous ventilatory activity provided a consistent means to assess atracurium-induced neuromuscular blockade in normothermic dogs, as evidenced by the observed closeness to the reported normothermic human data. In addition, the increased ventilatory drive produced during WBH in dogs provided a physiological means to monitor neuromuscular blockade. Dogs lack exocrine sweat glands and become tachypneic as a means to regulate body temperature during WBH (18).

An advantage of continuous infusion of atracurium is that total administered dose for a given period of neuromuscular blockade is less than that required for a single bolus to produce blockade for the same period of time. A single bolus of atracurium, 0.6 mg/kg, produces blockade for 44 min in dogs at 37.5°C (19). Using the 38°C infusion rate of 6.2 μg/kg/min, blockade can be produced using atracurium, 0.372 mg/kg, over 60 min. Similarly, using the 42°C infusion rate of 8.5 μg/kg/min, blockade can be produced over a 60-min period using atracurium, 0.51 mg/kg.

Atracurium can be infused at a single constant rate to provide continuous neuromuscular blockade during WBH at 42°C in dogs. The required infusion rate has an apparently linear relationship with change in core body temperature. Continuous infusion of atracurium produces effective neuromuscular blockade using less drug than a single bolus would require for the same period of blockade. The temperature-dependent Hoffmann degradation for termination of neuromuscular blockade may be useful when performing WBH in patients with renal and hepatic compromise.

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