Pharmacology

Influence of Acute Normovolaemic Hemodilution on the Dose-Response Relationship and Time Course of Action of Cisatracurium Besylate

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(*Br J Anaesth*, 98: 342–346, 2007)

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DOI: 10.1097/SA.0b013e3181925c6b

Acute normovolemic hemodilution (ANH) is an efficacious and cost-effective blood conservation strategy to avoid allogeneic blood transfusion. The potencies of succinylcholine, pancuronium, vecuronium, atracurium, and rocuronium are augmented with ANH. A neuromuscular blocking drug that is not influenced by ANH, thus requiring no dose adjustments, could be beneficial in patients undergoing surgery with ANH. This prospective, controlled, clinical, consecutive study investigated whether the potency of cisatracurium besylate is altered with ANH. The dose-response relationship and time course of action in patients undergoing surgery with and without ANH were assessed.

Sixty patients undergoing radical cystectomy, radical hysterectomy, or retropubic radical prostatectomy were randomly allocated to the ANH or control group and were stratified by gender and American Society of Anesthesiologists physical status classification. Patients in each group were then randomly allocated to receive initial cisatracurium doses of 30, 40, or 50 μg/kg followed by a second supplemental dose to reach a total dose of 100 μg/kg. Standard blood parameters were measured before and after ANH. A volume of 15 mL/kg blood was obtained from the cubital vein and stored to be simultaneously replaced by an equal volume of 6% HES. The patient's blood was ideally reinfused toward the end of the operation after the phase of major blood loss, or sooner if clinically indicated. Thereafter, anesthesia was induced with fentanyl and propofol and the trachea was intubated without using neuromuscular blocking drugs. Neuromuscular block at the adductor pollicis muscle was evaluated with the Relaxometer mechanomyograph. The ulnar nerve was stimulated supramaximally at the wrist with train-of-four (TOF) stimuli at intervals of 12 seconds. Data were continuously recorded until patients fully recovered from neuromuscular block, which was evaluated with the first twitch of the TOF (T_1) expressed as percentage of control response and TOF ratio (T_4:T_1). After T1 baseline stabilization, the designated cisatracurium dose was given, and maximum neuromuscular block was recorded. Dose-response curves were obtained. Doses required for 50%, 90%, and 95% T_1 depression (ED_{50}, ED_{90}, and ED_{95}) were calculated. Times until 25% first twitch and 0.8 TOF ratio recoveries were also determined.

The patients in the 2 groups were similar in demographic characteristics. There was no notable blood loss during the neuromuscular monitoring period of the study. Hemoglobin, hematocrit, and plasma proteins declined with ANH, from 13.6 to 8.7 g/dL, 41.7 to 28.6%, and 6.7 to 4.4 g/dL, respectively. The groups did not differ in the T_1 stabilization period, anesthesia induction period, skin and core temperatures, mean arterial pressure, estimated blood loss, fluid replacement, and propofol and remifentanil requirements during the neuromuscular monitoring period. Acute normovolemic hemodilution did not result in a shift in the cisatracurium dose-response curve, and there were no differences between the groups in cisatracurium onset time or maximum T_1 block. The ED_{50}, ED_{90}, and ED_{95} values for the controls were 28.2, 47.6, and 55.3 μg/kg, respectively, and those for the ANH group were 29.5, 50.4, and 58.7 μg/kg, respectively. The time until 25% first twitch and 0.8 TOF ratio recoveries between the ANH group (40.8 and 64.7 minutes) and the controls (42.2 and 66.5 minutes) were similar.

Acute normovolemic hemodilution did not alter the potency, dose-response relationship, and time course of cisatracurium as evident by the similar ED_{50}, ED_{90}, and ED_{95} in the 2 groups. The differences between cisatracurium and other neuromuscular-blocking drugs may arise from the different distribution characteristics. Dosing adjustments were not required, which would make cisatracurium the neuromuscular blocking drug of choice in patients undergoing surgery with ANH.

COMMENT

It has been shown previously with several neuromuscular-blocking agents that hemodilution increases the potency of these drugs. Based on the results of the current study, the authors suggested that cisatracurium, in contrast with other neuromuscular blocking agents, has a different volume of distribution. The authors' conclusion was based solely on the evaluation of the neuromuscular blocking effect of cisatracurium rather than blood concentrations of the drug, which were not provided. Until there are other data to support these results, this study leaves us with many unanswered questions concerning the mechanism(s) of the lack of enhanced effect of cisatracurium during hemodilution that differs from observations with other neuromuscular-blocking agents.

Comment by Reuven Pizov, MD