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Original contribution

Pharmacokinetics and pharmacodynamics of cisatracurium in patients undergoing surgery with two hemodilution methods

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ABSTRACT

Objective: To investigate the pharmacokinetics and pharmacodynamics of cisatracurium in patients undergoing surgery under acute normovolemic hemodilution (ANH) and acute hypervolemic hemodilution (AHH).
Methods: Ninety patients with orthopedic surgery were divided into ANH, AHH and control groups, which received hemodilution by hydroxyethyl starch 130/0.4 transfusion, Voluven transfusion and regular transfusion and infusion during surgery, respectively. Each group was divided into 3 sub-groups, administrated with cisatracurium at dosage of 0.1, 0.2 and 0.3 mg/kg respectively. The changes in plasma protein, pH and electrolytes from the hemodilution beginning to surgery finish were monitored. Before and after cisatracurium administration, the phamocodynamic indicators of muscle relaxant were observed, and the plasma drug concentration was measured.
Results: After hemodilution or regular transfusion, all three groups experienced a distinct drop in total plasma protein, albumin and pH. Compared with control group, the plasma concentrations of both K^+ and Ca^{2+} in ANH and AHH groups significantly dropped ($P < 0.05$), and those in each group after administration of cisatracurium also dropped, compared with before ($P < 0.05$). After administration with cisatracurium, the onset time of muscle relaxation in AHH group was extended notably, compared with AHH and control groups ($P < 0.05$), with no distinct difference of residual pharmacodynamics parameters ($P > 0.05$). In the same hemodilution or regular infusion, with increase of drug dosage, the onset time of muscle relaxation was shortened, and the period of no response to train-of-four stimulation, muscle relaxation blockade duration and action time of muscle relaxation blockade in body were extended ($P < 0.05$).
Conclusion: When using cisatracurium under AHH, the dosage should be increased appropriately, while it need not be adjusted under ANH.

1. Introduction

Due to the shortage of blood source, rising awareness of people in blood transfusion risk and religious belief, the blood protection has become an important part with the development of surgery [1]. Hemodilution, including acute normovolemic hemodilution (ANH) and acute hypervolemic hemodilution (AHH), is an important measure of blood protection, which can not only reduce or even avoid the heterologous blood transfusion, but also avoid the infection and spreading of blood-borne diseases and other transfusion-related complications [2,3]. Compared with ANH, AHH is easy to operate, economic in manpower and time, low in cost, and favorable in reducing the chance of blood pollution, thus boasting more advantages [4,5]. Hemodilution can incur the changes to the hemodynamics, electrolytes and activity of some enzymes in the plasma, and affect the plasma protein binding rate, distribution, elimination and discharge of various muscle relaxants, thereby influencing their muscle relaxing effect. Different methods of hemodilution may have different impacts on the muscle relaxant. It is reported that ANH can extend the elimination half-time of vecuronium bromide [6], and AHH can shorten the muscle relaxation onset time of vecuronium bromide in general anesthesia patients and speed up the recovery of muscle relaxation [7]. The same method of hemodilution may bring about different action effects on different muscle relaxants. For example, ANH can enhance the sensitiveness of patients to vecuronium bromide [8], rocuronium bromide [9] and atracurium [10], extend the action duration [11], yet weaken the muscle relaxation effect of pancuronium bromide and obviously shorten the onset time and action time of pipecuronium bromide [12].

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Cisatracurium Besylate is a cis-enantiomer of atracurium, which can form a competitive binding with the cholinergic receptor of motor end plate. It has a muscle relaxing effect similar with atracurium but about three times of atracurium in intensity of muscle relaxation [13]. Cisatracurium does not bring about a notable change to the hemodynamics and histamine releasing, which is the greatest advantage that differs from atracurium [14]. It also has advantages such as quick onset time, strong action, quick recovery and no accumulation, which make it a fairly ideal muscle relaxant currently [15]. At present, the impact of hemodilution on pharmacokinetics and pharmacodynamics of cisatracurium still lacks a systematic research.

This study systematically investigated the changes of blood pH, electrolytes and plasma protein under ANH and AHH and the impacts of these changes on the pharmacodynamics of cisatracurium during perioperative period. The objective was to provide a reference frame for reasonable use of the new muscle relaxant in hemodilution.

2. Patients and methods

2.1. Patients

This study was done in Gongli Hospital, Clinical Medicine of the Second Military Medical University (Pudong New Area, Shanghai, China) from January 2012 to January 2013. 90 patients with lower limbs orthopedic surgery were selected, with ASA grade I-II, ages between 35 and 60, hemoglobin before surgery ≥ 110 g/L, hematocrit (Hct) ≥ 35%, quantity of platelets ≥ 100×10^9 /L, and no abnormality spotted in thrombin, heart, lung, liver or kidney functions. The design and implementation of the experiment was in accordance with Helsinki Declaration. This study was approved by the Ethical Committee of Gongli Hospital, Clinical Medicine of the Second Military Medical University.

2.2. Grouping

Patients were divided into 3 groups in accordance with the random number table (n = 30) as follows: ANH group received the ANH, AHH group received the ANH, and control group received the regular transfusion and infusion. Each group was divided into 3 sub-groups (ANH1, ANH2, ANH3; AHH1, AHH2, AHH3; Control1, Control2, Control3; n = 10), administrated with cisatracurium (batch number: 20,060,869, Jiangsu Hengrui Medicine Co., Ltd., Lianyungang, China) at a dosage of 0.1, 0.2 and 0.3 mg/kg, respectively. Double blind was used in the experiment. The participant would be ruled out of the experiment when the operation time was <1 h or the participant was accompanied with any kind of serious complications such as wakening delay and drug allergy. The flow diagram was shown in Fig. 1.

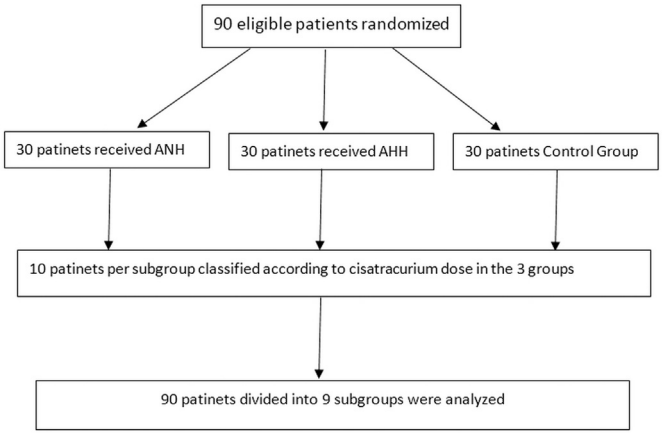

Fig. 1. Flow chart of patient selection.

2.3. Hemodilution method

Patients did not administrate medicine before the surgery and received a regular monitoring. The radial artery was catheterized under local anesthesia to monitor the blood pressure while right internal jugular vein was catheterized. Before anesthesia induction, the hemospasia of ANH group was 200–300 ml/10 min, while 6% hydroxyethyl starch 130/0.4 with medium molecular weight (Voluven, batch number: 732,702, Fresenius Company, Berlin, Germany) was injected via peripheral vein. The formula for hemospasia [16] was as follows: $V = EBV (H_0 - H_t) / H$ (EBV: estimated blood volume of whole body, 70 ml/kg for male, 60 ml/kg for female; H_0: initial Hct; H_t (constant value): medium dilution, 28%–30%; H: mean of H_0 and H_t). If the main hemospasia surgery was terminated or when necessary, the autologous blood was transfused within 6 h. In AHH group, 15–20 ml/kg Voluven was transfused at a speed of 30 ml/min to make Hct to drop to medium. Nitroglycerin (Shanghai Soho-Yiming Pharmaceuticals Co., Ltd., Shanghai, China) was infused with pump to avoid the overload of acute circulation. During the surgery, Voluven and Ringer's solution (Jiangsu Haosen Pharmaceutical Co., Ltd., Lianyungang, China) were continued to inject to ensure a high-circulating blood volume status and the diuresis was induced after the surgery. In control group, the regular transfusion and infusion were conducted.

2.4. General anesthesia and monitoring

After the status in control group was stable or the hemodilution in hemodilution groups met the standard, the neuromuscular conduction function of upper limb ulnar nerve and adductor pollicis were monitored (Orgallon muscle relaxation monitor, Holland) in the mode of train-of-four (TOF) stimulation. The intravenous injection of 0.03–0.05 mg/kg midazolam, 1–1.5 mg/kg propofol and 1–2 μg/kg remifentanil was taken for anesthesia induction within 5 s, and the intravenous injection of corresponding dosage of cisatracurium was taken at a single time. After tracheal intubation, the mechanical ventilation was applied. 4–12 $mg \cdot kg^{-1} \cdot h^{-1}$ propofol and 0.05–0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil were pumped to maintain the depth of anesthesia. During the surgery, the hemodynamics was maintained steady, with bispectral index value at 45–60 and $P_{ET}CO_2$ at 30–35 mm Hg.

2.5. Monitoring of hemodynamics, blood routine and pharmacodynamics

Changes of the body temperature, amount of bleeding, amount of urine, plasma protein and pH and electrolytes were monitored on 6 measurement time points, namely, before hemodilution or regular transfusion and infusion (T1) and immediately after hemodilution or regular transfusion and infusion (T2), completing muscle relaxant injection (T3), beginning of the surgery (T4), 1 h after surgery beginning (T5) and completing the surgery (T6). The onset time of muscle relaxation blockade (time from end of injection to T1 falling to 0), period of no response to TOF stimulation (time during which T_1 was kept at 0), blockade duration (the time from end of injection to T_1 restoring to 5%), muscle relaxation recovery index (the time in which T_1 restored from 25% to 75%), action time of muscle relaxation blockade in body (the time from muscle relaxant injection finished to T1 restored to 95%), time of TOF to 70% (the time from muscle relaxant injection finished until TOF ratio was 70%) and time of TOF to 90% (the time muscle relaxant injection finished until TOF ratio was 90%).

2.6. Measurement of plasma drug concentration

Blood sample (2 ml) was taken from the vein at 2, 4, 6, 8, 10, 12, 15, 30, 60, 90 and 120 min after the intravenous injection of cisatracurium, and then was put into anti-coagulant tube, followed by centrifugation at a speed of 6000 r/min for 5 min to separate plasma. 40 μl sulfuric acid (pH 3.0, Sigma-Aldrich Corp., MO, USA) was added, and the mixture