Journal of Clinical Anesthesia (2015) **27**, 632–637

ELSEVIER

Journal of Clinical Anesthesia

Original Contribution

Effects of mild hypoalbuminemia on the pharmacokinetics and pharmacodynamics of dexmedetomidine in patients after major abdominal or thoracic surgery☆,☆☆

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Received 5 September 2013; revised 14 April 2015; accepted 22 June 2015

Keywords:
Dexmedetomidine;
Pharmacokinetics;
Pharmacodynamics;
Hypoalbuminemia;
Abdominal surgery;
Thoracic surgery

Abstract

Study Objective: To explore the effects of mild hypoalbuminemia on pharmacokinetics and pharmacodynamics of dexmedetomidine in patients after major abdominal or thoracic surgery.

Design: A prospective cohort study.

Setting: University-affiliated teaching hospital.

Patients: The study was performed in 30 consecutive patients undergoing major abdominal or thoracic surgery. They were aged 18 to 65 years and graded as American Society of Anesthesiologists physical status I and II. All patients were scheduled to require more than 6 hours of postoperative sedation and mechanical ventilation. Nine of the patients had low plasma albumin levels (<35 g/L but >24 g/L; male/female, 6/3) after the operation, who were assigned to hypoalbuminemia group, and the remainder with normoalbuminemia (>35 g/L; male/female, 15/6) were assigned to normoalbuminemia group.

Interventions: All patients were administered a loading dose of dexmedetomidine 1.0 μg/kg infused over 10 minutes after admitted into intensive care unit and a maintenance dose of 0.4 μg/kg per hour followed for 6 hours.

Measurements: Plasma dexmedetomidine levels were determined by high performance liquid chromatography – mass spectrum. Sedation was evaluated using Ramsay sedation score. Heart rate and arterial pressures were monitored. Adverse events were recorded.

Main Results: Compared with patients with normoalbuminemia, maximum plasma concentration of dexmedetomidine decreased by 21.2% in patients with hypoalbuminemia ($P < .01$). Its volume of distribution at steady state increased by 40.5%; elimination half-life decreased by 33.5% ($P < .01$). However, heart rates, arterial pressures, and Ramsay sedation scores did not differ significantly between

☆ Supported by the research funding of the Renji Hospital (grant 10-03).
☆☆ The authors have no conflicts of interest to report.
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http://dx.doi.org/10.1016/j.jclinane.2015.06.002

the 2 groups. No serious adverse events occurred in either the patients with hypoalbuminemia or normoalbuminemia.

Conclusions: Sedation and adverse reactions of dexmedetomidine infusion did not differ significantly between patients with mild hypoalbuminemia and normoalbuminemia, although its volume of distribution at steady state increased and elimination half-life shortened in patients with hypoalbuminemia. This suggests that dexmedetomidine infusion can safely be used in mild hypoalbuminemia patients after major abdominal or thoracic surgery.

1. Introduction

Dexmedetomidine, a highly selective α_2-adrenoceptor agonist, has been widely used as a sedative agent in the patients after surgery because it has many desirable properties for this use: its effects are not limited to sedation but also include antianxiety, analgesia, and inhibition on the activity of sympathetic nervous system [1-3]. In addition, dexmedetomidine does not depress respiratory drive [4,5].

Approximately 94% of plasma dexmedetomidine is bound to albumin in healthy volunteers [6]. Hypoalbuminemia probably affects the pharmacokinetics and pharmacodynamics of dexmedetomidine due to the increase of its free fraction in plasma. Hypoalbuminemia is frequently observed in the patients after major abdominal or thoracic surgery. Data from critical care medicine indicate that more than 40% of patients admitted into the intensive care unit (ICU) have hypoalbuminemia [7-9]. However, there is little information on the effects of albumin levels on the pharmacokinetics and pharmacodynamics of dexmedetomidine in the patients after surgery. In this study, the effects of mild hypoalbuminemia on the pharmacokinetics and pharmacodynamics of dexmedetomidine were studied in the patients after major abdominal or thoracic surgery. We hypothesized that mild hypoalbuminemia might affect the pharmacokinetics of dexmedetomidine but its effect on the pharmacodynamics of dexmedetomidine was limited, if any, in these patients.

2. Materials and methods

The study was conducted in accordance with the ethical standards set forth in the Declaration of Helsinki. Written informed consent was obtained from each patient. The protocol was approved by the Ethics Committee of the Renji Hospital affiliated to School of Medicine, Shanghai Jiaotong University (ECRJ-10-07-02).

2.1. Patients

The prospective cohort study was performed in 30 consecutive patients undergoing the major abdominal or thoracic surgery in our hospital from January to December in 2011. They were aged 18 to 65 years and graded as American Society of Anesthesiologists physical status I and II. After the operation, 9 of the 30 patients had low plasma albumin levels (<35 g/L but >24 g/L; male/female, 6/3), who were assigned to hypoalbuminemia group, and the remainder with normal plasma albumin levels (>35 g/L; male/female, 15/6) were assigned to normoalbuminemia group. All patients were scheduled to require more than 6 hours of postoperative sedation and mechanical ventilation. Exclusion criteria included lactation or pregnancy, requirement for an infusion of neuromuscular blocking agent, or allergy to opioid drugs. Patients were also excluded if they had a history of hypertension, heart diseases, or central nervous system disease; had a hemoglobin level of less than 80 g/L and plasma albumin level less than 25 g/L before, during, or at the end of operation; or had liver or kidney dysfunction. These patients' characteristics are summarized in the Table.

2.2. Procedures

Anesthetic technique used before admission to ICU was chosen by the individual anesthetist. Dexmedetomidine infusion was started approximately 30 minutes after the patients had been in ICU and their blood pressure and heart rate varied less than 30% over a 5-minute period. All patients were administered a loading dose of dexmedetomidine 1.0 μg/kg infused over 10 minutes into a central vein with an infusion pump (Harvard Apparatus 22; Harvard Apparatus, South Natick, MA), and then a maintenance infusion rate of 0.4 μg/kg per hour followed for 6 hours. Blood samples of 5.0 mL each were drawn from basilic vein: before the dexmedetomidine infusion; at 5, 10, 15, 30, 45 minutes and 1, 2, 3, 4, and 6 hours during the dexmedetomidine infusion; and at 5, 10, 15, 30, and 45 minutes and 1, 2, 3, 4, and 6 hours after the infusion stopped. These samples were stored at −20°C until analyzed. Plasma dexmedetomidine level was determined by high-performance liquid chromatography with tandem mass spectrometric detection (PE Sciex API365 instrument; PE Sciex, Foster City, CA) as described previously [10]. The lower limit of reliable quantitation of the assay was 0.02 ng/mL. Interassay accuracy for the calibration standards ranged from 99% to 108%.

The individual plasma dexmedetomidine concentrations were fitted to the multiexponential function with the aid of a