Epinephrine, norepinephrine and dopamine infusions decrease propofol concentrations during continuous propofol infusion in an ovine model

Abstract  Objective: To determine the effects of exogenous ramped infusions of epinephrine, norepinephrine and dopamine on arterial and effluent brain blood concentrations of propofol under steady state intravenous anesthesia.  Design: Prospective, randomized animal study.  Setting: University research laboratory.  Subjects: Five adult female merino sheep.  Interventions: Induction (5 mg/kg) and continuous infusion of propofol (15 mg/min) with controlled mechanical ventilation to maintain PaCO₂, 40 mmHg. After 1 h of continuous anesthesia, each animal randomly received ramped infusions of epinephrine, norepinephrine (10, 20, 40 μg/min) and dopamine (10, 20, 40 μg·kg⁻¹·min⁻¹) in 3 × 5 min intervals followed by a 30-min washout period.  Measurements: Arterial and sagittal sinus whole blood for determination of propofol concentrations using high-pressure liquid chromatography. Cardiac output using a thermodilution method. Level of consciousness using an observational scale.  Main results: All three drugs significantly and transiently increased cardiac output in a dose-dependent fashion to a maximum of 146–169% of baseline. Baseline arterial and sagittal sinus propofol concentrations were not statistically different prior to catecholamine infusions. All three drugs significantly reduced mean arterial propofol concentrations (95% CI, p < 0.05): epinephrine to 41.8% of baseline (11.4–72), norepinephrine to 63% (27–99) and dopamine to 52.9% (18.5–87.3). There were parallel reductions of concentrations in sagittal sinus blood leaving the brain. The lowest blood concentrations were associated with emergence from anesthesia. Arterial concentrations were inversely related to the simultaneously determined cardiac output (r² = 0.74, p < 0.0001). Comparison of the data with the predictions of a previously developed recirculatory model of propofol disposition in sheep showed the data were consistent with a mechanism based on increased first pass dilution and clearance of propofol secondary to the increased cardiac output.  Conclusions: Catecholamines produced circulatory changes that reversed propofol anesthesia. These observations have potential clinical implications for the use of propofol in hyperdynamic circulatory conditions, either induced by exogenous catecholamine infusions or pathological states.

Key words  Catecholamines · Propofol · Cardiac output · First pass dilution · Infusions · Clearance · Pharmacokinetics
Introduction

Augmentation of mean arterial pressure and cardiac output with infusions of catecholamines is a cornerstone of critical care medicine. However, relatively little attention has been given to the influence of the pharmacodynamic effects of exogenous catecholamines on the pharmacokinetics of other drugs. Clinical experience has shown that the pharmacokinetics of drugs used in critically ill patients may be markedly different from those in normal individuals, as reflected by the substantially different dose requirements in these patients. A number of mechanisms may be invoked, depending on the drug and disease state of the patient. These include altered clearance and volumes of distribution secondary to changes in tissue blood flow, metabolic activity, protein binding, pH and drug interactions [1, 2, 3, 4]. Catecholamines may influence pharmacokinetics by one or more of these mechanisms.

Recently, our laboratory conducted a series of experiments on the effect of increasing doses of catecholamines on cerebrovascular hemodynamics in an instrumented sheep preparation, anesthetized with a constant rate propofol infusion. As expected, higher doses of catecholamines were found to increase blood pressure and cardiac output [5]. However, it was also noticed that the times of the peak catecholamine dose were associated with the emergence of the shee from propofol anesthesia. Given that both propofol and catecholamines are widely used in critical care medicine and the potentially important implications of such an interaction, we elected to quantitate this phenomenon in sheep as a first step in determining its mechanism and clinical significance.

Based on previous reports of an inverse relationship between cardiac output and propofol concentrations after short infusions [6], we hypothesized that this effect may also occur during longer propofol infusions when cardiac output was altered by catecholamine infusions. Our specific aims were, firstly, to document the effect of increasing doses of epinephrine, norepinephrine and dopamine on cardiac output, depth of anesthesia and the concentrations of propofol in arterial and effluent blood from the brain in instrumented sheep anesthetized with a constant rate propofol infusion. Secondly, to provide insight into the mechanisms involved; we wished to determine if a previously validated recirculatory model of propofol disposition in sheep [7, 8] could account for the observed changes in blood concentrations by altering the term for cardiac output in the model.

Materials and methods

Ethics statement

All experimental protocols were approved by the Animal Ethics Committee of the University of Adelaide. Care and handling of animals were in accordance with National Health and Medical Research Council guidelines.

Animal preparation

Female merino sheep of similar ages and body mass (40–50 kg) were used. Under halothane anesthesia, the animals were instrumented as described previously [9]. In summary, catheters were inserted into the descending aorta (for measurement of mean arterial pressure and sampling of arterial blood) and right atrium (for drug administration) via a femoral approach. A thermodilution cardiac output catheter was placed under pressure wave monitoring into the pulmonary artery. Via a craniotomy, a catheter was placed into the dorsal sagittal sinus which is the appropriate site for sampling cerebral venous blood in sheep [10].

Following this preparation, the sheep were recovered from anesthesia and housed in metabolic crates with free access to food and water [11]. A single dose of penicillin/streptomycin was administered perioperatively for antibiotic prophylaxis. Catheter patency was maintained by intraluminal heparin (10 IU/ml) locks.

Study design

At a later date, the sheep were re-anesthetized with propofol (5 mg/kg), endotracheally intubated and mechanically ventilated using a volume control ventilator (7000 Ventilator, Ohmeda, Madison, Wis., USA) to maintain an arterial carbon dioxide tension of 40 mmHg throughout the experiment. Anesthesia was maintained by continuous infusion of propofol at 15 mg/min throughout the protocol. Temperature and hydration were maintained throughout the experiment at baseline levels with external warming and intermittent infusions of saline according to central venous pressure, respectively. No muscle relaxant was used.

After 60 min of continuous intravenous anesthesia, pseudosteady state was assumed based on previous studies and mathematical modeling of propofol disposition [12]. Thereafter, each animal received consecutive ramped infusions of epinephrine, norepinephrine or dopamine in random order. One hour elapsed between each catecholamine infusion to allow clearance of the preceding catecholamine and for measured parameters to return to baseline values. Each ramped infusion had three rates, each of 5 min duration, corresponding to 10, 20, and 40 μg/min for epinephrine and norepinephrine and 10, 20, 40 μg/kg/min for dopamine. Infusions were delivered in equivalent volumes so that milliliters/hour represented microgram/minute for epinephrine and norepinephrine and microgram/kilogram per minute for dopamine. At the end of the study, the sheep were recovered from anesthesia and returned to their metabolic crates.

Measurements and drug analysis

The following measurements were made at baseline, 5, 10, 15 min (during the catecholamine infusion) and 20, 25, 35 and 45 min (during washout). Arterial and sagittal sinus blood samples were taken for measurement of whole blood propofol concentrations and stored at −20°C. They were subsequently assayed using a previously described method based on basic extraction and separation using a high pressure liquid chromatograph with fluorescence detection [9]. The limit of sensitivity was approximately 0.02 μg/ml. In each case, standard curves were prepared in blank blood taken immediately prior to the drug infusions with concentrations that spanned the expected concentration range. An assay was rejected