General Anesthesia

A dopamine infusion decreases propofol concentration during epidural blockade under general anesthesia

[Une perfusion de dopamine diminue la concentration de propofol pendant le bloc péridural sous anesthésie générale]

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Purpose: It is common clinical practice to use dopamine to manage the reduction in blood pressure accompanying epidural blockade. As propofol is a high-clearance drug, propofol concentrations can be influenced by cardiac output (CO). The purpose of the present study was to investigate the effects of dopamine infusions on propofol concentrations administered by a target-controlled infusion system during epidural block under general anesthesia.

Methods: 12 patients undergoing abdominal surgery were enrolled in this study. Anesthesia was induced with propofol and vecuronium 0.1 mg·kg⁻¹, and maintained using 67% nitrous oxide, sevoflurane in oxygen and constant infusion of propofol. Propofol was administered to all subjects via target-controlled infusion to achieve a propofol concentration at 6.0 µg·mL⁻¹ at intubation and 2.0 µg·mL⁻¹ after intubation. Before and after the administration of 10 mL of 1.5% mepivacaine from the epidural catheter and dopamine infusion at 5 µg·kg⁻¹·min⁻¹, CO and effective liver blood flow (LBF) were measured using indocyanine green. Blood propofol concentration was also determined using high-performance liquid chromatography.

Results: At one hour after epidural block and dopamine infusion, CO was significantly increased from 4.30 ± 1.07 L·min⁻¹ to 5.82 ± 0.98 L·min⁻¹ ($P < 0.0001$), and effective LBF was increased 0.75 ± 0.17 L·min⁻¹ to 0.96 ± 0.18 L·min⁻¹ ($P < 0.0001$). Propofol concentration was significantly decreased from 2.13 ± 0.24 µg·mL⁻¹ to 1.59 ± 0.29 µg·mL⁻¹ ($P < 0.0001$).

Conclusions: Propofol concentrations decrease with an increase in CO, suggesting the possibility of inadequate anesthetic depth following catecholamine infusion during propofol anesthesia.

Objectif : Il est courant d'utiliser la dopamine pour traiter la baisse de tension artérielle qui accompagne le bloc péridural. Comme le propofol est un médicament à clairance élevée, sa concentration peut être influencée par le débit cardiaque (DC). Nous avons vérifié les effets de perfusions de dopamine sur les concentrations de propofol administrées par un système de perfusion à concentration cible pendant le bloc péridural sous anesthésie générale.

Méthode : Douze patients devant subir une intervention chirurgicale abdominale ont participé à notre étude. L'anesthésie, induite avec du propofol et 0,1 mg·kg⁻¹ de vécuronium, a été maintenue avec du protoxyde d'azote à 67 %, du sévoflurane dans de l'oxygène et une perfusion constante de propofol. Le propofol a été administré à tous les sujets par une perfusion à concentration cible pour atteindre 6,0 µg·mL⁻¹ de propofol au moment de l'intubation et 2,0 µg·mL⁻¹ après l'intubation. Avant et après l'administration de 10 mL de mépivacaïne à 1,5 % par le cathéter péridural et la perfusion de dopamine à 5 µg·kg⁻¹·min⁻¹, le CO et le débit sanguin hépatique (DSH) ont été mesurés avec le vert d'indocyanine. La concentration sanguine de propofol a aussi été déterminée par chromatographie liquide haute performance.

Résultats : Une heure après le bloc péridural et la perfusion de dopamine, le CO s'était significativement élevé de 4,30 ± 1,07 L·min⁻¹ à 5,82 ± 0,98 L·min⁻¹ ($P < 0,0001$) et le DSH efficace était accru de 0,75 ± 0,17 L·min⁻¹ à 0,96 ± 0,18 L·min⁻¹ ($P < 0,0001$). La concentration de propofol a significativement baissé de 2,13 ± 0,24 µg·mL⁻¹ à 1,59 ± 0,29 µg·mL⁻¹ ($P < 0,0001$).

Conclusion : Les concentrations de propofol ont diminué avec l'augmentation de CO, ce qui soulève la possibilité d'un niveau

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anesthésique inadéquat après la perfusion de catécholamine pendant l'anesthésie au propofol.

PROPOFOL has been used widely for anesthesia during surgical procedures and for sedation of patients. Propofol is a short-acting drug with a large volume of distribution and high total body clearance.¹ Since the hepatic extraction ratio of propofol is high² and urinary excretion of unchanged propofol is minimal,³ hepatic metabolism is considered the primary elimination pathway and drug metabolism thus depends on liver blood flow (LBF).

Two cases of awareness during propofol anesthesia using target-controlled infusion have been reported.^{4,5} Propofol concentrations might be lower than predicted when cardiac output (CO) and LBF are increased resulting in an increased rate of propofol clearance. Previous reports have investigated the influence of CO on propofol concentrations,⁶⁻⁸ demonstrating an inverse relationship between CO and propofol concentration. However, these studies have been conducted in animals, and further investigations in humans are required.

Clinically, the reduction in blood pressure accompanying epidural block is frequently corrected by catecholamine infusions, resulting in a hyperdynamic state. The purpose of the present study was to investigate the effects of dopamine infusion during epidural block on CO and propofol concentration administered by target-controlled infusion.

Methods

Subjects

After Institutional approval, written informed consent was obtained from 12 patients scheduled to undergo total gastrectomy (eight males and four females; age 70 ± 5.0 yr; height 162 ± 6.4 cm; weight 59 ± 6.0 kg). All patients were classified as ASA physical status I–II, and individuals with hepatic or renal insufficiency, significant hemodynamic instability, or known allergy to eggs or propofol were excluded from the study.

Sampling procedure

Before induction of anesthesia, routine monitoring was established, including pulse oximetry, electrocardiogram and non-invasive blood pressure. An *iv* catheter was placed in an antecubital vein for infusion of anesthetics and for fluid replacement. After insertion of an epidural catheter (Th9/Th10) and admin-

istration of 3 mL of 1% lidocaine as a test dose, anesthesia was induced using vecuronium $0.1 \text{ mg}\cdot\text{kg}^{-1}$ and propofol, and was maintained with 67% nitrous oxide, sevoflurane in oxygen and constant infusion of propofol. During the study, the dose of sevoflurane was kept constant at 1%. Propofol was administered to all subjects by target-controlled infusion (Diprifusor; AstraZeneca International, Wilmington, DE) to achieve a propofol concentration of $6.0 \text{ }\mu\text{g}\cdot\text{mL}^{-1}$ at intubation and $2.0 \text{ }\mu\text{g}\cdot\text{mL}^{-1}$ after intubation throughout the study. A double lumen *iv* catheter was inserted into an internal jugular vein for infusion of dopamine and injection of indocyanine green as an indicator for CO and effective LBF. A cannula was placed in the left radial artery for invasive blood pressure monitoring and blood sampling. Thirty minutes after the start of the operation, the predicted propofol concentration of $2.0 \text{ }\mu\text{g}\cdot\text{mL}^{-1}$ was achieved and a constant infusion rate was established in all patients. Then, indocyanine green (20 mg) was injected for the measurement of CO and effective LBF. Blood samples were collected from the arterial cannula for measurement of blood propofol concentration. Mepivacaine (1.5%, 10 mL) was administered in the epidural catheter and a dopamine infusion at $5 \text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ were started. One hour after the administration of mepivacaine, 20 mg of indocyanine green were injected again for the measurement of CO and effective LBF, and blood samples were collected to determine propofol concentration.

Analytical procedure

Indocyanine green was used for the measurement of CO and effective LBF, as described in a previous report.^{9,10} Propofol concentrations in whole blood were measured using high performance liquid chromatography as reported previously.¹¹

Statistical analysis

Data are expressed as mean $\pm$ SD. Differences between propofol concentrations, CO, and effective LBF before and one hour after dopamine infusion were analyzed using a paired *t* test. A $P < 0.05$ was considered statistically significant.

Results

After dopamine infusion at a rate of $5 \text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, mean arterial pressure increased significantly from 74.6 ± 8.3 mmHg to 86 ± 10.1 ($n = 12$, $P < 0.001$). Heart rate also increased significantly from 72.6 ± 10.1 to 78.5 ± 7.1 ($n = 12$, $P < 0.01$). In four of the 12 patients, ephedrine 4 mg were administered since systolic blood pressure remained lower than 80

FIGURE 1 The relationship between cardiac index and propofol concentrations.

FIGURE 2 The relationship between effective liver blood flow and propofol concentrations.

mmHg within ten minutes after the administration of 1.5% mepivacaine. During the study, the amount of blood loss was less than 50 mL. CO increased significantly from $4.30 \pm 1.07 \text{ L}\cdot\text{min}^{-1}$ to $5.82 \pm 0.98 \text{ L}\cdot\text{min}^{-1}$ ($n = 12$, $P < 0.0001$). Effective LBF increased significantly from $0.75 \pm 0.17 \text{ L}\cdot\text{min}^{-1}$ to $0.96 \pm 0.18 \text{ L}\cdot\text{min}^{-1}$ ($P < 0.0001$). Propofol concentrations significantly decreased from $2.13 \pm 0.24 \mu\text{g}\cdot\text{mL}^{-1}$ to $1.59 \pm 0.29 \mu\text{g}\cdot\text{mL}^{-1}$ ($n = 12$, $P < 0.0001$). Propofol concentrations correlated negatively with cardiac index ($n = 24$, $R^2 = 0.418$, $P < 0.001$) and effective LBF ($n = 24$,

$R^2 = 0.433$, $P < 0.001$), respectively (Figures 1 and 2).

Discussion

The present study tested the hypothesis that a dopamine infusion during an epidural block would alter the pharmacokinetics of propofol. Our results confirm this hypothesis. To the best of our knowledge, this is the first study to describe a decrease in propofol concentration during its constant infusion when CO is increased in humans.

Propofol has been shown in various studies to affect the cardiovascular system, including CO and systemic vascular resistance.¹²⁻¹⁴ However, relatively little attention has been given to the influence of CO on propofol concentration. Upton *et al.*⁶ reported that the initial arterial concentration of propofol after a short infusion was inversely related to CO in sheep. Myburgh *et al.* and Kurita *et al.* reported a similar relationship during constant rate infusions of propofol in ovine and in swine, respectively.^{7,8} Wilson *et al.* reported that predosing with esmolol reduced the propofol requirements for induction of anesthesia by 25%.¹⁵ No investigations, however, have assessed the influence of changing CO on propofol concentrations during constant rate infusion in humans. Epidural anesthesia has been reported as exerting no influence on the pharmacokinetics of propofol.¹⁶ During clinical anesthesia, however, the decline of blood pressure with epidural block is frequently corrected by catecholamine infusion. This might produce a hyperdynamic state and bring about decreases in propofol concentration. We demonstrated that propofol concentrations became lower than predicted following dopamine infusion with epidural block in humans.

This phenomenon can be explained by two mechanisms. The first is the direct indicator dilution effect between venous injection site and arterial blood. A fixed dose in the presence of a higher CO results in less drug per unit blood volume, and therefore lower concentrations. Indeed, the contribution of the first pass dilution effect to steady state arterial concentration will simply be the drug clearance over the CO. This effect is therefore most significant for drugs with a high clearance.¹⁷ Secondly, higher CO implies higher blood flows to the organs of drug elimination and distribution, increasing the rate of clearance and distribution and resulting in lower concentrations. Since propofol is a high clearance drug, its concentration is considered to be greatly influenced by CO.

Johnson *et al.* reported arousal following isoprenaline administration during propofol anesthesia.⁴ They also examined the effect of *iv* epinephrine on bispectral index (BIS) and sedation, reporting that

mean BIS value increased from 63 to 76 and exogenous catecholamines seem to display an arousal effect.¹⁸ This could be due to changes in neurotransmitter levels in the brain. The adrenergic system has a role to play in the process of arousal from anesthesia, and this has been previously demonstrated.¹⁹ Beta receptors in the reticular activating system interact with information processing in the thalamus. In previous reports, however, another possible explanation, that propofol concentration decreased due to increased CO on administration of a catecholamine, had not been discussed. In the present study, we showed decreases in propofol concentration with increased CO.

In summary, propofol concentrations decrease with an increase in CO, suggesting the possibility of inadequate anesthetic depth following catecholamine infusion during propofol anesthesia.

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