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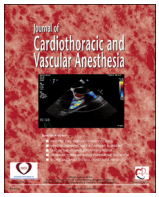

Original Article

Feasibility of Anesthesia Maintenance With Sevoflurane During Cardiopulmonary Bypass: A Pilot Pharmacokinetics Study

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Objective: Adequate maintenance of hypnosis during anesthesia throughout surgery using sevoflurane alone was investigated. In addition, sevoflurane pharmacokinetics during cardiopulmonary bypass were analyzed.

Design: This was a pilot pharmacokinetic study.

Setting: Tertiary care university hospital.

Participants: The study comprised 10 patients aged between 18 and 75 years who underwent elective mitral valve surgery.

Interventions: The end-tidal and sevoflurane plasma concentrations were measured throughout cardiac surgery procedures involving cardiopulmonary bypass. The sevoflurane plasma concentration was measured using gas chromatography. In addition, the ratio between sevoflurane alveolar concentration and inspired concentration over time (F_A/F_I) was analyzed to describe wash-in and wash-out curves.

Measurements and Main Results: Hypnosis was maintained adequately throughout surgery using sevoflurane alone. The bispectral index was maintained between 40 and 60 during cardiopulmonary bypass. The end-tidal sevoflurane was significantly different before and during cardiopulmonary bypass (1.86% ± 0.54% *v* 1.30% ± 0.58%, respectively; $p < 0.001$). However, the sevoflurane plasma concentration was not significantly different before and after cardiopulmonary bypass start-up (40.55 μg/mL [76.62-125.33] before cardiopulmonary bypass and 36.24 μg/mL [56.49-81-42] during cardiopulmonary bypass). This mismatch possibly can be explained by changes that occured after cardiopulmonary bypass start-up, such as reductions of body temperature (36.33°C ± 0.46°C *v* 32.98°C ± 2.38°C, respectively; $p < 0.001$) and hematocrit (35.62% ± 3.98% *v* 25.5% ± 3.08%, respectively; $p < 0.001$). The sevoflurane alveolar concentration varied according to sevoflurane plasma concentration and bispectral index values. No adverse events regarding sevoflurane administration during cardiopulmonary bypass were observed.

Conclusions: Sevoflurane end-tidal values were reliable indicators of adequate anesthesia during all cardiac surgery procedures involving cardiopulmonary bypass.

Key Words: sevoflurane; kinetics; bispectral index; cardiopulmonary bypass; anesthesia

EVERY YEAR, MORE than 1 million patients undergo cardiac surgery.[1] Despite improvements in perioperative management, morbidity and mortality still are commonplace. Several randomized controlled trials (RCTs) and meta-analyses suggested that volatile anesthetic use in cardiac surgery (in particular sevoflurane and desflurane), mimicking ischemic preconditioning, might reduce perioperative myocardial damage and postoperative mortality.[2–13]

Some authors[14] suggested that volatile anesthetic administration throughout surgery appeared to provide superior protective effects compared with administration only before

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http://dx.doi.org/10.1053/j.jvca.2016.12.018

1053-0770/

or after cardiopulmonary bypass (CPB). Moreover, these protective effects seemed to be related to the amount of volatile anesthetics administered.[11] These data confirmed that volatile anesthetic administration during coronary artery bypass graft surgery certainly is advantageous; therefore, it would be extremely interesting to identify the anesthetic regimen necessary to reduce perioperative morbidity and mortality.

To reach better levels of myocardial protection, precise and homogenous protocols for drug administration are necessary. According to these findings, an anesthetic plan based on the monopharmacologic maintenance of general anesthesia with volatile agents might be a useful option for cardiac anesthesiologists. Cardiac surgery, however, is a setting that presents a high risk of intraoperative awareness,[15] and the feasibility of halogenated monopharmacologic maintenance during CPB needs to be assessed. Anesthesia maintenance during CPB is challenging due to modifications in systemic blood flow (nonpulsatile blood flow), hypothermia, and hemodilution, with important changes in pharmacodynamics and pharmacokinetics.[16,17] In addition, the oxygenator and CPB circuit can bind different amounts of drugs administered to the patient, and hypothermia itself can lead to reduced consciousness, causing a change in anesthetic requirements during CPB.[17] To date, few studies have described volatile anesthetic complete kinetics in vivo during CPB.[18–25] Anesthetic wash-in is slower during the cooling phase, whereas wash-out during the rewarming phase is more similar to in vivo–model wash-out. Moreover, the degradation product hexafluoroisopropanol (HFIP) is a poorly studied molecule with implications in sevoflurane kinetics that are not understood fully.[26]

During the hypothermic phase there are increases in the blood/gas solubility coefficient and tissue capacity for halogenated anesthetics, leading to slower induction of and emergence from general anesthesia.[27] Several studies have underlined a decrease in anesthetic requirements during the hypothermic phase of CPB.[18–25,28] Despite these findings, feasibility of the monopharmacologic maintenance of general anesthesia with sevoflurane alone still is a matter of debate.

The primary endpoint of this pilot study was to evaluate the adequate maintenance of hypnosis during general anesthesia using sevoflurane as the only hypnotic agent throughout surgery, including CPB. Sevoflurane administration was titrated to maintain a constant and adequate level of bispectral index (BIS) between 40 and 60. Moreover, the authors defined the basis of sevoflurane pharmacokinetics during CPB.

Methods

Study Population

After receiving ethics committee approval, 10 consecutive patients were enrolled in the study. Written informed consent was obtained before surgery. Patients of both sexes aged between 18 and 75 years with good cardiac function (ejection fraction $> 50\%$ or end-diastolic diameter < 65 mm) who underwent elective mitral valve surgery (mitral valve replacement or mitral valve repair) with median sternotomy were included. Exclusion criteria were poor cardiac function (ejection fraction $< 50\%$ or end-diastolic diameter > 65 mm); coronary artery disease; diabetes mellitus; renal (serum creatinine > 1.5 mg/dL) or hepatic disease; use of angiotensin-converting enzyme inhibitors and sedative drugs (such as benzodiazepines); and a history of alcoholism.

Anesthetic Management

One hour before surgery all patients received intramuscular morphine (0.1 mg/kg) and scopolamine (0.25 mg) premedication. Standard intraoperative monitoring was performed, including electrocardiography, invasive arterial blood pressure, central venous pressure, pulse oximetry, capnography, vesical, temperature, and urine output. BIS was started before the induction of general anesthesia and was used to monitor sedation levels throughout surgery.[15]

General anesthesia was induced with fentanyl (3 μg/kg), sodium thiopental (3-5 mg/kg), and rocuronium (0.6-1 mg/kg) or succinylcholine (1 mg/kg) when required. After a BIS index value of < 60 was reached, patients underwent orotracheal intubation with a cuffed tube. After intubation, volume-controlled ventilation was applied with a Primus ventilator (Dräger, Lübeck, Germany) using an oxygen/air mixture and high fresh gas flows (> 8 L/min) to prevent rebreathing of the exhaled mixture (ventilator settings: tidal volume 8 mL/kg; fraction of inspired oxygen < 0.8; positive end-expiratory pressure 0; and respiratory rate titrated to avoid hypercapnia). Anesthesia was maintained using inhaled sevoflurane (Sevorane; Abbott, Abbott Park, IL; starting dose 1 end-tidal minimum alveolar concentration, equal to 2%); rocuronium bromide via continuous infusion (30-50 mg/h); and fentanyl boluses when needed. Maintenance was carried out throughout surgery using sevoflurane administered through a vaporizer (Vapor 2000; Dräger). Intraoperative administration of sevoflurane was titrated to keep the BIS level between 40 and 60[15] to obtain an adequate level of sedation.

Throughout surgery, hemodynamics were modified using vasopressors when necessary. Hemodynamic data, BIS level, and inspired and end-tidal sevoflurane concentrations were monitored and collected before induction and after 5, 10, 15, 20, 25, and 30 minutes. Blood samples were collected to perform arterial blood gas analysis and to evaluate the plasma concentration of sevoflurane and HFIP before induction and after 10, 20, and 30 minutes. Heparin (300 U/kg) was administered to patients before CPB to maintain an activated clotting time > 480 seconds. CPB was performed using the Affinity oxygenator (Medtronic, Minneapolis, MN) and Medtronic circuit. Mechanical ventilation was discontinued after CPB start, which then was carried out using moderate hypothermia (32-34°C). Myocardial protection during aortic cross-clamping was provided by antegrade and/or retrograde cold blood cardioplegia.

During CPB, fresh gas flow was adjusted to maintain acid-base balance. Sevoflurane administration was provided through a vaporizer (Vapor 2000) linked to a CPB oxygenator

Please cite this article as: Meroni R, et al. (2017), http://dx.doi.org/10.1053/j.jvca.2016.12.018