◇ This Month in

ANESTHESIOLOGY

■ Predicting Propofol Induction Dose. Kazama *et al.* (page 205)

Using pulse dye densitometry measurements to calculate cardiac output, blood volume, mean transit time, dye clearance, and central blood volume, Kazama *et al.* evaluated different variables for the ability to predict propofol induction dose at constant infusion rates of 40 mg · kg^{-1} · h^{-1} as a function of lean body mass. The study group included 75 unpremedicated patients (aged 10–85 yr), all scheduled to undergo intravenous induction of anesthesia for elective surgery.

In addition to these variables, patient characteristics, such as lean body mass, sex, age, hemoglobin concentration, and hepatic blood flow also were analyzed to determine their relation, if any, to induction dose. On the study day, a bolus injection of 0.3 mg/kg indocyanine green dye, 2.5 mg/ml, was administered to each patient. Researchers obtained dye densitogram measurements while patients rested on the operating table. The researchers then administered a flush of 20 ml lactated Ringer's solution. Propofol induction then proceeded with the drug infused at 40 mg · kg^{-1} · h^{-1} while level of consciousness was evaluated. Induction time was defined as the time from propofol administration until the patient did not responded to gentle verbal and physical stimulation; the induction dose was the amount of propofol administered up to this point. After consciousness was lost, the propofol infusion rate was decreased to 4 mg · kg^{-1} · h^{-1}.

Univariate least squares linear regression analysis was used to analyze the relation between propofol induction dose and each of the patient characteristics. Stepwise multiple linear regression models were used to select important predictors of induction dose.

Although the researchers found a significant correlation between induction dose and each of the eight variables evaluated, only age, lean body mass, and hepatic blood flow were associated independently with induction dose. At the infusion rate used in this study, the researchers concluded that propofol induction dose could be determined with use of the variables of age, lean body mass, central blood volume, and hepatic blood flow.

■ Is Hyperthermia during Epidural Anesthesia a Complication of the Anesthetic? Negishi *et al.* (page 218)

To explore the mechanisms of hyperthermia associated with epidural anesthesia, Negishi *et al.* recruited eight male volunteers to participate in four separate experiments on four study days. On each study day, an intravenous injection of 50 IU/g human recombinant interleukin (IL)-2 was administered to participants, followed by 100 IU/g of the drug 2 h later. The volunteers then were assigned randomly to one of four protocols: (1) control day without opioid or epidural anesthesia; (2) epidural analgesia using 0.2% ropivacaine alone; (3) epidural analgesia using 0.2% ropivacaine combined with 2.0 μg/ml fentanyl; or (4) intravenous fentanyl administered at a target plasma concentration of 2.5 ng/ml. Researchers allowed 2 weeks between the fentanyl day and the combined ropivacaine–fentanyl day to minimize drug tolerance.

Febrile responses to pyrogen were measured up to 8 h in each volunteer. Additional measurements included plasma concentrations of IL-6, IL-8, and tumor necrosis factor α, as well as blood pressure, heart rate, and arterial oxygen saturation. Core temperatures of the volunteers peaked at 38.7 ± 0.6°C on the control day, at 38.7 ± 0.7°C during epidural ropivacaine, and at 38.7 ± 0.9°C with combined epidural fentanyl and ropivacaine, but only increased to 38.1 ± 0.7°C on the day intravenous fentanyl was administered to the volunteers. The area under the temperature–time curve for fentanyl was roughly 50% less than for the other groups. Therefore, fentanyl significantly reduced febrile responses to pyrogen, whereas neither epidural ropivacaine nor epidural fentanyl–ropivacaine inhibited manifestation of fever as compared with controls.

From these results, the researchers concluded that hyperthermia during epidural analgesia is not caused by the anesthetic but should be considered as evidence of underlying infection or inflammation and should be treated seriously. In addition, because opioids tend to attenuate fever, the researchers recommended that threshold temperatures triggering investigations for infection be reduced approximately 0.5°C in patients to whom opioid analgesia is administered.

■ Influence of Hypothermia on Pharmacokinetics of Vecuronium in Rat Livers Investigated. Beaufort *et al.* (page 270)

Beaufort *et al.* used an isolated perfused rat liver model with a fairly constant perfusion rate to elucidate the influence of hypothermia on the uptake of vecuronium in the intact organ. The researchers divided each perfusion experiment into three phases: (1) a 950-μg bolus of vecuronium was administered, followed by a continuous infusion of vecuronium throughout the experiment; (2) temperature was reduced to 28°C; and (3) temperature was restored to 38°C. In control experiments, temperature was kept constant throughout the perfusion procedure. Concentrations of vecuronium and its metabolites were measured in the perfusion medium, in bile collected from the livers, and in liver homogenate.

The team found that hypothermia increased the amount of vecuronium in the perfusion medium and that, when normal temperatures were restored, this amount decreased. Although hypothermia reversibly reduced the net uptake of vecuronium to the liver, biliary excretion remained virtually intact. Hypothermia drastically reduced the biliary excretion rate of 3-desacetyl vecuronium in contrast to that of the parent compound. Researchers were able to measure metabolism of vecuronium in only one of three liver homogenate preparations, and they found in that case that hypothermia reduced the rate of conversion by a factor of 2. Pharmacokinetic analysis showed that the hypothermia-induced changes in the pharmacokinetics of vecuronium could be described adequately only by the combination of reduced hepatic net uptake and reduced metabolism. These results show the need for effective measurement of muscle relaxants during hypothermia to prevent overdosing.

■ Effects of Hypovolemia on Pharmacokinetics and Pharmacodynamics of Remifentanil in Pigs. Johnson *et al.* (page 322)

Building on their previous work with a porcine isobaric hemorrhagic shock model to investigate the influence of severe blood loss on the pharmacokinetics of fentanyl, Johnson *et al.* reported investigations using the same model while infusing remifentanil to shocked and control group pigs. A total of 16 pigs were assigned randomly to one of two groups: a control group and a shock group, in which animals were bled to a state of hemorrhagic shock. Remifentanil, 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$, was infused for 10 min in animals in both groups. Arterial samples were obtained for remifentanil concentration assays every 2 min during infusion and at designated intervals up to 65 min after the infusion was stopped. For pharmacokinetic analysis, the concentration-*versus*-time data for both groups was analyzed using several techniques. The electroencephalographic spectral edge was used as a measure of drug effect. Pharmacodynamics were characterized using a sigmoid inhibitory maximal effect model.

As hypothesized, the remifentanil blood concentrations were higher in the shock group. In addition, central clearance was slower and the central compartment was smaller in the shock group. No difference between shock and control groups was observed in the magnitude or the time course of the remifentanil-induced decrease in spectral edge. The results indicate that less remifentanil would be needed to maintain a target plasma concentration during hemorrhagic shock. However, because of its rapid metabolism, the impact of hemorrhagic shock on the concentration decrease of remifentanil after termination of the infusion was minimal. The authors also noted several limitations of the study—in particular, the differences between the controlled hemorrhage over time used in their experiment and the dynamic process of hemorrhagic shock during trauma or surgery.

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