

ANESTHESIOLOGY

■ Influence of Total Body Weight on Estimating Fentanyl Dose Requirements. Shibutani *et al.* (page 603)

Although opioid dosage regimens are often based on a patient's total body weight (TBW), the influence of body weight on the pharmacokinetics of fentanyl has not been established. Shibutani *et al.* examined the influence of TBW and other body mass indices on the accuracy of predicting plasma fentanyl concentrations in lean and obese patients.

For their study, the team recruited 70 patients undergoing major elective surgery with a body mass index of less than 30 and weighing less than 85 kg (Group L) and 39 patients with a body mass index greater than 30 and weights equal to or more than 85 kg (Group O). Types of surgery included major abdominal surgery, gastric bypass surgery, and spinal instrumentation for scoliosis. Procedures lasted, on average, 4 to 5 h.

Anesthesia was induced with fentanyl, sevoflurane, and atracurium, followed by a continuous infusion of fentanyl, the rate of which was adjusted by the participating anesthesiologists to meet clinical needs of each case. The fentanyl infusion was discontinued approximately 30 to 40 min before estimated end of surgery, and then resumed for analgesia after patients arrived in the postanesthesia care unit. Again, infusion rates were adjusted according to each patient's requirements. Arterial blood samples were obtained at three points during the surgery (Stages 1-3) and during the late postoperative period or on the following morning (Stage 4). Blood samples were stored and examined later by radioimmunoassay for fentanyl concentration. Pharmacokinetic models described by Shafer *et al.* and by Scott and Stanski were used to predict plasma concentrations of fentanyl. Results showed that the Shafer model systematically overestimated fentanyl concentration as weight increased. The authors used the exponential equation for Shafer performance error *versus* TBW to derive suggested dosing weights for obese patients. The pharmacokinetic mass *versus* TBW curve was essentially linear below 100 kg and approached a plateau above 140 kg. Total body clearance showed a strong linear correlation with pharmacokinetic mass, whereas the relationship with TBW was nonlinear. These results led the authors to conclude that using actual body weight overestimates fentanyl dose requirements in obese patients. The results are important in light of the increasing numbers of obese patients for whom anesthesiologists care.

■ Effects of Recruitment Maneuvers in Patients with Extrapulmonary Adult Respiratory Distress Syndrome Studied. Oczenski *et al.* (page 620)

Oczenski *et al.* conducted a prospective, randomized, controlled trial to quantify the benefits of recruitment maneuvers (RM) in patients with extrapulmonary adult respiratory distress syndrome (ARDS). Thirty consecutive postoperative patients with early ARDS were enrolled in the study. Early ARDS was defined as a need for mechanical ventilation for less than 72 h after diagnosis of ARDS. Patients were sedated with sufentanil/midazolam and paralyzed with rocuronium during the study period. Following a positive end-expiratory pressure (PEEP) trial, patients ventilated with low tidal volumes and high levels of PEEP were randomly assigned to either the control or RM group. Recruitment maneuvers were performed with 50 cm H₂O of continuous positive airway pressure and maintained for 30 s.

The PEEP trials resulted in significant improvement in oxygenation and venous admixture in both the RM and control groups. The ratio of the arterial oxygen partial pressure to the fraction of inspired oxygen (P_{aO_2}/F_{iO_2}) and Q_s/Q_t significantly improved 3 min after the RM in the group receiving that treatment. However, values returned to baseline values within 30 min. No significant differences in P_{aO_2}/F_{iO_2} and Q_s/Q_t were found between the RM and the control group at baseline or 30 min after the RM. In patients with early extrapulmonary ARDS who first underwent a PEEP trial, RM resulted in only a short-term improvement of oxygenation and venous admixture. It may be possible, however, that strategies other than the ones the authors used for setting PEEP or performing RM would produce different results. Further studies will be necessary to investigate the interaction of the effects of RM and the morphological aspects of extrapulmonary ARDS.

■ A Link between Inhaled Anesthetics and Neurodegenerative Disease? Eckenhoff *et al.* (page 703)

In an effort to elucidate possible mechanisms for the observed postoperative cognitive problems in the elderly, Eckenhoff *et al.* used a variety of techniques to test whether volatile anesthetics accelerate the formation of neurotoxic protein oligomers. Formed from amyloid B peptides, these oligomers are precursors to fibrillar pro-

tein accretions found in the brains of patients with Alzheimer's disease.

Light scattering, filtration assays, electron microscopy, fluorescence spectroscopy, and size-exclusion chromatography were used to characterize the concentration-dependent effects of halothane, isoflurane, propofol, and ethanol on amyloid B peptide oligomerization. Pheochromocytoma cells (PC-12 cells) were used to characterize cytotoxicity of amyloid oligomers with and without these same anesthetics.

The authors' data demonstrate that halothane and isoflurane increased amyloid B aggregation *in vitro* and that these increased oligomer concentrations seem to be associated with increased neuronal death. Ethanol and propofol inhibited oligomerization at low concentrations but enhanced it modestly at very high concentrations. Most of the experiments were conducted using higher halothane concentrations than those used in normal clinical practice and for exposure periods atypical in the clinical setting. The authors stress that their results do not point to a causative mechanism of Alzheimer's disease, but rather to a possible acceleration of underlying pathology and resulting increase in symptoms postoperatively in affected elderly individuals. Further study in both animal and clinical settings is warranted.

■ The Pharmacokinetics of Oral Transmucosal Fentanyl Citrate in Older People. Kharasch *et al.* (page 738)

Oral transmucosal fentanyl (OTF) citrate was the first drug specifically approved for breakthrough cancer pain. Approximately 25% is absorbed through the oral mucosa, whereas 75% is swallowed, resulting in bioavailability of 50%. Because cancer and breakthrough cancer pain are more common in the elderly, Kharasch *et al.* set

out to evaluate the effect of age on the disposition and clinical effects of OTF.

Twelve healthy volunteers, aged 67–71 yr, and 12 healthy younger volunteers, aged 26–32 yr, were enrolled in the study. Participants were asked to abstain from grapefruit products for at least 5 days before the study session and to eschew alcohol and caffeine for at least 24 h before. They fasted for a minimum of 8 h before the study period. Peripheral intravenous catheters were inserted for drug administration and blood sampling. All subjects received ondansetron, 4 mg. Thirty minutes later, they were given OTF (10 µg/kg), as either a 600 or 800 µg lozenge. They were instructed to rub the medication across the buccal mucosa, and not to bite, chew, or suck the lozenges. Venous blood samples were collected at baseline and at regular intervals during and after dosing, up to 10 h postadministration of OTF. Subjects' pupil diameters were also noted at blood sampling times, and participants rated their own response to the drug using a visual analog scale.

The investigators found no significant differences between young and elderly subjects in any pharmacokinetic parameter for fentanyl or norfentanyl. The maximum pupil diameter change from baseline to peak concentration was significantly less in older as compared to younger subjects. Subjective assessments of alertness/sedation, energy level, confusion, clumsiness, anxiety, and nausea did not differ between older and younger subjects. Based on these results, the authors do not believe that changes in OTF dosing based on age alone are necessary. However, this investigation was conducted in healthy volunteers. The effects of cancer, concomitant illness, or older age may indeed affect OTF dosing.

Gretchen Henkel