

ANESTHESIOLOGY

■ Does Gender Influence Minimum Alveolar Concentration? Two Perspectives. Eger *et al.* (page 1059); Wadhwa *et al.* (page 1062)

A recent study reported that elderly Japanese women given xenon have a significantly smaller minimum alveolar concentration (MAC) required to eliminate movement in response to surgical incision than men. In this issue of ANESTHESIOLOGY, two groups of investigators delve further into the controversies regarding whether gender influences MAC.

Eger *et al.* completed a retrospective review of previous studies that comprised an aggregate total of 258 patients (127 women and 131 men) anesthetized with desflurane, diethyl ether, halothane, methoxyflurane, sevoflurane, or xenon. Using logistic regression, the team recalculated the MAC value for the combined patients for each report. They then separately determined the MAC for female and male patients in each study. The MAC for the normalized combined data for women did not differ significantly from the normalized combined data for men. However, in two studies of sevoflurane, Japanese women were found to have significantly lower MAC values than men. Whereas the subset of patients given sevoflurane seem to have results consistent with the other Japanese report, another six anesthetic studies reviewed found no significant difference in MAC values between men and women. Although the findings of this retrospective study do not suggest that women generally have smaller MAC values than do men, it does leave open the question regarding subsets of patients. That is, do Japanese women have smaller MAC values than Japanese men, and would such a difference, if validated, increase with advancing age?

In another attempt to address the conundrum of gender-influenced pain sensitivity and anesthetic requirements, Wadhwa *et al.* designed a prospective study to test the hypothesis that MAC for desflurane would differ between men and women. The team recruited 34 study participants (17 men and 17 women), although final data analysis was restricted to 30 because of variances in adhering to study protocol. In patients scheduled to have skin incisions greater than 3 cm, anesthesia was induced by inhalation of 6–8% sevoflurane in 100% oxygen. After loss of the lash reflex, succinylcholine was given intravenously. Patients were maintained at their assigned end-tidal desflurane concentration (determined by the “Dixon up-and-down” method) for at least 10 min before skin incision.

Two independent investigators blinded to the end-tidal concentration of desflurane determined the patients’ responses to skin incision (movement or no movement). One investigator observed the upper extremities and head for movement; the other observed the lower extremities. The average time from induction of anesthesia to incision was 24 min in each group, and the average desflurane concentration required to prevent movement in 50% of the patients did not differ between men and women. The MAC of desflurane was $6.2 \pm 0.4\%$ in women and $6.0 \pm 0.3\%$ in men. The group of 15 female patients was comprised of equal numbers of those who were premenstrual, or in the peri-ovulatory or luteal phases of menstruation. Because women are most sensitive to ischemic, thermal, and pressure pain during the luteal phase, inclusion of women in various phases of their menstrual cycles may constitute a limitation of the study. However, the researchers observed no effect of menstrual status on the MAC of desflurane, indicating that although pain sensitivity in women is augmented, anesthetic requirements may not be.

■ Investigation of MDMA as a Trigger of Malignant Hyperthermia in Susceptible Swine. Fiege *et al.* (page 1132)

Acute toxicity after ingestion of 3,4-methylenedioxy-methamphetamine (MDMA, or “ecstasy”) is characterized by hyperthermia and other associated problems, such as renal failure and liver damage. In an effort to understand how MDMA triggers the hyperthermic effect, Fiege *et al.* exposed two groups of pigs to MDMA in cumulative doses of 0.5, 1, 2, 4, 8, and 12 mg/kg. Six of the animals were susceptible to malignant hyperthermia and six were normal. The investigators induced general anesthesia using ketamine and propofol, but neuromuscular blocking drugs were not used. The animals were monitored every 5 min during the experimental period for heart rate, mean arterial pressure, central venous pressure, cardiac output, end-tidal carbon dioxide concentration, body temperature, blood gas levels, and lactate levels. Blood samples were obtained every 20 min for gas chromatographic measurement of MDMA and 3,4-methylenedioxyamphetamine.

After measurement of baseline blood gas and body temperature levels, MDMA was administered intravenously. The clinical occurrence of malignant hyperthermia (MH) was defined by the presence of two of three

conditions: central venous $P_{CO_2} \geq 75$ mmHg, central venous pH ≤ 7.20 , and increase of body core temperature $\geq 2.0^\circ\text{C}$. When MH occurred, the investigators instigated standard therapy with dantrolene, sodium bicarbonate, and hyperventilation with 100% oxygen.

Administration of 8 mg/kg of MDMA triggered MH in all of the MH-susceptible swine. The normal swine also developed clinical signs of hypermetabolism. The changes attributed to MDMA administration in these animals tended to be moderate, even after administration of 12 mg/kg, compared to changes seen in the MH swine. The MDMA-induced MH crisis in the susceptible animals immediately responded to dantrolene therapy. From these results, the researchers assert that humans with established susceptibility to malignant hyperthermia should avoid the use of MDMA and related drugs. Because dantrolene seems to be effective therapy in swine, the authors believe that access to it should be given to all emergency departments and intensive care units that might treat MDMA-intoxicated patients.

■ Rates of IRB Approval and Informed Consent in Anesthesia Journals Surveyed. Myles and Tan (page 1209)

Myles *et al.* selected six highly ranked anesthesia journals and collected data on documented rates of institutional review board (IRB) approval and informed consent for all anesthesia studies related to human research published in 2001. The study types ranged from randomized controlled trials, to retrospective observational studies, to case series and reports. Thirty-seven percent of the 1,189 studies retrieved were classified as randomized controlled trials, 2% were nonrandomized trials, 28% were observational studies, 23% were case reports/series, and 10% were mechanistic studies. The latter included those that used human tissue or blood samples to ascertain anesthetic drug effect or other principles.

According to explicit statements in the published studies, IRB approval was documented in 71% (845) of the surveyed studies. Individual patient consent was documented in 56% (660), next-of-kin consent was obtained in 9.6% (114), and consent was waived in 2.9% (34) of the studies. IRB approval was obtained in most trials and mechanistic studies, but less often in prospective observational studies and case reports/series. Informed consent was obtained most often with randomized controlled trials (97%), and less with mechanistic studies (83%), nonrandomized trials (77%), prospective observa-

tional studies (75%), retrospective observational studies (41%), and case reports/series (3%).

Because of the wide variation in consent and approvals for different types of studies, the authors then restricted their analysis of approval rates to prospective studies. Following a logistic regression analysis, they found that the predictors of informed consent were type of publication, journal, and patient gender. Subsequent correspondence with the journal editors responsible for publication of randomized controlled trials without documentation of IRB approval or informed consent revealed that, in fact, such approval and consent had been obtained in all but one case. These facts were omitted from some of the published studies.

This survey found that rates of IRB approval and informed consent in leading anesthesia journals are at least as good as those in other specialty or general medical journals. However, the processes for obtaining, documenting, and publishing approvals and consent vary considerably between types of studies and journals. Noting that the World Medical Association's Declaration of Helsinki requires both IRB approval and informed consent for any research involving human subjects, the authors recommend more vigilance in confirming approvals by researchers, and in documenting those facts when the study is published. At risk is the violation of the principles of patient autonomy and undermining of the public's trust in scientific research.

■ Case Solved: Death by Succinylcholine Masked by Electrocardiogram Strips. Peters (page 1225)

In an unusual case report, Dr. Peters recounts his participation as an expert witness in a murder trial involving an anesthesiologist accused of murdering his 35-yr-old wife. The woman had been found dead by a paramedic team at the bottom of a stairway next to a vacuum cleaner. The husband, a trained anesthesiologist who had called the paramedics, reported that he had found his wife at the foot of the stairs unconscious, pale, and with a slow and weak pulse. He said he had administered cardiopulmonary resuscitation to his wife. He presented several electrocardiogram strips with date and time annotations showing consecutive sinus bradycardia, asystole, and ventricular fibrillation, which he said he had recorded before paramedics arrived using his portable electrocardiogram monitor/printer. The anesthesiologist suggested that his wife's blood pressure problems had possibly evoked the accident.

On the basis of suspected discrepancies between initial sinus bradycardia and stated resuscitation measures, a vial of succinylcholine missing from the anesthesiologist's emergency case, and testimony about the couple's disturbed relationship, the anesthesiologist was charged with murder using succinylcholine. However, succinylcholine or its degradation products were not detected in blood samples taken during the autopsy. Accordingly, the court sought the author's opinion of the authenticity of the electrocardiogram recordings furnished by the husband to paramedics.

After running test strips and examining the manufacturer's simulated recordings, Dr. Peters concluded that at least part of the electrocardiogram recordings secured from the murder scene were identical to the unique fibrillation pattern stored in and displayed by the particular simulator. Based on this evidence, the prosecutors were able to secure a confession from the anesthesiologist, who was convicted of and is now imprisoned for the murder of his wife.

Gretchen Henkel