trachea of a 4.2-kg infant. As a refinement, Benuomof suggested using a fiberoptic instrument in place of the catheter guide.3

Digitally assisted tracheal intubation may have been first performed as early as 154311 and has been described several times, especially in adults, over the past 100 yr.12-14 Our interest in digitally assisted tracheal intubation in pediatric anesthesiology arose from a recent report by Hancock and Peterson describing the role of "finger intubation" in their neonatal practice.15 They reported 39 successful digitally assisted intubations of neonatal tracheas with a mean time of 7 s per intubation. It occurred to us that the digital technique might make actual displacement of the tongue unimportant, and this proved to be the case. The palpating finger curved naturally around the tongue, to lie at once over the glottis.

The ability to perform digitally assisted tracheal intubation may help ensure the safety of the patient with mandibular hypoplasia and represents a valuable addition to the anesthesiologist's armamentarium of tracheal intubation techniques.

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Tolerance to Isoflurane during Prolonged Administration

John H. Arnold, M.D.,* Robert D. Truog, M.D.,† Joyce A. Molengraft, R.N.‡


* Instructor, Department of Anesthesia (Pediatrics), Harvard Medical School; and Assistant in Anesthesia, Children's Hospital.
† Assistant Professor, Department of Anesthesia (Pediatrics), Harvard Medical School; and Associate in Anesthesia, Children's Hospital.
‡ Staff Nurse, Multidisciplinary Intensive Care Unit, Children's Hospital.

TOLERANCE is defined as a reduction in physiologic response to a drug with repeated administration.1 Tolerance has been described during prolonged use of vir-

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Address reprint requests to Dr. Arnold: Multidisciplinary Intensive Care Unit, Farley 5, Children's Hospital, 300 Longwood Avenue, Boston, Massachusetts 02115.

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typically all the intravenous anesthetics. The phenomenon of tolerance is a particular problem in the intensive care unit, where profound levels of sedation are often required for prolonged periods of time. The use of potent volatile agents in the critical-care setting offers a reliable mode of administration, limited accumulation of toxic metabolites, and a rapid mode of excretion. The apparent development of tolerance to the anesthetic effects of isoflurane in a 4-yr-old patient over the course of 32 days of continuous administration is reported.

Case Report

A 4-yr-old boy ("G.D.") was treated at the referring hospital for Stage 4 Wilms' tumor. His therapy was complicated by the development of radiation pneumonitis, ventilator dependence, and bilateral pneumothoraces. He was referred to this hospital for further care. At the time of transfer, he was sedated with fentanyl by continuous infusion. His respiratory failure was managed with high-frequency oscillatory ventilation, during which he was sedated with fentanyl and midazolam by continuous infusion, as well as vecuronium for muscle relaxation. After 50 days of mechanical ventilation, the patient's sedation regimen included sufentanil (7 μg·kg⁻¹·h⁻¹), midazolam (230 μg·kg⁻¹·h⁻¹), and lorazeepam (1 mg·kg⁻¹·day⁻¹). He was also receiving vecuronium by infusion, dopamine (7.5 μg·kg⁻¹·min⁻¹), and inhaled β-agonists to provide bronchodilation. Given the requirement for large doses of intravenous agents to provide sedation, we elected to use isoflurane to enhance both sedation and bronchodilation. The goal of our therapy with isoflurane was to decrease or eliminate the need for additional sedatives, bronchodilators, or muscle relaxants. Isoflurane was administered via a Servo 900C Anesthesia System® (Siemens, Solna, Sweden) that included a calibrated liquid injection vaporizer (Siemens vaporizer 952®) and a reservoir-protected active scavenging system (Servo Eevac 180®). Inotropic and end-tidal gases were sampled at the proximal end of the endotracheal tube and subjected to continuous infra-red analysis (Ohmeda 5250 RGM®, Louisville, CO). Isoflurane administration was begun at an inspired concentration of 0.6% and the sufentanil infusion rate was decreased to 3.5 μg·kg⁻¹·h⁻¹. Shortly after initiation of isoflurane administration, the patient's systolic blood pressure decreased from 126 to 75 mmHg; a bolus of 5% albumin (5 ml/kg) and an increase in the dopamine infusion rate to 10 μg·kg⁻¹·min⁻¹ rapidly restored hemodynamic stability. He continued to receive muscle relaxants. At an end-tidal isoflurane concentration between 0.4 and 0.7%, dynamic lung compliance was increased and the requirement for β-agonists was decreased. After 5 days of isoflurane administration, the sufentanil and midazolam infusions were discontinued and intravenous methadone (1.7 mg·kg⁻¹·day⁻¹) was begun. After 6 days of isoflurane administration, the neuromuscular relaxants were discontinued and the patient was allowed to breathe spontaneously. At this time, the patient was receiving aminophylline, dopamine (2.5 μg·kg⁻¹·min⁻¹), methadone (0.4 mg/kg q 6 h), and isoflurane (end-tidal concentration 1.2–1.4%). The methadone dose was decreased gradually to 0.1 mg/kg every 6 h after 11 days. After 19 days of isoflurane administration with measured end-tidal concentrations between 0.8 and 1.2%, the patient was awake, fixing and following, and obeying commands. He was cooperative with routine care and occasionally watched television. The only differences noted between inspired and expired isoflurane concentrations occurred during the initiation of drug administration, which disappeared within 5 min, and, occasionally, when inspired concentrations were adjusted to acutely alter anesthetic depth (i.e., before endotracheal suctioning). The patient's highest measured inorganic fluoride concentration was 26.1 μM after 441 MAC-hours, and there were no significant changes in the patient's creatinine, serum osmolality, or urine output that would suggest inorganic fluoride toxicity. After approximately 75 days of mechanical ventilation and 32 days of continuous isoflurane administration, an attempt was made to aggressively separate the patient from the ventilator and the administration of isoflurane was discontinued. At this time, the only intravenous sedative the patient was receiving was methadone (0.1 mg/kg every 6 h). On discontinuation of isoflurane from an end-tidal concentration of 0.5%, the patient became increasingly alert and appeared agitated. The patient appeared dysphoric as soon as the end-tidal concentration reached approximately 0.5%, and a continuous infusion of midazolam (300 μg·kg⁻¹·h⁻¹) was begun to reduce anxiety and obvious agitation. Despite significant doses of midazolam by bolus (totaling 3 mg/kg over 1 h) the patient became increasingly agitated, diaphoretic, and hypertensive, and developed tachycardia and profuse diaphoresis. The patient's agitation was ultimately controlled after 6 h with pentobarbital and an increase in the midazolam infusion to 800 μg·kg⁻¹·h⁻¹. The patient's respiratory condition continued to deteriorate and he ultimately succumbed to intractable respiratory failure 31 days later.

Discussion

The use of volatile agents for sedation and analgesia has been reported in obstetric patients, in terminally ill patients with refractory pain, and, recently, for sedation in adult patients undergoing mechanical ventilation of their lungs. Volatile anesthetic agents have been used in the critical-care setting for the management of refractory status asthmaticus and status epilepticus. The potent volatile agents halothane and isoflurane offer the theoretic benefits of rapid titratability, bronchodilation, and the preservation of spontaneous ventilation. Previous experience in adults indicates that isoflurane produces limited cardiovascular or renal side effects. We feel that volatile agents in the intensive-care setting represent an important addition to the armamentarium available to critical-care physicians.

The patient we report was communicative, recognizing family members, and conversant while measured end-tidal isoflurane concentrations were between 0.8 and 1.2%, indicating tolerance to the anesthetic effects of isoflurane. Whether tolerance to inhalational anesthetic agents occurs during prolonged exposures is controversial. Animal studies have yielded conflicting results. Mice continuously exposed to subanesthetic...
concentrations of isoflurane for 63 days did not develop tolerance as assessed by loss of the righting reflex. However, rats intermittently exposed to halothane for 56 days did manifest tolerance to acoustic-evoked responses measured in the thalamic and hypothalamic regions, and mice intermittently exposed to either halothane, enfurane, and isoflurane manifested tolerance as measured by loss of the righting reflex. There are no human reports of tolerance to the anesthetic effects of halothane, enfurane, or isoflurane during prolonged exposures, although we have previously noted an apparent increase in the concentration of isoflurane required to control a movement disorder during the course of 112 h of continuous administration.

We also acknowledge that, in the present case, the previous development of tolerance to intravenous agents (both opioids and benzodiazepines) may have played a role in the development of tolerance to isoflurane.

In contrast, tolerance to nitrous oxide has been consistently noted in animals and has been associated with alterations in the density of opiate receptors in the brainstem. Similarly, tolerance to the analgesic effects of nitrous oxide has been reported in humans and may occur within 60 min of administration.

Furthermore, there is convincing electroencephalographic evidence that tolerance to nitrous oxide commonly occurs in humans. Whether the high frequency of tolerance associated with exposure to nitrous oxide implies a different mechanism of action than the potent volatile agents (halothane, enfurane, isoflurane) is an interesting speculation.

The patient we report also manifested abstinence symptoms that were noted shortly after the discontinuation of isoflurane administration. The patient had also received benzodiazepines and was receiving methadone at the time the symptoms were noted. It is possible that the symptoms were related to opioid abstinence that was precipitated by the steady decrease in opioid dosage that preceded the symptoms, and evidence of opioid withdrawal may have been masked by isoflurane administration. We feel this explanation is unlikely, because the patient we report was receiving 0.4 mg · kg⁻¹ · day⁻¹ of methadone at the time the abstinence symptoms were noted. It is also possible that the abstinence symptoms were caused by benzodiazepine withdrawal, because the patient had received significant doses of lorazepam that were discontinued during isoflurane administration. Although possible, we feel the immediate appearance of these symptoms following the discontinuation of isoflurane makes it the most likely etiology of our patient's symptoms. A withdrawal syndrome has been noted after administration of nitrous oxide, ethylene, cyclopropane, and diethyl ether to mice but has not been noted in animal studies after administration of isoflurane. Symptoms of abstinence associated with isoflurane administration have not been reported in humans. However, until further information becomes available, we suggest that inspired concentrations of isoflurane be gradually decreased in individuals receiving isoflurane for prolonged periods.

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