CASE REPORT

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Fatal Halothane Poisoning During Anesthesia with Other Agents

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ABSTRACT: A patient was inadvertently overdosed with halothane during the nitrous oxide phase of anesthesia induction. During the subsequent 2½-h resuscitation attempt, the oxygen via the anesthesia machine continued to be contaminated with 5% halothane. Brain death was pronounced when the patient may have been only very deeply anesthetized. The vaporizer had accidentally been left on the full ON position prior to the procedure. Poor design of vaporizer controls and operator neglect combined to allow protracted patient exposure to the toxic concentration of halothane. The medical examiner has a critical role in the adequate management of anesthesia/surgery related deaths.

KEYWORDS: toxicology, halothane, anesthetics

Intraoperative deaths secondary to anesthesia occur once in every 5000 to 10 000 anesthetic procedures [*1-6*]. Thus, anesthesia alone may account for 2000 deaths in the United States per year [*6*]. The majority of these deaths are secondary to airway insufficiency, inappropriate fluid therapy, and reactions to medication [*7,8*].

Eighty to ninety percent of anesthesia-related deaths are preventable or secondary to human error [*9-11*]. Although anesthesia accounts for only about 10% of all intraoperative deaths [*2,5*], a large percentage of the remaining deaths is also accidental. Intraoperative deaths, therefore, are more likely to be accidental compared to other hospital deaths. The relatively high frequency of accidents among operative deaths is one of the reasons many of the better medical examiner or coroner jurisdictions require notification for all intraoperative deaths. Intraoperative deaths in these jurisdictions are usually loosely defined as deaths occurring as a direct result of an anesthetic/surgical procedure. Unfortunately, many hospital personnel avoid reporting these deaths by pronouncing death outside the operative theater.

Notification of the medical examiner satisfies the legal requirements for reporting accidental deaths. The accidental nature of an intraoperative death, however, may not be initially apparent. As the case below illustrates, the medical examiner investigation may reveal an intraoperative death to be more complex than it appears initially.

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Case Report

A 61-year-old male was admitted for a prostatectomy for carcinoma of the prostate. One week before admission he had undergone general anesthesia with halothane for biopsy and diagnosis of prostatic cancer. The biopsy procedure was uneventful. The patient was otherwise in good health but had a vague history of myocardial infarction ten years previously.

On the day of the scheduled prostatectomy he received 75 mg of meperidine and 0.4 mg of atropine as preoperative medication 1 h prior to arriving in the operating suite. Anesthesia was induced without incident with 3 mg of curare, 300 mg of Pentothal®, 100 mg of succinylcholine, and 50% bottled nitrous oxide with oxygen from a wall outlet. An endotracheal tube was inserted without difficulty. Ten minutes after induction, before either the surgical procedure or the halothane anesthesia was begun, the patient became hypotensive (blood pressure 55/30 mm Hg). Within 15 min blood pressure was restored with phenylephrine drip. The nitrous oxide was discontinued and the patient received 5 L of oxygen delivered via the original anesthesia machine, which was used throughout the stay in the operating room. The anesthesia machine was equipped with a waste gas scavenging system.

Approximately 30 min after the blood pressure initially stabilized the patient developed ventricular dysrhythmias; the peripheral blood pressure was unobtainable. Over the ensuing hour the patient received Metaraminol, dopamine, lidocaine, and fluids to restore normal blood pressure and cardiac function. Blood pressure responded to drug therapy only to decline 10 to 15 min later. Four severe hypotensive episodes occurred during the 2½ h in the operating room. With aggressive antihypotensive therapy the patient's blood pressure was stabilized and he was transfered to the recovery room with a separate ventilator and wall oxygen. After 1 h in the recovery room (3½ h after induction of anesthesia) the patient remained totally unresponsive, without spontaneous respiratory activity, and with fixed, dilated pupils. On the assumption of brain death, ventilatory support was withdrawn and the patient died.

Autopsy examination was begun 6½ h later. Significant findings were a potentially resectable carcinoma of the prostate and minimal atherosclerotic coronary artery disease. There was no evidence of a previous myocardial infarction. Specimens of blood and liver were secured at autopsy; a sample of blood taken 2 h after induction of anesthesia for blood gas determinations was also secured from the original glass syringe.

The following day another patient anesthetized by the same anesthesia machine used on the decedent developed similar complications. The anesthetist for the second individual noted that the halothane vaporizer had been left on the maximum concentration setting (approximately 5%). The second patient's surgery proceeded uneventfully once the error was corrected. Reevaluation of the events surrounding the decedent's death indicated that one anesthetist had primed the anesthesia machine with the vaporizer on the 5% setting and had not turned the vaporizer off. The decedent's anesthetist *assumed* the vaporizer was off while inducing anesthesia and had *assumed* that only oxygen was being administered throughout the stay in the operating room. In reality a toxic (5%) dose of halothane was being given throughout that period (normal anesthetic dose is 1 to 2%). The clinical course while in the operating room was typical for halothane toxicity.

The physicians attempting resuscitation were unaware that halothane had been given at all and attributed the terminal unresponsiveness to hypotensive cerebral anoxic damage. In retrospect, life support may have been withdrawn from an anesthetized individual who may have recovered. The physicians were in violation of the state's brain death law, but the district attorney chose to take no action.

Method for Halothane Analysis

The gas chromatograph was a Varian Model 1200 equipped with a flame ionization detector and a 1.8-m (6-ft) by 3.2-mm (⅛-in.) stainless steel column packed with 0.4% Carbowax 1500 on a Carbopack A by Supelco Inc. Temperature settings were 100°C for the column,

175°C for the injector, and 190°C for the detector. Flow rates were 25 mL/min for the nitrogen carrier gas, the same for hydrogen, and 250 mL/min for air. A 200 μg/mL blood halothane standard was made by adding 1 mL of a 2.0 mg/mL aqueous halothane solution to 9 mL of whole blood. An aqueous solution of 10 μg/mL *l*-butanol was used as an internal standard. Prior to injection, 1 mL of internal standard solution was mixed with 1 mL of blood halothane standard. One millilitre of the blood sample to be tested was mixed in the same manner with internal standard and then 2.5 μL of each mixture was injected into the gas chromatograph. The retention time of halothane is 1.1 min and of *l*-butanol, 1.8 min, under the gas chromatographic conditions herein described. At an attenuation setting of $10^{-11} \times 1$ the 0.2 mg/mL blood halothane standard gives a 30% scale deflection on a 1-mV strip chart recorder and the *l*-butanol gives a 60% scale deflection at a setting of $10^{-11} \times 2$. Comparison of the peak height ratios between the standard and unknown blood specimen provides the basis for calculating the amount of halothane.

Confirmation of halothane identification was done by comparison gas chromatography/mass spectroscopy.

Toxicologic Results

Analysis for halothane was performed one month postmortem. The specimen had been stored at 4°C for two weeks and then at −70°C for two weeks.

Postmortem blood was positive for halothane (not quantified), was positive for trace amounts of lidocaine, and was negative for other organic bases and thiopental.

Antemortem blood contained 72 mg/100 mL of halothane, and the liver fluid contained 20 to 30 mg/100 mL of halothane.

Interpretation and Discussion

With the exception of those patients who are at high risk and die of recognized, nonpreventable complications of surgery, all operative deaths deserve competent medicolegal death investigation. Few death investigators are comfortable in their understanding of modern anesthesiology and should enlist the aid of a competent anesthesiologist in their investigations. Although only 10% of anesthesia-related deaths have positive gross or microscopic findings at autopsy [*12*], all such cases should undergo autopsy to rule out demonstrable abnormalities and thus better protect the interests of the victim's family, future patients, and the operating team [*13*]. The investigator must also remember to "autopsy" the operative suite, anesthesia machine, and the anesthesia/surgical report.

Careful toxicologic evaluation should augment the autopsy. Since inappropriate doses of drugs may easily (overtly and covertly) escape detection in the anesthetist's/anesthesiologist's memory or records, all potentially toxic drugs used during the anesthetic procedure should be assayed. The medicolegal investigator should also consider toxicologic examination for substances that could be present in the decedent but were not thought to have been used. The investigator should be wary of reported anesthesia control settings for these reasons and because malfunctioning anesthetic vaporizers can inadvertently deliver lethal levels of anesthetic agents to the patient.

There are many recognized forms of vaporizer failure leading to inadvertent overdose with an anesthetic agent. Tipping [*14*], overfilling [*15,16*], broken valves [*17*], or high flow into the vaporizer [*10*] can allow anesthetic agents direct access into the breathing circuit. Control values can be inaccurate [*18*]. The wrong vaporizer for a given agent, or vaporizers connected in series rather than parallel, can produce overdosage [*19*]. Accidental overdosage can also result from confusion of ON/OFF rotation directions of controls on different equipment [*20*] and inappropriate interchange of equipment [*21*]. Of increasing concern in many hospitals is the realization that vaporizers may also be left on by operating room personnel illicitly abusing halothane [*22-24*]. The above case report illustrates an unusual human error

involving a vaporizer and leading to a fatal halothane overdose. The decedent manifested typical symptoms of halothane toxicity, that is, hypotension and cardiac dysrhythmias. Toxicology revealed an abnormally high level of halothane both in the liver fluid and the blood. Anesthesiologists rarely use blood halothane levels to monitor anesthesia; anesthetic and toxic concentrations of halothane therefore are not well established. Animal and human studies have generally shown anesthetic blood levels from 5 to 30 mg/100 mL [*19,25-28*] and liver tissue halothane levels up to 63 mg/100 g [*27*]. Lethal halothane levels in humans are not well established and reflect occasional case report studies. Spencer and Green's report [*22*] of a halothane overdose includes a 65 mg/100 mL blood concentration. Animal studies have shown lethal halothane concentrations in rats in the range of 55 to 80 mg/100 mL [*29*].

The postmortem interval and specimen processing may contribute to making the interpretation of halothane concentrations hazardous. Halothane as a rather volatile liquid probably evaporates to some degree, even when refrigerated or frozen. Careful sample collection and speedy assay are reasonable precautions. Rubber-stoppered glass containers of blood may lose 1.8% of the initial halothane per day [*30*]. Similarly contained sections of liver and kidney may lose up to 0.4% of the initial halothane per hour [*30*]. In the present case the halothane analyses were done four weeks postmortem. The antemortem blood sample was in a rubber-stoppered glass tube and had been opened twice. The postmortem blood sample was in a loosely stoppered plastic container and the liver sample was in a loosely sealed plastic cup. Precise determination of original concentrations from the decay figures is not feasible in this case, but the original (true) antemortem and postmortem halothane concentrations were probably much higher than those actually detected. This case report illustrates the following points for toxicologic investigation of operative deaths:

1. Minimize the postmortem interval prior to autopsy.

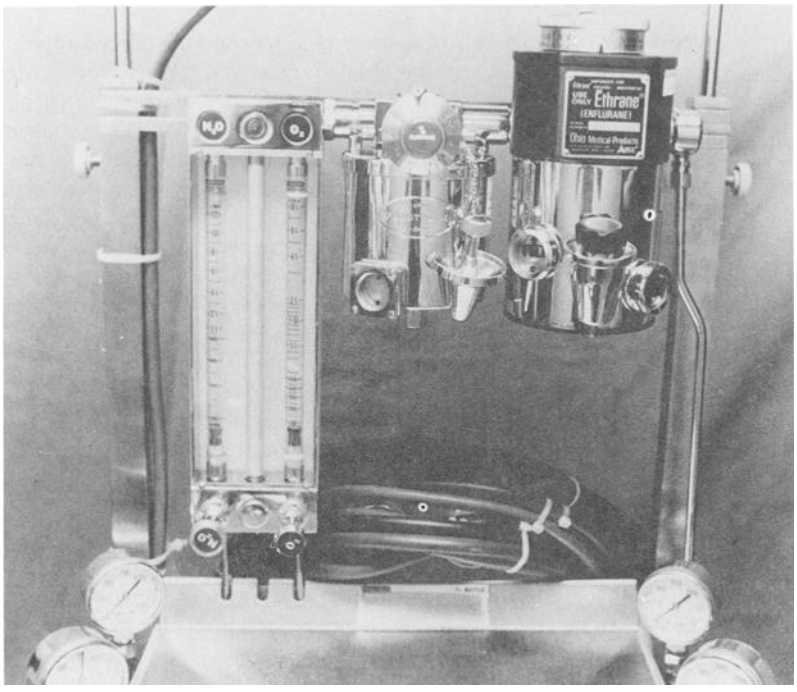

FIG. 1—*Anesthetic machine vaporizers* (on the right) *and flow meters* (on the left). *Note that although the vaporizers are on the OFF position, the design of the vaporizer valve settings does not attract the attention of the operator during a quick visual scan.*

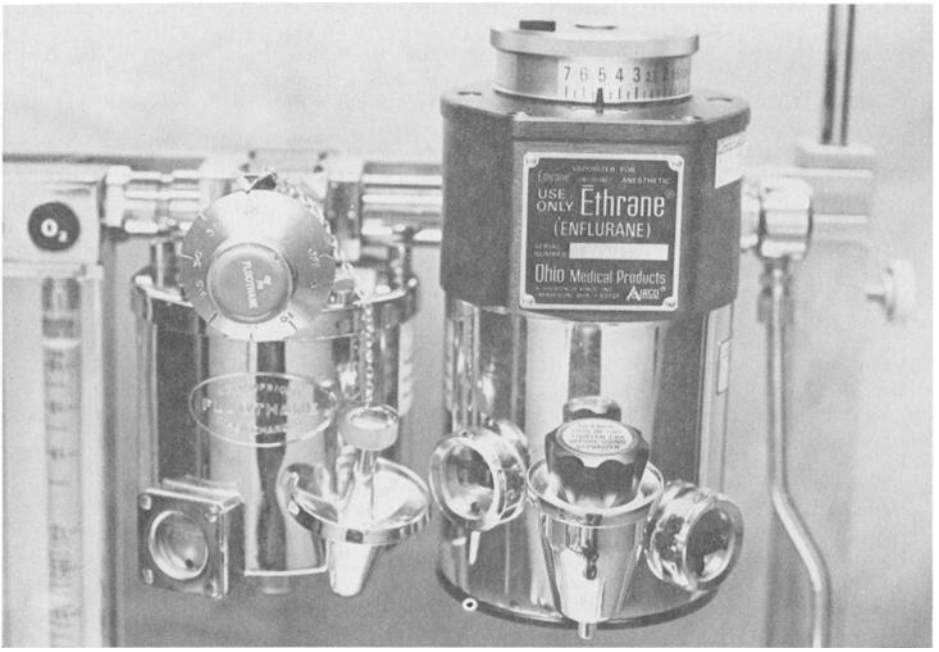

FIG. 2—*Close-up of the vaporizers shown in Fig. 1. The close-up illustrates the degree of visual attention the operator must expend to accurately assess the control valve settings.*

2. Collect toxicologic specimens for analysis not only for agents known to be present but also for agents that could be present.
3. Secure the specimens in well-stoppered, preferably glass, containers.
4. Expedite the transportation and the toxicologic assays with appropriate refrigeration or freezing.

More important than the human autopsy is the "investigation" of the equipment and situation surrounding the death. In the case at hand, additional history from operating room personnel and inspection of the anesthesia machine indicated the ease of administering an unsuspected overdose of halothane, particularly with waste gas scavenging to exhaust the halothane smell. As Fig. 1 illustrates, the OFF and ON control valve settings of most vaporizers are not readily differentiated, except on close examination (Fig. 2). Any machine to which lives are daily entrusted and which does not actively alert the operator to a dangerous mode of operation is a hazardous device in need of redesign. The potential for anesthetic vaporizers to allow easy delivery of toxic, nontherapeutic levels of agents also represents a dangerous and avoidable design flaw. In this case another anesthetist had primed the anesthesia machine prior to the operative procedure and had forgotten to turn the vaporizer off, illustrating the necessity of not *assuming* the vaporizer control setting to be off prior to the procedure.

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