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Overview

Anesthesia Update: Agents, Definitions, and Strategies

James E. Heavner, DVM, PhD

Anesthesiology, like most biomedical disciplines, is undergoing fast-paced changes. Decisions regarding the anesthesia management of laboratory animals, from evaluation of protocols to protocol implementation, should be based on contemporary knowledge of drugs and methods. Some of the major new concepts and drugs that are influencing or will influence the management of anesthesia in animal research environments will be presented here.

New anesthetic agents, techniques, and philosophies, and the availability of highly trained personnel have had major impact on the surgeries that can be done, the safety of anesthesia and surgery, how much anesthesia is used, which drugs are used before, during, and after anesthesia, and the speed of postoperative recovery. Major trends include development and use of anesthetics targeted for specific receptors (e.g., α_2-adrenergic agonists [1]), and/or which have pharmacokinetic profiles that permit rapid induction, rapid adjustment of anesthesia depth, and rapid recovery (e.g. desflurane [2]). Pre-operative and post-operative assessment and medication also are important components of anesthesia management. However, this review focuses principally on management of intra-operative anesthesia. Species-specific considerations, of which there are many, especially with respect to small rodents (3), are not featured.

Definitions of anesthesia depth and adequacy are being reconsidered. In some instances, the pharmacodynamics of drugs used to induce and maintain general anesthesia result in changes that do not fit neatly into traditional criteria for judging the anesthesia state. "Dissociative" anesthesia induced by ketamine is a good example (4). It is now known that a standard reference point for general anesthesia (minimum alveolar concentration [MAC]) of an inhalation anesthetic agent required to prevent a patient from making a directed response to a standard noxious stimulus) can be achieved without involvement of the brain (5, 6). Since the brain is generally considered the primary site for action of anesthetics, MAC may not be the best measure of anesthesia. As of this point in time, however, MAC is still used as a guide for administration of volatile anesthetics. Other guides of anesthesia depth and adequacy include hemodynamic and behavioral responses to noxious stimuli (7).

What is General Anesthesia and What Standard Determines its Adequacy?

General anesthesia is a drug-induced altered state of consciousness in which the patient is pain free, behaviorally depressed, and amnesic. A more traditional definition of general anesthesia is a drug-induced absence of all sensations (including pain) (8).

The moral and ethical standard for adequate anesthesia is that the anesthesia state should be adequate to prevent suffering during surgical intervention or recall of unpleasant intra-operative events and minimize postoperative pain. How can one know whether anesthesia is/was adequate in a non-verbal patient, such as a laboratory animal? Results from well-designed behavioral experiments involving human patients and animal models provide a solid base for making judgements about adequacy of anesthesia.

It has been known for some time that doses of general anesthetics that induce unconsciousness and amnesia are lower than are those that prevent autonomic and somatomotor reflex responses (9). Conversely, reflex responses can be blocked by use of selective pharmacologic agents (neuromuscular blocking agents [NMB], and sympathetic and parasympathetic antagonists), with little or no alteration in cognitive function. Use of anesthetic concentrations that result in unconsciousness and amnesia, together with NMBs to prevent reflex somatomotor responses, represents one contemporary approach to general anesthesia. In using this approach, results from behavioral studies are applied to subjective assessment of anesthesia adequacy. For example, 1.25 MAC of a sole volatile anesthetic will reliably induce adequate anesthesia. Depending on the anesthetic, the patient will awaken when the anesthetic concentration is decreased to 0.33 to 0.67 MAC (10).

Objective Measures of Anesthesia

Objective measures of adequate anesthesia, based on electrical activity of the brain, have been sought for some time. Efforts have been made to define electroencephalographic (EEG) patterns from the unprocessed or processed EEG, or changes in evoked responses (e.g., auditory brain stem evoked responses) that correlate with how deeply a patient is anesthetized. The bispectral index (BIS) is the first monitor approved by the Food and Drug Administration for the measurement of the hypnotic effects of drugs in humans, and there is interest in using it to guide anesthesia in animals.

The BIS is derived by applying stepwise regression analysis to EEGs from anesthetized subjects in known awake/sleep states. A set of EEG features describing power, frequency, biocoherence, β-activation, and burst suppression are combined to give a statistically based prediction of sedation or hypnosis during

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Department of Anesthesiology, Texas Tech University Health Sciences Center, 3601-4th Street, Room 1C-258, Lubbock, Texas 79430.

anesthesia. The regression equation is transformed into a 0 to 100 scale, where 0 = no brain electrical activity and 100 = maximal "organized" brain activity. To validate BIS in humans, volunteers were given propofol, midazolam, or isoflurane. Responses to voice were virtually nil when BIS was < 60 (11, 12). Gan and coworkers (13) found that use of BIS to titrate the hypnotic component of anesthesia reduced the dose of anesthetic and increased the speed of awakening. Investigations of BIS monitoring in animals are being pursued (14).

There was considerable discussion at the October 2000 meeting of the American Society of Anesthesiologists about whether a BIS number exists above which there is awareness and below which there is not. There was some agreement that BIS monitoring is similar to blood pressure monitoring—it is a monitor that must be interpreted in the context of other available information. For example, consideration should be given to the drug or drugs used for anesthesia, and presence or absence of autonomic responses to noxious stimuli, and the magnitude of the responses.

Anesthesia that "Walks a Line"

A concept that emerges from the foregoing discussion is anesthesia that "walks a line" so that anesthesia depth does not substantially exceed criteria that define adequate anesthesia. Even though it is difficult to objectively "walk the line," striving to do so is in the best interest of the patient and is economically advantageous. A risk of "walking the line" is that anesthesia may not be adequate for all patients, under all circumstances. Additionally, "walking the line" requires a sophisticated understanding of pharmacology for a variety of drugs and techniques, as a large number of drugs is used to tailor anesthesia and analgesia management for specific intra-operative and postoperative needs. In humans where "walking the line" is the norm, reports of awareness under anesthesia are rare, and rarer still are reports of patients experiencing pain during surgery. (15)

What are the pros and cons of using a more conservative approach (i.e., deeper depth of anesthesia)? One advantage of using depth of anesthesia that is further from the line that defines adequate anesthesia is greater assurance that the patient will receive adequate anesthesia. Disadvantages include potential for increased morbidity or mortality and higher costs (more drug used and longer recovery, with prolonged use of staffing and facilities). These disadvantages are magnified as anesthesia depth increases beyond the threshold for adequate anesthesia.

Anesthesia for Laboratory Animals

How does "walking the line" apply to anesthesia for animals in the experimental setting? Two boundaries with respect to anesthesia depth—too light and too deep—need to be considered. Modern anesthesia practice is moving away from the too deep boundary. Thus, investigators, technical staff, administrators, and regulatory personnel must recognize the trend toward lighter depths of anesthesia as they evaluate and/or administer anesthetic protocols. Statements such as "general anesthesia cannot be used because it blocks the response" must be evaluated in context. Generalizations about the use of anesthesia should not be based on observations associated with one or even a few anesthetic agents.

Volatile agents. Comprehensive reviews of volatile inhalation anesthetics are presented elsewhere (2, 16). Halothane, isoflurane, sevoflurane, and desflurane are the prominent modern inhalation agents. These agents have a much lower blood:gas partition coefficient than does methoxyflurane (and diethyl ether) (Table 1). The low coefficient permits rapid induction, quick responses to adjustments of anesthetic concentration, and rapid recovery. Such attributes make these agents compatible with the trends in anesthesia discussed previously. The newest agents, sevoflurane and particularly desflurane, are especially rapid in onset, and responses to concentration adjustments and recovery from anesthesia are remarkably rapid. One indicator of speed with which anesthesia can be induced by use of an inhalation anesthetic is how fast the lung alveolar concentration approaches the inspired concentration. As indicated in Fig. 1, the rank order from fastest to slowest is desflurane, sevoflurane, isoflurane, halothane, and methoxyflurane. Therefore, one must be prepared for abrupt recovery if anesthetic administration is stopped intentionally or unintentionally (e.g., vaporizer empty, delivery system disconnect).

The MAC values for halothane, isoflurane, sevoflurane, and desflurane for a number of animal species are shown in Table 2. In some instances, MAC varies considerably (e.g., desflurane in the rat). Reasons for the variability include possible differences in techniques for determining MAC (e.g., MAC for loss of righting reflex versus MAC for prevention of a response to a surgical stimulus) and genetic influences reflected as strain differences in MAC (17).

Table 1. Blood:gas partition coefficients*

Anesthetic	Blood:gas coefficient
Methoxyflurane	12.00
Halothane	2.54
Isoflurane	1.46
Desflurane	0.42
Sevoflurane	0.69

*Data from references 24 and 25.

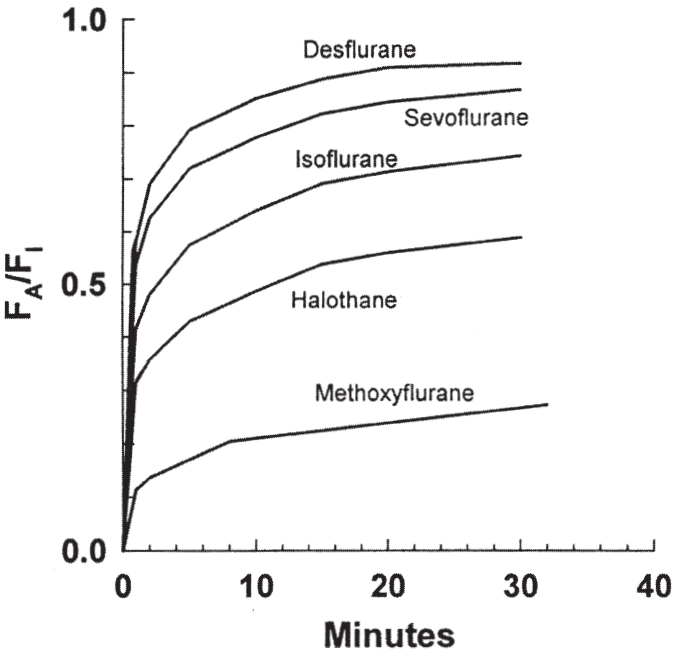

Figure 1. Increase in the alveolar (F_A) anesthetic concentration toward the inspired (F_I) concentration. Notice that the increase is most rapid in association with the anesthetic that has the lowest blood:gas partition coefficient, desflurane, and is slowest in association with methoxyflurane, the agent with the highest coefficient. All data are from studies of humans. Adapted from reference 2.

Table 2. Minimum alveolar concentration (MAC) values for a variety of species

Species	Halothane	Isoflurane	Sevoflurane	Desflurane
Cat	0.82 – 1.19	1.61 – 1.63	2.58	9.79
Dog	0.86 – 0.93	1.28 – 1.39	2.10 – 2.36	7.20
Horse	0.28	ND	2.31	ND
Monkey	0.88 – 1.15	1.46	ND	ND
Mouse	0.96 – 1.00	1.35 – 1.41	ND	ND
Calf	0.76	ND	ND	ND
Pig	0.91 – 1.25	1.45 – 2.04	1.97 – 2.66	10.00
Rabbit	0.80 – 1.56	2.05	3.70	8.90
Rat	0.81 – 1.23	1.17 – 1.52	2.40 – 2.50	5.72 – 7.10

ND = Not determined.
Data adapted from reference 2.

Apart from differences in speed of induction and recovery and/or responses to changes in inspired concentration of anesthetic, the predominant and clinically noteworthy difference among anesthetics is their effect on cardiovascular function. Halothane is a potent myocardial depressant and peripheral vasodilator. Isoflurane, sevoflurane, and desflurane also are potent vasodilators, but are less cardiodepressant than is halothane. Desflurane may cause transient tachycardia on initial exposure to high concentrations. Halothane, but not isoflurane, sevoflurane, or desflurane sensitizes the myocardium to catecholamines. Common to all modern volatile agents is the need to use precision vaporizers for safe administration. One feature that distinguishes desflurane from the other agents is its high vapor pressure. As a result, desflurane evaporates rapidly from open containers, and a special temperature-controlled vaporizer is required to administer it.

Other differences exist among these agents that may make one more (or less) advantageous than the others for a specific research requirement. Discussion of all differences that might be important to consider is beyond the scope of this review, so the reader is referred to the aforementioned references for further information.

Injectable agents. Comprehensive surveys of injectable agents are reported elsewhere (18, 19). Propofol is a unique and relatively new injectable anesthetic. Its pharmacokinetics favor rapid anesthesia induction, rapid responses to changes in infusion rates, and rapid recovery. Propofol generally is administered intravenously, first as a bolus for induction, than as a constant infusion for maintenance of anesthesia. Recovery may be prolonged if propofol is administered to dogs for longer than 30 min (20). Intramuscular administration to rabbits, even at relatively high doses, results only in sedation (21). The exact mechanism of action of propofol is not known, but it is a positive modulator of central γ-aminobutyric acid transmission (inhibitory action). Substantial systemic effects of propofol beyond its anesthetic action include relatively potent respiratory and cardiovascular depression. It is generally considered to be a poor analgesic but a good antiemetic.

Propofol is chemically different from other injectable anesthetics, such as the barbiturates and the α_2-adrenergic agonists, and is poorly water soluble. Clinical formulations of propofol use cremophor EL (a solution) or soybean oil, glycerol, and purified egg phosphatide (an emulsion) as vehicle. Cremophor has the disadvantage, however, of causing pain on injection. It has been documented to cause histamine release (e.g., in the dog [18]), or anaphylactic reactions in the rat and pig (22). The emulsion may also cause pain on injection since it does so when injected in humans. The emulsion also is an excellent medium for bacterial growth, so storage of opened ampules is not recommended.

α_2-Adrenergic agonists remain a popular class of anesthetic agents. They are principally sedative/analgesic drugs rather than general anesthetics. The prototype agent, xylazine, has been available for a long time. So too have the "newer" α_2-adrenergic agonists medetomide and detomidine (18). One advantage of these drugs is that a specific antagonist (atipamezole) is available to reverse their action.

Other agents: opioids, neuromuscular blocking agents, benzodiazepines. Opioids, neuromuscular blocking agents, anxiolytics, and amnesic drugs play important roles, particularly in "balanced anesthesia" techniques. Balanced anesthesia involves use of multiple drugs with complementary actions to induce and maintain anesthesia. The term was first applied to a "nitrous, narcotic" technique. In contemporary use, nitrous oxide (N_2O) and a potent opioid, such as fentanyl, are used to provide analgesia and change in conscious state, and a neuromuscular blocking agent is administered to induce muscular relaxation. Many modern anesthesia protocols are, in fact, a version of the balanced technique (e.g., sub-MAC or MAC potent volatile agent and N_2O supplemented with intravenous opioids plus a neuromuscular blocking agent and pre-operative or intra-operative administration of midazolam).

In keeping with contemporary trends in anesthesia (i.e., rapid induction and recovery, and quick responses to changes in drug administration), neuromuscular blocking agents, opioids, and adjuvants with pharmacokinetic properties similar to those of the newer anesthetics should be selected. Opioids used for intra-operative analgesia include alfentanil, sufentanil, fentanyl, and remifentanil, which is the newest of these agents. Newer neuromuscular blocking agents include mepivacurim and cis-atracurim (23).

Summary and Conclusions

The trend in modern anesthesia is to "lighten up." This generally involves use of several drugs with selective and complementary actions. The pharmacokinetic properties of such drugs should allow rapid onset, rapid recovery, and rapid responses to changes in delivered doses. Peri-operative management issues also are inherent to use of modern drugs and techniques. For example, provisions must be in place for postoperative analgesia if rapid recovery is anticipated.

Light anesthesia reduces morbidity and mortality, and reduces the drug, facility, and personnel costs associated with anesthesia. However, the requirements for anesthesia and the expertise of personnel administering anesthesia vary considerably. Many regulatory bodies and scientific journals require a description of how anesthesia adequacy and depth will be assessed, as well as extensive justification for the use of neuromuscular blocking agents. In environments where adequate experience and sophistication for the use of cutting edge drugs and methods are not available, older drugs and techniques may be adequate and preferable to protect animals from pain or distress.

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