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Minimum alveolar concentration: Key concepts and a review of its pharmacological reduction in dogs. Part 1

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ABSTRACT

Objective: To outline the major components of the minimum alveolar concentration (MAC) and review the literature in regard to pharmacological manipulation of the MAC of halothane, isoflurane, sevoflurane, enflurane, and desflurane in dogs. The pharmacologic agents included are alpha-2 agonists, benzodiazepines, propofol, maropitant, opioids, lidocaine, acepromazine, non-steroidal anti-inflammatory agents, and NMDA antagonists. Part 1 will focus on summarizing the relevance, measurement, and mechanisms of MAC and review the effects of alpha-2 agonists, benzodiazepines, and propofol on MAC.

Databases used: PubMed, Google Scholar, CAB Abstracts. Search terms used: minimum alveolar concentration, MAC, dog, canine, inhaled anesthetic potency, isoflurane, sevoflurane, desflurane, enflurane, and halothane.

Conclusions: Many drugs reduce the MAC of inhaled anesthetics in dogs, and allow for a clinically important decrease in inhalant anesthetic use. A decrease in MAC may decrease the adverse cardiovascular and pulmonary effects associated with the use of high concentrations of inhaled anesthetics.

1. Introduction

The concept of MAC was introduced by Merkel and Eger in 1963 in a study comparing halothane and halopropane in dogs (Merkel and Eger II, 1963), and soon thereafter MAC was suggested as a measure of anesthetic potency (Eger II et al., 1965). The MAC was originally defined as the minimum alveolar concentration of an inhaled anesthetic, at 1 atm, preventing purposeful movement in response to a noxious stimulus in 50% of individuals. Thus, MAC is a quantitative assessment of anesthetic potency, and is a measure that can be applied to all volatile anesthetics and across species. Due to the relative simplicity of its determination, and its reproducibility, the concept of MAC continues to be relevant.

It is of interest that only “gross purposeful movements”, such as twisting or jerking of the head or running or clawing movements of the limbs, were considered to be purposeful movements in response to the noxious stimulus, and coughing, swallowing or chewing were not deemed to be purposeful movements (Eger II et al., 1965). MAC represents the median effective dose (ED_{50}), and would appear to have limited clinical application as it is unacceptable for 50% of patients to move, in either a purposeful or non-purposeful manner, while undergoing a surgical procedure. Nevertheless, the MAC value of an anesthetic has proven to be a useful guide in clinical practice, and this is because the MAC dose-response curve for inhalational anesthetics is relatively steep, so a small increase in the end-tidal concentration over the MAC value will cause immobility in the vast majority of patients. For example, in human subjects the MAC value for methoxyflurane, halothane, and enflurane preventing movement in 95% of a population, defined as the AD_{95} (anesthetic dose preventing movement in 95% of patients), was only 20% greater than the MAC, although values varied by 5 to 40% (de Jong and Eger II, 1975). On the other hand, the steep slope of the curve may result in a patient moving if even small decreases occur end-tidal concentration, and this can occur rapidly with modern less soluble anesthetics.

Studies in inbred mice indicate that the MAC value is normally distributed within mouse strains and the variance is small. In comparison, differences of 39 to 55% existed in the MAC values among mouse strains, and were thought to represent the effect of multiple genes, because the pattern was distinctive for each anesthetic studied (Zhang et al., 2001). If an animal is selected at random from a population the probability of non-movement in response to a stimulus depends on genetic and environmental factors. The variance, measured as a partial pressure in percent of atmospheric pressure, in desflurane MAC in inbred mice was small (approximately 0.29%), and this was attributed to environmental influences because genetically similar animals should have the same MAC. The variance in MAC among the strains of mice

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studied was greater (0.85%), and because the experimental conditions were similar for both groups the variance was attributed to genetic differences (Zhang et al., 2001). This indicates that the effect of genetic variance on desflurane MAC among all strains of mice was 0.56%.

2. How do volatile anesthetics produce immobility?

As defined, MAC is a measure of the ability of the agent to produce immobility, but how volatile anesthetics produce immobility has long been debated. The brain, particularly the cerebral cortex, was considered to be the site of action of general anesthetics. However, monitoring cortical function does not accurately predict anesthetic depth in relation to the probability of a patient moving. It is obvious that the brain is affected by anesthetic drugs because general anesthesia is associated with unconsciousness; however, it is important to understand that the inhalant concentration required to produce unconsciousness is much less than that required to produce immobility (Eger II et al., 1965). Accordingly, it has been demonstrated that removal of the forebrain in rats did not affect the MAC of isoflurane (Rampil et al., 1993). Using an experimental preparation that allowed for selective perfusion of the goat brain and spinal cord, it was demonstrated that the MAC of isoflurane in the animal with an intact circulation was 1.2%; however, the MAC was 3% when the spinal cord was not perfused with isoflurane (Antognini and Schwartz, 1993), thus, supporting the role of spinal actions in volatile anesthetic induced immobilization. It was later demonstrated that isoflurane causes a greater suppression of ventral than dorsal horn neurons (Kim et al., 2007).

The molecular mechanism of action of inhaled anesthetics in production of immobility and unconsciousness is not completely understood; however, evidence exists for the involvement of multiple receptors including stimulation of glycine receptors (Zhang et al., 2003), inhibition of NMDA (Dutton et al., 2006), and inhibition of presynaptic sodium channels (Sonner et al., 2003). Spinal GABA receptors are thought to play less of a role than previously believed (Zhang et al., 2004). When two inhaled anesthetics are used in combination an additive effect is observed, implying that the different inhaled anesthetics are working via a common mechanism. Conversely, the combination of different intravenous anesthetics with each other or with inhaled anesthetics generally causes a synergistic effect in traditional MAC studies (Hendrickx et al., 2008) and an additive effect in studies of the MAC variant, MAC no movement, discussed later (Suarez et al., 2017). It is via this effect at different receptors affecting immobility, both spinally and supraspinally, that injectable drugs are thought to reduce the MAC of inhalant anesthetics (Stabernack et al., 2005).

3. MAC study design

MAC can be determined using one of two designs, bracketing or quantal, and both methods give the same results (Sonner, 2002). The bracketing design is the one most commonly used in animal studies, it can be performed using a relatively small number of animals, and was the method used in the initial MAC study in dogs (Merkel and Eger II, 1963). The animal is anesthetized with the volatile anesthetic delivered at a predetermined end-tidal concentration, and is observed for movement or absence of movement after application of a noxious stimulus. If movement occurs the anesthetic concentration is increased by 10 to 20%, depending on the volatile anesthetic in question, and the procedure is repeated until no movement is observed. After each adjustment in anesthetic concentration an equilibration period of 15 to 20 min is allowed. The MAC for that animal is considered to be the average of the lowest concentration preventing movement and the highest concentration allowing movement. MAC is generally determined in duplicate and the values are averaged. The MAC for the group is the average of the individual animal MAC values in the group.

The quantal design is used in human studies, but has also been used in dog studies, and in contrast to the bracketing technique, individual MAC values are not determined. Instead, MAC is determined for the population. The quantal dose-response is an “all-or-nothing” response in that there either is or is not a response to the stimulus. In this design, the patient is anesthetized and a target end-tidal concentration of inhalant is delivered. When a positive or negative response occurs the end-tidal concentration is increased or decreased, respectively, by a predetermined increment, for the next animal. This is often termed the “up-and-down” method (Dixon, 1965). For large populations, movement or non-movement is documented at multiple inhalant concentrations and a line of best fit is applied to the data points using a logistic or E_{max} equation, providing a dose-effect curve for the anesthetic. For small populations, cross-over pairs can be used to obtain MAC. A positive and negative response in two consecutive animals is termed a “crossover”, and an individual can only be used in one crossover. It is recommended that a minimum of four crossover pairs be obtained for MAC estimation; however, it is cautioned that analysis of quantal data using the up-down method may lead to incorrect estimates of MAC, and six cross-over pairs may yield more accurate results (Paul and Fisher, 2001). In this scenario, using cross-over pairs in a small population, mathematical averaging is used to obtain MAC. Quantal designs have been utilized in canine MAC studies (Barletta et al., 2016; Monteiro et al., 2016; Valverde et al., 2003). Because MAC is defined at 1 atm it is important that the atmospheric pressure at the study site is reported, especially if it differs significantly from 1 atm; alternatively, the MAC can be expressed as a partial pressure.

4. Variants of MAC

MAC, in the traditional sense, represents an ED_{50} but variants of MAC have been defined, thus providing further understanding of the gradations of anesthetic depth associated with inhalant anesthesia. The variants of MAC used in canine studies include MAC_{BAR} (Roizen et al., 1981), MAC_{NM} (Seddighi et al., 2012), and $MAC_{Extubation}$ (Barletta et al., 2016). MAC_{BAR} is the minimum alveolar concentration of an anesthetic, at 1 atm, blocking autonomic reflexes in response to a noxious stimulus in 50% of patients (Roizen et al., 1981). Changes in heart rate or blood pressure are used to gauge the autonomic response to stimulation, and a maximum change of 15% in either parameter has been allowed in dog studies (Columbano et al., 2012; Love et al., 2011; Seddighi et al., 2012; Yamashita et al., 2012; Voulgaris et al., 2013). In most studies, MAC_{BAR} is 20–40% higher than MAC; however, great variation exists depending on the agent and species (Voulgaris et al., 2013). In contrast to MAC, the slope of the dose-response curve for MAC_{BAR} is not steep, due to the variable adrenergic response among individuals, thus accounting for the great variation in MAC_{BAR} values (Roizen et al., 1981). Attenuating the autonomic response with inhalant agents alone is often associated with severe hypotension due to their effect on systemic vascular resistance and cardiac contractility and, for that reason, injectable drugs, particularly opioids, are used to decrease MAC_{BAR}.

More recently, MAC_{NM} has been defined as the end-tidal concentration at which no motor movement occurs in response to a noxious stimulus in all individuals in the study, an ED_{100} for study subjects. Although there is some variability among studies, MAC_{NM} is generally 10–20% higher than traditional MAC (Seddighi et al., 2011; Seddighi et al., 2012). Therefore, MAC_{NM} is thought to correspond to an ED_{95} for a population and may be more applicable in a clinical setting (Seddighi et al., 2012).

$MAC_{Extubation}$ represents the concentration of inhaled anesthetic at which the patient will no longer tolerate the endotracheal tube, and has only been determined in one canine study to date. The literature implies that $MAC_{Extubation}$ in dogs is 0.3–0.4 MAC (Barletta et al., 2016).

5. Selection of the noxious stimulus

In determination of MAC, MAC_{BAR}, and MAC_{NM}, a supramaximal noxious stimulus is applied (Eger II et al., 1965). A supramaximal