Research in Veterinary Science 118 (2018) 27–33

Contents lists available at ScienceDirect

Research in Veterinary Science

journal homepage: www.elsevier.com/locate/rvsc

Minimum alveolar concentration: Key concepts and a review of its pharmacological reduction in dogs. Part 2

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ARTICLE INFO

Keywords:
Minimum alveolar concentration
MAC
Dog
Inhalational anesthesia

ABSTRACT

Objective: To outline the major components of the minimum alveolar concentration (MAC) and review the literature regarding pharmacological manipulation of the MAC of halothane, isoflurane, sevoflurane, enflurane, and desflurane in dogs. The pharmacological agents included are alpha-2 agonists, benzodiazepines, propofol, opioids, lidocaine, acepromazine, non-steroidal anti-inflammatory agents (NSAIDs), maropitant, and NMDA antagonists.

Part 2 of this review will focus on the effect of opioids, lidocaine, NSAIDs, maropitant, acepromazine, and NMDA antagonists 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: Opioids, lidocaine, NSAIDs, maropitant, acepromazine, and NMDA antagonists have been shown to reduce the MAC of inhaled anesthetics in dogs and allow for clinically important decreases in inhalant anesthetic use. Thus, the use of these agents potentially decrease the adverse cardiovascular and pulmonary effects associated with the use of high concentrations of inhaled anesthetics.

1. Introduction

Part 1 of this review discussed the relevance, measurement, and mechanism of MAC determination in dogs, and provided an overview of the literature regarding the effect of alpha-2 agonists, benzodiazepines, and propofol on MAC. Part 2 will review the literature involving effect of opioids, lidocaine, acepromazine, maropitant, non-steroidal anti-inflammatory drugs, NMDA antagonists, and drug combinations on MAC.

2. Opioids

Opioids are the mainstay of acute pain management in dogs and, as such, are extensively used in the peri-anesthetic period. Their effect on MAC differs among species but opioids, in general, are associated with clinically important decreases in volatile anesthetic MAC in dogs (Muir et al., 2003; Steffey et al., 1994). Opioid receptors are located throughout the body both peripherally and within the central nervous system. Although opioid receptors are not thought to play a role in the immobility caused by inhaled anesthetics, their effect on MAC is thought to be a result of an indirect effect in modulating dorsal horn neurons involved in response to noxious stimuli (Sonner et al., 2003).

Morphine is the prototypical pure mu opioid agonist to which all other opioids are compared in terms of potency, efficacy, and adverse effects. An active metabolite of morphine, morphine-6-glucuronide is produced by canine hepatocytes in vitro (Mabuchi et al., 2004). However, the metabolite was not detectable in canine plasma after intravenous administration of 0.5 mg kg^{-1} of morphine (KuKanich et al., 2005). Additionally, this metabolite lacks the lipophilicity requisite to penetrate the blood-brain barrier and likely contributes little to MAC reduction. Morphine reduces MAC by as much as 67% when very high dosages are administered intravenously (Murphy and Hug, 1982b), whereas clinically relevant doses provide a more modest reduction in MAC ranging from 17% to 30% (Table 1) (Ko et al., 2009; Mahidol et al., 2015; Muir et al., 2003; Murphy and Hug, 1982b; Steffey et al., 1994). Morphine is commonly administered epidurally due to its long residence time in the epidural space attributed to its low lipid solubility. The effect of epidurally administered morphine on the MAC of halothane in dogs has been determined (Valverde et al., 1989). In that study, a dose of 0.1 mg kg^{-1} was injected epidurally after dilution in saline to a final volume of either 0.13 or 0.26 mL kg^{-1}, and MAC determination was made by applying the stimulus to a thoracic and pelvic limb, in turn. There was a 35–42% reduction in MAC across groups for

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https://doi.org/10.1016/j.rvsc.2018.01.009
Received 12 October 2017; Received in revised form 9 January 2018; Accepted 13 January 2018
0034-5288/ Published by Elsevier Ltd.

Table 1
Bolus doses, infusion rates, plasma concentration, and MAC effect in studies using pure mu agonist opioids.

Drug	Bolus mg kg^{-1} IV	Infusion rate μg kg^{-1} min^{-1}	Plasma concentration ng mL^{-1}	MAC effect	Reference
Morphine	0.5	N/A	ND	↓17% (E)	Murphy and Hug (1982b)
	2	N/A		↓32%	
	7	N/A		↓63%	
	27	N/A		↓67%	
Morphine	2	N/A	295	↓50% (I)	Steffey et al. (1994)
Morphine	1	N/A	ND	↓34% (I)	Ko et al. (2009)
Morphine	None	3.3	ND	↓48% (I)	Muir et al. (2003)
Morphine	0.5	3.3	ND	↓25% (S)	Mahidol et al. (2015)
Oxymorphone	0.05	N/A	ND	↓43% (I)	Machado et al. (2006)
Hydromorphone	0.1	N/A	ND	↓48% (I)	Machado et al. (2006)
Methadone	0.5	N/A	ND	↓35% (I)	Credie et al. (2010)
	1			↓48%	
Methadone	0.5	N/A	ND	↓30% (I)	Campagnol et al. (2012)
Meperidine	2.75	N/A	880[a]	↓48% (H)	Steffey et al. (1977)
	5.5		930	↓68%	
	11		1180	↓73%	
Fentanyl	0.015	0.05	3.1	↓33% (E)	Murphy and Hug (1982a)
	0.015	0.1	6.5	↓53%	
	0.03	0.2	11, 8.2[b]	↓57%, ↓56%	
	0.09	0.8	29	↓64%	
	0.27	3.2	99	↓66%	
Fentanyl	0.015	0.05	1	↓28% (E)	Schwieger et al. (1991a)
	0.045	0.2	3	↓44%	
Fentanyl	0.015	0.05	1	↓13% (E)	Salmenpera et al. (1994)
	0.045	0.2	4	↓40%	
Fentanyl	0.005	0.15	ND	↓35% (I)	Ueyama et al. (2009)
Fentanyl	0.01	0.3	ND	↓53% (I)	Hellyer et al. (2001)
Fentanyl (MAC_{NM})	0.015	0.1	3.25	↓39% (S)	Suarez et al. (2017)
Fentanyl (MAC_{NM})	0.0075	0.05	2.19	↓22% (S)	Reilly et al. (2013)
	0.015	0.1	5.13	↓35%	
	0.03	0.2	11.94	↓41%	
Fentanyl	0.005	0.15	ND	↓50% (I)	Simoes et al. (2016)
Fentanyl	33	0.2	6.2	↓42% (I)	Williamson et al. (2017)
	102	0.8	29.5	↓77%	
Remifentanil	None	0.055–5.5	10–15	Plateau at ↓63% (E)	Michelsen et al. (1996)
Remifentanil	None	0.15	ND	↓43% (I)	Monteiro et al. (2010)
		0.3		↓59%	
		0.6		↓66%	
		0.9		↓71%	
Alfentanil	0.0146	0.625	19	↓24% (E)	Hall et al. (1987b)
	0.0146	1.6	44	↓53%	
	0.072	8	223	↓69%	
	0.288	32	960	↓73%	
	0.720	80	2613	↓70%	
Sufentanil	0.0015	0.005	0.51	↓43% (E)	Hall et al. (1987a)
	0.003	0.015	0.92	↓57%	
	0.009	0.045	2.28	↓63%	
	0.120	0.405	17.43	↓67%	
	0.243	1.215	48.07	↓70%	

ND: not determined.
N/A: not applicable.
E = Enflurane.
S = Sevoflurane.
H = Halothane.
I = Isoflurane.
[a] Blood for plasma concentrations not drawn at exact time of MAC determination. MAC reduction percentage and associated plasma concentrations derived by the authors from figures provided in the original manuscript.
[b] Two groups received this treatment.

pelvic limb stimulation. A smaller reduction in MAC of 31–35% was noted for thoracic limb stimulation. Although morphine is absorbed systemically after epidural administration, the fact that there was a difference between the MAC decrease for the thoracic and pelvic limbs indicates that morphine was acting segmentally. There was no difference in the percent MAC decrease between the high and low volume treatments.

Oxymorphone and *hydromorphone* are pure mu agonists and, in comparison to morphine, are 5–10 times more potent and are also less likely to cause histamine release. Hydromorphone is commonly used in veterinary medicine due to its efficacy and low cost. A study investigating the effect of these agents on MAC revealed comparable reductions of 43% and 48% for oxymorphone and hydromorphone, respectively (Table 1) (Machado et al., 2006).

Methadone is a pure mu opioid agonist with similar potency to morphine and less potential for histamine release. Additionally, it has antagonistic activity at the NMDA receptor, making it unique among opioids. Clinically used dosages of methadone administered intravenously afford an isoflurane MAC sparing effect of 30–48% (Table 1) (Campagnol et al., 2012; Credie et al., 2010). Methadone's effect on MAC has also been investigated after epidural administration. A recent study compared the effect of methadone 0.5 mg kg^{-1} administered either intravenously or epidurally on the MAC of isoflurane (Campagnol et al., 2012). At 2.5-h post injection the MAC reduction