Various Systemic Effects of MK-467, A Peripherally Acting \( \alpha_2 \)-adrenoceptor Antagonist in Different Animal Species: An Overview

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Abstract

Most commonly used \( \alpha_2 \)-adrenoceptor agonist shows adverse cardiovascular effects during anaesthesia. They mainly depress the cardiovascular system by provoking vasoconstriction followed by bradycardia. Although \( \alpha_2 \)-adrenoceptor antagonist like atipamezole can reverse these effects along with that they also reverse the sedation and nociception. Concomitant administration of peripherally acting \( \alpha_2 \)-adrenoceptor antagonist MK-467 can reverse the adverse cardiovascular effect of \( \alpha_2 \)-adrenoceptor agonists without affecting the sedation and nociception. MK-467 has been successfully used in different animals like dogs, cats, sheep, horses along with different \( \alpha_2 \)-adrenoceptor agonist drugs. This review aims to summarize the effects of MK-467 on sedation, cardiopulmonary system, the minimum alveolar concentration of different inhalant anaesthetics, plasma drug concentration, plasma glucose and insulin in different animals.

Key words: \( \alpha_2 \)-adrenoceptor agonists, Atipamezole, Cardiopulmonary system, MK-467, Vatinoxan hydrochloride.

MK-467 is a potent \( \alpha_2 \)-adrenoceptor antagonist, preferably acting on the peripherally located \( \alpha_2 \) adrenoceptors. MK-467 (also known as L-659.066 or vatinoxan hydrochloride) is capable of crossing the blood-brain barrier minimally, as illustrated in rats and primates (Clineschmidt et al., 1988). Greater selectivity for \( \alpha_1 \) than \( \alpha_2 \) adrenergic receptors can be inferred from several in vivo and in vitro studies, which revealed the \( \alpha_1 \)-\( \alpha_2 \) receptor occupancy ratio to be 30:1 and 105:1, respectively (Clineschmidt, et al. 1988). The pharmacodynamic effects of MK-467 have been exhibited to be mediated mainly peripherally, in view of the fact that the brain/plasma ratio for MK-467 was 0.06 and 0.04 in rats and primates, respectively (Clineschmidt et al. 1988). Sedation and analgesia are some of the notable beneficial effects of \( \alpha_2 \)-agonists induced in the central nervous system (CNS), although many undesirable effects are observed in the cardiovascular system, outside the CNS. Hence, the combination of vatinoxan with \( \alpha_2 \)-agonists has the potential to diminish the \( \alpha_2 \)-agonist-mediated unfavourable peripheral cardiovascular effects with little or no impact on the desirable effects (Honkavaara et al. 2011, 2017a,b; Kaartinen et al. 2014; Salla et al. 2014 de Vries et al. 2016; Pypendop et al. 2017a; Siao et al. 2017). MK-467 when administered alone increases heart rate and lower systemic vascular resistance in dogs (Pagel et al. 1998). Absorption rates of medetomidine are increased following intramuscular administration of MK-467 (Restitutti et al., 2017). Co-administration of MK-467 also prevents dexametomidine-induced alterations in plasma insulin, glucose and lactate concentrations in healthy dogs (Restitutti et al., 2012). In mice, either the genetic absence of \( \alpha_2 \)-adrenoceptors or pharmacological blockade of all \( \alpha_2 \)-adrenoceptor subtypes with subtype non-selective antagonists leads to severe hypoglycaemia, when insulin release was stimulated with the clinically used antidiabetic drug glibenclamide (Fagerholm et al., 2008). Similar potentiation of glibenclamide-evoked insulin release and hypoglycaemia was also observed following treatment with MK-467 (Ruohonen et al., 2015).

This review provides an overview over the published literature on the various systemic effects, dosage and route of administration of MK-467 co-administered with \( \alpha_2 \)-adrenoceptor agonists viz: medetomidine, dexametomidine, romilidine and detomidine in different animal species.

Effects of MK-467 in different animal species

Haemodynamic and sedative effects

MK-467 efficaciously abates the initial vasoconstriction and the consequent hemodynamic disturbances induced by dexametomidine in dogs (Pagel et al., 1998; Honkavaara et al., 2008, 2011) without affecting the centrally mediated desired effects (Honkavaara et al., 2008; Restitutti et al., 2011). MK-467 also conduces to dose-dependent attenuation of the dexametomidine-induced increase in systemic vascular resistance and blood pressure and the...
sequential reductions in heart rate and cardiac index (Honkavaara et al., 2011). MK-467, when administered concurrently with medetomidine via IV or IM routes, reduced the cardiovascular adverse effects of medetomidine along with no detectable effect on sedation in dogs (Rolfe et al., 2012). MK-467 subsides certain undesired cardiovascular effects of medetomidine in dogs anaesthetized with isoflurane and the cardiovascular effects of medetomidine-MK-467 combination were equivalent to those of acepromazine-butorphanol combination (Salla et al., 2014a; Salla et al., 2014b). Classical haemodynamic effects of medetomidine can be attenuated by the co-administration of MK-467 IM in dogs (Restitutti et al., 2017). MK-467 when combined with medetomidine and butorphanol minimize the bradycardia induced by medetomidine in dogs as well advocate the adequate sedation required for diagnostic procedures (Kallo-Kujala et al., 2018a). In cats as well, the combinations of vatinoxan and α2-agonists have the potential to lessen the α2-agonist-induced adverse effects with little or no impact on the desired outcome. MK-467 dose-dependently nullifies the bradycardia and hypertension induced by dexmedetomidine along with reducing the duration of sedation and improving the cardiovascular tolerance of dexmedetomidine, co-administered intramuscularly or intravenously in cats (Honkavaara et al., 2017a; Honkavaara et al., 2017b). In a study, Pypendop et al., 2017a illustrated that following intravenous co-administration with dexmedetomidine, MK-467 effectively attenuated the dexmedetomidine-induced cardiovascular effects in cats resulting in a transient reduction in arterial blood pressure, without producing hypotension. Also, the intramuscular administration of MK-467 together with dexmedetomidine in isoflurane-anaesthetized cats attenuates the dexmedetomidine-induced unfavourable cardiovascular effects (Siao et al., 2017). Likewise in horses, MK-467 averts the cardiovascular alterations commonly observed with romifidine and detomidine, when administered in combination, without affecting the sedation quality (de Vries et al., 2016; Vainionpaa et al., 2013; Tapio et al., 2018; Pakkanen et al., 2015). A study conducted by Tapio et al. (2019) evaluated the effect of vatinoxan on cardiovascular function, gastrointestinal motility and on sedation level during CRI of medetomidine in standing horses. During this study, six healthy horses were given medetomidine hydrochloride, at the rate of 7 μg/kg IV without vatinoxan hydrochloride and at the rate of 140 μg/kg IV with vatinoxan hydrochloride, followed by CRI of medetomidine at 3.5 μg/kg/h for 60 min and they recorded the cardiorespiratory variables and borborygmi and sedation levels were also scored for 120 min. In accordance to the study, they concluded that Vatinoxan with a loading dose of medetomidine ameliorates the cardiovascular function and gastrointestinal motility during medetomidine CRI in healthy horses, although the sedation was slightly reduced during the first 20 min. Correspondingly in sheep also MK-467 attenuates medetomidine-induced cardiovascular adverse effects (Bryant et al., 1998; Adam et al., 2018). Raekallio et al. (2010) investigated whether the simultaneous administration of MK-467 and dexmedetomidine or premedication of dexmedetomidine with verapamil, would obviate the cardiovascular effects of dexmedetomidine in conscious sheep and the study indicated that MK-467 does prohibit the early systemic haemodynamic effects of dexmedetomidine, such as bradycardia and vasoconstriction, when the two drugs were simultaneously administered to sheep as a rapid intravenous bolus, although the initial haemodynamic influences of verapamil alone were similar to that of humans. However, premedication with verapamil was not able to arrest the dexmedetomidine-induced fall in heart rate and cardiac output, although it reduced the vasoconstriction. Still, MK-467 had no noticeable effect on the clinical sedation induced by dexmedetomidine.

Pharmacokinetic effects
MK-467 markedly influence the early disposition of dexmedetomidine without obvious effects on the plasma concentrations of the later in dogs, cats as well as sheep, whereas dexmedetomidine does affects the disposition of MK-467, but only minimally (Honkavaara et al., 2011; Pypendop et al., 2016; Adam et al., 2018). It has been analyzed that MK-467 elevates the early stage plasma concentration of both medetomidine and butorphanol when administrated IM in the same syringe and thereby results in deeper initial sedation for a shorter duration (Kallo-Kujala et al., 2018a; Restitutti et al., 2017). Bennett et al. (2016) outlined the plasma disposition of dexmedetomidine in dogs when given together with MK-467. In the study they demonstrated that MK-467, following co-administration with racemic medetomidine, did not alter the degree of initial medetomidine-evoked sedation, though it does reduce the antinociceptive efficacy of medetomidine and shortened the duration of its sedative action, corresponding to the approximately 50% reductions in the concentrations of dexmedetomidine in plasma when co-administered with MK-467. Owing to the results, they concluded that MK-467 increased the clearance and decreased the concentration of dexmedetomidine in plasma and further stated that the partial loss of efficacy can be compensated by administering a higher dose of medetomidine with MK-467. Administration of vatinoxan in isoflurane anaesthetized cats has been characterized by a small volume of distribution and low metabolic clearance (Py pendop et al., 2019b). In horses, MK-467 has shown to reduce the plasma concentrations of detomidine and butorphanol (Vainionpaa et al. 2013; Pakkanen et al. 2015).

Effect on minimum alveolar concentration (MAC) of different inhalant anaesthetics
Hector et al. (2017) examined the effects of low and high dose infusions of dexmedetomidine and MK-467, on sevoflurane minimum alveolar concentration (MAC) in dogs. In this research, they hypothesized that MK-467 has no
influence on sevoflurane MAC, while dexmedetomidine dose-dependently decrease sevoflurane MAC and the results for dexmedetomidine came as they assumed in their hypothesis, however, unexpectedly, a significant increase in sevoflurane MAC with high MK-467 infusion dose was recorded. Effects of dexmedetomidine, with or without vatinoxan, on the minimum alveolar concentration of isoflurane (MAC) in cats, have been investigated by Pypendop et al. (2019a) and they advocated that vatinoxan increases the MAC of isoflurane in cats along with diminishing the potency of dexmedetomidine in reducing MAC.

Antinociceptive effect
Huuuskonen et al. (2020) researched concerning the effect of simultaneous administration of vatinoxan on the antinociceptive efficacy of medetomidine in dogs, at doses providing circulating dexmedetomidine concentration equivalent to those produced by medetomidine alone. This randomized crossover study was performed in eight healthy beagle dogs, each receiving 3 intravenous treatment: medetomidine (20 μg/kg), medetomidine (20 μg/kg) with vatinoxan (400 μg/kg) and medetomidine (40 μg/kg) with vatinoxan (800 μg/kg), respectively and the sedation score, visceral and somatic nociception and the plasma drug concentration were assessed. Following the results, they suggested that medetomidine coadministered with vatinoxan does not reduce the visceral antinociception in case the plasma dexmedetomidine concentrations were comparable to those produced by medetomidine alone.

Effect on plasma glucose, insulin, non-esterified fatty acid and acetate
The concomitant use of MK-467 in dogs treated with dexmedetomidine averted the major alterations in plasma concentrations of glucose, insulin, non-esterified fatty acid and lactate (Restitutti et al., 2012). A review by Kallio-Kujala et al. (2018b) also illuminates the effects of dexmedetomidine and MK-467 combination in canine glibenclamide-induced hypoglycaemia model to predict its safety in hypoglycaemic dogs undergoing sedation. They opined that the potentiation of glibenclamide-evoked hypoglycaemia was not observed when the MK-467 was co-administered with dexmedetomidine and thereby stated that the co-administration of MK-467 and dexmedetomidine appears to be safe in the glibenclamide induced canine hypoglycaemia model. However, MK-467 should be employed with caution in dogs having the risk of hypoglycaemia owing to its insulin-releasing effect. Pakkanen et al. (2018) conducted a study to explore whether or not the intravenous (IV) administration of romifidine or vatinoxan induce any variation in the plasma concentration of glucose or some metabolites and stress-related hormones in horses and also if vatinoxan can antagonise the possible adverse effects of romifidine when these agents are administered simultaneously. As per the study, the Plasma glucose concentration differed in all the three intravenous treatments: romifidine (80 μg/kg), vatinoxan (200 μg/kg) and the combination of both, with the glucose concentration to be highest following romifidine administration and the lowest following vatinoxan. The baseline serum concentration of insulin varied widely amongst individual horses while no differences were detected in serum insulin, cortisol or plasma adrenocorticotropic hormone (ACTH) concentrations during the treatments. The plasma lactate, serum triglyceride or blood sodium and chloride concentrations also did not differ from the baseline or between the treatments concentrations. Compared with baseline, the plasma glucose concentration increased after romifidine was given as well as after co-administration of both romifidine and vatinoxan. The serum cortisol, FFA and base excess increased after all the three treatments whereas the plasma ACTH concentration increased only after vatinoxan administration. The serum insulin concentration reduced after vatinoxan treatment while the blood potassium levels were found to be decreased after all the treatments. Considering the results, they infered that vatinoxan can partially prevent the romifidine induced hyperglycaemia, despite the variations in baseline levels of serum insulin.

Other effects
Effects of MK-467 on organ blood flow detected by contrast-enhanced ultrasound (CEUS) have been evaluated in dogs treated with dexmedetomidine (Restitutti et al., 2013) and the research depicted that MK-467 effectively attenuates the effects of dexmedetomidine in organ blood flow as detected via contrast-enhanced ultrasound (CEUS). Rossi et al. (2019) elucidated the effect of general anaesthesia in dorsal recumbency with and without vatinoxan on bronchoalveolar lavage cytology of healthy horses. They proposed that anaesthesia in dorsal recumbency did not consistently affect lung cytology with or without vatinoxan.

CONCLUSION
MK-467, as a peripherally acting α₂-adrenoceptor antagonist, has shown to exert numerous efficacious systemic effects in different animal species viz. dog, cat, horse, sheep. It has exhibited to be highly competent in attenuating the haemodynamic disturbances produced by α₂-adrenoceptor agonists without modifying their desirable effects, namely sedation and analgesia. In addition to significantly influencing the pharmacokinetics of medetomidine and dexmedetomidine, MK-467 has also shown to affect the minimum alveolar concentration (MAC) of various inhalant anaesthetics as well as alter the plasma glucose and insulin concentrations. Hence, in the view of these valuable beneficial effects, MK-467 represents a clinically potent agent which should be administered along with α₂-agonist drugs during surgical procedures. In recent past, a multitude of studies have been conducted to establish the positive implications of vatinoxan in dog, cat, sheep and horse yet further research to assess these effects in other animal species is a need of today’s veterinary surgery.
Despite of being a highly efficient peripherally acting α₂-adrenoceptors antagonist, MK-467 has still not gained much popularity as a regular clinical anaesthetic drug in veterinary practice. However clinical application of MK-467 together with the commonly practised α₁-agonist drugs, such as medetomidine and dexmedetomidine will give us an opportunity to eliminate the detrimental effects of these drugs during general anaesthesia.

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