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Dexmedetomidine: Systemic effects and clinical application in animals

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Abstract

Dexmedetomidine, the latest α -2 agonist, is an active optical isomer of racemate medetomidine. It produces dose dependent sedation and analgesia in animals. In veterinary practice it is used for premedication and as an adjunct to general anaesthesia in several species. Similar to other alpha-2 agonists it exerts its effects through the action on alpha-2 adrenergic receptors. The sedative and anxiolytic effects are mediated by activation of supraspinal autoreceptors located in the pons whereas analgesic effects are mediated by activation of heteroreceptors located in the dorsal horn of the spinal cord. Dexmedetomidine has been shown to have an anaesthetic sparing effect on injectable as well as inhalation anaesthetics and decreases the requirements for postoperative analgesics. Cardiovascular effects of dexmedetomidine are not very much different from the classic biphasic pattern of changes in arterial blood pressure reported for other alpha-2 agonists. Dexmedetomidine causes a transitory decrease in respiration, but can obtund the stress response when administered systemically. The present review describes in detail the mechanism of action, effects on various body systems and clinical application of dexmedetomidine in animals.

Keywords: Dexmedetomidine, sedation, alpha-2 agonists, premedication

Introduction

Alpha-2 agonists like xylazine, detomidine, romifidine and medetomidine constitute a group of drugs that have been used in veterinary practice for a long time to induce sedation and analgesia. They are frequently used as sole agents to sedate the animals or combined with opioids to produce different levels of sedation and analgesia. Use of alpha-2 agonists with dissociative agents like ketamine has been very popular to produce anaesthesia in a variety of animal species. These agents attenuate the stress response to anaesthesia and surgery; reduce anaesthetic and opioids requirements and produce good sedation and analgesia (Gertler *et al.*, 2001) [28].

Dexmedetomidine, the latest α -2 agonist, is an active optical isomer of racemate medetomidine, which is used as a sedative and preanaesthetic in veterinary practice. Studies have shown that dexmedetomidine may offer additional sedative and analgesic benefits over medetomidine. In dogs, dexmedetomidine produces dose dependent sedation and analgesia and the intensity of these effects is similar to that produced by twice the dose of medetomidine (Kuusela *et al.*, 2000) [46].

Dexmedetomidine is a sedative from α -2 agonist class of drugs with a molecular weight of 236.7 and chemical name (+) -4-[1-(2, 3-dimethylphenyl) ethyl]-1H-imidazole. In the racemic mixture of parent compound medetomidine, dexmedetomidine is the active optical enantiomer and displays specific and selective alpha-2 receptor agonism; whereas levomedetomidine is considered to be pharmacologically inactive. Dexmedetomidine hydrochloride is a white to almost white powder that is freely soluble in water and has a pKa of 7.1 (Abbott lab., 2000) [1]. Dexmedetomidine is the first isomer specific drug to be licensed in animals and represents a jump forward in the development and use of stereospecific agents instead of the use of non specific racemic mixtures.

Dexmedetomidine is used in both human and veterinary medicine. In human medicine it is used as a short term medication (<24 hr) for analgesia and sedation in the intensive care units (Shukry and Miller, 2010) [65]. The major applications in human medicine include premedication, anaesthetic adjunct to the regional and general anaesthesia and as postoperative sedative and analgesic; similar to benzodiazepines but it appears to have more beneficial effects (Gertler *et al.*, 2001) [28]. In veterinary practice it is used for premedication and as an adjunct to general anaesthesia in several species (Ahmad *et al.*, 2013; Kuusela, 2001, Kutter, 2006; Sano *et al.*, 2010; Santosh *et al.*, 2013) [61, 47, 4, 44].

Mechanism of action

Alpha-2 agonists exert their effects through the action on alpha-2 adrenergic receptors. Alpha-2 receptors are located presynaptically and postsynaptically in neuronal as well as nonneuronal tissues and extrasynaptically in the vasculature. Alpha-2 receptors present on noradrenergic neurons are called "autoreceptors" and those on nonnoradrenergic neurons are called "heteroreceptors" (Lemke, 1997) [20]. The sedative and anxiolytic effects of α -2 agonists are mediated by agonism of supraspinal autoreceptors situated in the pons (*Locus coeruleus*) whereas analgesic effects are mediated by agonism of heteroreceptors located in the dorsal horn of the spinal cord (Lemke, 1997) [20].

Like other α -2 agonists, dexmedetomidine acts on the presynaptic α -2 receptors on various neuronal and non-neuronal sites and inhibits the release of noradrenaline from sympathetic nerve terminals. Dexmedetomidine mediated activation of the α -2 adrenergic receptor results in activation of G-proteins, which modulate cellular activity by signalling a second messenger system, leading to the inhibition of adenylate cyclase which in turn results in decreased formation of 3', 5'-cyclic adenosine monophosphate (cAMP) (Birnbaumer *et al.*, 1990, Cotecchia *et al.*, 1990) [15, 25]. All these events result in efflux of K⁺ through an activated channel causing hyperpolarization and suppression of neuronal firing. Entry of Ca⁺⁺ into the nerve terminals is also reduced by α -2 adrenoreceptor activation, which may be responsible for its inhibitory effects on secretion of neurotransmitters (Hayashi *et al.*, 1995, Khan *et al.*, 1999) [30, 38]. When delivered directly into the locus coeruleus, dexmedetomidine produces a dose dependent hypnotic response, which can be antagonized by atipamezole (Correa-Sales *et al.*, 1992a, b) [23, 24].

In rat, dexmedetomidine has been shown to bind to α -2A adrenoreceptors on the cell membrane of neurons of locus coeruleus and leads to opening of inward rectifying potassium channels, resulting in hyperpolarization of membrane (Chiu *et al.*, 1995) [21]. The neuronal hyperpolarization may be a key element in the mechanism of action of α -2 adrenoreceptor agonists from the view point of an anaesthesiologist (Birnbaumer *et al.*, 1990) [15].

Metabolism

Dexmedetomidine has been administered via various routes in different species. Dexmedetomidine undergoes extensive first pass metabolism in humans with oral bioavailability of 16%. Bioavailability is complete following intramuscular administration. Bio-availability upon buccal administration was found as much as 82% and thus it can be used as an alternative to i.v. or i.m. administration (Anttila *et al.*, 2000) [46]. Dexmedetomidine undergoes hydroxylation by cytochrome P450 system followed by glucuronidation in the liver and the most of the metabolites of dexmedetomidine are excreted by liver. The average protein binding of dexmedetomidine is 94% (Gertler *et al.*, 2001; Kuusela *et al.*, 2000) [28, 46].

Excretion and elimination of dexmedetomidine is delayed in old animals. In a pharmacokinetic study of dexmedetomidine in mature and old ponies, a significant difference was found in the half-life of the drug (Bettschart *et al.*, 2005).

Anaesthetic sparing action

Alpha-2 agonists have a potent anaesthetic sparing effect and more specific the drug is at α -2 adrenoceptors more potent is

the anaesthetic sparing effect (Sinclair, 2003) [66]. Dexmedetomidine has been reported to cause a marked reduction in the anaesthetic requirements of general anaesthetics. Compared to midazolam, dexmedetomidine is more effective in decreasing the need for intraoperative ketamine and reducing ketamine-induced adverse central nervous system alterations (Levanen *et al.*, 1995) [51]. It may decrease isoflurane and sevoflurane MAC by 35%-50% and 0%-17%, respectively (Bloor *et al.*, 1992) [17]. Bloor *et al.*, (1992) [17] reported up to 89% decrease in the total requirement of isoflurane in dogs treated with dexmedetomidine. Another study reported a decrease of 18 to 59% in MAC of isoflurane when dexmedetomidine was given as continuous intravenous infusion. This decrease in MAC of isoflurane was further enhanced when a combination of lidocaine-dexmedetomidine was used (Acevedo-Arcique *et al.*, 2014) [2]. Kuusela *et al.* (2001) [47] reported that the combined mean end-tidal isoflurane concentration was higher in dogs treated with medetomidine than that treated with dexmedetomidine, implying that the analgesic effect of dexmedetomidine was more pronounced than medetomidine. In the same study, the authors could not find any significant difference in propofol requirements after premedication with medetomidine or dexmedetomidine. Dexmedetomidine has been shown to have a greater anaesthetic sparing effect as compared to acepromazine when continuous rate infusion of alfaxalone was used to maintain anaesthesia in dogs undergoing ovariohysterectomy (Herbert *et al.*, 2103) [31]. The authors attributed this effect to the antinociceptive effects of dexmedetomidine. Similar findings were reported by Mendes *et al.* (2003) [53] in cats in which dexmedetomidine significantly reduced the mean induction dose of propofol. In contrast to the earlier studies, Hunt *et al.* (2013) [34] reported a reduction in the dose of propofol for anaesthetic induction in dogs when premedicated with dexmedetomidine but found no effect on the dose of alfaxalone. But in cats, dexmedetomidine was associated with a reduction in the dose of alfaxalone however, propofol dose was not affected. Since two anaesthetists were involved in this study the difference was attributed to variability in anaesthetic practice.

Sedative effects

Sedative effects of dexmedetomidine are attributed to its action on supraspinal autoreceptors in pons. Intravenous dexmedetomidine results in a dose dependent sedation in dogs (Sabbe *et al.*, 1994) [59]. However, it was also observed that 10 μ g/kg of dexmedetomidine intravenously induced maximum sedation; increasing the dose only increased duration of sedation not intensity (Kuusela *et al.*, 2000) [46]. Another study also revealed that dose dependency is limited to a certain level and increasing the dose beyond certain level leads to the reversal of sedation, possibly because of α -1 receptor activation or desensitization of α -2 receptors (Ansah *et al.*, 2000) [11]. Kuusela *et al.* (2000) [46] compared the clinical and pharmacokinetic effects of dexmedetomidine and medetomidine and found that overall sedative effects of dexmedetomidine did not differ from that of medetomidine but analgesic effect of dexmedetomidine was of longer duration than racemate medetomidine. The degree of sedation induced by dexmedetomidine is not affected by exercise or pretreatment with dexamethasone (Raekallio *et al.*, 2005) [58]. Dexmedetomidine provides a reliable and effective sedation to children undergoing diagnostic imaging studies without adversely affecting respiratory rate and end-tidal CO₂ values

and maintained hemodynamic stability in clinically acceptable range for pediatric population (Mason *et al.*, 2006) [52]. Dexmedetomidine-bupivacaine combination produced greater sedation than that produced by combinations of ketamine-bupivacaine or fentanyl-bupivacaine in dogs operated for castration under epidural anaesthesia (Nour *et al.* 2013) [56]. Hunt *et al.* (2013) [34] demonstrated that dexmedetomidine provided greater sedation than acepromazine in cats but not in dogs. The authors opined that this difference could be due to the adjustment of the dose of dexmedetomidine not that of acepromazine to metabolic body size. As a result of which the relative dose of dexmedetomidine would have been higher than that of acepromazine in low body weight animals i.e. cats, explaining the observed difference in sedation. Status of palpebral reflex has been used as a measure of sedation as it gives a fairly good idea about CNS depression in clinical settings (Leppanen *et al.*, 2006; Ahmad *et al.*, 2013) [4, 50]. When used alone, dexmedetomidine produces mild depression of palpebral reflex (Huncke *et al.* 2010; Ahmad *et al.*, 2013) [4, 33]. It does not produce adequate sedation to allow painful procedures. Ko *et al.* (2000) [41] did not advocate use of medetomidine alone for sedation of dogs undergoing moderately to severely painful procedures. For deep sedation a combination of drugs is preferred to achieve variable level of sedation, muscle relaxation, analgesia and anaesthesia that would meet clinical demands in a variety of diagnostic and therapeutic procedures without major side effects (Ahmad *et al.*, 2013; Santosh *et al.*, 2013). [61, 4]

Analgesic effects

Analgesic effects of dexmedetomidine are mediated through 2A subtypes of alpha-2 adrenoceptors. Alpha-2 adrenoceptor 2A subtypes, have been identified in the substantia gelatinosa of the dorsal horn of the spinal cord and stimulation by specific agonists of these alpha-2 adrenoceptors inhibits the firing of nociceptive neurons stimulated by peripheral A δ and C fibres (Howe *et al.*, 1983; Guo *et al.*, 1996) [29, 32]. Agonism of these receptors also inhibits the release of substance P by primary afferents of the dorsal horn (Kuraishi *et al.*, 1985) [43] and suppress the activity of wide dynamic range neurons evoked by noxious stimulation (Murata *et al.*, 1989) [54]. The antinociception produced by alpha-2 agonists may be due in part to acetylcholine release in the spinal cord (Bouaziz *et al.*, 1995; Klimscha *et al.*, 1997) [19, 39]. Dexmedetomidine has been shown to act on dorsal horn of spinal cord by interrupting the nociceptive pathway to the ventral root, thus reducing the spinal reflexes (Kending *et al.*, 1991; Savola *et al.*, 1991) [37].

Status of withdrawal reflex has been used in clinical settings as a measure of depth of analgesia since it is easy to use and repeat, and avoids tissue destruction and sensitization after numerous repetitions (Kuusela, 2004, Leppanen *et al.*, 2006; Ahmad *et al.*, 2013) [45, 50, 4]. Kuusela, (2004) [45] considered withdrawal reflex as a valid parameter when evaluating α_2 -agonist mediated analgesia. Dexmedetomidine alone doesn't abolish pedal reflex in dogs and provides a mild level of analgesia, however, it can be enhanced by addition of midazolam, butorphanol, fentanyl or ketamine (Selmi *et al.*, 2003 [53]; Ahmad *et al.*, 2013 [4], Santosh *et al.*, 2013 [61]). Valtolina *et al.* (2009) [70] demonstrated that continuous rate infusion of dexmedetomidine was equally effective as that of morphine infusion at providing postoperative analgesia with no clinically significant adverse reactions. The study suggested potential application of dexmedetomidine for a

balanced multimodal postoperative analgesia regimen in dogs. Dexmedetomidine premedicated dogs, undergoing ovariohysterectomy under continuous infusion rate of alfaxalone; were less responsive to surgical stimulation as compared to those premedicated with acepromazine (Herbert, *et al.*, 2013) [31]. Nour *et al.* (2013) [56] reported significantly lower pain scores in dogs undergoing castration after administration of a combination of dexmedetomidine-bupivacaine epidurally as compared to the dogs administered with bupivacaine alone or a combination of bupivacaine with fentanyl. Dexmedetomidine has been shown to enhance the action of local anesthetics via peripheral α -2A adrenoceptors in a dose dependent manner (Yoshitomi *et al.*, 2008) [71]. The combination alpha-2 agonist with local anaesthetics produced a direct inhibition of tetrodotoxin-resistant Na⁺ channels contributing to the antinociceptive effects (Oda *et al.*, 2007) [57].

Perioperative administration of dexmedetomidine has resulted in a decrease in postoperative analgesics. Human patients who received dexmedetomidine for postsurgical pain, had significantly slower early postoperative heart rate and showed a decrease in requirement of morphine by more than 66% compared with a control group receiving only morphine. However, mean arterial pressure, respiratory rates, sedation and nausea scores did not differ significantly between the treatment groups (Arain *et al.*, 2004) [12].

Cardiovascular effects

Cardiovascular response of dexmedetomidine is not very much different from the classic biphasic pattern of changes in arterial blood pressure reported for other alpha-2 agonists. However, the dose and concurrent use of other preanaesthetics and anaesthetics may alter the cardiovascular response of dexmedetomidine. Further, species specific hemodynamic response may occur following administration of dexmedetomidine (Flacke *et al.*, 1990; Ebert, *et al.*, 2000) [26, 27]. In humans and rodents dexmedetomidine causes an increase in arterial blood pressure for 5 to 10 min followed by a decrease in blood pressure (Bloor *et al.*, 1990) [18]. Small doses of medetomidine alone causes a small rise followed by a decrease in the MAP but do not produce hypotension (Alibhai *et al.*, 1996) [7]. However, no such biphasic response has been reported in dogs and blood pressure remains increased despite a decrease in sympathetic tone, but cardiac output may decrease as much as 70%. In humans, a high degree of postoperative bradycardia has been reported, especially with increasing doses of dexmedetomidine (Aho *et al.*, 1993) [6]. The decrease in heart rate is thought to be of parasympathetic origin and not due to reduced sympathetic tone (Bloor *et al.*, 1992) [17]. Talke *et al.* (1997) [68] observed postoperative sympatholytic effects of dexmedetomidine and reported that plasma norepinephrine and epinephrine concentration decreased on an average by 72% which could attenuate postoperative increase in heart rate and blood pressure but did not entirely abolish sympathetic tone. Dexmedetomidine would preserve blood flow to the most vital organs (brain, heart, liver, kidney) at the expense of organs like skin and pancreas and this distribution of blood flow is not affected by the type of anaesthesia (Lawrence *et al.*, 1996) [48]. However, the pattern of cardiovascular changes may be affected by the dose used and the type of anaesthetic combined with dexmedetomidine.

Kuusela *et al.* (2001) [46] studied various premedicant doses of dexmedetomidine administered intravenously in dogs under

propofol and isoflurane anaesthesia and found that dose level of 20 µg/kg preserved blood pressure but profound bradycardia occurred. Dose level of 2 µg/kg resulted in more stable cardiovascular effects but the effect was short term and a stable plane of anaesthesia was difficult to maintain necessitating increased isoflurane concentration. In dogs, a significantly greater increase in mean arterial blood pressure followed by a decrease has been reported, when ketamine was coadministered along with dexmedetomidine (Ahmad *et al.*, 2011 [5]; Ahmad *et al.*, 2013 [4]; Santosh *et al.*, 2013 [61]). In equines sedated with dexmedetomidine, heart rate and central venous pressure did not differ significantly from pre-sedation values but decrease in stroke volume and blood pressure occurred (Bettschart *et al.*, 2005) [14]. Dexmedetomidine induced only a transient decrease in heart rate and cardiac output in sheep anaesthetized with sevoflurane (Kastner *et al.*, 2005). A short lived increase in mean arterial pressure (MAP) and systemic vascular resistance (SVR) was followed by a significant decrease in MAP and SVR. In sheep and goat anaesthetized with sevoflurane, Kutter *et al.* (2006) [44] found that arterial, pulmonary arterial, pulmonary capillary wedge and central venous pressures increased and heart rate and cardiac output decreased significantly after dexmedetomidine administration.

Respiratory effects

Administration of dexmedetomidine results in decrease in respiratory rate with minimal effects on blood gases in dogs (Vainio, 1989; Acevedo-Arcique *et al.*, 2014) [2]. At higher doses dexmedetomidine induces mild metabolic acidosis accompanied by a compensatory increase in arterial bicarbonate concentration (Kuusela *et al.*, 2001) [47]. In small ruminants dexmedetomidine has been associated with a significant decrease in PaO₂ along with sudden and prolonged decrease in dynamic compliance and a significant increase in airway resistance, shunt fraction, and alveolar dead space (Kästner *et al.*, 2005; Kutter *et al.*, 2006) [44]. Bettschart-Wolfensberger, (2005) [14], reported a decrease in respiratory rate throughout the 60 min observation period, but no change in arterial PO₂ or PCO₂ when dexmedetomidine was administered intravenously in ponies. A transitory decrease in respiratory rate has been observed after a single administration of dexmedetomidine in cats (Ansah *et al.*, 1998 [10]; Selmi *et al.*, 2003 [53]). Concurrent administration of dexmedetomidine with butorphanol, midazolam, fentanyl and ketamine resulted in a significant decrease in respiratory rate in both dogs and cats (Selmi *et al.*, 2003 [53]; Ahmad *et al.*, 2011 [5]; Ahmad *et al.*, 2013 [4]; Santosh *et al.*, 2013 [61]). Contrarily, isoflurane anaesthesia in dogs has been shown to cause more respiratory depression when used alone than when used along with medetomidine or dexmedetomidine (Bloor *et al.*, 1989 [16]; Nguyen *et al.*, 1992). It could be due to a decreased requirement of isoflurane to maintain anaesthesia. Systemic administration of dexmedetomidine resulted in a dose dependent depression in the rate and slope of CO₂ response curve whereas intrathecal or epidural dexmedetomidine caused little change in the rate and or slope of CO₂ function suggesting that these actions could be mediated supraspinally (Sabbe *et al.*, 1994) [59].

Endocrine effects

Alpha-2 agonists directly or indirectly obtund the stress response when administered systemically. Reduction in the

perception of stressors is thought to be achieved indirectly through sedation and analgesia and directly by inhibiting neuroendocrine response. Preoperative administration of medetomidine has resulted in delayed ACTH and cortisol response was observed in dogs undergoing ovariohysterectomy. The plasma cortisol did not change significantly from baseline at least up to 60 min after extubation (Benson *et al.*, 2000) [13]. Dexmedetomidine being an active isomer of medetomidine is likely to behave in the similar manner.

Serum insulin levels decrease significantly following medetomidine administration in dogs and cats and return to base values only after several hours. Although glucose concentration increases after medetomidine administration but it remains within physiological limits (Burton *et al.*, 1997, Ambrisko and Hikasa, 2002, Kanda and Hikasa, 2008). Xylazine produces a dose dependent increase in plasma glucose in contrast to medetomidine, which does not produce the same effect after increasing the dose (Ambrisko and Hikasa, 2002). Dexmedetomidine resulted in a decrease in blood glucose concentration at 30 min of its administration, which returned to baseline at 90 min in beagle dogs (Raekallio *et al.*, 2005) [58]. In the same experiment plasma cortisol concentration decreased significantly in the dogs, which received dexamethasone with or without exercise. Ahmad *et al.* (2012) [3] reported a decrease in blood glucose concentration at 30 min followed by a significant increase at 120 min after intramuscular administration of 20 µg/Kg dexmedetomidine with correspondingly significant decrease in blood insulin concentration. High doses of dexmedetomidine resulting in prolonged recumbency could be related to delayed increase in blood glucose.

Clinical usage

The recommended dose of dexmedetomidine is 50% that of racemate mixture medetomidine. The dose is based on the demonstrated lack of pharmacological effect of the the levo form of the drug (Kuusela, 2004) [45]. The doses of dexmedetomidine for iv and im uses are 375 µg/m² and 500 µg/m², respectively. Dose ranges from 10 µg/kg for premedication to 40 µg/kg for deep sedation are recommended in dogs while in cats dexmedetomidine is used @ 40 µg/kg intramuscularly.

Continuous rate infusion (CRI) of dexmedetomidine in healthy dogs is being recommended as an adjunct to general anaesthesia as it reduces the dosage of general anaesthesia, provides a stable plane of anaesthesia and additional analgesia (Uilenreef *et al.*, 2008; Valtolina *et al.*, 2009 [70]; Congdon *et al.*, 2013).

The major concern over the use of the alpha-2 agonists has been the marked cardiovascular changes associated with high doses of these drugs. The bradycardia induced by alpha-2 agonists may be prevented by prior administration of anticholinergic agents. However, such a procedure may not be recommended and may be contraindicated in several cases because the resultant hypertension and dysrhythmias (premature ventricular depolarizations) could be fatal in dogs with cardiovascular diseases (Alvaides *et al.*, 2008) [8]. Pulsus alternans has been reported in dogs in which atropine has been administered concurrently with medetomidine (Ko *et al.*, 2001) [42]. To minimize these side effects a combination of drugs should be preferred over a single agent to produce deep sedation as a synergistic interaction between the drugs not only reduces the dose requirements of the drugs and hence

minimize the unwanted side effects associated with either drug but also improve recovery.

Dexmedetomidine has been studied for its efficacy and safety with butorphanol, buprenorphine or diazepam. It was concluded that dexmedetomidine along with butorphanol, buprenorphine, diazepam, midazolam, fentanyl, ketamine and these combinations have been found both effective and safe in healthy dogs (Levanen *et al.*, 1995^[51]; Selmi *et al.*, 2003^[53]; Leppanen *et al.*, 2006^[50]; Ahmad *et al.*, 2011^[5]; Ahmad *et al.*, 2013^[4]; Santosh *et al.*, 2013^[61])

Future research and applications:

Dexmedetomidine, being a very specific alpha-2 agonist, exerts well defined effects on different system organs in the body. It preserves the cardiovascular function better than other alpha-2 agonists, inspite of being more potent compound. In veterinary practice it is being used mainly in small animals like dogs and cats. Extensive studies are required to elucidate its application in clinical anaesthesia in ruminants, which are sensitive to common alpha-2 agonists like xylazine. It should also be evaluated as an adjunct to different anaesthetics and analgesics for general and epidural anaesthesia and pain management in bovine and equine species. Being a very potent alpha-2 agonist, dexmedetomidine may be used for sedation and capture of wild animal species, where small quantities of the drugs are desired for ease of injection.

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