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Dexmedetomidine prolongs spinal anaesthesia induced by levobupivacaine 0.5% in guinea-pigs

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Abstract

Alpha-2 adrenoceptor agonists have been used in association with local anaesthetic to increase the duration of spinal anaesthesia. Intrathecal administration of clonidine prolonged motor blockade induced by local anaesthetic. Since the affinity of dexmedetomidine (DEX) to alpha-2 adrenoceptors is eight-times greater than clonidine, it is expected that DEX could be advantageous in clinical anaesthesia. We investigated the duration of motor nerve block induced by spinal injection of 0.5% levobupivacaine (LVB) associated with intrathecal or intraperitoneal administration of DEX. Seventy-two guinea-pigs were randomly divided in 12 groups, which were all treated with intrathecal injection of 50 μL of LVB. DEX was injected intrathecally with LVB in 6 groups or injected intraperitoneally after LVB in another 6 groups. Intrathecal DEX (0.1, 0.2 and 0.4 μg) increased the LVB-induced motor anaesthesia from 48 (41–66) min to 84.5 (52–91) min ($P<0.05$), 101.5 (83–115) min ($P<0.05$) and 105 (97–114) min ($P<0.05$), respectively. Similarly, intraperitoneal DEX (20 and 40 μg kg^{-1}) increased the motor blockade from 48.5 (33–59) min to 88 (71–114) min ($P<0.05$) and 114.5 (103–156) min ($P<0.05$), respectively. Pre-treatment with yohimbine reduced the duration of motor block from 101.5 (83–115) to 76.5 (68–86) min ($P<0.05$) or from 114.5 (103–156) to 90 (83–93) min ($P<0.05$) when DEX was administered by the intrathecal or intraperitoneal routes. Motor block induced by spinal injection of LVB was prolonged by intrathecal and systemic administration of DEX, which was partially dependent on activation of alpha-2 adrenoceptors.

Introduction

Activation of alpha-2 adrenoceptor has been associated with several important physiological and pharmacological effects, such as sedation (Drew et al 1979), analgesia, decreasing of sympathetic outflow and anaesthetic-sparing effect (Jaakola et al 1991; Correa-Sales et al 1992; Eisenach et al 1996). Alpha-2 adrenoceptors are located both in the peripheral organs and in the central nervous system (CNS). These receptors are scattered over the superficial laminae in the spinal cord (Eisenach et al 1996) and are located in the locus coeruleus (Correa-Sales et al 1992). The use of alpha-2 adrenoceptor agonists in anaesthesia increased with the elucidation of their actions in the CNS. Clonidine, the prototype alpha-2 adrenoceptor agonist, has been used in association with local anaesthetic to enhance the duration of spinal anaesthesia (Bonnet et al 1989; Dobrydnjov et al 2003). Intrathecal injection of alpha-2 adrenoceptor agonists induces antinociception (Eisenach et al 1994, 1996; Talke et al 2003). Prolongation of sensory and motor blockade induced by local anaesthetic was observed with simultaneous intrathecal administration of clonidine (Dobrydnjov et al 2003; Rochette et al 2004). The mechanisms underlying this effect are not completely understood, although a direct interaction of clonidine with the nerve fibres has been demonstrated (Gaumann et al 1992; Butterworth & Strichartz 1993). Since the affinity of dexmedetomidine for alpha-2 adrenoceptors is eight-times greater than clonidine, it is expected that dexmedetomidine could be advantageous in clinical anaesthesia (Jaakola et al 1991; Bhana et al 2000). Dexmedetomidine is used in several countries as a short-term sedative but recently Shahbaz et al (2004) reported that it reduced postoperative pain after major surgery. There are no data regarding the association of dexmedetomidine and local anaesthetic during spinal anaesthesia. In this study we

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investigated the duration of motor nerve block induced by spinal injection of 0.5% levobupivacaine associated with intrathecal or intraperitoneal injection of dexmedetomidine. Also, the involvement of alpha-2 adrenoceptor activation by dexmedetomidine was investigated in guinea-pigs pre-treated with intraperitoneal injection of yohimbine.

Materials and Methods

The following protocols were approved by the Animal Care and Use Committee at Universidade Federal do Rio de Janeiro.

Animal preparation and spinal anaesthesia

Seventy-two male guinea-pigs, 400–500 g, were randomly divided in two sets of six groups (6 guinea-pigs in each group). After dermal anaesthesia with lidocaine (1%), a 30G size needle was used for intrathecal drug injection at L5/L6. The correct position of the needle in the spinal space was confirmed by the immediately symmetrical loss of muscle strength and movements of the hind paws after injection of 0.5% levobupivacaine. The motor block was evaluated by two different observations: firstly, pulling hindpaws of guinea-pigs from the experimental table to certify if they were unable to keep their walking position and, secondly, lifting the forepaws 6–7 cm from the table to observe if they were unable to sustain themselves and walk (Nishiyama & Hanaoka 2004). Only the guinea-pigs that were successfully anaesthetized with motor block were used in this study. A dose–response curve for levobupivacaine-mediated motor block was obtained after intrathecal injection of different doses of levobupivacaine (75–250 μg) to six guinea-pigs for each dose intrathecally (0.1, 0.2 and 0.4 μg) or intraperitoneally (5, 10, 20 and 40 $\mu g\,kg^{-1}$).

Protocol 1: motor block induced by intrathecal injection of levobupivacaine and dexmedetomidine

Thirty-six guinea-pigs divided in 6 groups were injected intrathecally with 50 μL of levobupivacaine (0.5%) either added to saline (control, G1) or to three different doses of dexmedetomidine (0.1, 0.2 or 0.4 μg) (G2, G3, G4, respectively) (Table 1). In the two additional groups, yohimbine at a dose of $2\,mg\,kg^{-1}$ (G5) or $4\,mg\,kg^{-1}$ (G6) was injected intraperitoneally 30 min before intrathecal administration of 50 μL of levobupivacaine and dexmedetomidine (0.2 μg). The duration of motor block was determined (in minutes) from the installation of anaesthesia up to complete recovery of guinea-pig movements.

Protocol 2: motor block induced by intrathecal injection of levobupivacaine and intraperitoneal dexmedetomidine

Thirty-six guinea-pigs were randomly allocated into six different groups as described in Table 1. Fifty microlitres of levobupivacaine (0.5%) was spinally injected in all guinea-pigs. In the control group (G7), saline was injected intraperitoneally immediately after intrathecal levobupivacaine. In two groups, guinea-pigs were treated with intraperitoneal injection of $20\,\mu g\,kg^{-1}$ (G8) or $40\,\mu g\,kg^{-1}$ (G9) dexmedetomidine. In two other groups, yohimbine $4\,mg\,kg^{-1}$ (G10) or $10\,mg\,kg^{-1}$ (G11) was administered intraperitoneally 30 min before levobupivacaine followed by $20\,\mu g\,kg^{-1}$ of dexmedetomidine intraperitoneally. In group G12, the dose of yohimbine was the same as used in G11 ($10\,mg\,kg^{-1}$, i.p.) before levobupivacaine followed by $40\,\mu g\,kg^{-1}$ of intraperitoneal dexmedetomidine. The duration of motor block was measured from installation of anaesthesia up to complete recovery of guinea-pig movements as described in Protocol 1.

Table 1 Experimental groups used to determine duration of motor block

Groups	n	LVB (intrathecal)	DEX	YO[a]
G1	6	50 μL (250 μg)	—	—
G2	6	50 μL (250 μg)	1 μL (0.1 μg) intrathecally	—
G3	6	50 μL (250 μg)	2 μL (0.2 μg) intrathecally	—
G4	6	50 μL (250 μg)	4 μL (0.4 μg) intrathecally	—
G5	6	50 μL (250 μg)	2 μL (0.2 μg) intrathecally	$2\,mg\,kg^{-1}$ intraperitoneally
G6	6	50 μL (250 μg)	2 μL (0.2 μg) intrathecally	$4\,mg\,kg^{-1}$ intraperitoneally
G7	6	50 μL (250 μg)	—	—
G8	6	50 μL (250 μg)	$20\,\mu g\,kg^{-1}$ intraperitoneally	—
G9	6	50 μL (250 μg)	$40\,\mu g\,kg^{-1}$ intraperitoneally	—
G10	6	50 μL (250 μg)	$20\,\mu g\,kg^{-1}$ intraperitoneally	$4\,mg\,kg^{-1}$ intraperitoneally
G11	6	50 μL (250 μg)	$20\,\mu g\,kg^{-1}$ intraperitoneally	$10\,mg\,kg^{-1}$ intraperitoneally
G12	6	50 μL (250 μg)	$40\,\mu g\,kg^{-1}$ intraperitoneally	$10\,mg\,kg^{-1}$ intraperitoneally

LVB, isobaric levobupivacaine (0.5%); DEX, dexmedetomidine ($100\,\mu g\,mL^{-1}$); YO, yohimbine; n, no. of experiments.
[a]Yohimbine was administered 30 min before spinal anaesthesia.

Drugs

Commercially available formulations of levobupivacaine (0.5%) and dexmedetomidine (100 μg mL^{-1}, 2 mL vial) were provided by Cristália Produtos Químicos e Farmacêuticos Ltda (São Paulo, Brazil) and Abbott Laboratories (São Paulo, Brazil), respectively.

Statistics

All data were expressed as median (range) and differences between groups were considered statistically significant when $P < 0.05$. For comparison between two groups, the Mann–Whitney test was used for non-normal distribution of the data. For comparison between multiple groups, we used the Kruskal–Wallis one-way analysis of variance on rank followed by Dunn's method as a post-hoc test when necessary.

Results

Motor block induced by intrathecal injection of levobupivacaine and dexmedetomidine

Spinal injection of levobupivacaine alone promoted motor block in a dose-dependent manner with a duration of 48 (41–66) min when guinea-pigs were treated with 250 μg. The dose necessary to promote 50% of maximal duration of motor block induced by levobupivacaine was 68 μg. In contrast, no motor block was observed in the guinea-pigs treated with dexmedetomidine alone when it was administered either intrathecally (0.1, 0.2 and 0.4 μg) or intraperitoneally (5, 10, 20 and 40 μg kg^{-1}). The duration of motor block induced by intrathecal levobupivacaine (0.5%) alone in the control group (G1) was significantly increased from 48 (41–66) min to 84.5 (52–91) min (G2) ($P < 0.01$) and 101.5 (83–115) min (G3) ($P < 0.01$) when 0.1 or 0.2 μg of dexmedetomidine was added to levobupivacaine solution. However, no further increase (105 (97–114) min, G4) was observed when a higher dose of dexmedetomidine (0.4 μg) was added to levobupivacaine solution (Figure 1).

Systemic treatment of guinea-pigs with yohimbine significantly reduced the effect of dexmedetomidine to prolong the duration of levobupivacaine-induced anaesthesia. Thus, the motor block duration was significantly reduced from 101.5 (83–115) (G3) to 81.5 (69–98) min (G5, $P < 0.05$), and to 76.5 (68–86) min (G6, $P < 0.05$) after pre-treatment with 2 and 4 mg kg^{-1} of yohimbine, respectively (Figure 1).

Motor block induced by intrathecal injection of levobupivacaine and intraperitoneal dexmedetomidine

The duration of motor block induced by levobupivacaine was also increased by systemic administration of dexmedetomidine. Motor block was prolonged from 48.5 (33–59) min (G7) to 88 (71–114) min ($P < 0.01$) or 114.5 (103–156) min ($P < 0.01$) after treatment with 20 μg kg^{-1} (G8) or 40 μg kg^{-1} (G9) of dexmedetomidine intraperitoneally immediately after spinal anaesthesia with levobupivacaine (Figure 2).

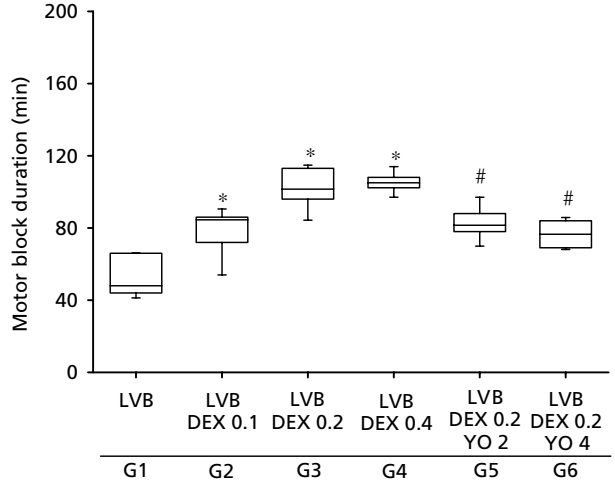

Figure 1 Box and whisker plot of motor block duration induced by spinal injection of levobupivacaine 0.5% (LVB) associated with dexmedetomidine (DEX). Guinea-pigs were treated with spinal injection of 50 μL of LVB in the control group (G1) and associated with incremental amounts of intrathecal DEX 0.1 μg (G2), 0.2 μg (G3) and 0.4 μg (G4). Guinea-pigs in groups G5 and G6 had spinal anaesthesia with 50 μL of LVB associated with DEX 0.2 μg intrathecally and were previously treated with intraperitoneal yohimbine (YO) 2 mg kg^{-1} (G5) and 4 mg kg^{-1} (G6). Boxes show interquartile range and whiskers the maximal and minimum values. The horizontal line in the box represents the median value. *$P < 0.05$, compared with LVB group, G1; $^{\#}P < 0.05$, when compared with G3; n = 6 guinea-pigs in each group.

Yohimbine (10 mg kg^{-1}) was only effective in reducing the prolonged duration of motor block when dexmedetomidine was injected intraperitoneally at 40 μg kg^{-1} (G12) ($P < 0.01$). Even in this condition, yohimbine was not able to completely reduce the effect of dexmedetomidine. Yohimbine at 4 mg kg^{-1} intraperitoneally (G10) or 10 mg kg^{-1} intraperitoneally (G11) did not significantly reverse the effect of dexmedetomidine (20 μg kg^{-1}, i.p.) (Figure 2).

The results observed with dexmedetomidine either injected intraperitoneally or intrathecally indicate that the increase in motor blockade was significantly different ($P < 0.05$) between groups G2 (dexmedetomidine 0.1 μg, i.t.), 84.5 min (52–91) and G9 (dexmedetomidine 40 μg kg^{-1}, i.p.), 114.5 min (103–156). However, no significant difference was observed when comparing other groups. Yohimbine partially reversed the action of dexmedetomidine when administered intraperitoneally or intrathecally, with no significant difference between both experimental conditions.

Discussion

In this study, we demonstrated that motor block duration induced by intrathecal injection of levobupivacaine was

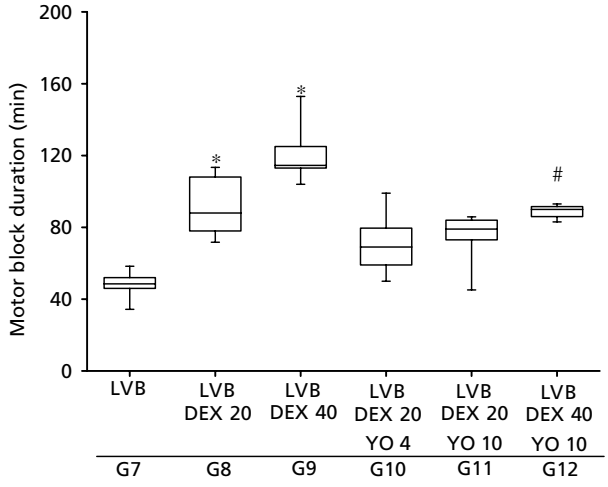

Figure 2 Box and whisker plot of motor block duration induced by spinal injection of levobupivacaine 0.5% (LVB) associated with dexmedetomidine (DEX). Guinea-pigs were treated with spinal injection of 50 μL of LVB in the control group (G7) and associated with incremental amounts of intraperitoneal DEX 20 $\mu g\,kg^{-1}$ (G8), 40 $\mu g\,kg^{-1}$ (G9). Guinea-pigs in groups G10 and G11 had spinal anaesthesia with 50 μL of LVB associated with DEX 20 $\mu g\,kg^{-1}$ intraperitoneally and were previously treated with yohimbine (YO) intraperitoneally, 4 $mg\,kg^{-1}$ (G10) and 10 $mg\,kg^{-1}$ (G11). Guinea-pigs in group G12 had spinal anaesthesia with 50 μL of LVB associated with DEX 40 $\mu g\,kg^{-1}$ intraperitoneally and were previously treated with YO intraperitoneally, 10 $mg\,kg^{-1}$. Boxes show interquartile range and whiskers the maximal and minimum values. The horizontal line in the box represents median value. $^{*}P < 0.05$, compared with LVB group, G7; $^{\#}P < 0.05$, when compared with G9; n = 6 guinea-pigs in each group:

potentiated by dexmedetomidine in a dose-dependent manner. The analgesic action of alpha-2 adrenoceptor agonists is well established. Clonidine, the prototype alpha-2 adrenoceptor agonist, has been used in association with compounds such as opioids (Grace et al 1995; Siddall et al 2000; Ackerman et al 2003) and local anaesthetics (Dobrydnjov et al 2003) to enhance their analgesic action.

The mechanism for the potentiation of motor block by alpha-2 adrenoceptor agonists is unknown. One possible mechanism for the prolonged motor block induced by dexmedetomidine could be a synergistic interaction of dexmedetomidine as a local anaesthetic. This hypothesis arises from experiments performed in the sciatic nerve of rats in which clonidine and guanfacine, also an alpha-2 adrenoceptor agonist, produced a reversible tonic and phasic block of nerve conduction (Butterworth & Strichartz 1993). In another study, it was demonstrated that clonidine enhanced hyperpolarization (Erne-Brand et al 1999); this effect could shift the membrane potential toward a more negative value, reducing the safety for action potential conduction. However, the efficiency of clonidine as a single agent to induce motor block after intrathecal injection was not observed in human studies even at a higher dose than 450 μg (Filos et al 1994; Malinovsky & Bernard 1996). Thus, clonidine should be considered as an adjuvant drug to produce anaesthesia, since it is not potent enough to be used as a single drug. Similar investigations have not been conducted with dexmedetomidine.

Combination of two drugs that are from different classes, and one of them lacks efficacy, may produce synergistic interaction. Dexmedetomidine failed to produce motor block when used alone intrathecally or intraperitoneally. This work showed that the combination of levobupivacaine and dexmedetomidine, which are from different classes (local anesthetic and alpha-2 adrenergic agonist), produced a synergism, resulting in a prolonged spinal anaesthesia induced by levobupivacaine. Similar synergism was observed by Raffa et al (2001) and Porreca et al (1990), who described this interaction with the combination of two drugs of different classes in which one of them had no efficacy. A fixed intrathecal dose of levobupivacaine (250 μg) was used to investigate the effect of increasing doses of dexmedetomidine, which did not permit a better analysis of the interaction between the two drugs.

The effect of dexmedetomidine was not dependent on the route of administration because the prolongation of motor block occurred either after intrathecal or intraperitoneal injection. Our results showed that when intrathecal dexmedetomidine (0.4 μg) was used, the maximal effect was an increase of 118%. No significant difference was observed after administration of a high dose of dexmedetomidine intraperitoneally (40 $\mu g\,kg^{-1}$), with an increase of 136%. Prolonged duration of levobupivacaine-induced motor block by intraperitoneal injection of dexmedetomidine could involve more than one mechanism, still unknown. The dose used by the intraperitoneal route was approximately 50 times higher than the one administered by the intrathecal route. Distribution of dexmedetomidine to supraspinal sites is higher when administered intraperitoneally because of its high plasma concentration and dexmedetomidine is highly lipid-soluble and easily crosses the blood–brain barrier. Liu et al (1995) reported that prolonged spinal anaesthesia after premedication with 0.2 mg of oral clonidine was consequent to its interaction with alpha-2 adrenoceptors at spinal and supraspinal sites within the CNS.

Another possible mechanism to explain the prolonged motor block could be the interference of dexmedetomidine with neuromuscular activity. Talke et al (1999) reported that simultaneous administration of dexmedetomidine with rocuronium increased the neuromuscular blockade in human subjects. That effect was consequent to a pharmacokinetic mechanism increasing the unbound plasma concentration of rocuronium by an unclear process and not due to a direct effect on neuromuscular transmission.

Interaction of dexmedetomidine with the descending noradrenaline (norepinephrine) fibres could also be an important mechanism in the prolongation of levobupivacaine-induced motor block. Activation of descending noradrenaline neurons, whose cell bodies are located in the locus coeruleus and the nerve terminal in the ventral horn, facilitates the motor component of the spinal reflex (Strahlendorf et al 1980). The physiological function of adrenoceptors in the ventral horn is not completely elucidated. Binding and autoradiography studies have demonstrated the presence of

alpha adrenoceptors in the grey matter of the spinal cord (Jones et al 1982; Roudet et al 1994). Systemic administration of high dose of levodopa ($>50\,mg\,kg^{-1}$) activates post-synaptic alpha-1 adrenoceptors, which also increases the activity of motoneurons (Ono & Fukuda 1995) that can be inhibited by prazosin, an alpha-1 adrenoceptor antagonist. These results suggest that the activation of alpha-1 adrenoceptors could promote activation of motoneurons in the ventral horn. In contrast, activation of alpha-2 adrenoceptors by clonidine inhibited the spinal monosynaptic and polysynaptic reflex, which was reversed by the alpha-2 antagonist, piperoxan (Ono & Fukuda 1995).

Central activation of alpha-2 adrenoceptors inhibits the excitatory regulation of the noradrenaline pathway on the spinal motor reflex. We consider that systemic or spinal injection of dexmedetomidine reduces the motor block activity through the reduction of noradrenaline release in the ventral horn or of the activation of somata of the locus coerulus located at A6 and A7 of the brain stem. Yohimbine was used to demonstrate the importance of alpha-2 adrenoceptor on potentiation of motor block induced by dexmedetomidine. Yohimbine partially inhibited the action of dexmedetomidine after its injection at the spinal and intraperitoneal sites. As a highly lipid-soluble agent, yohimbine quickly crosses the blood–brain barrier, promoting effects on the CNS and thus antagonizing the effects of dexmedetomidine (Owen et al 1987; Guthrie et al 1990). The maximal effect of yohimbine was an inhibition of 30% of dexmedetomidine effect. These results indicate that enhancement of levobupivacaine-induced motor block duration by dexmedetomidine is probably not totally dependent on alpha-2 adrenoceptor activation. Rather, the contribution of alpha-2 receptor activation is a minor effect. Thus, it is possible that the combination of the anaesthetic-like effect of dexmedetomidine and alpha-2 adrenoceptor activation could explain the prolongation of levobupivacaine-induced motor block after spinal injection. However, we can not discard alternative mechanisms.

According to our results, dexmedetomidine is a potentially interesting agent to be used in association with local anaesthetic to prolong the motor block duration in different surgical procedures that require muscle relaxation. Dexmedetomidine is commercially available as a hydrochloride salt, well tolerated when administrated by intravenous injection. However, there are no studies addressing neurotoxicity after its administration by the intrathecal route. A complete neurotoxicological investigation with dexmedetomidine is still needed.

In conclusion, we report that the duration of motor block induced by spinal injection of levobupivacaine could be prolonged by intrathecal or systemic administration of dexmedetomidine. This effect is not only dependent on the activation of alpha-2 receptor but also by still unknown additional mechanisms.

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