Laboratory Investigation

Different effects of olprinone on contractility in nonfatigued and fatigued diaphragm in dogs

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Purpose: To evaluate the effects of low-dose olprinone, a phosphodiesterase III inhibitor, on contractility and its mechanism in nonfatigued and fatigued diaphragm in dogs.

Methods: Thirty six pentobarbitone-anesthetized dogs were studied. In Group Ia (n=6), animals without fatigue, received no study drug. In Group Ib (n=6), dogs were given a bolus injection (10 µg·kg⁻¹) followed by continuous infusion (0.1 µg·kg⁻¹·min⁻¹) of olprinone. In Groups IIA, IIB, and IIC (n=8 each), diaphragmatic fatigue was induced by intermittent supramaximal bilateral electrophrenic stimulation at a frequency of 20-Hz applied for 30 min. After producing fatigue, Group IIA received no study drug; Group IIB was infused with olprinone (10 µg·kg⁻¹ loading dose plus 0.1 µg·kg⁻¹·min⁻¹ maintenance dose); Group IIC was infused with nicardipine (5 µg·kg⁻¹·min⁻¹) during olprinone administration. Diaphragmatic contractility was assessed by transdiaphragmatic pressure (Pdi).

Results: No difference in Pdi was observed between Groups Ia and Ib. After fatigue, in Groups IIA, IIB, and IIC, Pdi at low-frequency (20-Hz) stimulation decreased from prefatigued (baseline) values (P<0.05), whereas there was no change in Pdi at high-frequency stimulation (100-Hz). In Group IIB, during olprinone administration, Pdi at both stimuli increased from fatigued values (P<0.05). In Group IIC, the augmentation of Pdi to each stimulus in fatigued diaphragm by olprinone was abolished with an infusion of nicardipine.

Conclusion: Low-dose olprinone does not affect contractility in nonfatigued diaphragm, but increases contractility in fatigued diaphragm via its effect on transmembrane calcium movement in dogs.

Objectif : Évaluer les effets d’une faible dose d’olprinone, un inhibiteur de la phosphodiésterase III, sur la contractilité et sur son mécanisme sur le diaphragme fatigué ou non, chez des chiens.

Méthode : Trente-six chiens anesthésiés au pentobarbital ont été étudiés. Dans le groupe la (n=6), les animaux non fatigués n’ont pas reçu de médicament à l’étude. Dans le groupe Ib (n=6), les chiens ont reçu l’injection d’un bolus (10 µg·kg⁻¹) d’olprinone, suivie d’une perfusion continue (0.1 µg·kg⁻¹·min⁻¹). Dans les groupes IIA, IIB, et IIC (n=8 chacun), on a induit la fatigue diaphragmatique par une stimulation électrophrénique intermittente supramaximale bilatérale à une fréquence de 20 Hz appliquée pendant 30 min. Après l’induction de cette fatigue, les chiens du groupe IIA n’ont pas reçu de médicament; ceux du groupe IIB ont reçu une perfusion d’olprinone (10 µg·kg⁻¹ en dose de charge plus 0.1 µg·kg⁻¹·min⁻¹ comme dose de maintien); ceux du groupe IIC ont reçu de la nicardipine (5 µg·kg⁻¹·min⁻¹) pendant l’administration d’olprinone. La contractilité diaphragmatique a été évaluée par pression transdiaphragmatique (Pdi).

Résultats : Aucune différence de Pdi n’a été observée entre les groupes la et Ib. Après la production de fatigue chez les animaux des groupes IIA, IIB, et IIC, la Pdi sous stimulation à basses fréquences (20 Hz) a diminué par rapport aux valeurs précédant la fatigue (valeurs de base), P<0.05, tandis qu’il n’y a pas eu de changement de Pdi sous stimulation à hautes fréquences (100 Hz). Dans le groupe IIB, pendant l’administration d’olprinone, la Pdi a augmenté par rapport aux valeurs du muscle fatigué et ce, sous stimulation à toutes les fréquences utilisées (P<0.05). Dans le groupe IIC, l’augmentation de Pdi par l’olprinone pour chaque stimulus du diaphragme fatigué a été abolie avec une perfusion de nicardipine.

Conclusion : Une faible dose d’olprinone n’a pas d’effet sur la contractilité d’un diaphragme non fatigué, mais accroît celle d’un muscle fatigué par ses effets sur le déplacement du calcium transmembranaire chez les chiens.

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PHOSPHODIESTERASE (PDE) III inhibitors have been developed, and investigated clinically and pharmacologically to evaluate their therapeutic potential for the treatment of congestive heart failure.\textsuperscript{1-3} In addition to these pharmacological properties, we have shown that amrinone and milrinone improve diaphragmatic muscle function,\textsuperscript{4,5} and that olprinone is more effective than milrinone for the improvement of contractility in fatigued diaphragm.\textsuperscript{6} However, high-dose (> 0.3 µg·kg\textsuperscript{-1}·min\textsuperscript{-1}) olprinone occasionally causes severe hypotension by its direct relaxing effect on vascular smooth muscle.\textsuperscript{7} This study was undertaken to determine the effects of low-dose (0.1 µg·kg\textsuperscript{-1}·min\textsuperscript{-1}) olprinone and its mechanism in nonfatigued and fatigued diaphragm in dogs.

Methods
The protocol was approved by our animal research committee, and the care of the animals was in agreement with guidelines for ethical animal research. Thirty-six healthy mongrel dogs weighing 10-15 kg were anesthetized with pentobarbital (25 mg·kg\textsuperscript{-1} loading dose plus 2 mg·kg\textsuperscript{-1}·hr\textsuperscript{-1} maintenance dose) iv to abolish spontaneous movement. No muscle relaxant was used. Animals were placed in the supine position, their tracheas were intubated with a cuffed tracheal tube, and the lungs were mechanically ventilated with a mixture of O\textsubscript{2} and air (F\textsubscript{O\textsubscript{2}}=0.4) to maintain Pa\textsubscript{O\textsubscript{2}} > 100 mmHg, Pa\textsubscript{CO\textsubscript{2}} 35-40 mmHg, and pH\textsubscript{a} 7.35-7.45. The right femoral artery was cannulated to monitor arterial blood pressure and to obtain blood samples for blood gas analysis. The right femoral vein was cannulated to administer maintenance fluids (10 mL·kg\textsuperscript{-1}·hr\textsuperscript{-1} lactated Ringer’s solution), pentobarbital, and bicarbonate to keep the plasma HCO\textsubscript{3} concentration within normal ranges. The left femoral vein was cannulated for the administration of olprinone. A flow-directed pulmonary artery catheter was advanced via the right external jugular vein into the pulmonary artery to measure cardiac output (CO) by thermodilution technique. Rectal temperature was monitored continuously and maintained at 37 ± 1°C.

The phrenic nerves were exposed bilaterally at the neck, and stimulating electrodes were placed around them. Transdiaphragmatic pressure (Pdi) was measured by using two thin-walled latex balloons: one positioned in the stomach, the other in the middle third of the esophagus. The balloons were connected to a differential pressure transducer (TP-604 T; Nihon Kohden, Tokyo, Japan) and an amplifier (Type 1257; Nihondenki San-ei, Tokyo, Japan). While one balloon catheter was open to atmosphere, the position of the other was changed to obtain appropriate pressure. Then the position of the balloons in the esophagus and the stomach was confirmed. Supramaximal electrical stimuli (10-15 volts) of 0.1-msec duration were applied for two seconds at low-frequency (20-Hz) and high-frequency (100-Hz) stimulation with an electrical stimulator (SEN-3301; Nihon Kohden). Isometric contractility of the diaphragm was evaluated by the measurement of the maximal Pdi after airway occlusion at FRC. Transpulmonary pressure (Ptp), the difference between airway and esophageal pressure, was kept constant (nearly - 5 cm H\textsubscript{2}O) by maintaining the same lung volume before each phrenic stimulation. End-expiratory diaphragmatic geometry and muscle fibre length during contraction were kept constant by placing a close-fitting plaster cast around the abdomen and lower third of the rib cage. The electrical activity of crural (Edi-cru) and costal (Edi-cost) parts of the diaphragm was recorded by two pairs of fishhook electrodes placed through a midline laparotomy; electrodes were positioned into the anterior portion of crural part near the central tendon and the anterior portion of costal part (away from the zone of apposition) in the left hemidiaphragm. Each pair was placed in parallel fibres 5-6 mm apart. The abdomen was then sutured in layers. The signal was rectified and integrated with a leaky integrator (Type 1322; Nihondenki San-ei) with a time constant 0.1 sec and was regarded as the integrated diaphragmatic electrical activity (Edi-cru, Edi-cost).

Twenty-eight dogs were randomized among four groups: Groups Ia (n=6), Ib (n=6), IIA (n=8) and IIB (n=8); Group IIC (n=8) was added after the previous results had been obtained. In Groups Ia and Ib, after the baseline measurements of Pdi, Edi-cru, Edi-cost, and hemodynamic variables, including heart rate (HR), mean arterial pressure (MAP), right atrial pressure (RAP), mean pulmonary arterial pressure (MPAP), pulmonary artery occlusion pressure (PAOP), and CO, Group Ia received no study drug; Group Ib was given a bolus injection (10 µg·kg\textsuperscript{-1}) followed by a continuous infusion (0.1 µg·kg\textsuperscript{-1}·min\textsuperscript{-1}) of olprinone iv via an infusion pump for 30 min. At 30 min after the onset of olprinone infusion, in Group Ib, Pdi, Edi-cru, Edi-cost, and hemodynamic variables were measured, and CO was evaluated by thermodilution technique. In Group Ia, these measurements were made at 30 min to verify the stability of this preparation.

In Groups IIA, IIB, and IIC, after measuring prefatigued (baseline) values of Pdi, Edi-cru, Edi-cost, and hemodynamic variables, and CO, diaphragmatic fatigue was induced by intermittent supramaximal