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Original Research

Cardiopulmonary Effects and Recovery Quality of Remifentanil–Isoflurane Anesthesia in Horses

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ABSTRACT

Remifentanil is a potent opioid with minimum alveolar concentration–sparing effects in humans and dogs, but its effects in horses have not been reported. We proposed to evaluate the cardiopulmonary effects, the duration, and recovery quality of remifentanil in isoflurane-anesthetized horses. Ten horses were premedicated with xylazine (1 mg/kg IV), induced with ketamine and diazepam (2.2 mg/kg/0.1 mg/kg IV), and maintained with isoflurane in oxygen delivered by a mechanical ventilator. Each horse was anaesthetized twice in a randomized order, with 1 week between treatments. In both treatment groups, a bolus of 0.5 μg/kg and a 120-minute infusion of remifentanil (0.375 μg/kg/min) or sterile water (delivered at the same rate per volume as the remifentanil) commenced when an end-tidal isoflurane concentration of 1.2%–1.4% was reached. Cardiopulmonary variables, arterial blood gas variables, time to extubation, and recovery scores were not significantly different between groups. The time to first movement was significantly different, which is longer for the placebo group (25.6 ± 17.7 minutes) than that for the remifentanil group (11.33 ± 5.38 minutes). The time to standing was significantly different; in the placebo group, it was 47 ± 20 minutes, and in the remifentanil group, it was 30.7 ± 9.3 minutes.

1. Introduction

Balanced anesthesia is the concomitant administration of multiple anesthetic and analgesic drugs so that no single drug is given at a dosage sufficient to produce toxicity during or after surgery. In humans and small animals, balanced anesthesia with opioids provides perioperative analgesia and improves hemodynamics by minimizing the necessary inhalation concentration for general anesthesia [1–3].

Remifentanil, a synthetic opioid, is the methyl ester of 4-methoxycarbonyl-4-[(1-oxopropyl) phenylamino]-l-piperidinepropionic acid and is marketed as a hydrochloride salt [4]. Remifentanil exhibits μ-opioid receptor-mediated effects, analogous to those of structurally related phenylpiperidine derivatives such as fentanyl and sufentanil [5]. Remifentanil produces physiological changes in humans consistent with potent μ-receptor agonist activity, including analgesia and sedation. Remifentanil adverse effects include ventilatory depression, nausea, vomiting, muscular rigidity, bradycardia, and pruritus [6]. Most of these adverse effects have not been reported in horses.

Because remifentanil does not cause histamine release on injection, it has fewer adverse hemodynamic effects than morphine [7]. In humans, the reduced heart rate (HR) caused by remifentanil can be completely antagonized by naloxone [5,8]. Remifentanil is synergistic with hypnotic drugs thereby yielding a decrease of minimum alveolar anesthetic concentration [5], but opioids may produce a different effect in horses.

The presence of a methyl ester on the propionic acid side chain of the piperidine ring increases the susceptibility of remifentanil to hydrolytic cleavage by blood and tissue

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nonspecific esterases, leading to relatively rapid clearance in humans and measured as a plasma half-life of 8–10 minutes [4,7], which prevents accumulation of the drug. Remifentanil can thus be classified as an ultrashort-acting phenylpiperidine opioid analgesic agent [9]. Previously reported evidence suggests that remifentanil is metabolized in the horse in much the same way as in humans and canines, namely by hydrolysis to 4-methoxycarbonyl-4-[(1-oxopropyl) phenylamino]-1-piperidinepropionic acid. This same metabolite has also been identified in canine urine samples [6,10].

The assumption is that remifentanil and fentanyl have similar potency in horses [11,12]. The peak analgesic effect is produced 1–3 minutes after the administration of the drug, which is faster than that produced by fentanyl.

The recovery period is a critical phase of anesthesia in all species, especially in horses, because excitement in recovery can lead to increased morbidity or even mortality in this species.

Extremely high dosages of μ-agonist opioids administered intraoperatively may cause unacceptable excitement in horses during recovery [13], but administration of clinically relevant dosages of μ-agonists causes no difference in recovery quality compared with administration of lesser potent opioids [14], and recovery quality is actually better in horses receiving potent μ-agonist opioids than those not receiving any opioid [15,16]. Recoveries from remifentanil alone have not been evaluated.

Because of the potent analgesia, minimal cardiovascular adverse effects, rapid onset of action, and lack of accumulation, remifentanil could be an advantage in medically compromised horses that are undergoing surgery, for example horses undergoing colic surgery. The objective of this study was to evaluate the cardiopulmonary effects, recovery duration, and recovery quality in horses anesthetized with remifentanil and isoflurane. Our hypothesis was that remifentanil can be used in horses as a continuous infusion during inhalation anesthesia giving proper hemodynamic stability and good recovery quality from anesthesia.

2. Materials and Methods

2.1. Horses

The study was approved by the Animal Care and Use Committee of the Universidad Nacional del Centro de la Provincia de Buenos Aires. A total of 10 mature and healthy crossbred horses (two stallions, one gelding, and seven mares), American Society of Anesthesiologist 1 score with a mean age (±standard deviation [SD]) of 7.45 ± 5.09 years (range, 2–15), and a mean weight of 433.1 ± 58.35 kg (range, 358–507) were used. Food, but not water, was withheld from the horses for 12 hours before beginning each study.

2.2. Experimental Design

Each horse was anesthetized twice in a randomized order, with 1 week between treatments. The left jugular vein was percutaneously catheterized after local anesthesia using a 14-ga, 51-mm length Teflon catheter (Abbocath-T, Hospira Inc, IL) facilitated the administration of drugs. Both anesthetic events were premedicated with xylazine (1 mg/kg body weight IV; Xylazina 10%, Pro Ser S.A., Buenos Aires, Argentina) and induced to the anesthesia with ketamine and diazepam (2.2 mg/kg IV; Ketamina 100 mg, Pro Ser S.A. or 0.1 mg/kg body weight IV; Viazepam, Bio-amer, Buenos Aires, Argentina). Horses were placed on a foam surgical pad (Shanks Dorsal/Lateral equine surgery table, Shanks Veterinary Equipment, IL) in dorsal recumbency. Each horse was intubated with a 22-, 24-, or 26-mm inner diameter cuffed orotracheal tube (SurgiVet, Smiths Medical, OH) and connected to semiclosed anesthetic circuit (Model 2800 BC; Mallard Medical Inc, CA) maintained with isoflurane (IsoSol; Vedco Inc, St. Joseph) in oxygen delivered by using intermittent positive pressure ventilation. When an end-tidal isoflurane (ETiso) concentration of 1.2%–1.4% was reached, either remifentanil or sterile water was administered:

Remifentanil (Remicit, Astrazeneca S.A., Buenos Aires Argentina): bolus of 0.5 μg/kg and a 120-minute infusion of 0.375 μg/kg/min (Medifusion; Medex Inc, GA)
Placebo: bolus and a 120-minute infusion of sterile water (delivered at the same rate/volume [Medifusion; Medex Inc] as the remifentanil)

A base–apex lead electrocardiogram was used to monitor HR and rhythm. The submaxillary artery was catheterized with a 21-ga winged needle infusion set (Butterfly, Hospira Inc) and connected to a calibrated pressure transducer (IV monitoring Kit; Trasnpac, Hospira Inc). Zero pressure was considered at the level of the right atrium, using the sternal manubrium as the external reference point. The systolic, diastolic, and mean arterial blood pressures (ABPs) were recorded and their values displayed on a pressure monitor (Dre, Dre Inc, KY). Hemoglobin saturation of oxygen ($SatO_2$) was continuously measured using a pulse oximetry probe placed on the tongue.

Respiratory rate, end-tidal CO_2 ($ETCO_2$), and the fraction of isoflurane (fractional inspired isoflurane concentration/fractional expired isoflurane concentration) were continuously monitored (Dre, Dre Inc) using exhaled gases drawn from sampling port at the Y-piece. The gas analyzer was calibrated at the beginning of the study with the appropriate gas mixture.

End-tidal isoflurane was maintained at 1.2%–1.4% throughout the entire anesthetic period. Data collection begins as soon as the infusion was started for 120 minutes.

Minute ventilation was manipulated to maintain $ETCO_2$ 35–45 mm Hg. Arterial blood samples were anaerobically

Table 1
Scoring system used to grade recoveries.

Scores	Description
1	1 attempt to stand, no ataxia
2	1–2 attempts to stand, some ataxia
3	>2 attempts to stand but quiet recovery
4	>2 attempts to stand, excitation
5	Severe excitation