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Review Article

Effects of Yohimbine Over Pharmacokinetic and Pharmacodynamic and Behavioral Parameters in Horses Sedated With Detomidine

Sergio Recillas-Morales [a], Edgar Osornio-Plata [a], José Antonio Ibancovichi-Camarillo [a], José Mauro Victoria-Mora [a], Moisés Cipriano-Salazar [b], Pedro Sánchez-Aparicio [a,*]

[a] Department of Pharmacology, Anaesthesia and Analgesia, Facultad de Medicina Veterinaria y Zootecnia, Universidad Autónoma del Estado de México, Toluca, México

[b] Unidad Académica de Medicina Veterinaria y Zootecnia, Universidad Autónoma de Guerrero, Altamirano, México

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ABSTRACT

The aim of this study was to review the safety of the detomidine (DET) in horses and the effects of yohimbine (YOH) over pharmacokinetic, pharmacodynamic, and behavioral parameters in horses sedated with DET. A literature search was made on PubMed (National Center for Biotechnology Information, United States National Library, Bethesda, MD) and SCOPUS (Elsevier Research Intelligence) for studies that had evaluated the effects of DET or YOH on clinics pharmacodynamics and pharmacokinetics parameters in horses plus experimental studies with the effect of YOH on the pharmacokinetics, pharmacodynamics, and behavioral parameters in horses sedated with DET. Additionally, information was obtained from studies where DET or YOH was administered alone or in their combination in treatment of horses. Three investigations described the pharmacokinetics or physiologic effects of YOH when administered after DET to reverse the behavioral and physiologic effects of DET. The studies with DET showed that it was more absorbed when administered intramuscular than when administered sublingual. In those studies, they noted important implications, both from therapeutics and regulatory prospective. They demonstrated intravenously administered DET is effective in sedation with effects on cardiovascular effects.

1. Introduction

There is a wide group of alpha-2 adrenergic adrenoreceptor agonists such as xylazine, detomidine (DET) (DET is alpha-2 adrenergic adrenoreceptor agonists), medetomidine, and romifidine. In veterinary practice, xylazine and medetomidine are the most commonly used drugs for horses. DET is a potent agonist of both centrally and peripherally located alpha-2 receptors in many animal species [1,2] and is characterized by rapid distribution and metabolism to two main metabolites with subsequent elimination [3]. DET is commonly used in equine medicine for procedures requiring sedation, chemical restraint, or analgesia and is most commonly administered parenterally [3–7]. The effects of DET on the pharmacokinetics and pharmacodynamics parameters in the horse following either intravenous (IV) or intramuscular (IM) administration have been well described [2,8–11].

Alpha-2 adrenergic antagonists are often used to reverse the sedative, cardiovascular depressant [3] and central nervous system (CNS) effects of alpha-2 adrenergic receptor agonists following IV or IM administration. The three antagonist most commonly used in veterinary

* Corresponding author at: Pedro Sánchez-Aparicio, El Cerrillo Piedras Blancas, Toluca, Estado de México 50090.
E-mail address: pedrosanchezaparicio0@gmail.com (P. Sánchez-Aparicio).

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medicine are yohimbine (YOH) (alpha-2 receptor antagonist), atipamezole, and tolazoline. In equine medicine, the only Food and Drug Administration (FDA) approved alpha-2 adrenergic antagonist is tolazoline [1]. Yohimbine is an indole alkaloid derived from several biological or botanical sources, including the bark of the *Pausinystalia yohimbine* tree and the Rauwolfia root [2,3]. Yohimbine enhances sympathetic outflow via the neurotransmitter, norepinephrine. It is a potent antagonist of centrally and peripherally located alpha-2 receptors in humans and many animal species [12–14]. In veterinary medicine, YOH is almost exclusively used to reverse the sedative or cardiovascular effects of the alpha-2 receptor agonists, especially DET [2]. In horses, YOH has been shown to antagonize the ventricular bradycardia and atrioventricular (AV) conduction disturbances observed following administration of DET [3]. Yohimbine appears to be widely distributed as evidenced by a large volume of distribution and rapidly cleared following IV administration to the horse [5]. In the human, YOH is rapidly metabolized by the cytochrome P450 enzymes to two hydroxyl-yohimbine metabolites [15]. To our knowledge, there are no reports in the literature regarding YOH metabolites in the horse [5]. Hydroxylation is the major pathway for elimination of YOH in the horse. However, although hydroxylation of YOH in humans has been attributed to CYP450 enzymes, namely CYP3A4 and CYP2D6, the identity of the enzymes responsible for metabolism of YOH in the horse has yet to be elucidated [5]. Based on the evidence of experimental studies on its efficacy, the aim of this study was to systematically review the safety of the drug in horses and the effects of YOH over pharmacokinetic, pharmacodynamic, and behavioral parameters in horses sedated with DET.

2. Methods

A literature search was made on PubMed (National Center for Biotechnology Information, United States National Library, Bethesda, MD) and SCOPUS (Elsevier Research Intelligence) from its inception on May 26, 2015. In the review, experimental studies involving the evaluation of the effects of DET administered enterally or parenterally in horses on clinics pharmacodynamics and pharmacokinetics parameters were included. Experimental studies that determined the pharmacokinetics or pharmacodynamics profile of intravenously administered YOH in horses were also included. Finally, experimental studies evaluating the effect of YOH on the pharmacokinetics, pharmacodynamics, and behavioral parameters in horse sedated with DET were included. A review of titles and, if available, abstracts was performed by two of the investigators who eliminated duplicate manuscripts and studies evaluating the effects of other alpha-2 adrenergic antagonists on horse. Five manuscripts were retrieved for further revision. Disagreements between the investigators were resolved by consensus.

Data abstraction was performed by three other investigators. From the experimental studies performed in horses, the following variables were obtained: animal species, sex, age, dosage, administration route, clinics effects, changes in behavior, cardiac and blood parameters, pharmacokinetics and pharmacodynamics effects. Of the 26 retrieved studies, the information was obtained from 14 selected reports [1,3–7].

3. Results

The following studies reporting treatments in horses which employed DET or YOH when administered alone or in combination were identified. Three in vivo experimental studies with horses characterized pharmacokinetics, pharmacodynamics, sedative, and clinical effects of DET. The DET was administered at different doses enterally or parenterally. DET doses of 0.03 mg kg^{-1} was most frequently chosen for two reasons, it is the dose commonly used for sedation in horses, and this dose has demonstrated the minimum effects on alveolar concentration of isoflurane in horses [7]. However, studies with this drug do not use this suggested dose. The first study characterized the pharmacokinetics of a novel DET gel product after sublingual (SL) administration indicated slight differences in absorption and plasma DET concentrations. Carboxydetomidine and hydroxydetomidine were detected in urine samples. The elimination of DET differed between sedentary and active horses. For the second experiment, area under the curve and maximal plasma concentration (C_{max}) showed that IM and SL routes of administration were not bioequivalent. The onset of sedation was very fast with IV administration. However, the time to the onset of sedation was longer after SL and IM administration. Part of the gel is likely to be swallowed and, due to extensive first-pass metabolism, does not reach the systemic circulation. In two experiments, no adverse effects were observed in horses that were treated via SL. Other study showed the pharmacokinetics parameters of DET where the clearance was considerably faster and the volume of distribution markedly higher compared to previous reports in the some specie (Table 1).

Three experimental studies characterized the pharmacokinetics or pharmacodynamics profile and determine the half-life of YOH when administered to horses. The studies were conducted in a randomized fashion at different doses administered intravenously where in each horse received 0.075, 0.1, 0.12, 0.15, 0.2, or 0.4 mg/kg of YOH. Mean plasma YOH concentration in the first 15 minutes following IV administration of 0.4 mg/kg YOH corresponded to 105 or 220 ng/mL (Table 2). Immediately following administration, some horses showed signs of sedation which persisted for approximately 1 hour, as indicated by a slight drop in head height (chin-to-ground distance). Gastrointestinal (GI) sounds increased in most horses at all doses studied; nevertheless, a dose-dependent response was evident with GI sounds.

Another three investigations described the pharmacokinetics or physiologic effects of the YOH when administered after the DET to reverse the behavioral and physiologic effects of DET. The experimental studies with DET showed that DET had been absorbed when administration route was SL but was less absorbed than when given IM. In these studies (references), the authors noted important implications, both from therapeutics and regulatory prospective. These studies demonstrated that intravenously administered DET was effective in sedation, but with negative effects on cardiovascular (Table 3).