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"A SYSTEMATIC REVIEW OF EXPERIMENTAL STUDIES OF YOHIMBINE EFFECTS OVER PHARMACOKINETIC , PHARMACODYNAMIC AND BEHAVIORAL PARAMETERS IN HORSES SEDATED WITH DETOMIDINE"

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EDGAR GERARDO OSORNIO PLATA

Asesores:

DR. PEDRO SÁNCHEZ APARICIO

DR. JOSÉ ANTONIO IBANCOVICHI CAMARILLO

DR. SERGIO RECILLAS MORALES

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TÍTULO

"A SYSTEMATIC REVIEW OF EXPERIMENTAL STUDIES OF YOHIMBINE EFFECTS OVER PHARMACOKINETIC , PHARMACODYNAMIC AND BEHAVIORAL PARAMETERS IN HORSES SEDATED WITH DETOMIDINE"

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INTRODUCCIÓN

La detomidina (DET) 4-(2,3-Dimethylbenzyl)-1H-imidazole, es un alfa-2 adrenérgico, agonista potente y específico de uso común en el ámbito de la medicina veterinaria, utilizado como sedante a nivel clínico y de campo en la especie equina en procedimientos que requieren sedación, restricción o contención química e incluso analgesia (diMaio Knych y Stanley, 2011). Este fármaco ha sido administrado frecuentemente por vía parenteral (Kaukinen *et al*., 2011; Knych *et al*., 2012; Knych y Stanley, 2014) y sus efectos sobre parámetros farmacocinéticos y farmacodinámicos en el caballo han sido descritos cuando son administrados por vía intravenosa (IV) o intramuscular (IM) (Hubbel *et al*., 2009; Knych *et al*., 2012). No obstante, la DET ha sido administrada recientemente por vía enteral en una presentación farmacéutica novedosa de gel, cuyos efectos sobre estos parámetros aún no han sido adecuadamente dilucidados.

Los efectos sedantes y depresores cardiovasculares de los fármacos agonistas alfa-2 adrenérgicos pueden ser revertidos efectivamente por el antagonista del receptor alfa-2 (Knych *et al*., 2012). Los tres antagonistas comúnmente utilizados en el área de la medicina veterinaria son yohimbina (YOH), atipamezol y tolazolina. En el ámbito de la medicina equina, el único fármaco antagonista alfa-2 adrenérgico aprobado por la Food and Drug Administration es tolazolina, aunque yohimbina y atipamezol también se han utilizado para revertir los efectos de los agonistas alfa-2 adrenérgicos (Knych y Stanley 2014). Los antagonistas alfa-2 adrenérgicos se utilizan a menudo para revertir los efectos depresores en el sistema cardiovascular y sistema nervioso central (SNC) causados por los agonistas alfa-2 adrenérgicos cuando estos han sido administrados por vía IV, IM e incluso sublingual.

La YOH es un alcaloide indol derivado de diversas fuentes biológicas o botánicas en las que se incluye a la corteza del árbol de *Pausinystalia YOH* y la raíz de *Rauwolfia* (Dimaio Knych *et al.*, 2011a; Dimaio Knych y Stanley, 2011b). Este fármaco incrementa el flujo del neurotransmisor noradrenalina a través de la vía simpática. Además de ser un potente antagonista de los receptores alfa-2

adrenérgicos situados a nivel central y periférico en los seres humanos y en diversas especies animales mamíferas (Kollias-Baker *et al.,* 1993; Ramseyer *et al.,* 1998; Hubell y Muir, 2006). En el ámbito de la medicina veterinaria, la YOH se utiliza casi exclusivamente para revertir el efecto sedante o los efectos cardiovasculares negativos generados por los agonistas alfa-2 adrenérgicos, especialmente de la DET (Dimaio Knych *et al*., 2011a). Diversos experimentos han demostrado que en los caballos, la YOH antagoniza la bradicardia ventricular y aurículo-ventricular (AV), las cuales han sido reportadas después de la administración de DET por vía enteral (Knych *et al*., 2012). Aparentemente, la YOH puede tener un óptimo volumen de distribución en el organismo y puede aclararse rápidamente tras su administración intravenosa en la especie equina (DiMaio Knych *et al*., 2011a). Se ha demostrado que en el ser humano, la YOH se metaboliza rápidamente a tráves de enzimas del citocromo CYP450 a dos metabolitos secundarios, siendo el más importante, el hidroxil-yohimbina (LeCorre *et al*., 1999). Hasta donde se sabe, no hay informes en la literatura científica que indique cuántos y cuáles son los metabolitos de la YOH que intervienen en el metabolismo del fármaco en el caballo (Dimaio Knych *et al.,* 2011). No obstante, se sabe que la hidroxilación es la principal vía de eliminación de la YOH en el caballo. Sin embargo, mientras que la hidroxilación de la YOH en los seres humanos se ha atribuido a las enzimas CYP450, hay evidencia de que las enzimas CYP3A4 y CYP2D6 han sido identificadas como responsables del metabolismo de la YOH en el caballo (*Knych et al*., 2012). Con base en la evidencia de estudios experimentales sobre la eficacia de la YOH, el objetivo de este estudio consiste en revisar sistemáticamente la seguridad de la droga en los caballos, sus parámetros farmacocinéticos, farmacodinámicos y los parámetros de comportamiento farmacológico en caballos sedados previamente con DET.

REVISIÓN DE LITERATURA

1.- Efecto de la detomidina sobre parámetros farmacocinéticos, farmacodinámicos y de comportamiento farmacológico en caballos.

Son contados los artículos científicos especializados que se han enfocado a la caracterización de los parámetros farmacocinéticos y farmacodinámicos de la DET cuando ha sido administrada por vía enteral o parenteral. Uno de los estudios más importantes fue realizado por DiMaio Knych y Stanley (2011b), quienes caracterizaron la farmacocinética y farmacodinámia de la DET cuya presentación farmacéutica fue en gel y se administró vía sublingual en caballos previo a una competencia. En dicho estudio, se incluyeron 12 caballos adultos pura sangre clinicamente saludables en competencia activa. En este estudio se demostraron cambios farmacocinéticos y farmacodinámicos, los cuales se vieron reflejados en la concentración de DET en plasma que fue de 168±83.7 ng/mL. Esta concentración es considerada como elevada, pues es señal que la DET se absorbe bien en la mucosa sublingual hacia la circulación sistémica. La concentración plasmática de la DET más alta se logró rápidamente tras su administración sublingual en un tiempo máximo de 36±10 minutos posteriores a la administración del fármaco. Su vida media de eliminación fue de 1.5±1.0 horas, lo cual puede constatarse con las concentraciones de la DET a nivel urinario, ya que sus niveles de metabolitos en muestras de orina estuvieron por debajo del límite de detección por 3 días después de la administración. La vida media de eliminación tras su administración sublingual es prolongada, si se compara con el tiempo de eliminación después de la administración IV o IM. Las concentraciones del compuesto original y sus metabolitos pueden estar por debajo del límite de detección en orina hasta 3 días después de su administración. En sintesis, se sabe que el gel de la DET (40 µg/kg) parece inducir un grado moderado de sedación cuando se administra por vía sublingual.

Un estudio dirigido por Kaukinen *et al. (*2011), permitió identificar la absorción, biodisponibilidad y efecto sedante de la DET cuando es administrada a los caballos por vía enteral con una presentación farmacéutica novedosa en gel y se contrasto con la administración intravenosa e intramuscular de la DET en solución inyectable. El estudio fue realizado con nueve caballos, cada caballo fue asignado al azar. Se colectaron muestras de sangre antes y después de la administración del fármaco, con la intención de medir las concentraciones de la DET en el suero. Las variables farmacocinéticas fueron estimadas para cada caballo y para el momento en que fueron dosificadas. Las variables evaluadas en los previos al muestreo de sangre fueron sedación, frecuencia cardíaca (FC), ritmo cardiaco y efectos adversos. La dosis utilizada fue de 40 µg/kg de DET IV, IM o sublingual con un período de lavado de 7 días entre cada tratamiento. La concentración máxima de la DET cuando es administrada por vía sublingual fue inferior, respecto a cuándo se administró por vía IM (4.16 *vs*. 11.16 ng/mL) y el tiempo máximo (t_{max}) fue de 1.83 *vs.* 1.06 horas. En el estudio, se concluyó que la DET se absorbe en menor cantidad cuando se administra por vía sublingual respecto a su administración vía intramuscular ya que parte del fármaco no llega a la circulación sistémica.

Vainionpää *et al.* (2013), indagaron sobre las concentraciones plasmáticas del fármaco antagonista alfa-2-adrenérgico MK-467 (anteriormente conocido como L-659'066), su efecto sedante a nivel periférico y sobre la motilidad intestinal en caballos sedados con DET administrada vía intravenosa. En su estudio utilizaron seis yeguas clínicamente saludables, la profundidad de la sedación, sonidos intestinales, actitud, postura, altura de la cabeza, apertura de los párpados y el movimiento de las orejas fueron registrados antes y después del tratamiento. Además realizaron un electrocardiograma. Posterior a la toma de muestra sanguínea, se analizaron las concentraciones de DET y MK467 en plasma. La dosis utilizada fue de 10 µg/kg de DET (Equisedan, Vetcare, Finlandia) administrada vía IV sola y en combinación con 250 µg/kg de MK467 (Merck & Co., Inc., NJ, EE.UU.) vía IV en un diseño cruzado aleatorizado con 14 días de periodo

de lavado entre tratamientos. En el estudio se detectó una reducción significativa de la FC después de la administración de la DET, y la frecuencia respiratoria fue significativamente mayor después de la administración de DET-MK467. Los investigadores determinaron que la DET-MK467 reducen la concentración plasmática de la DET así como el área bajo la curva, favorece el incremento en su volumen de distribución y el periodo de aclaramiento. Finalmente se identificó que el MK467 no afecta la calidad de la sedación inducida por la DET, aunque si reduce la duración del efecto farmacológico, lo que puede haber sido causado por los efectos del MK467. En este sentido, los investigadores sugirieron que el MK467 puede ser clínicamente útil como agente farmacológico para prevenir ciertos efectos secundarios a nivel periférico causados por la administración de la DET en caballos.

2.- Efecto de la Yohimbina sobre parámetros farmacocinéticos, farmacodinámicos y de comportamiento farmacológico en caballos.

Contados son los artículos especializados que han caracterizado los cambios farmacocinéticos y farmacodinámicos. El estudio dirigido por Dimaio Knych *et al*. (2011) determinaron el perfil farmacocinético de la YOH cuando fue administrada por vía IV en caballos. En el experimento se utilizaron ocho caballos adultos sanos, no medicados. Se obtuvieron muestras de sangre que fueron procesadas en diferentes momentos antes y hasta 72 horas después de la administración de los fármacos. Las muestras de sangre en plasma se analizaron mediante cromatografía líquida por espectrometría de masas y los datos fueron analizados utilizando un modelo farmacocinético no compartimental y otro compartimental. La dosis utilizada en dicho estudio fue de 0.12 mg/kg de YOH (Yobine, Lloyd laboratorios, Shenandoah, IA, EE.UU.), dosis que fue administrada vía IV lenta durante 1 minuto. La concentración plasmática máxima fúe de 114.5±31.8 ng/mL y fue registrada a las 0.09±0.03 horas posteriores a la administración del fármaco. El volumen de distribución y el aclaramiento sistémico fueron de 13.5±2.1 mL/min/kg y 3.3±1.3 L/kg en el análisis farmacocinético no compartimental. La vida media de

eliminación terminal fue de 4.4±0.9 horas. Para el análisis compartimental, la concentración de YOH en plasma se ajusta mejor en términos de tiempo a un modelo de dos compartimentos, el aclaramiento sistémico y el volumen en estado de equilibrio de la distribución de la YOH fue de 13.6±2.0 mL/min/kg y 3.2±1.1 L/kg. Se detectaron los metabolitos hidroxi-yohimbina en las muestras de orina en cualquiera de los puntos de tiempo muestreados. Dos caballos presentaron efectos sedantes, incluyendo un ligero descenso en la posición y altura de la cabeza y una postura caracterizada por relajación de miembros posteriores, mientras que en los restantes seis caballos no hubo cambios en su conducta. Los signos de sedación persistieron durante aproximadamente 1 hora en ambos caballos. Los sonidos Gastrointestinales (GI) se incrementaron moderadamente en comparación con el valor basal, mientras que la consistencia fecal parecía normal. Esta investigación, permite sugerir que la YOH se caracteriza por tener una vida de eliminación prolongada, muy probablemente como resultado del secuestro y liberación lenta de sus metabolitos. Una dosis de 0.12 mg/kg administrada por vía intravenosa en caballos, ha permitido identificar que el volumen de distribución es elevado y el aclaramiento sistémico es muy lento, la cual está determinado por su vida media de eliminación.

En un estudio especializado, los investigadores Dimaio Knych, Steffey, y Stanley (2011), demostraron la farmacocinética y farmacodinámica de la YOH cuando es administrada por vía intravenosa en el caballo. En esta investigación se utilizaron nueve caballos adultos sanos no medicados. Las muestras de sangre se recogieron varias veces antes y hasta 24 horas después de la administración del fármaco. Dichas muestras se analizaron mediante cromatografía líquida por espectrometría de masas utilizando tanto el análisis no compartimental como el compartimental. En dicho estudio se utilizó una dosis de 0.1, 0.2, y 0.4 mg/Kg de YOH (Yobine; Lloyd laboratorios, Iowa) administrada por vía intravenosa lenta durante 1 minuto. La concentración plasmática máxima fúe de 106.0±28.9, 156.7±34.3 y 223.0±44.5 ng/mL para la dosis de 0.1, 0.2, y 0.4 mg/Kg y ocurrió a las 0.09±0.03 horas posteriores a la administración del fármaco. El aclaramiento sistémico y el volumen de distribución fueron de 12.0, 12.2 y 17.9 mL/min/kg y 2.1,

2.6 y 2.9 L/kg en el análisis no compartimental. La vida media de eliminación terminal fue de 43.6, 3.3 y 2.9 horas para las dosis de 0.1, 0.2, y 0.4 mg/Kg. Para el análisis compartimental, el aclaramiento sistémico y el volumen de distribución de la YOH fueron de 11.1 mL/min/kg y 2.3 L/kg. Dos caballos mostraron signos de sedación, un caballo presento excitación y los restantes seis no se apreciaron conductualmente afectados. Se observaron episodios de taquicardia a pocos minutos de la administración de las distintas dosis en los caballo. Sin embargo, no hubo correlación entre las respuestas de comportamiento y el incremento del ritmo cardíaco. 63 % de los caballos exhibieron bradicardia antes de la administración del fármaco y mejoraron transitoriamente conforme aumento el tiempo, fueron desapareciendo los efectos adversos. Las respuestas de comportamiento tras la administración de YOH parecen ser consistentes en los caballos, las cuales son independientes de la dosis. En todos los caballos, la YOH tuvo profundos efectos sobre la frecuencia y el ritmo cardiaco, la frecuencia cardíaca máxima fue superior a 100 latidos por minuto en algunos de los caballos bajo estudio. En general, los efectos de la YOH parecen ser muy variables entre los caballos, y a pesar de que actualmente no hay indicación terapéutica respecto a la administración de la YOH en caballos, se sugiere administrarla con precaución, ya que existe la posibilidad de efectos adversos impredecibles.

Jernigan *et al*. (1988), caracterizaron el perfil farmacocinético y determinaron la vida media del clorhidrato de YOH con dos dosis diferentes en caballos. En su diseño experimental, consideraron dos grupos de caballos y determinaron si la vida media varió cuando la dosis fue diferente. En el estudio se colectaron muestras de sangre en diferentes momentos antes y hasta 3 horas posteriores a la administración del fármaco. Las concentraciones séricas de YOH fueron determinadas por un método de cromatografía líquida de alta eficacia (HPLC). Para el análisis farmacocinético, se utilizó un modelo farmacocinético no compartimental utilizando la teoría estadística metodo de los momentos. El clorhidrato de yohimbina (Sigma Chemical Co., St. Louis, Missouri) se preparó como un 0.4% peso/volumen 0.075 (siete caballos) o 0.15 (cuatro caballos) mg/Kg y fueron inyectados en la vena yugular. Las dosis utilizadas se basaron en las

concentraciones para antagonizar la xilazina y la ketamina en los caballos. No hubo diferencias significativas en ninguno de los parámetros farmacocinéticos entre las dosis pequeñas y grandes de YOH. El volumen de distribución de YOH fue de 39.6±16.6 *vs*. 34.0±19.4 mL/min/kg y 4.6±1.9 *vs*. 2.7±1.0 L/kg en los caballos que recibieron dosis grandes y pequeñas respectivamente. La vida media eficaz fue de 76.1±23.1 min y 52.8±27.8 min en los caballos que recibieron dosis grandes y pequeñas de YOH. La administración de YOH no produjo cambios conductuales en los caballos, se mantuvieron relajados y sin evidencia de ansiedad. El volumen de distribución fue elevado debido a la solubilidad del fármaco en los lípidos y a su capacidad para atravesar membranas.

3. Efecto de la Yohimbina sobre parámetros farmacocinéticos, farmacodinámicos y de comportamiento farmacológico en caballos sedados con detomidina.

Heather Dimaio Knych *et al*. (2012), describieron la farmacodinamia y los efectos de la YOH en caballos sedados previamente con DET. Nueve caballos adultos fueron usados en el estudio, en los cuales se obtuvieron muestras de sangre en distintos momentos, desde antes y hasta 72 horas después de la administración del fármaco. Las muestras se analizaron mediante cromatografía líquida por espectrometría de masas y las evaluaciones de comportamiento fueron subjetivas, las cuales se realizaron durante el estudio. Además se incluyó el monitoreo de los signos de sedación, excitación y/o agitación. Los efectos del fármaco sobre el comportamiento, la frecuencia y el ritmo cardiaco, el nivel de glucosa, el volumen de paquete celular (PCV) y la concentración de proteínas plasmáticas fueron medidas. En dicho estudio se emplearon tres regímenes de dosificación. 1) 0.03 mg/kg DET (Dormosedan, Pfizer Salud Animal, Pennsylvania, EE.UU.) IV. 2) 0.2 mg/kg YOH (Yobine, Lloyd laboratorios, IA, EE.UU.) IV. 3) 0.03 mg/kg DET IV seguido por 0.2 mg/kg de YOH vía IV. Cada caballo recibió los tres tratamientos y se consideró un periodo de lavado mínimo de 1 semana entre tratamientos. Se

identificó que dos caballos mostraron signos de sedación. La YOH regulo efectivamente la frecuencia cardíaca y el porcentaje de alteraciones de la conducción atrio-ventricular, estos valores se demostraron cuando se administró la YOH 15 minutos posteriores a la administración de DET. Antes de la administración del fármaco, la frecuencia cardíaca disminuyó significativamente en todos los caballos bajo estudio. La bradicardia inducida por la DET persistió durante 1 hora.

Los niveles de glucosa fueron obtenidos, identificando hiperglucemia causada por efecto de la DET, la cual desapareció por un efecto benéfico de la YOH. Las concentraciones de glucosa en plasma aumentaron significativamente durante un máximo de 3 horas después de la administración de DET (31 mg/dL) en el grupo de los caballos tratados solamente con DET. La DET es eficaz en la inducción de la sedación con efectos pronunciados sobre los efectos cardíacos, incluyendo una notable disminución en la frecuencia cardíaca y una mayor incidencia de bloqueos de la conducción AV. Los investigadores determinaron que la administración intravenosa de YOH resulta ser eficaz para revertir los efectos sobre cardiovasculares de la DET.

Knych *et al*. (2012), describieron la farmacocinética de la DET y YOH, en el estudio se incluyeron nueve caballos adultos clínicamente sanos, cada caballo recibió tres regímenes de dosis con periodo de lavado de 1 semana entre cada tratamiento. Se recolectaron muestras de sangre y se analizó la concentración de la DET y de la YOH mediante cromatografía líquida por espectrometría de masas. Los Datos fueron analizados mediante un análisis no compartimental y otro compartimental. Las muestras de sangre se recolectaron en el momento 0 (antes de administrar DET) y 1 hora (antes de la administración del antagonista) y a los 5, 10, 15, 30, 45 minutos y 1, 1. 5, 2, 2.5, 3, 4, 5, 6, 8, 12, 18, 24, 36, 48 y 72 horas después de la administración de la DET y YOH. En el estudio se emplearon tres regímenes de dosificación. 1) 0.03 mg kg^{-1} DET (Dormosedan, Pfizer Salud Animal, Pensilvanya, EE.UU.) IV, 2) 0.2 mg/kg YOH (Yobine, Lloyd laboratorios, IA, EE.UU.) IV y 3) 0.03 mg/kg DET IV seguido por 0.2 mg/kg YOH IV 15 minutos

después. Los investigadores señalaron que la vida media de eliminación de la YOH no se afecta por la administración de la DET.

Knych y Stanley (2014), describieron los efectos de los antagonistas alfa 2-adrenérgicos de la DET cuando esta es aplicada por vía sublingual en el caballo. En el estudio se incluyeron nueve caballos sanos que fueron divididos en cuatro tratamientos, en los cuales cada caballo recibió todos los tratamientos considerando como mínimo una semana entre tratamientos. Se obtuvieron muestras de sangre y se analizaron las concentraciones de YOH, atipamezol y tolazolina mediante cromatografía líquida por espectrometría de masas. Las muestras se recogieron en el momento 0 (antes de la administración de DET) y 1 hora después de la administración de DET (antes de la administración del antagonista) y a los 5, 10, 15, 30, 45 minutos y 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 18, 24, 36, 48 y 72 horas después de la administración del antagonista. Se administraron cuatro tratamientos: 1) 0.04 mg/kg DET (Dormosedan Gel, Pfizer Salud Animal, Nueva York, EE.UU.) vía Sublingual (SL). 2) 0.04 mg/kg DET SL y 1 hora más tarde se continuó con la administración de 0.075 mg/kg de YOH (Yobine, Lloyd laboratorios, IA, EE.UU.) vía intravenosa (IV). 3) 0,04 mg/kg DET SL, una 1 hora después se administraron 4 mg/kg de tolazolina (Tolazolina, Lloyd Laboratories) IV. 4) 0.04 mg/kg de DET SL, una hora más tarde se administró 0.12 mg/kg de atipamezol (Antisedan, Salud Pfizer Animal) vía IV.

La administración de DET aumentó significativamente la prevalencia de trastornos a nivel Atrio Ventricular. La YOH efectivamente disminuye la prevalencia de los bloqueos Atrio Ventriculares. Se determinó que la DET aumentó significativamente las concentraciones de glucosa a los 45 minutos posteriores a la administración del fármaco y así se mantuvo hasta por 3 horas. Por el contrario, la administración de YOH atenuó significativamente la hiperglucemia inducida por la DET. Las concentraciones de glucosa en plasma que se registraron fueron de (111±17 y 93±14 mg/dL) a los 45 minutos y 3 horas después de la administración de la YOH.

JUSTIFICACIÓN

En el ámbito clínico de expertos en el área de equinos a nivel internacional, mucho se ha comentado sobre el uso, aplicación y efecto de fármacos como la YOH en caballos sedados previamente con DET. Entre estos hallazgos, se destacan las experiencias de médicos a nivel clínico en los que se han hecho observaciones de las respuestas clínicas y conductuales en el caballo por efecto de la DET. Sin embargo, son escasos los estudios de carácter científico realizados con pacientes equinos que permitan identificar con claridad y precisión, los efectos del fármaco en el animal y su comportamiento farmacocinético, farmacodinámico y de carácter comportamental desde el punto de vista farmacológico. En este sentido, consideramos necesario y oportuno, realizar una revisión de carácter sistemático que permita identificar de manera global y con precisión farmacológica, cuales son los efectos respecto al uso de la YOH en caballos que han sido sedados previamente con DET. En esta revisión sistemática se pretende identificar inicialmente los efectos de ambos fármacos cuando se administran solos y cuando se administran después del proceso de sedación. Además existe la intención de identificar los efectos de estos fármacos a nivel farmacocinético, farmacodinámico y de comportamiento farmacológico en pacientes a los que se les ha administrado previamente DET como un agente sedante.

HIPÓTESIS

La caracterización del efecto de la YOH sobre los parámetros farmacocinéticos y farmacodinámicos en equinos sedados previamente con DET, permitirán al clínico establecer un criterio sobre el uso adecuado de la YOH, y así poder tomar decisiones terapéuticas en pacientes equinos.

OBJETIVOS

Describir y caracterizar de manera certera y precisa los efectos farmacocinéticos y farmacodinámicos de la yohimbina en caballos sedados previamente con Detomidina a partir de una revisión bibliográfica sistemática.

Específicos

- Identificar los efectos farmacocinéticos y farmacodinámicos de la DET en el caballo.
- Identificar los efectos farmacocinéticos y farmacodinámicos de la YOH en el caballo.
- Caracterizar los efectos farmacocinéticos y farmacodinámicos de la YOH en caballos sedados previamente con DET.

MATERIAL Y MÉTODO

Diseño experimental.

Se realizó una búsqueda en PubMed (Centro Nacional de Información sobre Biotecnología, Biblioteca Nacional de Estados Unidos, Bethesda, MD) y SCOPUS (Elsevier Inteligencia Investigación) desde su creación el 26 de mayo de 2015. En la revisión se incluyeron estudios experimentales que involucraron el analisis de los parámetros farmacodinámicos y farmacocinéticos en equinos clínicamente sanos tras la administración de la DET por vía enteral o parenteral. También se incluyeron los estudios experimentales que determinaron la farmacocinética, la farmacodinamia y el perfil farmacológico de la YOH en caballos. Finalmente se consideraron los estudios experimentales que abordaron el efecto de la YOH sobre la farmacocinética, farmacodinámica y parámetros de comportamiento en el caballo sedado previamente con DET.

El resultado de la búsqueda, permitió obtener una determinada cantidad de estudios científicos, de los cuales se realizó una selección de las investigaciones enfocadas específicamente a evaluar los efectos de la DET, YOH y de la YOH cuando previamente se administró DET. Los documentos obtenidos fueron el resultado de una revisión y análisis de los títulos, y se eliminaron manuscritos duplicados y aquellos estudios que evaluaron los efectos de otros fármacos alfa-2 adrenérgicos agonistas o antagonistas en el caballo, distintos a la DET y YOH. También se excluyeron aquellos documentos que abordaron especies animales distintas a la equina.

Posteriormente se inició con el análisis de los documentos que consideraron el uso de la DET en equinos, posteriormente se revisarón los artículos que incluyeron la administración de la YOH y finalmente, se analizarón los documentos que evaluaron el efecto de la YOH en pacientes equinos previamente sedados con DET. En los tres casos, el primer criterio de análisis consistió en evaluar las variables sexo, fin zootécnico, edad, dosis, presentación farmaceútica, vía de administración, efectos clínicos, cambios en el comportamiento, entendiendo por

estos, los parámetros cardíacos y sanguíneos, además de los parámetros farmacocinéticos y farmacodinámicos.

El artículo de carácter científico resultado de la revisión sistemática que se basa en los efectos de la YOH sobre parámetros farmacócineticos, farmacodinámicos y de comportamiento farmacológico en caballos sedados con DET se adecuo a las instrucciones a los autores de la revista indexada Journal of Equine Veterinary Science (JEVS). A continuación se describen las características de la guía a los autores de esta revista, las cuales se encuentran publicadas en su portal.

Guía de autor:
General

Journal of Equine Veterinary Science (JEVS) is an international publication designed for the practicing equine veterinarian, equine researcher, and other equine health care specialists. Published monthly, each issue of *JEVS* includes original research, reviews, case reports, short communications, and clinical techniques from leaders in the equine veterinary field, covering such topics as laminitis, reproduction, infectious disease, parasitology, behavior, podology, internal medicine, surgery and nutrition. *JEVS* is also an official publication of the Equine Science Society.

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A systematic review of experimental studies of the effects of yohimbine on pharmacokinetic, pharmacodynamic and behavioural parameters in horses sedated with detomidine

Short title: Yohimbine effects on pharmacokinetic, pharmacodynamic and behavioural parameters in horses sedated with detomidine

S. Recillas-Morales[a], E. Osornio-Plata[a], J. A. Ibancovichi-Camarillo[a], J. M. Victoria-Mora[a], Moisés Cipriano Salazar, P. Sánchez-Aparicio[a*]

[a]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.

*Corresponding author: El Cerrillo Piedras Blancas, Toluca, Estado de México C.P. 50090 Tel-fax 0052 (722) 2965548 ext 126 pedrosanchezaparicio0@gmail.com

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, pharmacodynamics, and behavioural parameters in horses sedated with detomidine. A literature search was made on PubMed[1] and SCOPUS[2] 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. Aditionally, 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 physiologics effects of YOH when administered after DET to reverse the behavioural and physiological effects of DET. The

[1] PUBMED: National Center for Biotechnology Information, United States national Library, Bethesda, MD.
[2] SCOPUS: Elsevier Research Intelligence.

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 therapeutic and regulatory prospective. They demonstrated intravenously administered DET is effective in sedation with effects on cardiovascular effects.

Key words: Detomidine, Yohimbine, Pharmacokinetic, Pharmacodynamics, Behavioural change.

Introduction

There is a wide group of alpha-2 adrenergic adrenoreceptor agonists such as xylazine, detomidine (DET)[3], 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 (Jochle & Hamm 1986; Salonen *et al*., 1989), and is characterized by rapid distribution and metabolism to two main metabolites with subsequent elimination (Knych *et al*., 2012). DET is commonly used in equine medicine for procedures requiring sedation, chemical restraint or analgesia and is most commonly administered parenterally (Kaukinen *et al*., 2010; DiMaio and Stanley, 2011; Knych *et al*., 2012; Knych and Stanley, 2014; Vainionpää *et al.*, 2013). The effects of DET on the pharmacokinetics and pharmacodynamics parameters in the horse following either intravenous (IV)[4] or intramuscular (IM)[5] administration have been well described (Salonen *et al.*, 1989; Grimsrud *et al*., 2009; Hubbel *et al*., 2009; Mama *et al*., 2009; DiMaio and Stanley, 2011).

Alpha-2 adrenergic antagonists are often used to reverse the sedative, cardiovascular depressant (Knych *et al*., 2012) and central nervous system (CNS) effects of alpha-2 adrenergic receptor agonists following IV or IM administration. The three antagonists most commonly used in veterinary medicine are yohimbine (YOH)[6], atipamezole and tolazoline.

[3]Det: Detomidine is alpha-2 adrenergic adrenoreceptor agonists.
[4] IV: Intravenous
[5] IM: Intramuscular
[6] YOH: alpha-2 receptor antagonist.

In equine medicine, the only FDA[7] approved alpha-2 adrenergic antagonist is tolazoline (Knych & Stanley 2014). YOH is an indole alkaloid derived from several biological or botanical sources, including the bark of the *Pausinystalia yohimbine* tree and the Rauwolfia root (Dimaio Knych *et al*., 2011; Dimaio Knych and Stanley, 2011). YOH enhances sympathetic outflow neurotransmitter, norepinephrine. It is a potent antagonist of centrally and peripherally located alpha-2 receptors in humans and many animal species (Kollias-Baker *et al*., 1993; Ramseyer *et al*., 1998; Hubell & Muir 2006). In veterinary medicine, YOH is almost exclusively used to reverse the sedative or cardiovascular effects of the alpha-2 receptor agonists, especially DET (Dimaio Knych *et al*., 2011). In horses, YOH has been shown to antagonize the ventricular bradycardia and atrioventricular (AV)[8] conduction disturbances observed following administration of DET (Knych *et al*., 2012). YOH appears to be widely distributed, as evidenced by a large volume of distribution and rapid clearance following IV administration to horses (DiMaio Knych *et al.*, 2011). In humans, YOH is rapidly metabolised by the cytochrome P450 enzymes to two hydroxyl-yohimbine metabolites (LeCorre *et al.*, 1999). To our knowledge, there are no reports in the literature regarding YOH metabolites in the horse (Dimaio Knych *et al*., 2011). Hydroxylation is the major pathway for the 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 hase yet to be elucidated (Knych *et al.*, 2012). Based on the evidence of experimental studies on its efficacy, the aim of this study was to systematically review the safety of this drug in horses and the effect of YOH over pharmacokinetic, pharmacodynamics, and behavioural parameters in horses sedated with DET.

Method

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 26 May, 2015. In the review, experimental studies involving the evaluation of the effects of DET administered enterally or parenterally in

[7] FDA: Food and Drug Administration.

[8] AV: Atrio-ventricular

horses on clinics pharmacodynamics and pharmacokinetics parameters were inlcuded. 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 behavioural 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, and pharmacokinetics and pharmacodynamics effects. Of the 26 retrieved studies, information was obtained from 14 selected reports (Dimaio Knych *et al.*, 2011; Dimaio Knych *et al*., 2012; Di Maio Knych & Stanley 2011; Di Maio Knych *et al*., 2011; Jernigan *et al*., 1988; Kaukinen *et al*., 2010; Kaukinen *et al*., 2011; Knych *et al.*, 2012; Knych & Stanley 2014; Mama *et al*., 2009; Vainionpää *et al.*, 2013; Salonene *et al*., 1989; Jochle & Hamm, 1986; Hubbel *et al*., 2009) .

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 (Dimaio Knych *et al*., 2012). 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)[9] administration indicated slight differences in absorption and plasma DET concentrations.

[9] SL: Sublingual

Carboxydetomidine and hydroxydetomidine were detected in urine samples. The elimination of DET is differed between sedentary and active horses. For the second experiment, AUC[10] and Cmax[11] show 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 species (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 h, 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 pharmacokinetic or physiologic effects of the YOH when administered after the DET to reverse the behavioural 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, they noted important implications, from both therapeutic and regulatory perspectives. These studies demonstrated that intravenously administered DET was effective in sedation, but with negative effects on cardiovascular system (Table 3).

[10] AUC: Area under the curve.
[11] C_{max}: Maximal plasma concentration.

The behavioural effects of the alpha-2-receptor antagonist, YOH, appears to be highly variable between horses. Regardless of the variability in response when administered alone, YOH was effective in resolving naturally occurring as well as DET-induced AV conduction disturbances.

Discussion

In relation to administration of DET in horses, it has been shown individual variability in pharmacokinetics parameters can be attributed to factors such as dose, loss of drug, dose lost via expulsion from the mouth or swallowing, or DET metabolism by enzymes in the GI tract wall or first-pass effects (di Maio Knych & Stanley, 2011). DET is a lipophilic weak base with an acid dissociation constant (Pka) of 7.2; thus, absorption is favoured in an alkaline environment, mouth and small intestine included. Oral cavity in horses tends to be alkaline, which makes it possible that slight differences. SL administration of DET gel was well tolerated by horses, barely perceptible diffuse erythema of the oral mucous membranes was reported in horses formulation. Salonen *et al*. (1989) indicated that due to extensive first-pass metabolism, the drug does not reach the systemic circulation. SL administration of DET is apt to reach the heart before distribution to the brain because the mucosal capillaries drain directly into the jugular veins, which run directly to the heart. However, blood must travel throughout the body before reaching the brain (di Maio Knych & Stanley, 2011).

The highest plasma DET concentration was 168±83.7 ng/mL, which indicated that the drug was absorbed well from the SL mucosa into the systemic circulation. In SL administration, drainage from the submucosal region was via the jugular vein. In this respect, it is important to know whether if collection of samples was via a jugular vein immediately following absorption. Although DET appeared to be absorbed well following SL administration, there was a great degree of variability in C_{max} and T_{max} among horses. The C_{max} differed substantially as a result of the site used for collection of samples and the time after drug administration (di Maio Knych & Stanley, 2011).

The elimination of drugs has been reported to differ between sedentary and active horses (di Maio Knych & Stanley, 2011). Previous studies have reported the elimination half-life of DET to be 26 to 71 minutes (Knych *et al*., 2012). Vainionpää *et al*. (2013) reported a

half-life of 37 minutes, resulting in observations analogous with the previously reported findings. The mean half-life of the elimination of DET following SL administration reported by di Maio Knych & Stanley (2011) was 1.5±1 hours and longer than after IV administration which was 26.4 minutes. Terminal half-life of DET was longer after SL than after IM administration, but sedation lasted longer after IM administration (Kaukinen *et al*., 2011). This can be explained by the lesser bioavailability of DET as a oromucosal gel, compared to the injectable solution, reflecting the dose-dependent duration of DET sedation (Kamerling *et al*. 1988).

DET administration SL and IV produced profound sedation in all horses studied as evidenced by an observable decrease in chin-to-ground distance (Dimaio Knych *et al*., 2012; di Maio Knych & Stanley 2011)). Kaukinen *et al.* (2011) reported that sedation started sooner after IM administration than after the administration of the oromucosal gel. This can be explained by the lower mean C_{max} and the longer mean t_{max} after SL administration via IM injection, indicating that DET is absorbed more rapidly when given IM to horses. DET produces cardiovascular side effects and ataxia (Dimaio Knych *et al*., 2012); in the study of Kaukinen *et al*. (2011); However, those effects were less pronounces after SL administration. No adverse events were observed in the oromucosal gel group, with the exception of only adverse effect after IM treatment was mild bradycardia observed in one horse. It has been shown that some horses exhibit signs of ataxia (stable but swaying lightly) between the 40 to 90 minute assessment points after oromucosal gel administration. The bradycardia and conduction disturbances observed following DET administration may be attributable to a centrally mediated decrease in peripheral sympathetic tone, presynaptic inhibition of norepinephrine release from fibres innervating the heart, or enhancement of vagal reflexes (di Maio Knych & Stanley 2011).

Dimaio Knych *et al*. (2012) noted a marked increase in glucose concentrations 30 minutes post-DET.. Hyperglycemia has been detected in horses (Dimaio *et al.*, 2012; Knych & Stanley 2014) and has been attributed to inhibition of insulin release from the pancreas beta cells. di Maio Knych and Stanley, (2011) reported no apparent pattern for glucose concentrations over the 6 hours sample collection period although there was a large variability among horses, suggesting the possibility of a non-drug-related phenomenon and simply a result of food being withheld from the horses before and throughout the glucose-

monitoring period. There is need for additional studies to characterize these effects in horses. In relation to the administration of YOH, it has been shown than there are variation in the pharmacokinetics parameters. It is possible that the differences observed were caused by age, physical condition, intrinsic clearance, amount of body fat, and tissue blood flow (Jernigan *et al*., 1988). The pharmacokinetic parameters calculated for YOH, as the large volume of distribution, was due to its rapid dispersed (2.0 - 5.7 L/Kg). The lipid solubility and lipophilic compound of YOH may allow it to cross the blood-brain barrier to a potential site of action in the CNS. The same researchers indicated extensive tissue distribution and ability to cross membranes, which helps to explain its duration and action when used for arousal from anesthesia.

The mean half-live of YOH was 86.6 min in horses given a small dose of 0.075 mg/Kg and 57.8 minutes in horses given a large dose of 0.15 mg/Kg (Jernigan *et al.,* 1988). The relatively long serum half-life and mean residence time of YOH indicated that this would be present in the body until after most anesthetics or sedatives were no longer effective. In steers and dogs, the half-life ranged from 87 to 164 minutes, respectively. In other studies, the investigators were able to detect YOH in plasma samples at 12 hours postdrug administration and have demonstrated that plasma versus time concentration data were best described by a two-compartment open model (Dimaio Knych *et al.,* 2011; Dimaio Knych & Stanley, 2011). They suggest that it was a result of sequestration and slow release over time.

The clearance and terminal elimination half-life can differ substantially between studies because of the ability to collect and detect YOH in plasma samples. However, renal blood flow may be the limiting factor in the clearance of YOH in the form of metabolite. However, additional studies are necessary to be conclusive. The large volume of distribution coupled with the slower systemic clearance is the reason for the longer terminal elimination half-life (Dimaio Knych *et al*., 2011).

Based on analysis of plasma and urine samples in horses, it has been reported that hydroxylation also appears to be the predominant pathway for elimination of YOH. One metabolite was hydroxy-yohimbine in urine samples (Dimaio Knych *et al*., 2011). YOH is eliminated by a first-order process, and it is possible that this could have a very prolonged half-life with small serum concentrations due to release of the drug from tissue reservoirs

(Dimaio Knych *et al*., 2011). A more sensitive YOH assay and determinations of renal and hepatic clearance are necessary to define further a possible prolonged elimination of YOH (Dimaio Knych *et al*., 2012).

YOH has been shown to decrease the incidence of naturally occurring nonpathological AV conduction disturbances following IV administration in horses (Di Maio Knych & Stanley, 2011; Dimaio Knych *et al.,* 2011). Similar effects were reported when administered alone, with maximal resolution of AV blocks occurring within 2 minutes of administration (Dimaio Knych *et al.*, 2012).

The clearance and $t_{1/2el}$[12] of YOH following SL DET administration (22.9 mL minute^{-1} kg^{-1}), 1.87 hours ($t_{1/2el}$) reported on a study (Knych & Stanley 2014) differs from previous report of YOH disposition following IV DET administration (6.8 mL minute^{-1} kg^{-1}); 4.4 hours ($t_{1/2el}$) (Knych *et al*., 2012). Knych & Stanley (2014) reported total YOH plasma clearance to ranged from 18.6 to 41.2 mL minute^{-1} kg^{-1}, indicating that it is a high hepatic extraction ratio drug with extra hepatic metabolism. Similar findings were reported in horses (di Maio Knych & Stanley 2011; Knych *et al*., 2012).

DET IV administration in horses produced a decreased heart rate of 15 bpm. This maximal change was observed at 2 minutes postdrug administration, and it is likely attributable to large concentrations of drug delivered to the heart. The heart rate increased 16 bpm in horses receiving YOH subsequent to DET (Dimaio Knych *et al.*, 2012). This change was slightly more rapid, 2 minutes post-YOH administration than that observed when YOH was administered alone. Antagonism of the DET-induced cardiac effects was most pronounced with YOH and tolazoline and least with atipamezole (Knych & Stanley 2014). In addition to their effects on heart rate, administration of DET has been associated with AV conductions blocks an increasing incidence of AV blocks (Dimaio Knych *et al.*, 2012) following enteral administration. It was reported 48% of the AV signals were blocked following DET administration alone, with the maximal number of conduction blocks occurring by 5 min post-DET administration. The bradycardia and the conduction disturbances may be due to a centrally mediated decrease in peripheral sympathetic tone, presynaptic inhibition of norepinephrine release from fibres innervating the heart or the enhancement of vagal reflexes. Dimaio Knych *et al.* (2012) noted that DET induced

[12] $t_{1/2el:}$ terminal elimination half-life.

conduction blocks immediately post YOH administration. The percentage of AV conduction disturbances returned to pre-DET values within 2 minutes of YOH administration.

DET administration following subsequent administration of YOH generates differences in behaviour, including a return toward baseline chin-to-ground distances, which were observed within 3 to 5 minutes of YOH administration. This initial period of arousal was followed by 10 minutes of sedation. Although the animals were obviously sedate, signs were less pronounced than those observed upon initial administration of DET (Dimaio Knych *et al.*, 2012). Horses treated with YOH showed signs of alertness within 5 minutes followed by a return to sedation (Knych & Stanley 2014).

Plasma glucose concentrations increased following DET administration which decreased toward baseline much faster in groups that received YOH subsequent to DET as compared to horses that did not receive the alpha-2 adrenergic receptor antagonists. It is possible that the faster return to baseline glucose concentrations was due to displacement of DET from receptors. This is supported by the lack of effect of YOH on plasma glucose concentrations (Dimaio Knych & Stanley 2011), suggesting that YOH by itself had no effect on plasma glucose concentrations (Dimaio Knych *et al*., 2012). Probably, the inhibition of insulin release was mediated through postsynaptic adrenoreceptors located on the pancreatic cells, specifically the alpha-2 adrenergic subtype and that of alpha-2 adrenergic receptor antagonists, such as YOH, blocking the hyperglycemic effect of alpha-2 adrenergic agonists (Oda *et al.,* 1991 in (Knych & Stanley 2014)). YOH decreased DET-induced hyperglycaemiadue likely to cessation of DET-induced effects as opposed to being due to atipemezole. The antihyperglycaemic effect may be dose dependent, and a higher dose of atipamezole may be necessary to reverse the alpha-2-agonistic effect and in turn result in decreased plasma glucose concentrations (Knych & Stanley 2014).

DET pronounced generating cardiac effects, including a notable decrease in heart rate and an increased incidence of AV conduction blocks. Conversely, the behavioural effects of the alpha-2 receptor antagonist, YOH, appears to be highly variable between horses. Regardless of the variability in response when administered alone, YOH was effective in resolving naturally occurring as well as DET-induced AV conduction disturbances. Overall, YOH was effective in reversing the behavioural and cardiovascular effects of IV

administered DET. The antagonistic effects of YOH on HR and rhythm changes and behavioural effects elicited by SL-administered DET appear to be incomplete.

Conclusion

In recent years, DET administration in horses has become popular, in part, due to the existence of a pharmaceutic form supplied as a gel for the oral administration coupled with a YOH administration increment to reverse the DET effects. Although YOH is not an FDA-approved drug for the equines and it is indicated as an alpha-2 antagonist, YOH has been used for this purpose. Scientific evidence shows multiple variation of pharmacodynamics, pharmacokinetic, and cardiovascular parameters for individual horses; therefore, YOH should be used cautiously in order to avoid serious and unpredictable undesired side effects. Until the causes of variation between individual horses is resolved, it is important to determine if the source of variation relays just in the individuality of each animal or if there is a relationship with determinant factors such as age, sex, body fat or physical condition, renal clearance, or any other condition.

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Table 1. Effects of detomidine in horses on clinics, pharmacodynamics or pharmacokinetics parameters.

Authors	Objective	Experimental model	Dose and administration route	Pharmacokinetics or pharmacodynamics changes	Conclusion
(di Maio Knych & Stanley, 2011)	Characterise pharmacokinetics and pharmacodynamics of DET gel administered in horses before competition.	Twelve healthy fit actively competing adult Thoroughbred racehorses were included. Horses were assessed as healthy and free of cardiovascular disease. Horses did not receive any sedative or analgesic agents; they continued to be exercised throughout the sample collection period, except for the	0.04 mg/kg DET (Dormosedan Gel, Pfizer Animal Health, New York, NY) administered SL.	Highest plasma DET concentration was 168±83.7 ng/mL. Peak DET plasma concentration was rapidly with mean±SD Tmax[13] at 36±10 min after drug administration. Half-life of elimination was 1.5±1 h. Concentrations of DET as well as its metabolites in urine samples were below	DET gel appeared to have been absorbed well from the SL mucosa into the systemic circulation. The half-life of elimination following SL administration was prolonged, compared with IV or IM administration, with detectable concentrations of DET or its metabolites in plasma for up to 24 hours after administration.

[13] T_{max}: Time of maximal plasma concentration

		day of drug administration, during which no exercise was performed.		the limit of detection LOD[14] by 3 days after administration.	
(Kaukinen *et al.*, 2011)	Determine the absorption, bioavailability and sedative effect of DET administered to horses as an oromucosal gel compared to IV and IM administration DET injectable solution.	Nine healthy horses were given (five Standardbreds and four warmbloods) were used. Each horse was allocated by computer-generated randomisation to receive DET via each route in a randomised order. Blood samples were collected before and after drug administration for the	40 µg⁄kg DET route IV, IM or administered under the tongue with a 7-day wash-out period between treatments. DET was given as a bolus into the jugular vein, as an IM injection into the neck muscles (Domosedan 10	Slow absorption leads to fewer and less pronounced adverse effects than the more rapid absorption after IM injection. Maximum concentration for DET given via SL route was lower than following IM administration (geometric mean 4.16 *vs.* 11.16 ng/mL) and the t_{max} was longer	Less DET is absorbed when given SL than when given IM, because part of it does not reach the circulation. SL administration of DET oromucosal gel at 40 µg⁄kg produces safe sedation in horses. Slow absorption leads to fewer and less pronounced adverse effects than the more rapid absorption after IM injection.

[14] LOD: Limit of detection.

		measurement of DET concentrations in serum. Pharmacokinetic variables were estimated for each horse and each dosing occasion.	mg⁄mL solution, Orion Pharma, Espoo, Finland), or as an oromucosal gel (Domosedan Gel 7.6 mg⁄mL, Orion Pharma, Turku, Finland).	(1.83 *vs.* 1.06 h).	
(Vainionpää *et al.*, 2013)	Investigate plasma drug concentrations and the effect of the peripherally acting alpha-2-adrenoceptor antagonist MK-467 (L-659′066) on sedation, HR and gut motility in horses	Six healthy Finnhorse mares were used. They were not pregnant and in winter anoestrus. The depth of sedation, intestinal sounds, attitude, posture, height of the head, eyelid aperture and movement of the ears were scored before and after treatment.	10 μg⁄kg^{-1} DET (Equisedan, Vetcare, Finland) was administered IV alone and in combination with MK467 250 μg⁄kg^{-1} (Merck & Co., Inc., NJ, USA) IV in a	AUC_{sed} was significantly higher with DET than DET+MK467, but maximal sedations scores did not differ significantly between treatments. MK467 lowered the AUC of the plasma concentration of DET, and increased its	MK467 prevented DET induced bradycardia and intestinal hypomotility. MK467 did not affect the clinical quality of DET-induced sedation, but the duration of the effect was reduced, which may have been caused by the effects of MK467 on the plasma concentration of DET. MK467 may be useful

	sedated with IV DET.	An electrocardiogram was recorded continuously, HR and rhythm were evaluated before and after of the injection. Blood was collected after drug administration.	randomised, crossover design with a minimum of 14 days between treatments.	volume of distribution and clearance. A significant reduction in HR was detected after DET. HR was significantly higher after DET-MK467 than DET. DET induced intestinal hypomotility, was prevented by MK467.	clinically in the prevention of certain peripheral side effects of DET in horses.

Table 2. Effects of yohimbine in horses on clinics, pharmacodynamics or pharmacokinetics parameters.

Authors	Objective	Experimental model	Dose and administration route	Pharmacokinetics, pharmacodynamics or behavioural changes	Conclusion
(Dimaio Knych *et al*. 2011)	Determine the pharmacokinetic profile of IV administered YOH in horse.	Eight healthy non-medicated adult horses including seven thoroughbreds and one Standardbred. Blood samples were collected prior and at various times up to 72 h post drug administration. Data analysed using both non-compartmental and compartmental analysis.	0.12 mg/Kg YOH (Yobine, Lloyd Laboratories, Shenandoah, IA, USA) an IV dose administered slowly over 1 min.	Peak plasma concentration was 114.5±31.8 ng/mL, occurred at 0.09±0.03 h. Systemic clearance and steady-state volume of distribution were 13.5±2.1 mL/min/Kg and 3.3±1.3 L/Kg following non-compartmental analysis. Terminal elimination half-life was 4.4±0.9 h. For compartmental	They were able to detect YOH in plasma samples at 12 h post drug administration, suggests that YOH is characterised by prolonged elimination, most likely as a result of sequestration and slow release over time. A dose of 0.12 mg/Kg IV to horse has a large volume of distribution. Large volume of distribution coupled with slower systemic clearance determined support the

				analysis, plasma YOH *vs.* time data were best fitted to a two compartment model, systemic clearance and steady-state volume of distribution of YOH were 13.6±2.0 mL/min/Kg and 3.2±1.1 L/Kg.	longer terminal elimination half-life.
(H. K. Dimaio Knych, Steffey, and Stanley 2011)	Investigate the pharmacokinetics and pharmacodynamics of YOH when administered IV to horse.	Nine healthy non-medicated adult horses including 8 Thoroughbreds and 1 Standardbred A minimum of 1 week was allowed to elapse between administrations of additional doses to the same horse.	0.1, 0.2, and 0.4 mg⁄Kg YOH (Yobine; Lloyd Laboratories, Iowa), IV administered slowly over 1 min.	Peak plasma concentration was 106.0±28.9, 156.7±34.3 and 223.0±44.5 ng/mL for doses of 0.1, 0.2, and 0.4 mg⁄Kg, occurred at 0.09±0.03 hours. Systemic clearance and steady-state volume of distribution	Behavioural responses following YOH administration are highly variable between horses. YOH had profound effects on heart rate and rhythm, with maximal heart rates exceeding 100 beats/minute in some horses. YOH should be used with

	Blood samples were collected prior and at various times up to 24 h post drug administration, were analysed using liquid chromatography–mass spectrometry. Data analysed using both non-compartmental and compartmental analysis.	were 12.0, 12.2 and 17.9 mL/min/Kg and 2.1, 2.6 and 2.9 L/kg following non-compartmental analysis. Terminal elimination half-life was 43.6, 3.3 and 2.9 h for doses of 0.1, 0.2, and 0.4 mg/Kg. For compartmental analysis, plasma YOH *vs.* time data were best fitted to a two compartment model, systemic clearance and steady-state volume of distribution of YOH were 11.1 mL/min/Kg and 2.3 L/kg.	caution as there is the potential for unpredictable harmful effects.

(Jernigan *et al*. 1988)	Characterise the pharmacokinetics profile and determine the half-life of YOH with two dosages in horses.	Two groups of horses (11 Crossbred horses; seven geldings and four mares) were used to determine whether the half-life varied when the dose was changed. Blood samples were collected prior and at various times up to 3 h post drug administration. For pharmacokinetic analysis, a non-compartmental approach using statistical moment theory was used.	YOH hydrochloride (Sigma Chemical Co., St. Louis, Missouri) was prepared as a 0.4% w/v. 0.075 (seven horse) or 0.15 (four horse) mg⁄Kg was injected into the apposite jugular vein.	No significant differences in any of the pharmacokinetic parameters between doses of YOH. Systemic clearance and steady-state volume of distribution of YOH were 39.6±16.6 *vs*. 34.0±19.4 mL/min/Kg and 4.6±1.9 *vs*. 2.7±1.0 L/kg in horses given doses. The mean effective half-life for YOH was 76.1±23.1 min and 52.8±27.8 min in horses given small or large doses of YOH.	The large volume of distribution, due to YOH's lipid solubility and ability to cross membranes was seen. Their results indicated relatively long serum half-live of YOH in horses.

Table 3. Effects of yohimbine on changes in behaviour, pharmacodynamics or pharmacokinetics parameters of detomidine in the horse.

Authors	Objective	Experimental model	Dose and administration route	Pharmacokinetics, pharmacodynamics or behavioural changes	Conclusion
(Heather K. Dimaio Knych, *et al*., 2012)	Describe pharmacodynamics effects of DET and YOH when administered alone and in sequence.	Nine adult horses (eight Thoroughbreds and one Standardbred). Blood samples were obtained prior and at various times up to 72 h post drug administration. Plasma samples were analysed using liquid chromatography–mass spectrometry. Behavioural effects, heart rate and rhythm, glucose, packed cell	Three dose regimens were employed. 1) 0.03 mg kg^{-1} DET (Dormosedan, Pfizer Animal Health, PA, USA) IV. 2) 0.2 mg kg^{-1} YOH (Yobine, Lloyd Laboratories, IA, USA) IV. 3) 0.03 mg kg^{-1} DET IV	Heart rate decreased significantly for all horses, following DET administration. The maximal decrease (15 bpm) was present 2 min post-DET. Bradycardia persisted for up to 1 h post-DET administration. YOH returned heart rate and the percent of AV conduction disturbances to pre-DET values when	DET is effective in inducing sedation with pronounced effects on cardiac effects, including a notable decrease in heart rate and an increased incidence of AV conduction blocks. IV administration of YOH is effective in reversing the behavioural and cardiovascular effects of IV administered DET. YOH induced sedation, bradycardia, AV heart

		volume (PCV) and plasma proteins were monitored.	followed 15 min later by 0.2 mg kg^{-1} YOH IV. Each horse received all three treatments with a minimum of 1 week between treatments.	administered 15 minutes post-DET. Plasma glucose concentrations increased by 30 min post-DET administration, both for the DET only and the DET+YOH dose groups (44 and 32 mg/dL^{-1}).	block and hyperglycaemia.
(Knyche*t al*., 2012)	Describe the pharmacokinetics of DET and YOH when administered in combination.	Nine adult horses (eight Thoroughbreds and one Standardbred) were studied. Each horse received all three dose regimens with a minimum of 1 week in between subsequent regimens. Blood samples were	Three dose regimens were employed. 1) 0.03 mg kg^{-1} DET (Dormosedan, Pfizer Animal Health, PA, USA) IV. 2) 0.2 mg kg^{-1} YOH	The Cl system and V_d of DET were not significantly different for either treatment. The maximum measured DET concentrations were 76.0 and 129.9 ng mL^{-1} for the DET and DET-YOH treatments,	DET increases plasma YOH concentrations and decreases the Cl and V_d compared to administration of YOH by itself. The elimination half-life of YOH remained unaffected when administered subsequent to

	collected at time 0 (immediately prior to DET administration) and at 1 h post DET administration (immediately prior to antagonist administration) and at 5, 10, 15, 30, 45 min and 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 18, 24, 36, 48 and 72 h post administration of the DET and YOH treatment. Plasma was analysed for DET and YOH concentrations by liquid chromatography-mass spectrometry. Data were analysed using	(Yobine, Lloyd Laboratories, IA, USA) IV. 3) 0.03 mg kg^{-1} DET IV followed 15 min later by 0.2 mg kg^{-1} YOH IV.	respectively. Systemic clearance and V_d of DET were not significantly different for either treatment. There was a significant increase in the maximum measured YOH plasma concentrations from YOH (173.9 ng mL^{-1}) to DET-YOH (289.8 ng mL^{-1}). Both the Cl and V_d for YOH were significantly less (6.8 mL $minute^{-1}$ kg^{-1} and 1.7 L kg^{-1}) for the DET-YOH as compared to the YOH treatments (13.9 mL	DET. However, the increased plasma concentrations in the presence of DET has the potential to cause untoward effects and therefore further studies to assess the physiologic effects of this combination of drugs are warranted.

		both non-compartmental and compartmental analysis.		minute^{-1} kg^{-1} and 2.7 L kg^{-1}).	
(Knych & Stanley 2014)	Describe the effects of alpha-2-adrenergic receptor antagonists on the pharmacodynamics of SL DET in the horse and evaluate effects of alpha-2-adrenergic receptor antagonists in reversing its sedative and	Nine healthy horses consisting of eight Thoroughbreds and one Quarter Horse were studied. Four treatment groups were studied and each horse received all treatments with a minimum of 1 week between treatments. Blood samples were obtained and plasma analysed for YOH, atipamezole and tolazoline concentrations by liquid	Four treatments were administered 1) 0.04 mg kg^{-1} DET (Dormosedan Gel, Pfizer Animal Health, NY, USA) SL. 2) 0.04 mg kg^{-1} DET SL followed 1 h later by 0.075 mg kg^{-1} YOH (Yobine, Lloyd Laboratories,	DET administration significantly increased the prevalence of AV[15] conduction disturbances. YOH effectively decreased the prevalence of the AV blocks initially, although the number of AV blocks increased again by 1–2 hours for all drugs. DET significantly increased glucose concentrations by 45 min post	At the doses of 0.075 mg kg^{-1}, the effects of YOH on cardiac and behavioural effects elicited by SL administration of DET are transient and incomplete.

[15] AV: Atrioventricular.

	cardiovascular effects.	chromatography-mass spectrometry. Samples were processed according to the methodology described by (Knych & Stanley 2014).	IA, USA) IV. 3) 0.04 mg kg^{-1} DET SL followed 1 h later by 4 mg kg^{-1} tolazoline (Tolazine, Lloyd Laboratories) IV. 4) 0.04 mg kg^{-1} DET SL followed 1 h later by 0.12 mg kg^{-1} atipamezole (Antisedan, Pfizer Animal Health) IV.	administration with concentrations remaining elevated for 3 h (121±11 and 127±43 mg dL^{-1}). YOH significantly attenuated the DET induced hyperglycaemia.

CONCLUSIÓN

La yohimbina ejerce efectos benéficos sobre los parámetros farmacocinéticos y farmacodinamicos en equinos sedados previamente con detomidina, lo que permite revertir efectivamente los efectos adversos generados por la Detomidina. No obstante, es necesario se realicen más investigaciones con el uso de estos agonistas y antagonistas, pues aun no quedan claros los efectos de ambos sobre los niveles de glucosa en el paciente además de los efectos sobre el comportamiento de los equinos.

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