Induction of general anaesthesia by blowpipe darting in a fractious companion horse

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TITLE OF CASE ***Do not include "a case report"***

Induction of general anaesthesia by blowpipe darting in a fractious companion horse.

SUMMARY ***Up to 150 words summarising the case presentation and outcome (this will be freely available online)***

A fractious nine-year-old, 520 kg, castrated Swiss Warmblood was presented with a history of anorexia, progressive weight loss and mild hind-limb lameness. Because of its temperament, standard physical examination was considered to be only feasible under general anaesthesia. For safety reasons, general anaesthesia was planned to be induced by blowpipe darting. Two attempts are described and discussed in the present report. The first attempt, using a combination of medetomidine and tiletamine-zolazepam, was unsuccessful. Conversely, detomidine combined with butorphanol, followed by a second dart of detomidine and tiletamine-zolazepam, proved to be adequate to induce anesthesia. Factors that could have influenced the outcome, such as different therapeutic approach, drug protocol and dosages, stress level or genetic mutations, are presented and discussed.

BACKGROUND ***Why you think this case is important – why did you write it up?***

Induction of general anaesthesia by remote delivery is an uncommon practice in domestic horses. Nevertheless, this technique might represent the most suitable option for administering anaesthetic drugs in a safe and effective way to animals with a fractious temperament.

Blowpipe darting, a simple and practical remote delivery method, allows precise dart injection when within a few meters of an animal by experienced personnel. The lower dart velocity when compared to compressed air projectors or gunpowder cartridge rifles, minimizes the risk of impact tissue trauma. [1] For these peculiarities, blowpipe darting can be seen as an adequate choice to deliver drugs avoiding animal handling in clinical settings.

The ideal drug combination for remote immobilization must be effective and safe. It should also be concentrated enough that the volume does not exceed the dart capacity, non-irritant to allow intramuscular administration, provide rapid and smooth onset of action and be reversible. A number of different drugs and drug combinations have been described for chemical immobilization of non-domestic equids. Etorphine, a highly potent opioid, is one of the most commonly used drugs for this purpose;[2-3] succinylcholine, a depolarizing neuromuscular blocking agent, has been described for the immobilization of feral horses;[4] ketamine-medetomidine has been reported for Przewalski's horses and "Judas donkeys";[5,6] while tiletamine-zolazepam (TZ) for feral horses, Przewalski's horses and zebras.[7–9]

To our knowledge, no drug combinations and effective dosages have been reported for intramuscular induction of general anaesthesia in fractious companion horses so far. In the present report, two consecutive attempts to induce general anaesthesia through remote delivery of sedatives and anaesthetics in a fractious domestic horse are described. While the first attempt failed, the second was successful. Potential reasons for failure and success are presented and discussed.

CASE PRESENTATION ***Presenting features, clinical and environmental history***

A nine year old, castrated male, Swiss Warmblood, and of estimated weight 520 kg, was presented to the Swiss Institute of Equine Medicine (ISME) with a history of anorexia, progressive weight loss and mild hind-limb lameness. The horse was known for its fractious temperament and had a history of highly aggressive reactions towards medical interventions and specifically towards injections. This has been noticed since the very early age but was exacerbated after surgical castration. Previously, the horse had been anaesthetized at the same hospital for sarcoid removal. On that occasion, a high level of danger was perceived by the personnel involved whenever contact with the horse was necessary. Even under deep sedation, the horse had still reacted violently to an intravenous injection, by targeted harsh kicking. A standard physical examination including oral examination, blood sampling and imaging was considered to be only feasible under general anaesthesia. To this end, induction of general anaesthesia by remote drug delivery followed by conventional anaesthetic maintenance was planned.

On the morning of the planned procedure, the horse was transported to the hospital. Upon arrival, the horse was unloaded from the trailer and led by the owner directly into the anaesthetic induction box through the backdoor, which is accessible from the outside

pathway. The animal was left alone inside and free to move around. Care was taken to guarantee a quiet environment, with auditory contact to other horses. The horse showed a curious but calm attitude. A 3 ml gas pressurized dart (Mini-Ject 2000 Nylon syringe cylinder; Dist-inject) containing medetomidine (0.04 mg/kg) (Zalopine; 10 mg/ml, Orion Pharma, Espoo, Finland) and TZ (2 mg/kg) (Zoletil 100; Tiletamine 250 mg, Zolazepam 250 mg, Virbac AG, Opfikon, Switzerland) was prepared. To reduce the total volume to be injected, medetomidine (2 ml) was used to dilute 1000 mg of TZ, resulting in a total volume below 3 ml. The dart, equipped with a woolen tailpiece and a smooth needle (1.5 x 35 mm) sealed with a silicon sleeve for impact protection, was fired by blowpipe (Mini-Inject Blowpipe 11mm; Dist-Inject) into the hindquarter musculature. The horse reacted immediately with a strong kick and became excited, showing attempts to escape and jump.

Thirty-five minutes later, the horse showed signs of minimal sedation but was severely ataxic. While standing on a corner, he still reacted with aggressive behavior when approached and exhibited exaggerated behavioral reactions to external stimuli. Thus, a second dart containing TZ (1 mg/kg) and medetomidine (0.04 mg/kg) was shot. Twenty to thirty minutes later, the horse was mildly sedated but it still aroused in response to noise and remote tactile stimulation. Profuse sweating and increased urination were observed. At this time point approaching the horse for direct injections of further drugs was still deemed too dangerous. A third dart with additional medetomidine and TZ was considered unsafe and likely ineffective. Therefore, the decision was made to abandon the procedure and plan an alternative approach in the future. The horse recovered uneventfully and was sent home 7 hours after the second dart.

Nineteen days later, the horse was readmitted to the hospital. For this occasion, two consecutive darts were planned, the first one to sedate and the second one to induce general anaesthesia. A 5 ml dart (Mini-Ject 2000 Nylon syringe cylinder; Dist-inject) containing detomidine (0.05 mg/kg) (Equisedan; 10 mg/ml, Graeub AG, Bern, Switzerland) and butorphanol (0.03 mg/kg) (Morphasol; 10 mg/ml, Graeub AG, Bern, Switzerland) was prepared. Again, the dart was fired by blowpipe into the hindquarter muscles. Fifteen minutes later, clear sedative effects, including lowered head, wide stance and decreased responsiveness, became apparent. A second 5 ml dart containing TZ (4 mg/kg) and detomidine (0.02 mg/kg) was immediately fired. This dart did not empty completely. At visual inspection, it was estimated that half of the volume remained in the dart. Thus, a third dart with TZ (2 mg/kg) and detomidine (0.02 mg/kg) was shot. Within five minutes, severe ataxia with partial loss of posture was observed, followed by recumbency and unresponsiveness to stimulation. A 13-gauge catheter (Intranule; Vygon, Ecouen, France) was placed in the right jugular vein, and blood was withdrawn for complete hematology and chemistry profiles. The trachea was intubated with a 26 mm cuffed endotracheal tube. The horse was hoisted and positioned in dorsal recumbency. Because nystagmus was present, thiopental (0.5 mg/kg) (Thiopental Inresa; 50 mg/ml, Ospedalia AG, Hünenberg, Switzerland) was administered intravenously before moving into the operating room.

Once in the operating room, the endotracheal tube was connected to a large animal circle

breathing system (Matrx VML Large Animal Anaesthesia System) equipped with a cycled ventilator (DHV 1000 Large Animal Ventilator, Surgivet, Smiths Medical). Anesthesia was maintained with Isoflurane (Attane; Provet AG, Lyssach, Switzerland) in oxygen and air mixture (50%-50%). Intermittent positive pressure ventilation was started once connected to the breathing circuit using a respiratory rate (RR) of 6 breaths/min, a tidal volume from 6 L and a positive end-expiratory pressure of 5 cm H_2O. After the first blood gas analysis tidal volume was reduced to 5 L. Heart rate and rhythm, invasive systolic, diastolic and mean arterial pressure (SAP, DAP, MAP), RR, SpO_2, $EtCO_2$ and EtIso were continuously monitored with a multi-parameter-anesthetic monitor (Datex Ohmeda S/5, GE) and recorded every 5 minutes. Fluid therapy was initiated with lactated Ringer's solution at a rate of approximately 5 ml/kg/h and a urinary catheter connected to a collection bag was placed into the bladder. Once an adequate anaesthesia depth was achieved, the planned medical procedures were started. These included oral examination, dental floating, gastroscopy, carpal x-rays and vaccination. Penicillin (30000 IU/kg) (Penicillin Natrium; 10 Mio, Streuli Pharma SA, Uznach, Switzerland), gentamicin (6.5 mg/kg) (Pargenta; 50 mg/ml, Graueb AG, Bern, Switzerland) and flunixin meglumine (1.1 mg/kg) (Fluniximin; 50 mg/ml, Graueb AG, Bern, Switzerland) were administered intravenously. Due to the unique behavior displayed by the horse, an additional blood sample was taken for genomic sequencing.

Arterial blood was sampled three times (25, 75 and 135 minutes after onset of recumbency) for blood gases and lactate analysis. At those time points, $PaCO_2$ was 36.7, 44.1 and 51.6 mm Hg respectively and PaO_2 was 193, 142, 157 mm Hg respectively. Lactate levels ranged between 1.9 and 2.5 mmol/l. Heart rate oscillated around 30 bpm; EtIso fluctuated between 0.83% and 1.0%. The lowest SpO_2 value recorded was 85%, which was at the time of the first reading, and thereafter it stayed above 95%; $EtCO_2$ values ranged between 31 and 44 mm Hg; FiO_2 was maintained between 51-61% throughout anesthesia. Seventy-five min after onset of recumbency, MAP decreased below 70 mm Hg. From this time point onwards, dobutamine (Dobutrex; 5 mg/ml, Teva Pharma AG, Basel, Switzerland) administered at a rate of 0.3 µg/kg/min, was sufficient to keep MAP above 70 mmHg until the completion of anesthesia. Total urine collected during anesthesia was 15 l. Bloodwork was unremarkable.

Once the procedures were finished, isoflurane was discontinued. Total anaesthesia time, from onset of recumbency until discontinuation of isoflurane, was 165 min. The horse was disconnected from the breathing system, transferred to the recovery box, and positioned in left lateral recumbency. At this time point he had a rectal a temperature of 34.7°C and was wet; therefore the horse was dried by rubbing paper towels and covered with blankets. Mechanical ventilation with 100% oxygen was provided via a Hudson demand valve at a frequency of 6 breaths/min. Twenty minutes later, the frequency was reduced to 3 breaths/min until the horse started to breath spontaneously. At this time point the endotracheal cuff was deflated and oxygen (10 l/minute) was insufflated through the endotracheal tube. Phenylephrine (Phenylephrine HCl 15%; Grosse Apotheke Dr. G. Bichsel AG, Interlaken, Switzerland) was administered intranasally at a volume of 10 ml in both nares. Seventy minutes after isoflurane discontinuation the horse had recovered the

swallowing reflex and was extubated. Romifidine (0.01 mg/kg) (Sedivet; 10 mg/ml, Boehringer Ingelheim, Basel, Switzerland) was administered IV and the jugular catheter was removed. The horse was then allowed to recover unassisted in the padded box. Muscle stiffness, shivering and limb rigidity were observed while the horse was recumbent. The horse stood up on the first attempt, 260 minutes after the end of anesthesia, moving directly from lateral recumbency to standing position. He was slightly ataxic but standing on all four limbs with minimal proprioceptive deficits. A recovery score of 2 (1: Excellent, 5: Very poor; adapted from Young and Taylor) was assigned. [10]

INVESTIGATIONS ***If relevant***

Genomic sequencing was performed to investigate genetic factors that could have influenced drug response.

DIFFERENTIAL DIAGNOSIS ***If relevant***

Stress, genetic mutations, altered pain state, drug resistance and behavioural problems, were suspected as potential alterations influencing the outcome.

TREATMENT ***If relevant***

OUTCOME AND FOLLOW-UP

Three hours after standing the horse was sent home.

DISCUSSION ***Include a very brief review of similar published cases***

Two attempts to induce general anaesthesia by blowpipe darting in a fractious domestic horse are described in the present report. In the first, two darts, one containing medetomidine (0.04 mg/kg) and TZ (2mg/kg) followed by a second one containing medetomidine (0.04 mg/kg) and TZ (1 mg/kg) failed to achieve recumbency 35 minutes apart. The second attempt resulted adequate to induce anaesthesia. It consisted in a two-staged approach where sedation was achieved with the first dart using detomidine (0.05 mg/kg) and butorphanol (0.03 mg/kg), followed by detomidine and TZ at an estimated dose of 0.03 mg/kg and 4 mg/kg respectively. This is the first description of successful IM general anaesthesia in a fractious companion horse.

When planning general anaesthesia for this horse a number of issues were encountered. Safety of the horse as well as of the personal involved in the procedure must always be a priority on equine anaesthesia. To address safety in horses with aggressive reactions towards medical interventions a possibility is to undergo behavioral therapy and postpone the procedure until the animal is desensitized. It has been reported an efficient rehabilitation in equine cases with positive-reinforcement based habituation. [11] However, due to relative urgency of the procedure and the extreme fractious temperament of the horse, it was considered not feasible within a reasonable time frame in this case. Therefore, because the main concern was minimizing risks, darting was considered to be the best drug delivery method. Darts can be projected via blowpipe, compressed air projector, or gunpowder cartridge rifle.[1] Among available delivery systems, blowpipe was selected because of being an accurate method for short distances, being silent and producing a limited und thus safer projectile velocity.[1] Darting injuries have been attributed to misuse of the drug-delivery system and inexperience of personnel.[12] The anesthetist was trained and familiar with the delivery method optimizing the effectiveness of drug administration as well as safety for the horse and personnel. The darts used were gas-pressurized, constructed of lightweight plastic. This dart type was selected as it has a lower risk of causing injuries than the rapid-injection darts,[13] which expel their content by powder charge. However, as seen in the second attempt of the present case, it might happen that the pressurized gas is not enough to expel the whole dart content because of insufficient charge or depressurization before or during the flight. This is a common problem causing incomplete discharge, which is difficult to notice before darting.

The main issue confronted in the current case was the impossibility to induce anaesthesia at the first attempt. As a result of the failed attempt, an alternative approach was devised with modifications to the drug protocol and dosages for the following attempt. A two-stage sequence of darts was planned: the first to sedate the horse, containing detomidine (0.05 mg/kg) and butorphanol (0.03 mg/kg); and the second one to induce anaesthesia, containing TZ at a higher dose than the one used on the first attempt (4 mg/kg) combined with detomidine (0.02 mg/kg). It was planned to administer the second dart only in case of evident sedation following the first dart, mimicking the approach used in routine equine clinical anaesthesia. Due to incomplete discharge of the second dart, containing TZ and a second dose of detomidine, a third dart was delivered to reach the planned dosages. On this occasion the time interval between the two darts was short, so that the onset of anaesthetic action can most probably be attributed to the sum of both.

Whether the success of the second attempt can be credited to the increased drug dosages, the reduced dosing interval, the modifications to the drug protocol, or to the two-stage approach remains unclear. However, those factors are the most likely to have influenced the successful attempt. While detomidine-butorphanol combinations are commonly used for equine premedication and have highly predictable effects, high doses of medetomidine combined with tiletamine-zolazepam had not been described in fractious companion horses before. On the other side, reports of successful anaesthetic induction using combinations of a dissociative agent with an α2-agonist in non-domestic equids, as well as in a variety of wild animals justify the choice of drugs used in the first attempt.[14–18]

Another key issue was the selection of drugs to be used for darting. Although a number of different drug combinations have been reported for chemical immobilization of non-domestic equids, no specific information about intramuscular anaesthetic induction in fractious companion horses was found in the literature.

Etorphine, a potential effective choice according to previous reports,[2-3] was discarded because of its limited access. Etorphine is in the Yellow list of the International Narcotics Control Board listed in the Schedule I in accordance with the Single Convention on Narcotic Drugs, 1961.[19] Currently, there are not authorized products containing etorphine in Switzerland, and although it is possible to import it with Swissmedic's approval,[20] the process of getting the required licenses may take several weeks. Furthermore, etorphine presents risk of fatal complications for humans manipulating it because of its high potency.

Similarly, succinylcholine was excluded for a number of reasons. It leads to immobilization as an abrupt collapse of support muscles, which could cause severe injuries, and it produces tachyarrhythmia and hypertension in horses.[4] Moreover, succinylcholine does not provide anaesthesia or analgesia making its use ethically unacceptable.

The use of ketamine (2.1 mg/kg) in combination with medetomidine (0.09 mg/kg) has been reported to be successful to immobilize Przewalski's horses using a CO_2 injection rifle.[5] This drug combination also worked appropriately to immobilize "Judas donkeys" with dose rates of 0.14 mg/kg medetomidine and 4.1 mg/kg ketamine.[6] However, the characteristics of the present case, being a 520 kg horse, to be darted by blowpipe, and the concentration

of the ketamine available (100 mg/ml), made this combination unpractical because of the high volume needed, which would have been a minimum of 15 ml.

As an alternative to ketamine, tiletamine has been widely used for the immobilization of wild animals. Tiletamine is a dissociative anesthetic that is commercialized combined with zolazepam, a benzodiazepine derivative, in equal mixture. TZ has been reported in feral horses in combination with xylazine and butorphanol,[7] and in zebras and Przewalski's horses in combination with romifidine with successful results.[8] One benefit of TZ is that it is available as a powder; therefore, it can be reconstituted in high concentrations minimizing the final volume to be injected. The disadvantages are the longer onset, longer duration of action, and impossibility to antagonize it.[21]

Among α2-agonists, medetomidine was chosen because of the availability of a highly concentrated solution (Zalopine 10 mg/ml). This, used to solve TZ, resulted in a total injection volume suitable for a 3-ml dart. The dose rate of medetomidine (0.04 mg/kg) chosen for the first dart might be equipotent to 4 mg/kg of xylazine.[22] Xylazine doses ranging from 2.6 to 4.1 mg/kg, combined with TZ and butorphanol, have been reported to be adequate to anaesthetize feral horses.[7] Unfortunately, only slight sedation and strong ataxia were observed in the present case after the first dart, but also when the same drugs were administered again 30 minutes later at the same doses. Since increasing the dose of α2-agonists has been shown to prolong the duration of action without enhancing the potency,[23] a ceiling effect might have been responsible for the lack of sedative efficacy of the second dart. While comparing equisedative doses of xylazine and medetomidine, it is described that medetomidine elicits stronger and longer ataxia than xylazine.[22] This might help to explain the severe ataxia observed in the present case. It is also possible that the dose of TZ used (3 mg/kg) was insufficient, as it is in the lower range of doses reported as effective in non-domestic equids, which are 3.2, 3.5 and 5.0 mg/kg in feral horses,[7] 3.3 mg/kg in Przewalski's horses and 1.8 mg/kg in Hartmann mountain zebras.[8] Furthermore, the 30-minute delay between the first and the second dart could have been too long, since it has been recommended to redose within 20 minutes if the first dose of drugs is not effective.[7]

Avoiding stress and fear for the animal before and during the anaesthetic induction procedure was identified as a key factor to enhance the probability of success. Stress and excitation, accompanied by a high catecholamine levels, are known to impair the efficacy of alpha-2 agonists. Indeed, in race horses after strenuous exercise, doses required to induce sedation and anaesthesia are much higher than in horses at rest.[24,25] Thus, efforts were made to avoid handling by unknown people, to minimize the time spent in the hospital environment and to maintain an overall quiet atmosphere. However, at the first attempt excitation and fear were clearly recognizable after the first dart was shot, and from that moment on throughout the entire process. This stress level might have influenced the unsuccessful outcome. Despite following a very similar approach for the second attempt, a lower level of excitation was noticed and a good level of sedation was reached soon after the first dart. This could have been because of adaptation to the repeated situation. It has been

described that the transport-induced stress response in horses, indicated by cortisol release and changes in heart rate, decreases with repeated transport.[26]

The exaggerated behavioral responses of this horse to routine medical interventions, and the resistance showed to the anaesthetic drugs on the first attempt were found to be exceptional. Therefore, a genomic sequencing was performed. The potential for genetic factors to influence drug response should be considered when observing variations from the normal effects.[27] When sequencing the genome of this horse, no protein-changing variants were detected within the three genes that encode for separate subtypes of α2 adrenoreceptors, *ADRA2A*, *ADRA2B* and *ADRA2C.*[28] However, heterozygous intronic private variants were found in the pain-associated genes *SCN11A* and *TRPA1*. The *SCN11A* gene encodes a member of the sodium channel family, and is highly expressed in nociceptive neurons of dorsal root ganglia and trigeminal ganglia.[29] Variants in this gene have been described to influence pain thresholds regulated by inflammatory mediators in mice.[30] TRP channels appear to be involved in the transduction of several nociceptive stimuli.[29] Variants in the *TRPA1* gene have been associated with increased pain sensitivity in humans.[31] Therefore, it is possible that the horse was suffering from an altered sensitivity to painful stimuli, which might have accounted for its unique behavior. However, these variants were located in introns of the respective genes, which reduce the possibility of having a functional effect. On the other hand, other private variants were found to be more prone to have a functional effect. The *CACNA1G* gene, a calcium voltage-gated channel, which is involved in synaptic transmission, and the *C15orf59* gene, involved in postsynaptic inhibition, which may have an influence on the nociceptive pathway.

In conclusion, this case presented a challenge because of the importance of assuring safety, the scarce information about intramuscular anaesthetic induction in companion horses, the limitations on drug selection, and the drug resistance encountered on the first attempt. In addition, it also proved that general anaesthesia in a fractious companion horse can be achieved by blowpipe darting, and it may suggest that separating sedation and induction in two sequential darts could be beneficial. Furthermore, we highly recommend to plan diligently the approach and to make effort for minimizing horse stress and anxiety.

LEARNING POINTS/TAKE HOME MESSAGES ***3 to 5 bullet points – this is a required field***

- Safety of the personnel and of the horse must always be a priority in equine anaesthesia.
- General anaesthesia in a fractious companion horse can be achieved by blowpipe darting.
- Diligent planning of the approach is required and special effort should be made to minimize stress and anxiety in fractious horses.

REFERENCES ***Vancouver style***

1 Isaza R. Remote drug delivery. In: West G, Heard D, Caulkett N, eds. *Zoo Animal and Wildlife Immobilization and Anesthesia*. Wiley-Blackwell 2014. 155--79.

2 Seal US, Siniff DB, Tester JR, *et al.* Chemical immobilization and blood analysis of feral horses (Equus caballus). *J Wildl Dis* 1985;**21**:411–6.

3 Plotka ED, Seal US, Eagle TC, *et al.* Rapid reversible immobilization of feral stallions using etorphine hydrochloride, xylazine hydrochloride and atropine sulfate. *J Wildl Dis* 1987;**23**:471–8.

4 Gallagher L V, Borchard RE, Klavano PA, *et al.* Physiologic responses of feral horses to succinylcholine chloride immobilization. *J equine Vet Sci* 1983;**3**:48–52.

5 Matthews NS, Petrini KR, Wolff PL. Anesthesia of Przewalski's Horses (Equus przewalskii przewalskii) with Medetomidine/Ketamine and Antagonism with Atipamezole. J. Zoo Wildl. Med. ;**26**:231–6. doi:10.2307/20095466

6 Woolnough AP, Hampton JO, Campbell S, *et al.* Field immobilization of feral 'Judas' donkeys (Equus asinus) by remote injection of medetomidine and ketamine and antagonism with atipamezole. *J Wildl Dis* 2012;**48**:435–43. doi:10.7589/0090-3558-48.2.435

7 Matthews N, Myers M. The use of tiletamine-zolazepam for darting feral horses. *J equine Vet Sci* 1993;**13**:264–8.

8 Wiesner H, von Hegel G. [The immobilization of wild equines with STH 2130 and tiletamine/zolazepam]. *Tierarztl Prax* 1990;**18**:151–4.

9 Zabek MA, Wright J, Berman DM, *et al.* Assessing the efficacy of medetomidine and tiletamine-zolazepam for remote immobilisation of feral horses (Equus caballus). *Wildl Res* 2014;**41**:615. doi:10.1071/WR14108

10 Young SS, Taylor PM. Factors influencing the outcome of equine anaesthesia: a review of 1,314 cases. *Equine Vet J* 1993;**25**:147–51.

11 Torcivia C, McDonnell SM. Case series report: Systematic rehabilitation of specific health care procedure aversions in 5 ponies. *J Vet Behav* 2018;**25**:41–51. doi:10.1016/j.jveb.2018.02.003

12 Jessup DA. Reducing Capture-Related Mortality and Dart Injury. *Wildl Soc Bull* 1973;**29**:751–2.

13 Cattet MRL, Bourque A, Elkin BT, *et al.* Evaluation of the Potential for Injury With Remote Drug-Delivery Systems. *Wildl Soc Bull* 2006;34:741-9.

14 Barasona J, López-Olvera J, Beltrán-Beck B, *et al.* Trap-effectiveness and response to tiletamine-zolazepam and medetomidine anaesthesia in Eurasian wild boar captured with cage and corral traps. *BMC Vet Res* 2013;**9**:107. doi:10.1186/1746-6148-9-107

15 Muller LI, Osborn DA, Doherty T, *et al.* Optimal Medetomidine Dose When Combined

with Ketamine and Tiletamine-zolazepam to Immobilize White-tailed Deer. *J Wildl Dis* 2012;**48**:477–82. doi:10.7589/0090-3558-48.2.477

16 Naples LM, Langan JN, Kearns KS. Comparison of the Anesthetic Effects of Oral Transmucosal Versus Injectable Medetomidine in Combination with Tiletamine-Zolazepam for Immobilization of Chimpanzees (Pan troglodytes). *J Zoo Wildl Med* 2010;**41**:50–62. doi:10.1638/2009-0096.1

17 Stegmann GF, Jago M. Cardiopulmonary effects of medetomidine or midazolam in combination with ketamine or tiletamine/zolazepam for the immobilisation of captive cheetahs (Acinonyx jubatus). *J S Afr Vet Assoc* 2006;**77**:205–9.

18 Jacquier M, Aarhaug P, Arnemo JM, *et al.* Reversible Immobilization of Free-ranging African Lions (Panthera leo) with Medetomidine-tiletamine-zolazepam and Atipamezole. *J Wildl Dis* 2006;**42**:432–6. doi:10.7589/0090-3558-42.2.432

19 International Narcotics Control Board. Yellow list: List of narcotic drugs under international control. 1961.http://www.incb.org/

20 Der Schweizerische Bundesrat. Verordnung über die Tierarzneimittel 812.212.27. 2004.http://www.vetpharm.uzh.ch

21 Staffieri F. Field Anesthesia in the Equine. *Clin Tech Equine Pract* 2007;**6**:111–9. doi:10.1053/J.CTEP.2007.05.003

22 Bryant CE, England GC, Clarke KW. Comparison of the sedative effects of medetomidine and xylazine in horses. *Vet Rec* 1991;**129**:421–3.

23 Grimsrud KN, Ait-Oudhia S, Durbin-Johnson BP, *et al.* Pharmacokinetic and pharmacodynamic analysis comparing diverse effects of detomidine, medetomidine, and dexmedetomidine in the horse: a population analysis. *J Vet Pharmacol Ther* 2015;**38**:24–34. doi:10.1111/jvp.12139

24 Hubbell JA, Hinchcliff KW, Schmall LM, *et al.* Cardiorespiratory and metabolic effects of xylazine, detomidine, and a combination of xylazine and acepromazine administered after exercise in horses. *Am J Vet Res* 1999;**60**:1271–9.

25 Rankin DC, Greene SA, Keegan RD, *et al.* Anesthesia of horses with a combination of detomidine, zolazepam, tiletamine, and isoflurane immediately after strenuous treadmill exercise. *Am J Vet Res* 1999;**60**:743–8.

26 Schmidt A, Hödl S, Möstl E, *et al.* Cortisol release, heart rate, and heart rate variability in transport-naive horses during repeated road transport. *Domest Anim Endocrinol* 2010;**39**:205–13. doi:10.1016/j.domaniend.2010.06.002

27 Belle DJ, Singh H. Genetic factors in drug metabolism. *Am Fam Physician* 2008;**77**:1553–60.

28 Schmutz I, Jagannathan V, Diez Bernal S, *et al.* Exclusion of adrenoceptor alpha 2 variants in a horse insensitive to medetomidine. *Anim Genet* Published Online First: 23

January 2018. doi:10.1111/age.12636

29 Foulkes T, Wood JN. Pain Genes. *PLoS Genet* 2008;**4**:e1000086. doi:10.1371/journal.pgen.1000086

30 Priest BT, Murphy BA, Lindia JA, *et al.* Contribution of the tetrodotoxin-resistant voltage-gated sodium channel NaV1.9 to sensory transmission and nociceptive behavior. *Proc Natl Acad Sci U S A* 2005;**102**:9382–7. doi:10.1073/pnas.0501549102

31 Kim H, Mittal DP, Iadarola MJ, *et al.* Genetic predictors for acute experimental cold and heat pain sensitivity in humans. *J Med Genet* 2006;**43**:e40. doi:10.1136/jmg.2005.036079

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