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Case Report
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Use of Alprazolam to Facilitate Mare-Foal Bonding in an Aggressive Postparturient Mare

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A healthy 11-year old, 577 kg maiden Quarter Horse mare was examined at the Lloyd Veterinary Medical Center with a 4-day old colt because the mare would bite or kick the foal when the foal attempted to suckle. The owner bottle fed the foal small amounts of mare's milk over the first 4 days of life, but the foal became progressively weaker over time and was recumbent and nonresponsive at presentation. Furthermore, although gestational length and parturition were reportedly normal, the mare had apparently not been producing adequate amounts of milk since the foal was born.

Upon presentation (Day 1), the foal weighed 36.8 kg and was severely dehydrated, undernourished, unresponsive, hypothermic (32.2°C; reference range [RR], 37.2–38.6°C), bradycardic (40 beats/min; RR, 96–108 beats/min), hypoglycemic (28 mg/dL; RR, 101–226 mg/dL), hyperlactatemic (4.2 mmol/L; RR, <2.5 mmol/L), and had a low serum immunoglobulin G (IgG: 400–800 mg/dL[a] ; RR, >800 mg/dL). A CBC revealed leucopenia ($3.41 \times 10^3/\mu L$; RR, 5.1–10.1 $\times 10^3/\mu L$) characterized by neutropenia ($2.15 \times 10^3/\mu L$; RR, 3.21–8.58 $\times 10^3/\mu L$) and relevant serum biochemistry derangements included hypoproteinemia (3.5 g/dL; RR, 5.3–7.9 g/dL), hypoalbuminemia (1.9 g/dL; RR, 2.8–3.7 g/dL), and hyperbilirubinemia (4.61 mg/dL; RR, 0.5–3.9 mg/dL).

The foal was treated for failure of transfer of passive immunity and polymicrobial sepsis confirmed via blood culture yielding *E. coli* and *Citrobacter sp*. Treatment included administration of 2 L of equine plasma, which increased the serum IgG to >800 mg/dL, fluid resuscitation and treatment, antimicrobial treatment consisting of ceftiofur (Naxel[b]) (5 mg/kg IV q12h) and gentamicin[c] (10 mg/kg IV q24h) for 10 days followed by sulfamethoxazole-trimethoprim[d] (30 mg/kg PO q12h) for 7 days, nasoesophageal tube feedings and supportive and nursing care. The mare was treated with domperidone[e] (1.1 mg/kg PO q24h) to increase milk production. The foal was able to ambulate by Day 4 and by Day 6, was bright and alert and attempted to suckle from the mare frequently. However, the mare consistently demonstrated aggressive behavior toward the foal; therefore the mare's head was tied in a stationary position and periodic sedation (detomidine, Dormosedan,[b] 0.011 mg/kg IM q6h) was administered while the hindlimbs were hobbled to allow the foal to suckle under strict supervision. Although the foal was able to suckle voluntarily, the mare continued to display violent behavior and attempted to bite and kick the foal, but was constrained by the applied restraints.

Abbreviations:

C_{max}	maximum serum concentration
CNS	central nervous system
LD_{50}	median lethal dose

In an attempt to facilitate mare-foal bonding and provide a means for the foal to suckle unsupervised without maternal sedation or restraint, the mare was administered alprazolam[f] (0.035 mg/kg PO q8h) on Day 7. On Day 8, 24 hours after the initial dose of alprazolam, the mare had a quieter demeanor and demonstrated less aggression toward the foal. The next day (Day 9) the mare was not aggressive toward the foal and allowed the foal to suckle regularly. Over the next 2 days, the mare was untied, the hobbles were removed and the foal was allowed to suckle without incident. On Day 11, the mare's physical examination was within acceptable parameters, but the mare appeared mildly sedate; therefore the frequency of alprazolam administration was decreased to twice daily (0.035 mg/kg PO q12h). On Day 14, the foal weighed 44 kg and was suckling regularly without threat from the mare. The mare and foal were subsequently discharged with instructions to administer alprazolam (0.035 mg/kg PO q12h for 3 days, then 0.018 mg/kg PO q12h for 5 days). One week after discharge the owner reported that the mare demonstrated no aggression toward the foal when suckling, and 6 months after presentation the mare and foal were reportedly healthy.

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Serum alprazolam concentrations from blood samples collected from the mare were subsequently measured at various time points. Specifically, after owner permission was obtained on Day 7 of hospitalization, 12 mL of blood was collected from the mare, just before the first dose of alprazolam administration (Time 0) and at Times 5, 10, 15, 30, 45, and 60 minutes as well as at 2, 4, 6, 8, 12, 24, 36, and 48 hours after the first alprazolam dose and placed in clot tubes; serum was then harvested and frozen at −80°C until further analysis. Alprazolam and its active metabolite, α-hydroxyalprazolam, concentrations in extracted serum samples were measured via liquid chromatography-ion trap mass spectrometry in positive ion mode. Four daughter ions of the parent pseudomolecular ions at a mass-to-charge ratio of 310.2 and 326.2, respectively, were used for quantification. Hydroxyalprazolam-D5 was used as an internal standard. Separation was achieved on a core-shell C18 column[g] and guard column with a mobile phase consisting of water and acetonitrile each containing 0.1% formic acid. Retention times were 5.2 minutes for alprazolam and 4.8 minutes for α-hydroxyalprazolam. Using this method, standard curves were linear from 0.2 to 50 ng/mL for both compounds, with a coefficient of determination of >0.99 and a coefficient of variation of 2.25% for alprazolam and 2.41% for α-hydroxyalprazolam. After oral administration, alprazolam was quantifiable in plasma by 10 minutes, and α-hydroxyalprazolam by 30 minutes (Fig 1). The maximum concentrations for alprazolam (16.35 ng/mL) and α-hydroxyalprazolam (1.39 ng/mL) were reached at 4 and 6 hours, respectively. Multiple dose administration every 8 hours led to apparent accumulation of drug at the 24, 36, and 48 hour time points (Fig 1).

Normal mare-foal behavior and bonding has been previously described in detail.[1–4] Difficulties with mare-foal bonding are relatively rare, and with the exception of a severely physically compromised foal, most problems that occur result from inadequate or abnormal maternal behavior.[1] Some aspects of postparturient behavior can appear to be antagonistic or aggressive toward the foal, but can in reality be normal maternal behavior. For example, it is not uncommon for a mare to demonstrate disapproving behavior such as threats to bite or kick or swishing of the tail toward the foal during bumping of the udder and suckling.[2] This must be differentiated from inadequate or abnormal maternal behavior, which can be observed in primiparous or multiparous mares, but is more common in the former situation.[1,4] These behavioral abnormalities have been divided into distinct forms: ambivalence, fear of foal, nursing avoidance, extreme protective, and savage attack behavior.[1–4]

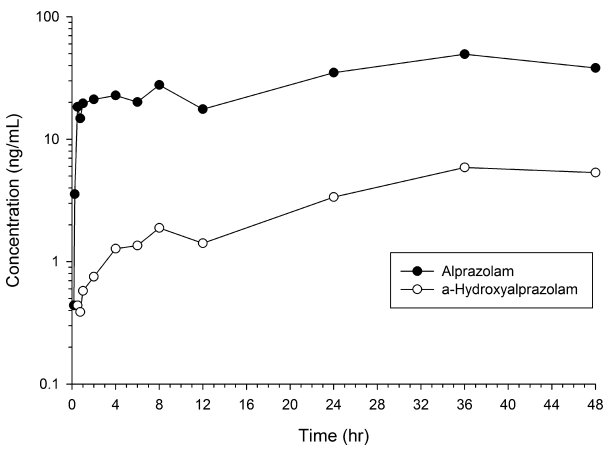

Fig 1. Serum alprazolam concentrations at various time points measured from blood samples collected from a mare administered 0.035 mg/kg of alprazolam PO, q8h. Arrows indicate when alprazolam was administered. Time 0 was just before the first dose of alprazolam administration.

Ambivalence behavior of the mare toward the foal is characterized by lack of attention, bonding and protective behavior whereas fear of the foal behavior is typified by maternal avoidance of the foal whenever the foal approaches.[1,5] Nursing avoidance behavior implies aggressive behavior of the mare toward the foal only during suckling.[1,5] Extreme protective behavior is observed when maternal aggression is directed at humans or other animals and in the process the foal is injured (ie, mare tramples or pushes the foal into an obstacle when trying to intervene between the foal and the perceived threat).[1] Finally, savage attack behavior of the mare against the foal is the most violent and severe abnormal behavior and can be life-threatening to the foal.[1] Maternal behavior in the mare in this report can be described as a combination of ambivalence and nursing avoidance. In the case described here, the nursing avoidance behavior was aggressive enough toward the foal that the foal could not be left unattended with the dam. When common methods of correcting nursing avoidance (ie, supervised nursing with physical restraint of the mare, repeated sedation) were unsuccessful, alprazolam was administered and facilitated the development of appropriate mare-foal behavior over a 2–3 day time period in this case.

Alprazolam is a short-acting anxiolytic of the benzodiazepine class of psychoactive medications and is prescribed to treat anxiety and panic disorders in people as well as dogs and cats.[6–8] The exact mechanism of action is unknown, but similar to other benzodiazepines, alprazolam readily crosses the blood brain barrier and interacts with inhibitory neurotransmitter receptors that are directly activated by gamma-amino-butyric acid receptors ($GABA_A$) within the central nervous system (CNS). The net result is general slowing of brain activity producing dose-related CNS depression that can vary from mild cognitive impairment (ie, sedation) to hypnosis.[6] In people, alprazolam has a fast onset of action and is readily absorbed after oral administration with plasma concentrations and clinical benefits achieved within the first 1–2 hours of administration.[6] The dosage for alprazolam administration in people ranges from 0.25 to 0.5 mg, PO, q8h for anxiety disorders and up to 10 mg daily for panic disorders. A single 1 mg dose of alprazolam in people resulted in a maximum serum

concentration (C_{max}) between 12 and 22 ng/mL 1–2 hours after administration.[6] Similarly, serum alprazolam concentrations were detected in the mare described in this report and reached measurable and comparable plasma concentrations to those in people within 1 hour of administration (serum concentration at 1 hour – 14.1 ng/mL; C_{max} of 16.35 ng/mL at 4 hours). In human medicine, optimal reduction in anxiety associated with panic disorder occurs at steady-state plasma alprazolam concentrations of 20–40 μg/mL.[9] After a multiple dose regimen every 8 hours, trough concentrations of alprazolam in the mare of this report were within this target range for the third and sixth dose. Although an exact therapeutic dosage has not been established in horses, the 20 mg (0.035 mg/kg) dose administered to the mare in this report resulted in notable behavioral changes within 24 hours of commencement of alprazolam administration. This coincides with plasma concentrations within the therapeutic range for humans.

Adverse effects of alprazolam administration in people include drowsiness, fatigue, weakness, ataxia, and sedation; however, the medication has a wide safety margin evidenced by the very high median lethal dose of alprazolam that will kill 50% of rats (LD_{50}, 331–2171 mg/kg).[6,10] After accidental ingestion of alprazolam in dogs at doses as high as 5.55 mg/kg, clinical signs were similar to those reported in people and included ataxia and disorientation, depression, hyperactivity, gastrointestinal distress, weakness, tremors, vocalization, increased heart and respiratory rate, hypothermia, and increased salivation developing within 10–30 minutes postingestion.[11] Despite the high doses ingested, death was not reported in any of those dogs, emphasizing the safety of this drug. Mild sedation was noted 96 hours after the initial oral administration in this mare at which point the frequency of administration was decreased to twice daily.

Alprazolam can increase the risk of congenital abnormalities in women when used during the first trimester, thus caution should be used in pregnant mares.[12] Furthermore, the pharmacokinetics of alprazolam in breast milk is similar to that in blood of lactating women, suggesting that the medication readily passes into the milk.[6] Alprazolam concentrations were not determined from milk samples from the mare, or serum samples from the foal in this report, however, it is likely that drug was present in the mare's milk and therefore could have been absorbed to some extent by the foal. Although no sedation or other behavioral abnormalities were noted in the foal here, it is advisable to use the lowest dosage of alprazolam necessary to achieve the desired maternal behavioral changes, and the duration of administration should be as brief as possible. Preferably, discontinuation of daily alprazolam administration in people involves tapering the dose gradually to zero over several weeks to reduce rebound clinical signs. In the mare in this report, the dose was tapered over a short period of time (days) with no perceived untoward effects.

In summary, administration of alprazolam at a dose of 0.035 mg/kg, PO, q8–12 h was an affordable (< $0.50/dose) method to facilitate healthy mare-foal bonding and behavior in an aggressive mare and ultimately allowed the foal to nurse from the mare while reducing the risk of maternally induced injury to the foal. Of note, however, administration of alprazolam to horses is not approved by the Food and Drug Administration and would be classified as extralabel use.

Footnotes

[a] Snap Foal IgG Test Kit, IDEXX Laboratories, Westbrook, ME
[b] Pfizer Animal Health, New York, NY
[c] Gentacin, MWI, Boise, ID
[d] Sulfamethoxazole and Trimthoprim, Amneal Pharmaceuticals, Glasgow, KY
[e] Equidone, Dechra Veterinary Products, Overland Park, KS
[f] Alprazolam, Sandoz Inc., Princeton, NJ
[g] Kinetix C18 column 100 × 2.1 mm, Phenomenex, Torrance, CA

Acknowledgment

Conflict of Interest Declaration: The authors disclose no conflict of interest.

Off-label Antimicrobial Declaration: The authors declare no off-label use of antimicrobials.

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