



Procaine

Background

Procaine is commonly used in a variety of forms in equine veterinary medicine.ⁱ It is assigned 3/B in the ARCI's Uniform Classification of Foreign Substances. Procaine is rarely administered alone for its anesthetic effect but rather as a constituent of Penicillin G Procaine (PGP), an economic, effective, and commonly used antibiotic with a very low toxicity.ⁱⁱ PGP is a crystalline complex that acts as a depot of

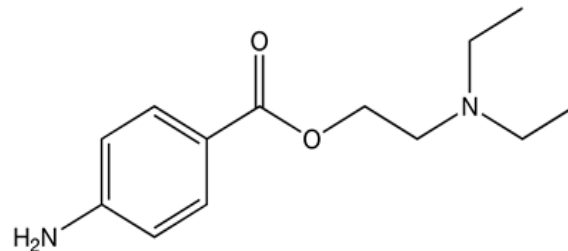


Figure 1:

<http://itech.dickinson.edu/chemistry/wp-content/uploads/2008/04/procaine.png>

penicillin G and delays its rapid absorption. Procaine is a prescription medication and can only be dispensed from or upon the request of a veterinarian. It is a constituent of multiple commercially available systemic and topical penicillin-containing products including Flo-cillin™ and Forte Topical™.ⁱⁱⁱ PGP has excellent activity against Gram Positive bacteria including anaerobes; with dosages varying based upon administration protocols, co-administration of other medications, and practitioner preference. Typically, the doses of Procaine Penicillin-G administered to horses greatly exceed the manufacturer's label recommendation.^{iv} Its twice daily intramuscular approach is often preferred to, for example, intravenous doses of potassium penicillin every 6 hours. Combining procaine with penicillin increases the duration of penicillin's effectiveness and can ease the discomfort associated with a large-volume intramuscular injection.

Procaine, as a local anesthetic agent, has the potential to be used as an infiltrative nerve block or intra-articularly enabling a horse compromised by musculoskeletal disease to perform beyond its physical limitations establishing increased risk of injury for the horse and others on the racetrack with it.^v Though not well studied, the use of Procaine in large doses as a CNS stimulant to improve performance in racehorses has been reported. Large procaine doses (concentrations exceeding 600 ng/mL) have been shown to produce excitation in horses.^{vi} Horses exposed to this dosage began pacing, pawing, circling and had a deep-blowing respiratory pattern. However, the effectiveness of this dosage as a CNS stimulant seems to be marginal since many horses quickly became ataxic and uncoordinated, demonstrating exaggerated startle and escape responses.^{vii} It is for these reasons that the use of procaine in proximity to a race must be controlled.

Procaine crosses the cell membrane and will distribute widely throughout the body of the horse.^{viii} Hydrolysis of procaine is the same regardless of its administration as PGP or procaine hydrochloride. Therefore, it is not possible to distinguish procaine administered in conjunction with penicillin for treating an infection from procaine administered alone for its local aesthetic properties.^{ix}

Research Studies

Multiple studies have been performed to determine the pharmacokinetics of procaine following multiple administration protocols.

When administered subcutaneously as a local anesthetic agent, procaine was detectable for a range of 2 to 12 hours in plasma and 23 to 54 hours in urine.^x The detection interval was dependent on the dose given and analytical method applied. As an anesthetic it has a rapid onset of effect with a dose-dependent duration of 10 to 90 minutes.^{xi} Notably, the addition of epinephrine substantially extended the period of analgesia to a range of 180-420 minutes. Even in the absence of measurable effect, low doses of procaine administered subcutaneously result in detectable concentrations in plasma.^{xii}

As noted above, epinephrine can have a profound effect on the duration of local anesthetic activity. The combination of epinephrine and procaine has been demonstrated to provide the same degree of analgesia for up to 3 hours post administration, and a horse could experience maximum analgesic effect with a plasma procaine concentration less than 0.2 ng/ml. This led some to conclude that plasma procaine concentrations poorly correlate with the anesthetic effect resulting from the co-administration of epinephrine and procaine.^{xiii}

When administered intramuscularly, as procaine penicillin-G as an antibacterial agent at therapeutic doses, procaine was detectable for a range of 3 to 36 hours in plasma and of 30 to 425 hours (17 days) in urine depending on dose, frequency and duration of treatment, and analytical method applied.^{xiv} While any local anesthetic effect of procaine resulting from a procaine penicillin-G administration would not be expected to affect race performance, the prolonged detection interval associated with this method of administration confounds making a distinction between therapeutic and illicit use.

After oral and topical administrations, and despite that procaine was not present in detectable concentrations in plasma, urine procaine concentrations were detectable for 54 hours and 30 hours respectively.^{xv}

Scientific Advisory Committee (SAC) Recommendation

Procaine, as PGP, is a valuable medication in the ethical care of racehorses and the SAC supports its appropriate use and recognizes that the use of withdrawal guidance consistent with the detection times as described above, would render the use of PGP impractical. In order to ensure the availability of PGP to veterinarians and prevent the inappropriate use of procaine as a local anesthetic on race day a combination control strategy was devised.

The SAC recommended a multi-pronged regulatory approach for a horse administered therapeutic procaine penicillin-G. It requires 4 following conditions:

1. Notification to the state veterinarian of therapeutic use when treatment is initiated;
2. Discontinuation of PGP by the date of race entry;
3. Mandatory surveillance of the horse for the 6 hours prior to the scheduled post-time, (at owner expense), and
4. A post-race sample plasma procaine concentration of less than 25 ng/mL.

Failure to meet any one of these prongs results in a rule violation.

Practice Tips

Veterinarians should educate clients on the four requirements that must be met when procaine penicillin is used in racing horses as it is the trainer's decision to enter a horse and trainer's responsibility to implement the required pre-race surveillance. Trainers and veterinarians should be vigilant in making treatment-history inquiries for horses transferred to their care. In addition, some dosages and administration methods of procaine penicillin-G can result in plasma concentrations above the 25 ng/ml threshold even after the discontinuation of the drug days before. Clearance testing may be warranted for horses undergoing extended treatment protocols.

References

- ⁱ Tobin, T., *et al*, *Pharmacology of Procaine in the Horse: Pharmacokinetics and Behavioral Effects*, *Am J Vet Res*, 1977; 38(5): 637–47.
- ⁱⁱ Wintser, H.J., *et al*, *Pharmacokinetics of Procaine Injected into the Hock Joint of the Horse*, *Equine Vet. J.*, 1981; 13(1):68-9.
- ⁱⁱⁱ FDA Green Book. Available online at:
<https://animaldrugatfda.fda.gov/adafda/views/#/search>
- ^{iv} https://ohiostate.pressbooks.pub/osuvmcabxuse/chapter/abx_penicillin-equine/
- ^v Tobin, T., *et al.*, *Am J Vet Res*, 1977.
- ^{vi} Tobin, T., *et al.*, *Pharmacology of procaine in the horse: a preliminary report*, *Am J Vet Res* 1976; 37(9): 1107-1110.
- ^{vii} Tobin, T., *et al.*, *Am J Vet Res*, 1976; Sundlof, S., *et al*, *Procaine in the Urine of Racing Greyhounds: Possible Sources*, *Am J Vet Res* 1983; 44(8):1583-1587.
- ^{viii} Tobin, T., *et al*, *Pharmacology of Procaine in the Horse: Pharmacokinetics and Behavioral Effects*, *Am J Vet Res*, 1977; 38(5): 637–47.
- ^{ix} Uboh, C., *et al*, *Pharmacokinetics of Penicillin G Procaine versus Penicillin G Potassium ad Procaine Hydrochloride in Horses*, *Am J Vet Res*, 2000; 61(7):811-15.
- ^x Tobin, T., *et al*, *Am J Vet Res*, 1977; Stevenson, A.J., *et al*, *Plasma Elimination and Urinary Excretion of Procaine after Administration of Different Products to Standardbred Mares*, *Equine Vet. J.*, 1992; 24(2): 118-124; Kuchembuck, N.L., *et al*, *Plasma Concentration and Local Anesthetic Activity of Procaine Hydrochloride Following Subcutaneous Administration to Horses*, *Am J Vet Res*, 2007; 68(5): 495-500; Harkins, J.D., *et al*, *Regulatory Significance of Procaine Residues in Plasma and Urine Samples: Preliminary Communication*, *Equine Vet. J.*, 1996; 28(2):21-125.
- ^{xi} Kuchembuck, N.L., *et al.*, *Am J Vet Res*, 2007; Harkins, J.D., *et al*, *Equine Vet. J.*, 1996; Kamerling, S.G., *et al*, *Differential Effects of Phenylbutazone and Local Anesthetics on Nociception in the Equine*, *Eur. J. Pharmacol.*, 1985; 107: 35-41.
- ^{xii} Kuchembuck, N.L., *et al.*, *Am J Vet Res*, 2007.
- ^{xiii} Kuchembuck, N.L., *et al.*, *Am J Vet Res*, 2007.

^{xiv} Tobin, T., *et al.*, Am J Vet Res, 1977; Stevenson, A.J., *et al.*, Equine Vet. J., 1992; 24(2); Uboh, C., *et al.*, Am J Vet Res, 2000.

^{xv} Stevenson, A.J., *et al.*, Equine Vet. J., 1992.