Equine Communications

A digest of clinical notes and letters.

Letters may include preliminary communications discussing recent developments, first observations of a new disease, a new pathological finding, or any other brief article or case history of outstanding importance or general interest.

Practical review articles and case histories should be written to provide instructive information on a particular technique, disease, or condition that will be relevant for the equine veterinarian in practice.

"Equine Communications" is intended to complement the Journal's editorial and to open the lines of communication among the equine practitioners. Your frequent participation is encouraged. All contributions will be promptly acknowledged.

Pharmacology Review: A Review of the Pharmacology of Procaine in the Horse

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Local anesthetics are drugs which block nerve conduction when applied locally and thus provide relief from pain. They act rapidly on both sensory and motor nerves at the point of injection, and the more lipid soluble ones act when applied directly to mucous membranes. The actions of all commercially available local anesthetics are rapidly reversible. Cocaine was the first local anesthetic discovered, but because of its abuse potential it is no longer available for this use. Procaine was first synthesized in 1905, and since then many other local anesthetics have been synthesized and introduced into clinical medicine.

Procaine is a highly lipid soluble drug which distributes widely and rapidly in the horse. Therefore, after injection by any route, procaine HCl is well and rapidly absorbed and widely distributed. To delay its absorption, procaine for local administration is often given with 1:10,000 epinephrine, which produces local vasoconstriction and thus delays absorption of the drug. Similarly, penicillin-procaine is a poorly absorbed complex of procaine and penicillin, which has the same effect, *i.e.*, slows the absorption of procaine.

In the horse, procaine is rapidly broken down in the blood stream by plasma esterases, and probably also by liver esterases. In blood, procaine has a half-life of about 9 minutes, though its half-life in the horse is considerably longer (50 minutes) because procaine is widely distributed outside the circulatory compartment. Procaine is almost completely metabolized in the horse, less than 1.0% of the total dose being excreted unchanged in the urine. The major metabolites of procaine in the horse appear to be para-aminobenzoic acid and diethylaminoethanol. No information on the fate of diethylaminoethanol in the horse is available.[5]

When used for local anesthesia in joints or for conduction block of nerves, relatively small amounts of procaine are sufficient. In our experiments, 8 ml of a 2% solution of procaine[a] was infused into the synovial sac of the intercarpal joint, using aseptic precautions. After administration by this route, plasma levels of the drug peaked at about 30 minutes at the very low level of about 20 ng/ml. Thereafter, plasma levels of the drug fell away rapidly and were no longer detectable by about 5 hours after dosing.[3]

In contrast to the low and rapidly declining levels observed in plasma, urinary concentrations of procaine after this dose level were high and declined slowly. Urinary concentrations peaked at about 300 ng/ml 6 hours after dosing and then declined slowly. At 24 hours after dosing they were about 20 ng/ml and reached the limits of detection by about 30 hours. Thus, quite substantial and easily detectable urinary levels of procaine were found for about 30 hours after the intra-articular injection of a small amount of procaine HCl.[3]

In another series of experiments, a large amount of procaine (4 grams) was given intramuscularly (IM) to a group of horses. This dose represents about the largest dose of procaine HCl which could be given by any route, since any higher dose will cause signs of central nervous system excitation. In this case, plasma levels peaked at about 500 ng/*ml* about 15 minutes after dosing and declined with a half-life of about 3

[a] Novocain®, Winthrop Laboratories, New York, NY.

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hours to less than detectable levels after 24 hours. As previously, urinary concentrations of the drug peaked at about 1 μg ml 6 hours after dosing and then declined slowly. to reach undetectable levels about 3 days after dosing. These experiments suggest that, after use of large doses of procaine HCl for infiltration anesthesia, at least 3 to 4 days should be allowed for procaine to clear from equine urine.[4]

In another series of experiments, we administered large doses of penicillin-procaine (15 million units IM, containing about 6 grams of procaine) and followed plasma and urinary concentrations of procaine. After administration of this dose, plasma levels of procaine peaked at about 250 ng/ml 1 hour after dosing. This is about one-half to one-third the level of procaine required to produce excitation of the central nervous system, so very much larger doses of procaine-penicillin would be required to produce stimulant effects. Thereafter, plasma levels of procaine fell slowly at first, with a half-life of about 8–10 hours, and then even more slowly. with a half-life of about 24 hours, to become undetectable by the fifth day. This very slow decline in plasma levels of procaine is presumably a reflection of its slow absorption from the injection site.[4]

Urinary concentrations of procaine after procaine-penicillin peaked at 1.5 μg/ml about 24 hours after dosing and then declined slowly. Initially, the apparent half-life of procaine in equine urine paralleled its 8–10-hour half-life in plasma, but thereafter the rate of decline slowed, to give an apparent half-life for procaine in equine urine of about 3 days. Urinary concentrations of procaine were variable, however, with urinary concentrations apparently influenced by the pH of the urine. Urinary levels of procaine were still detectable 13 days after dosing, suggesting that at least 14 days should be allowed after a large dose of procaine-penicillin for the drug to clear the urine.[3]

One unusual aspect of the kinetics of procaine in the horse has been the very prolonged urinary levels of the drug observed. In experiments where this drug was given intravenously, it was cleared from plasma with a half-life of about 50 minutes and was no longer detectable by about 3 hours after dosing. However, substantial levels of the drug were still found in urine by 24 hours after dosing. Because the drug had been given by intravenous (IV) injection, there was no possibility of delayed absorption of the drug accounting for this discrepancy. and these prolonged urinary levels of the drug are not readily explainable.[2,3]

It therefore appears for these experiments that small doses of procaine such as those used to produce local blocks of nerves or joints should be cleared from equine within 30 hours and certainly by 48 hours. After larger doses, such as might be associated with a large infiltration type block. up to 4 days may be required for the drug to clear. After large doses of procaine-penicillin, up to 14 days at least are required to allow the drug to clear. After repeated doses of procaine-penicillin, which would be associated with a prolonged therapy. an even longer time period should be allowed.

Experiments were also conducted to determine the effects of treatment with furosemide[6] on plasma and urinary concentrations of procaine after procaine HCl. These experiments showed no effect whatsoever of furosemide on plasma or urinary levels or clearance times for procaine. Furosemide, therefore, does not act to either "flush" procaine out of the body or to decrease its concentration in urine.[7] About the only way to influence the concentration of procaine in equine urine would be to render the urine alkaline by administering sodium bicarbonate. As a basic drug, procaine distributes less readily into a basic urine and its concentrations in alkaline urine are always lower than those observed in an acidic urine.[1]

The principal forensic problem with procaine is that of distinguishing between procaine administered as penicillin-procaine and that administered as procaine HCl for nerve or joint blocks.[6] Since the only difference between these drugs in the body lies in their different rates of absorption, this provides the only means known to this author of distinguishing between them. Procaine HCl is absorbed rapidly from its local injection site, so blood levels of this drug rise and fall rapidly, with a half-life of not more than 3 hours. In the case of penicillin-procaine, however, blood levels increase slowly and then fall very slowly indeed. The upshot of this is that if an animal is positive for procaine in the urine, a blood sample should be drawn within 12 hours after the first test. If it is still positive for procaine, the drug administered was probably penicillin-procaine. However, in the case of procaine HCl, the drug is cleared from the plasma within 12 hours, so a clear second sample suggests procaine HCl. It should be pointed out that precautions must be taken to block the procaine esterases[5] in equine plasma for these tests, or no procaine whatsoever will be found in any plasma sample.

[6] Lasix®, National Laboratories, Somerville, NJ.

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Other workers have suggested that procaine HCl may be distinguished from penicillin-procaine by virtue of the fact that it exists complexed with the penicillin molecule in the blood and urine. In a series of experiments this investigator was unable to find any evidence for the existence of this postulated complex. To date, therefore, the only way to distinguish between procaine HCl and procaine penicillin would seem to be by virtue of the different rates of decline in their plasma levels.[6]

Another of the reasons that procaine is a banned drug is that it has central stimulant actions in the horse. Studying these actions, we found that horses are highly sensitive to the central stimulant action of procaine, being about 20 times more sensitive to these actions than are humans. In the horse the first signs of central nervous stimulation begin to appear at plasma levels of about 0.6 μg/ml. By the time the plasma level reaches 1.0 μg/ml, the animal is quite excited, pacing, circling, and showing fine muscle tremors along its back. The pacing may be quite poorly coordinated, and the animal stumbles readily. If the dose is increased, the animals become uncontrollable and, in our experiments, usually broke away from the infusion apparatus. Because of the incoordinated and uncontrollable nature of the excitement, procaine would not be a useful stimulant drug prerace. Further, its unusually rapid absorption means that it must be given quite close to race time (15 minutes) to be effective during a race. All of these factors militate strongly against its usefulness as a stimulant drug.[4]

A further problem with procaine from the horsemen's point of view is that it is relatively easy for the analyst to detect. By virtue of the free NH_2 group on the procaine molecule, it derivatizes readily with many chemical markers, which facilitates its detection. Other local anesthetics which lack the free NH_2 group were much more difficult to detect until the recent introduction of the nitrogen phosphorus detector. Now, however, most local anesthetics are, in principle, about equally susceptible to detection.

In summary, procaine is an unpredictable central stimulant which is unlikely to improve the performance of a horse. For reasons which are not clear, urinary concentrations of procaine can be much higher than and persist much longer than plasma levels of the drug. After injection of a small amount of this drug for a local block, at least 30 hours should be allowed for the urine to clear. After a large dose, such as might be used for infiltration anesthesia, 4 days are required. After a large dose of penicillin-procaine, up to 2 weeks may be required. The only method for distinguishing between procaine HCl and penicillin-procaine appears to be on the basis of the very slow clearance of penicillin-procaine from equine plasma and urine.

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