The Pharmacology of Narcotic Analgesics in the Horse. I. The Detection, Pharmacokinetics and Urinary "Clearance Time" of Pentazocine

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Publication # 27 from the Kentucky Equine Drug Research Program, Department of Veterinary Science, College of Agriculture, University of Kentucky, Lexington, KY 40506. Published as Kentucky Agricultural Experiment Station article 78-4-36 with the permission of the Dean and Director, College of Agriculture. Supported by grants from the Kentucky Equine Research Fund and the Patricia Hewitt Foundation.

The data presented in this paper represent part of a dissertation by J. Richard Miller, submitted in partial fulfillment of the requirements for the degree of Master of Science in Toxicology in the Graduate Toxicology Program, University of Kentucky, 1978.

After intravenous (IV) injection, pentazocine[a] (1 mg/kg) was distributed widely in the horse (V_d = 5.7 l/kg) and was extensively (80%) bound to plasma proteins. Pentazocine was distributed relatively slowly in the horse, with an α phase half-time of 27 minutes and an apparent β, or metabolic phase, half-life of about 138 minutes. After intramuscular (IM) injection of 0.66 mg/kg, peak plasma levels occurred at about 30 minutes, and plasma levels thereafter declined in a multi-exponential fashion with a very slow terminal half-life.

About 30% of a dose of pentazocine administered to horses was eliminated in urine as a glucuronide metabolite. Complete hydrolysis of all β-glucuronidase releasable pentazocine from equine urine required at least 16 hours incubation at 37°C with very high glucuronidase concentrations. When analyzed in this way, pentazocine was detectable in urine for up to five days after administration and had an apparent urinary half-life of about eight hours or more. Equine practitioners and horsemen should be aware of this prolonged "clearance time" for pentazocine and avoid racing within six days of pentazocine administration.

Introduction

Pentazocine[a] is a benzomorphan derivative which has some analgesic activity and little dependence potential in man.[1] It is reported to possess between one-fourth and one-sixth of the narcotic potency of morphine and to have a low incidence of side effects.[2] Its pharmacokinetic properties have been studied in some detail in man,[1] and Davis and Sturm[3] have reported on its plasma levels after IM injection in various domestic animals, including the pony.

Pentazocine is occasionally used in equine medicine as a narcotic analgesic and has been detected in postrace drug screening in Kentucky[b] and other states.[3] Because pentazocine is detected in urine primarily as the glucuronide[1] and is excreted for relatively long periods after drug administration, we undertook to study the pharmacokinetic properties of pentazocine in the thoroughbred horse with particular emphasis on the excretion of its metabolites in urine.

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[a] Talwin. Winthrop Laboratories, Sterling Drug Company, New York, NY.

[b] J.W. Blake: *Personal communication*, Kentucky Equine Drug Testing Program (1977).

A further reason for studying the disposition of pentazocine in the horse was to investigate the effects of furosemide on the urinary excretion of drugs eliminated as glucuronides. Because pentazocine is excreted in relatively high concentrations in equine urine as a glucuronide metabolite,[b] it was selected as a starting point for studies on the effects of furosemide on urinary concentrations of drugs eliminated as glucuronide metabolites. Preliminary communications have been reported.[7,9]

Materials and Methods

Animals

Care and maintenance of horses, administration of drugs, and collection of blood and urine samples were as previously described.[8] Unless otherwise noted, all experimental points are the means ± standard errors of the means of experiments on at least four different horses.

Determination of Pentazocine

To allow detection of low nanogram levels of pentazocine in plasma, a derivative of the extracted drug with heptafluorobutyric anhydride (HFBA) was formed and quantitated by gas chromatography with electron capture detection. This method was not satisfactory for urine because of the very high background values obtained after the urine was incubated with β-glucuronidase.[7,9] For detection in this medium, gas chromatography of urine extracts using a nitrogen detector was used.[7]

Pentazocine Determination by Electron Capture Detection. To 2 ml of spiked aqueous or plasma samples, 4 ml of a saturated solution of sodium tetraborate, pH 9.5, and 5 ml of dichloromethane were added, and the whole rotoracked for 20 minutes. At the end of this period the tubes were centrifuged at 3000 xg for 10 minutes and the organic layer was removed. The dichloromethane was evaporated to dryness under vacuum at a temperature of 40°C. The residue was then dissolved in 1 ml of benzene. The benzene was transferred to a 16 × 125 mm culture tube and 100 μl of heptafluorobutyric anhydride (HFBA) was added. The reaction mixtures were incubated at room temperature for 20 minutes. At the end of this period, the reaction mixture was washed with 10 ml of saturated sodium tetraborate, pH 9.5. After centrifugation, the benzene layer was removed and aliquots taken for analysis.

Gas chromatography was on a gas chromatograph[c] equipped with a ^{63}Ni electron capture detector. Separation was on a three-foot glass column (ID 2 mm) packed with 3% OV 101 on 100/120 gas chrom Q. Nitrogen as the carrier gas was set to flow at 30 ml/minute. The injector temperature was 230°C, the column temperature was 205°C, and the detector temperature was 280°C.

[c] Varian 3700, Varian Instruments, Palo Alto, CA.

Pentazocine Determination by Nitrogen Detection. To 0.5 ml of urine, 1.0 ml of saturated KH_2PO_4, pH 5.0, and 0.8 ml of bovine liver β-glucuronidase[d] were added. These were then incubated for 16 hours at 37°C (Figure 3). At the end of the incubation period, 3 to 4 drops of concentrated NH_4OH were added to bring the pH of the system to about 9.5. Then 4 ml of dichloromethane was added, the whole rotoracked for five minutes and centrifuged at 1000 xg for five minutes. The dichloromethane phase was separated and evaporated to dryness at 55°C in a water bath. To the residue, 0.5 ml of benzene was added and aliquots of this taken for gas chromatography.

Chromatography was on a gas chromatograph[e] equipped with a three-foot glass column (ID 2 mm) packed with OV 101 and a nitrogen-phosphorous detector. The injection temperature was 210°C, column temperature 220°C, and the detector manifold temperature was 250°C. Gas flows were 1 ml/minute. H_2 at 8 psi and 100 ml/minute air at 30 psi.

Pentazocine recovered from equine urine had the same retention time as authentic pentazocine at three different column temperatures.

Formation of pentafluoro propionic anhydride (PFPA) derivative of material recovered from urine after administration of pentazocine to horses also yielded material which chromatographed with retention times similar to those of authentic pentazocine treated with PFPA.

Plasma Protein Binding of Pentazocine

Five ml of fresh horse plasma were pipetted into bags of dialysis tubing.[f] These plasma samples were placed in 300 ml Erlenmeyer flasks containing 200 ml of phosphate buffer, pH 7.4, with pentazocine added in concentrations from 10 to 1000 ng/ml. The flasks were sealed[g] and gently shaken in a water bath at 37°C for 18 hours.[8] At the end of the incubation period, 5 ml of buffer and 2 ml of plasma were extracted and analyzed for pentazocine by electron capture detection as described previously. The percentage of drug bound to plasma proteins was determined as previously described.[8]

Chemicals and Reagents

Authentic pentazocine base[h] was used to prepare standards. Injectable pentazocine[i] (30 mg/ml) was the

[d] Glucurase, Sigma Chemical Co., New York, NY.

[e] Perkin Elmer 3920A, Perkins Elmer, Norwalk, CT.

[f] Spectrapor, Spectrum Medical Industries, Los Angeles, CA.

[g] Parafilm, American Can Company, Neenah, WS.

[h] Provided by Sigma Chemical Company, St. Louis, MO.

[i] Talwin, Winthrop Laboratories, Sterling Drug Company, New York, NY.

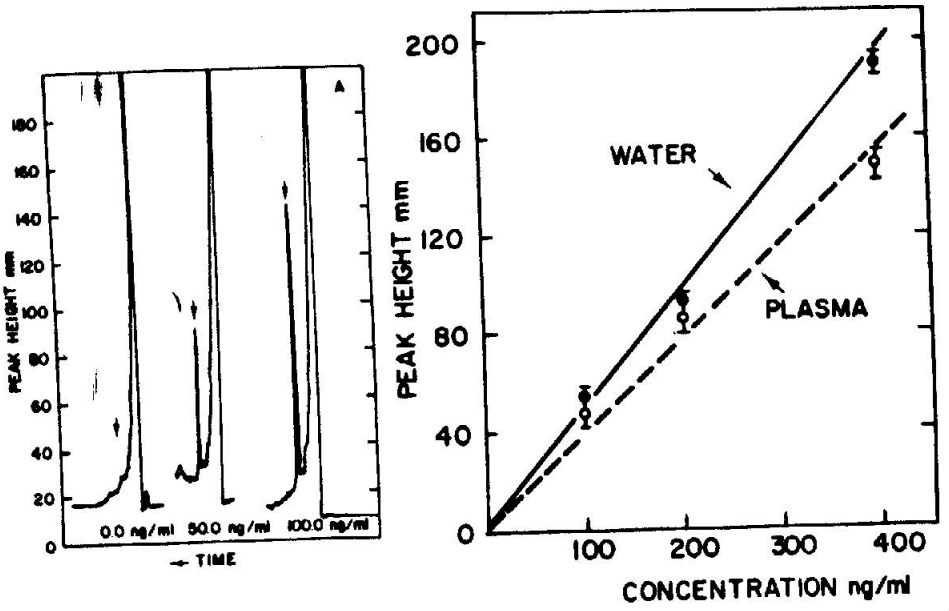


Figure 1. Chromatograms of the pentazocine-heptafluorobutyrate and recovery and quantitation of pentazocine from equine plasma. The left-hand panel shows gas liquid chromatography of the HFBA derivative of 0, 50, and 100 ng/ml of pentazocine extracted from equine plasma as outlined in "Methods." The right-hand panel shows recovery of the indicated concentrations of pentazocine added to water (solid circles, ●-●) or equine plasma (open circles, ○-○). All experimental points represent means ± standard errors of the means of four independent experiments.

drug form used throughout these experiments. Except for liver β-glucuronidase,[j] all other solvents used were of nanograde purity. All glassware used in these experiments was silanized in a 1% solution of dichlorodimethylsilane in toluene.[k]

[j] Provided by Sigma Chemical Company, St. Louis, MO.

[k] Aldrich Chemical Company, Milwaukee, WI.

Results

Figure 1 shows typical chromatograms for the HFBA derivative of pentazocine. When chromatographed as described previously for electron capture detection, the pentazocine gave a sharp peak with a retention time of about 57 seconds, with no interfering peaks. As shown in the right-hand panel, peak height (or detector response)

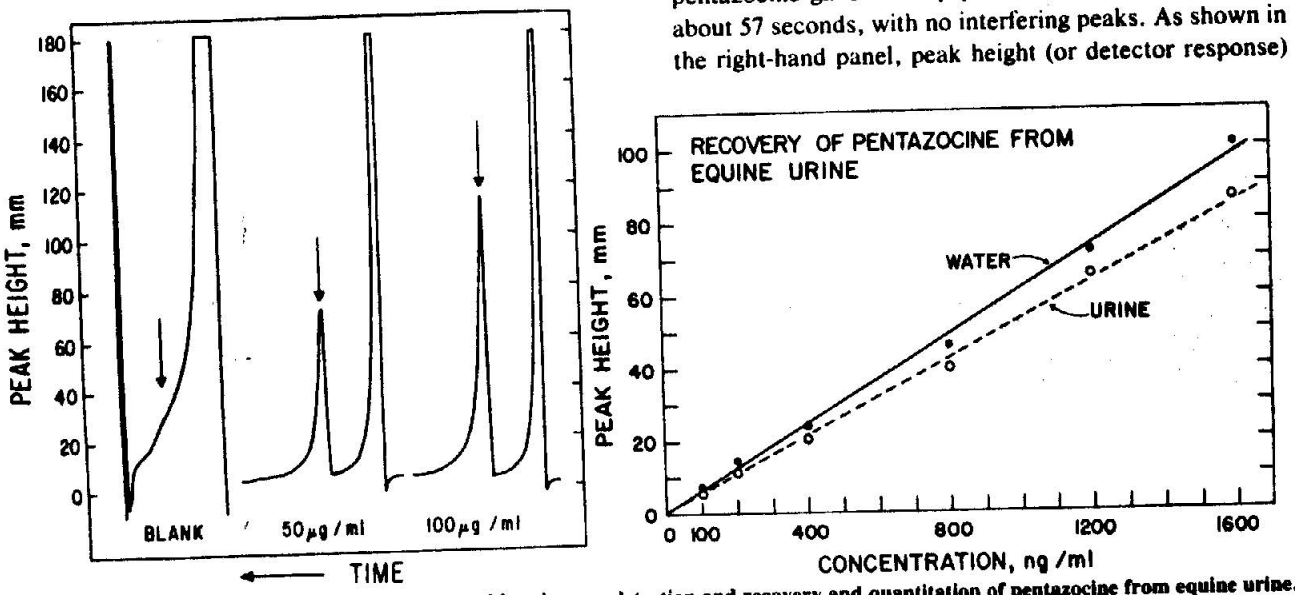


Figure 2. Chromatograms of pentazocine detected by nitrogen detection and recovery and quantitation of pentazocine from equine urine. The left-hand panel shows gas-liquid chromatograms of 0, 50, and 100 μg/ml of pentazocine extracted as described in "Methods" and detected with the nitrogen detector. The right-hand panel shows recovery and quantitation of the indicated concentrations of pentazocine added to water (solid circles, ●-●) or equine urine (open circles, ○-○). All experimental points are the means ± standard error of the means of four independent experiments.

was directly related to the concentration of pentazocine added to the system. As shown in the right-hand panel, the recovery of pentazocine from equine plasma was about 80% of that from water.

Figure 2 shows typical chromatograms of pentazocine recovered from aqueous solutions containing the indicated concentrations of pentazocine according to the method for nitrogen detection. As shown in the right-hand panel, the detector response was linear over the range of 0.0 to 1.6 μg of pentazocine/ml, and recovery from urine was about 90% of that from aqueous solution.

One of the problems experienced in the determination of pentazocine in urine was that of obtaining complete hydrolysis of all β-glucuronidase releasable pentazocine. In early experiments with 10-fold smaller concentrations of β-glucuronidase and about 14-fold larger volumes of urine, complete hydrolysis of all β-glucuronidase releasable pentazocine was not obtained. Figure 3 shows that when the concentration of β-glucuronidase was increased about 10-fold and the volume of urine reduced considerably, no further release of β-glucuronidase releasable pentazocine was obtained after about 16 hours incubation at 37°C.

Figure 4 shows binding of pentazocine to equine plasma proteins at concentrations corresponding to those found *in vivo*. The experiments show that pentazocine was about 80% protein-bound to equine plasma proteins under these conditions.

Figure 5 shows plasma levels of pentazocine after rapid intravenous injection of 1 mg/kg pentazocine in four horses. Plasma levels of pentazocine fell relatively rapidly

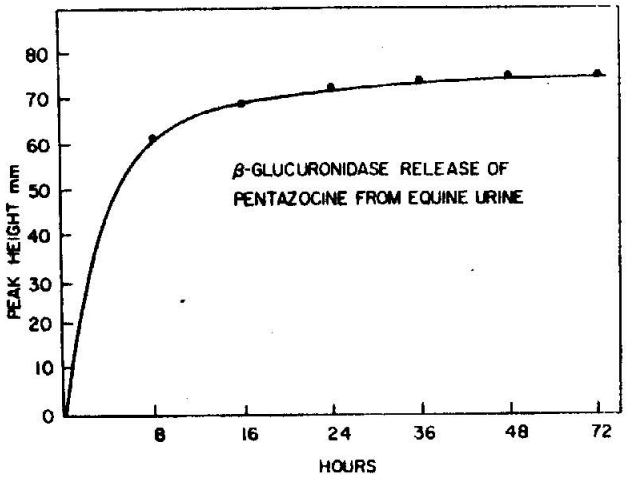


Figure 3. Release of pentazocine from urine by β-glucuronidase. Aliquots of 0.5 ml of equine urine from horses dosed with 1 mg/kg pentazocine were incubated with β-glucuronidase as described in "Methods." The solid circles (●-●) show the amounts of pentazocine released from the urine at the end of the indicated incubation periods. Data points are means of separate experimental determinations on three different urine samples.

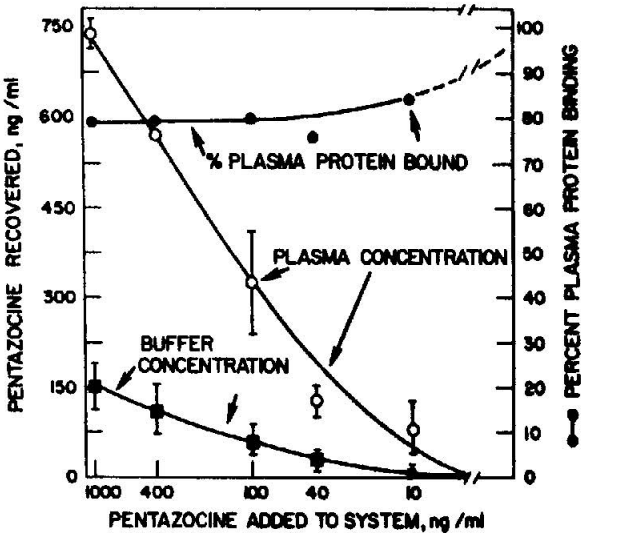


Figure 4. Plasma protein binding of pentazocine. The indicated concentrations of pentazocine were added to 5 ml freshly drawn equine plasma in a spectrophor dialysis bag or to 50 ml of 50 mm phosphate buffer, pH 7.4. The system was then gently shaken at 37°C for 16 hours. At the end of the incubation period aliquots of the plasma and buffer samples were taken for analysis. The solid squares (■-■) show pentazocine concentrations in the buffer; the open circles (○-○) show pentazocine concentrations in the plasma. The solid circles (●-●) show the proportion of pentazocine plasma protein-bound at the indicated concentrations. All data points are the means ± standard error of means of experiments on three different plasma samples.

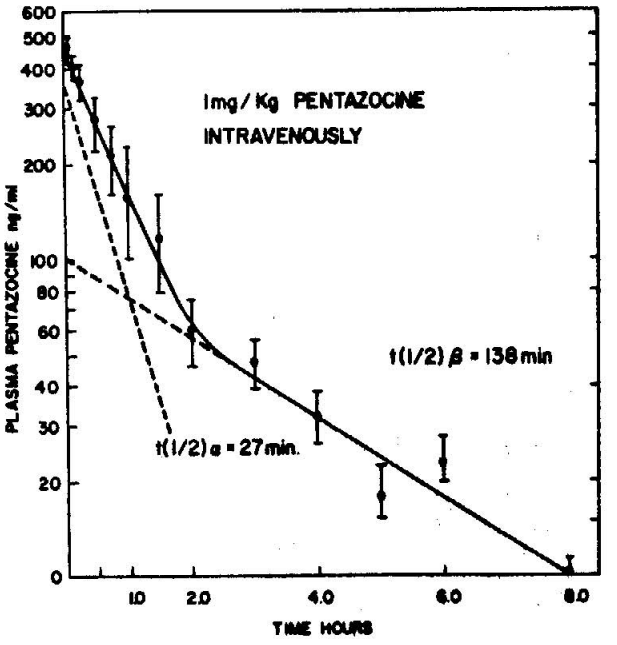
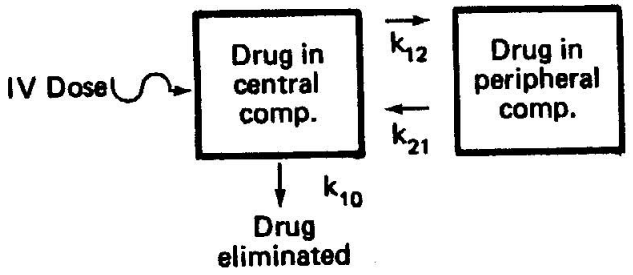


Figure 5. Plasma concentrations after rapid intravenous injection of 1 mg/kg pentazocine. The solid circles (●-●) show plasma concentrations of pentazocine after rapid IV injection of 1 mg/kg pentazocine. The β phase half-life was determined by fitting a linear regression to all data points from two hours on, and is represented by the solid line from two and one-half hours on. The α phase half-life was determined by subtracting the projected β phase from all data points prior to two hours. All data points are the means ± standard errors of the means of determinations on at least four different horses.

for the first two hours, then more slowly, with an apparent terminal half-life of about 138 minutes from a linear regression analysis of all points from 2.5 hours on. This regression line was extrapolated back to a zero time intercept of 102 ng/ml. Curve peeling the half-time for the α, or distribution phase, was determined to be 27 minutes, and the zero time intercept for this phase was 365 ng/ml. From these data and the equations describing a two-compartment open model[4] the pharmacokinetic parameters describing a two-compartment open model derived from and fitting the data of Figure 5 were calculated (Table 1).

TABLE 1

Possible two-compartment open model and kinetic parameters for pentazocine in the horse.



Kinetic Parameters:

k_{10} = 0.0134 min^{-1}
k_{21} = 0.0095 min^{-1}
k_{12} = 0.0076 min^{-1}
A = 365 ng/ml
B = 103 ng/ml
α = 0.0256 min^{-1}
β = 0.005 min^{-1}
$t_{1/2}\alpha$ = 27 min
$t_{1/2}\beta$ = 138 min
V_1 = 2.14 L/kg
Apparent V_d = 2,970 L or 5.7 L/kg
Corrected V_d = 14,850 L or 38.5 L/kg

Figure 6 shows urinary concentrations of pentazocine following intravenous (IV) injection of 1 mg/kg. Urinary concentrations of pentazocine declined rapidly at first, then more slowly, to yield an eventual urinary half-life of about eight hours over the following four days. Pentazocine was detectable in equine urine for up to 100 hours after its intravenous administration.

Figure 7 shows plasma levels of pentazocine after IM injection of 0.66 mg/kg. Plasma levels of the drug rose

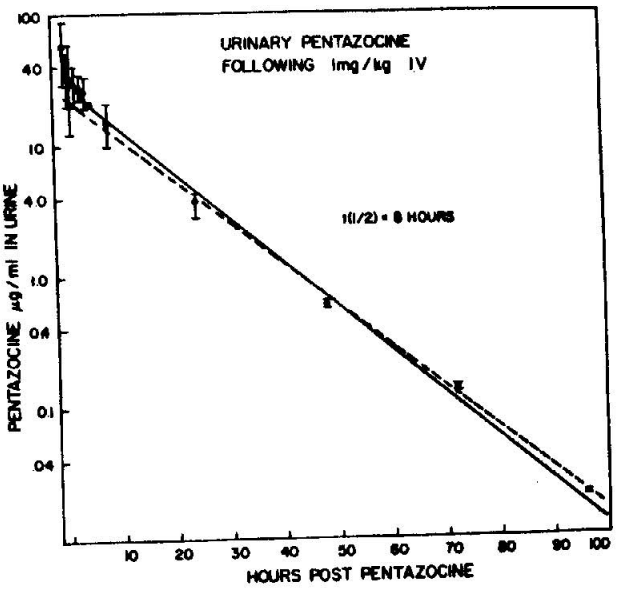


Figure 6. Urinary concentrations of pentazocine following 1 mg/kg intravenously. The solid circles (●-●) show urinary concentrations of pentazocine following 1 mg/kg IV. The solid line was fitted to the data points by eye. The dotted line represents a least squares regression fit to all the points from 10 hours on. All points are the means ± the standard errors of the means of determinations on at least four different horses.

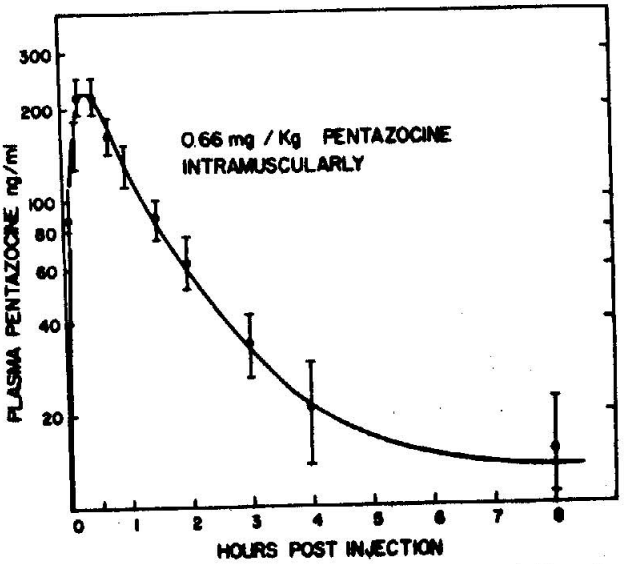


Figure 7. Plasma levels of pentazocine following 0.66 mg/kg intramuscularly. The solid circles (●-●) show plasma levels of pentazocine after 0.66 mg/kg pentazocine was administered by deep intramuscular injection. All data points are means ± the standard errors of the means of determinations on four different horses.

slowly, peaked at about 30 minutes and then declined. This decline was relatively rapid at first, with a half-life of about one hour, but the later decline was slow, with a half-life of about eight hours in the terminal phase. Comparison of the areas under the curves and correction for differences in doses indicated that pentazocine was essentially completely absorbed after IM injection.

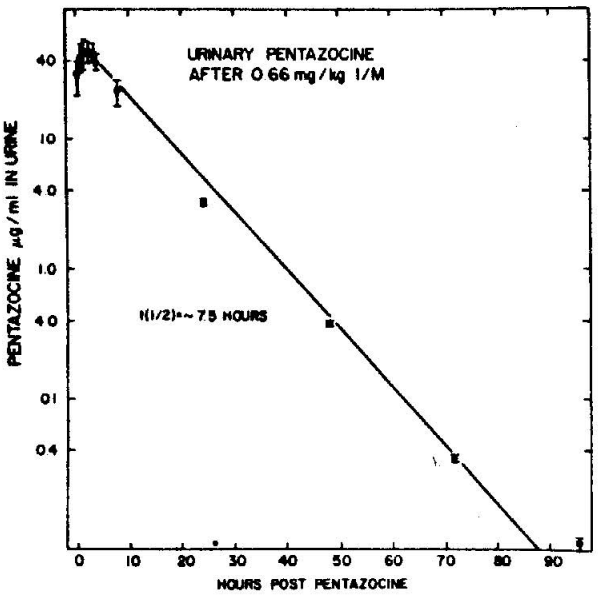


Figure 8. Urinary levels of pentazocine following 0.66 mg/kg intramuscularly. The solid circles (●-●) show urinary levels following administration of 0.66 mg/kg pentazocine by deep intramuscular injection. All points are the means of determinations on at least four different horses.

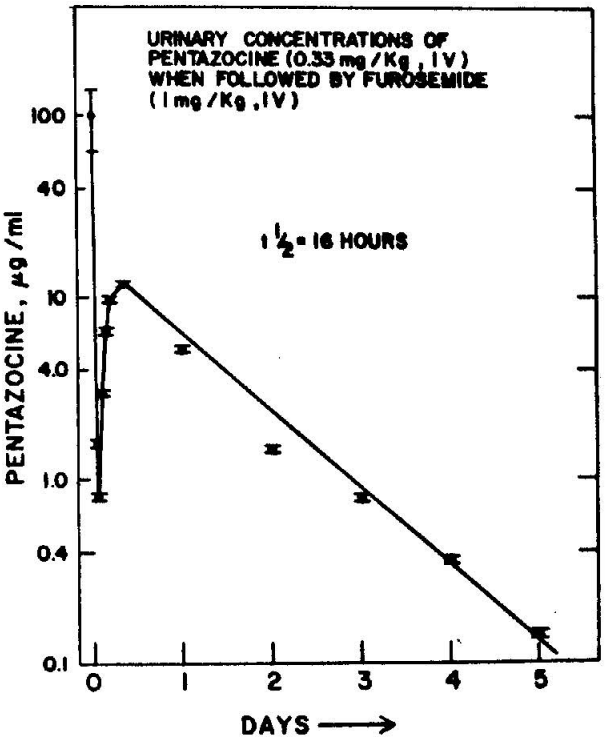


Figure 9. Urinary concentrations of pentazocine (0.33 mg/kg IV) when followed by furosemide (1 mg/kg IV). The solid circles (●-●) show urinary concentrations following IV injection of 0.33 mg/kg pentazocine and 1 mg/kg furosemide IV at 30 minutes. All data points are the means ± standard errors of the means of determination on at least four different horses.

Figure 8 shows urinary levels of pentazocine after rapid IM injection of 0.66 mg/kg of pentazocine. Urinary concentrations of the drug increased for the first three hours, but thereafter declined exponentially with a half-life of about 7.5 hours to become undetectable in equine urine by the fith day after dosing.

Figure 9 shows urinary concentrations of pentazocine when an intravenous (IV) dose of 0.33 mg/kg was followed by 1 mg/kg furosemide IM at 30 minutes. Urinary concentrations of the drug fell very rapidly at first, to less than 1 μg/ml. This value compares with values of about 40 μg/ml in control experiments reported elsewhere.[7] Thereafter, urinary concentrations of the drug increased until the eighth hour after dosing, from which point on plasma levels of the drug again declined exponentially, with an apparent half-life of about 16 hours, to become undetectable on the sixth day postdosing.

Discussion

Two analytical methods were required for this study because of the difficulty in detecting this drug in equine plasma and urine. For detection of pentazocine at the dose levels used in these studies, formation of the HFBA derivative and electron capture detection was the only method available to us which was sufficiently sensitive to detect pentazocine at low nanogram levels in equine plasma. Despite the high sensitivity of this method, the dose of the drug had to be increased to 1 mg/kg to allow detection of an apparent β, or elimination phase.

Pentazocine could not be detected in equine urine by electron capture detection because of overwhelming background problems. Prolonged enzymatic hydrolysis of equine urine, such as was required for complete hydrolysis of conjugated pentazocine, apparently released large quantities of other materials which reacted readily with HFBA and chromatographed with similar retention times to pentazocine-HFBA. To get around this problem, nitrogen detection was utilized. The relative specificity of the nitrogen detector allowed unhindered detection of pentazocine and eliminated the background problems encountered with the electron capture detection method.

A further problem encountered in the recovery of pentazocine from equine urine was the difficulty of obtaining complete hydrolysis of all conjugated pentazocine. Thus, earlier experiments utilizing incubation conditions routinely used in equine drug testing laboratories (*e.g.* 1 ml of β-glucuronidase, 6 to 8 ml of urine, incubation at 40° C for up to five hours) did not hydrolyze more than a fraction of the pentazocine available in our urine samples. To overcome this problem, the amount of urine added to the system was reduced to 0.5 ml and the incuba-

tion time extended to up to 72 hours. Under these conditions about 95% of the available pentazocine was released within 16 hours, with the remainder being released very slowly.

The reason for this very slow release of pentazocine from pentazocine glucuronide is not clear. It may be that the pentazocine-glucuronide bond is sterically hindered and poorly accessible to β-glucuronidase. However, a more likely explanation is that many other glucuronides in equine urine compete for the available β-glucuronidase catalytic sites and therefore act as competitive inhibitors of the reaction of interest. In any event, it is clear that for accurate quantitative work on glucuronide metabolites of pentazocine or other drugs in equine urine, careful hydrolytic procedures and relatively specific detection methods are required.

After IV injection, pentazocine was distributed relatively slowly to the tissues ($t\frac{1}{2}\alpha$ = 27 minutes), and this phase was followed by an even slower decline in drug levels with an apparent half-life on the order of about 138 minutes. One possible interpretation for this is that the kinetics of pentazocine in the horse may be described by a simple two-compartment open model (Table 1) and the terminal half-life observed in Figure 5 may be the true terminal half-life for pentazocine in the horse.

The principal problem with this interpretation is the observation of the very slow terminal half-life of pentazocine after its IM injection, and its similarly slow urinary half-life. These observations are consistent with the hypothesis that the true plasma half-life of pentazocine in the horse may be longer than that observed in the IV experiments, and that the limitations of sensitivity in the IV experiments prevent detection of the true β-phase half-life which is presumably about eight hours or greater. Although urinary volumes were not measured in these experiments, it seems reasonable to assume that urinary output in these three sets of horses over periods of up to six days were approximately constant, and that the urinary half-life of the drug represents its rate of plasma level decline.

This possibility of a slow plasma half-life for pentazocine is in good agreement with recent work in this laboratory on the behavioral effects of narcotic drugs in horses. These experiments have shown that motor responses to narcotic drugs in the horse decay very slowly indeed, with apparent half-lives of up to eight hours. It is thus more than likely that the true plasma half-life of pentazocine in the horse is the eight-hour figure suggested by the urinary and IM data, and not the figure suggested by the IV data.

Independently of the route by which pentazocine was administered, urinary elimination of its glucuronide metabolite was slow, and urinary levels were found for considerable times. Thus, after IV administration of 1 mg/kg, urinary levels of pentazocine were detectable for four days postdosing, and urinary levels of the drug declined with an apparent half-life of about eight hours. Similarly, after IM administration of 0.66 mg/kg of pentazocine, urinary concentrations of the drug again declined slowly and the drug was detectable for up to 100 hours postdosing. Finally, after IV administration of an even lower dose (0.33 mg/kg), which was followed by a dose of furosemide, urinary levels of the drug declined even more slowly ($t\frac{1}{2}$ = 16 hours), and the drug remained detectable for up to five days postdosing.

Studying plasma levels of pentazocine in man, Berkowitz *et al.*[2] observed peak plasma levels of 140 ng/ml after doses of 0.66 mg/kg, somewhat less than those observed in this study. In contrast to the results reported here, Berkowitz *et al.*[2] observed good correlation between the terminal half-lives of pentazocine in man after IV and IM administration, with a terminal half-life in both cases of about 120 minutes. The reason for the prolonged plasma half-life of pentazocine after IM administration in the studies reported here remains unclear. In addition, the half-time for the α phase reported by both Berkowitz *et al.*[2] and Beckett *et al.*[1] appears to be very much faster than that observed in these experiments in horses.

Berkowitz *et al.*[2] also reported the relationship between plasma levels of pentazocine and its analgesic effect. After IM injection, the analgesic effect followed plasma levels of the drug with about a 15-minute lag time. Thus, after IM injection of pentazocine in the horse, peak analgesic effect might be expected at about one hour. It is somewhat more difficult to estimate the time of peak analgesic effect after IV administration, but 30 minutes to one hour postadministration appears the likely time for peak effect, in view of the slow distribution of the drug from plasma. It is, however, considerably more difficult to estimate how good the analgesic effect is likely to be in the horse. In his studies, Berkowitz apparently required plasma levels of about 30 to 50 ng/ml of pentazocine to attain moderate to good analgesia. If one can assume that analgesia in the horse is associated with the same plasma level of pentazocine as in humans, analgesia might be expected in the horse for about three hours after both 1 mg/kg IV and 0.66 mg/kg IM.

Studying the clinical response to pentazocine in a colic model, Lowe[5] reported little or no analgesia due to pentazocine[1] at 1.1 mg/kg and only about 90 minutes of

[1] Talwin. Winthrop Laboratories, Sterling Drug Company, New York, NY.

analgesia at four times this dose.[7] These data would seem to suggest that higher plasma levels of pentazocine are required to effectively combat pain in the horse than in the human. It should be borne in mind, however, that one of the basic pharmacological actions of all narcotic analgesics is to increase tone in the gastrointestinal tract, and that this component of the pharmacological action will tend to aggravate colic pain. It may be, therefore, that the horse and human attain analgesia at about the same plasma levels of pentazocine and that discrepancies between data in the horse[6,7] and the human[2] are due to the particular model[6,7] used to estimate the analgesic response to pentazocine in the horse.

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