J. vet. Pharmacol. Therap. 18, 397–406, 1995.

A review of the pharmacology, pharmacokinetics, and regulatory control in the US of local anaesthetics in the horse

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(Paper received 1 August 1994; accepted for publication 12 April 1995)

INTRODUCTION

The first local anaesthetic (LA) was cocaine, derived from the leaves of the *Erythroxylon coca* shrub in the Andes Mountains. The drug was first isolated in 1860. When touched to the tongue, it has a bitter taste, and the tongue becomes numb and loses sensation. Cocaine was first used clinically as a LA in ophthalmology and dentistry. Procaine, a non-addictive LA, was developed as the first synthetic analogue of cocaine in 1905.

Local anaesthetics block the conduction of nerve impulses when applied locally to nerve tissue. Ideally, a LA should (1) be non-irritating to local tissue, (2) be able to penetrate body tissues well, (3) cause no permanent damage to nerve tissue, (4) possess low systemic toxicity, (5) be effective when applied topically or injected, (6) have a rapid onset, and (7) have a moderate duration of action to allow adequate time to perform surgery but not require excessive time for recovery. The advantages of local versus general anaesthesia include decreased expense, increased safety, low toxicity and minimal recovery problems.

MECHANISM OF ACTION

Block of the nerve signal by LAs is due to inhibition of voltage-gated Na^+ channels through interference with the changes in conformation that occur during channel activation. Channel inhibition of LAs increases with repeated depolarization, a phenomenon called phasic block. Because either more channels are susceptible to LAs during depolarization or LAs bind to the channel conformations during depolarization with greater affinity, phasic block causes increased binding of LAs (Butterworth & Strichartz, 1990). A nerve at rest offers little opportunity for the anaesthetic agent to inhibit the Na^+ channels, but a recently stimulated nerve (e.g. an afferent nerve from a painful fetlock joint) will attain a greater degree of block from the LA (Courtney & Strichartz, 1987).

Peripheral nerves contain both sensory and motor, myelinated and unmyelinated neurons. Generally, small, unmyelinated nerve fibres are more susceptible to the action of the LAs than are larger fibres. However, anatomical fibre type also determines susceptibility to LAs, so there is overlap of fibre sensitivity. For example, some myelinated A-δ fibres are blocked earlier and with less LA than most unmyelinated C fibres (Nathan & Sears, 1961). Pain is the first sensory modality to disappear, followed by cold, warmth, touch and deep pressure (Ritchie & Greene, 1990).

ONSET AND DURATION OF ANAESTHESIA

Injection of a LA into or around a peripheral nerve provides a high degree of anaesthesia with relatively small amounts of anaesthetic agent. The areas of sensory and motor denervation usually begin a few centimetres distal to the injection site. The rate of onset of anaesthesia varies with the agent used (Table 1).

Published as Kentucky Agricultural Experiment Station Article No. 93-4-175 with the approval of the Dean and Director, College of Agriculture and Kentucky Agricultural Experiment Station.
Published as no. 186 from the Kentucky Equine Drug Testing and Research Programs, Department of Veterinary Science and the Graduate Center for Toxicology, University of Kentucky.

Table 1. Local anaesthetic agents commonly used in horses (adapted from Lumb & Jones, 1984)

Anaesthetic	Dose (mg)	No. of positives	Clearance time (days)	Relative toxicity	Potency	RCI class	Onset	Duration (min)
Procaine	80–1600	73	30+	1.0	1	3	Slow	30–90
Lidocaine	100–400	2	2.5+	1.0–1.4	1.5–2	2	Fast	45–180
Mepivacaine	60–300	4	2‡	1.5	1.5–2	2	Fast	120–180
Bupivacaine	50–200	1	1‡	< 1.0	8	2	Intermediate	180–600
Benzocaine	> 800	7	> 2	NA	NA	5	NA	NA

*Clearance times cited are the longest clearance times reported in the literature. † From Chalmers *et al.* (1987). ‡ From Agriculture Canada (1991). NA, not applicable.

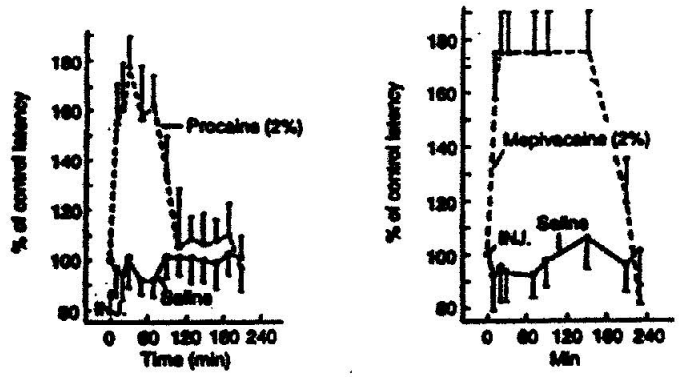


Fig. 1. Nerve block action of 2% procaine and 2% mepivacaine on hoof withdrawal reflex latency. Values are expressed as per cent of mean pre-treatment (control) latency. Reproduced with permission from Kamerling *et al.* (1985).

Lidocaine provides anaesthesia within about 3 min, while onset of anaesthesia with bupivacaine takes about 15 min.

The duration of a nerve block depends on the physicochemical characteristics of the anaesthetic agent used. The more potent agents are more lipid soluble, and agents with longer durations of action are highly protein bound to membrane proteins (Day & Skarda, 1991). Procaine anaesthesia has a relatively short duration (30–90 min), lidocaine and mepivacaine are intermediate in duration (45–180 min) and bupivacaine has a relatively long duration of action (180–600 min). The duration of anaesthesia can be extended by injecting a larger volume of anaesthetic agent, but this strategy has practical limitations.

Prolonging contact time increases the duration of effect of a LA. The LAs used clinically often contain a vasoconstrictor (usually adrenaline or phenylephrine), which prolongs the anaesthetic effect by reducing the rate at which the anaesthetic is absorbed from the site of injection.

EFFECT ON PAIN PERCEPTION

In equine medicine, anaesthetic agents are frequently administered locally around peripheral nerves and intrasynovially to localise pain and diagnose lameneses (Lindsay *et al.*, 1981; Taylor, 1991). When anaesthetics are administered locally, the hair should be clipped, and the skin should be scrubbed with a surgical disinfectant. Additional precautions are required to prevent the introduction of infection during intrasynovial injections, including sterile gloves and, very importantly, a new, unopened bottle of anaesthetic (Taylor, 1991).

Lindsey *et al.* (1981) demonstrated the pain-relieving effect of intra-articular anaesthesia. A 4-year-old Quarter horse mare was examined because of a grade III lameness after considerable exercise. Five minutes after 2% mepivacaine hydrochloride (HCl) injection into the affected hock joint, lameness was no longer evident. Duration of the pain relief was not reported.

Kamerling *et al.* (1985) studied the effect of anaesthetic agents administered locally around peripheral nerves in horses. Pain perception was examined using radiant thermal stimuli from a heat lamp. Time of hoof withdrawal was measured to determine the degree of anaesthesia provided by anaesthetic agents. Figure 1 illustrates the significant increase in pain threshold in horses following procaine and mepivacaine administration. Onset of anaesthesia was quicker and longer lasting with mepivacaine. In contrast, phenylbutazone had no effect on nociception (Kamerling *et al.* (1985).

INTRA-ARTICULAR ANAESTHESIA

The effect of anaesthetic agents on equine synovial fluid has been investigated (White *et al.*, (1989). Intra-articular lidocaine HCl and mepivacaine HCl significantly altered synovial fluid of the injected joint. Total nucleated cell count and absolute monocyte count of the synovial fluid were significantly increased following separate injections of both agents. Additionally, intra-articular mepivacaine HCl increased the number of neutrophils in synovial fluid. This study did not detect any significant differences between the response of synovial fluid to the two anaesthetic agents. Furthermore, the change in synovial fluid cellularity confirmed results of an earlier study (Wagner *et al.*, (1982) suggesting injurious effects from both arthrocentesis and intra-articular injection.

LOCAL ANAESTHETICS OF CLINICAL IMPORTANCE

Procaine is the most commonly confirmed positive among LAs in racehorses owing to its presence in procaine penicillin; procaine HCl is seldom used as a LA in veterinary medicine. Lidocaine hydrocloride has replaced procaine as the LA of choice in veteri-

nary medicine and produces local anaesthesia that is faster in onset, longer lasting and more extensive than that of procaine. The pharmacological properties of mepivacaine (Carbocaine®) are very similar to those of lidocaine, however the onset of anaesthesia is more rapid and the duration is longer than that of lidocaine. Bupivacaine (Marcaine®, Sensorcaine®) is one of the longest acting LAs. The drug has little tendency to accumulate; therefore, the likelihood of systemic toxicity is low. Benzocaine is poorly soluble in water and its use is limited to topical preparations.

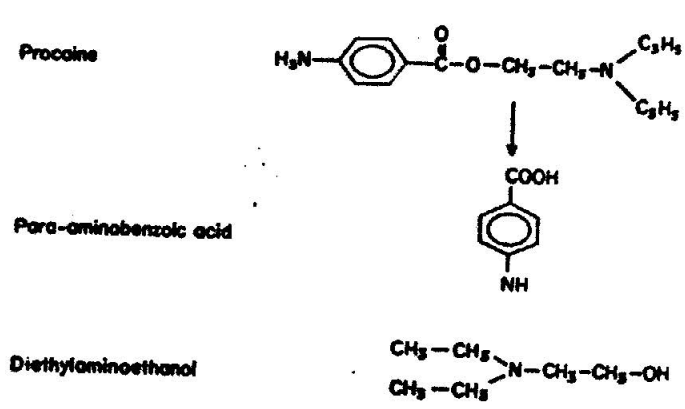


Fig. 2. Structure of procain and its major metabolites.

PROCAINE

Disposition and metabolism

In the horse, plasma (and probably liver) esterases rapidly hydrolyse procaine with half-lives of 9.0 and 7.5–12 min respectively (Tobin *et al.*, 1976a, 1977). Less than 1% of a dose of procaine is excreted unchanged in the urine. *para*-Aminobenzoic acid and diethylaminoethanol are the products of procaine hydrolysis (Fig. 2; Tobin *et al.*, 1976b). Procaine is also excreted in the urine as a conjugate with glucuronic acid. The short *in vitro* half-lives are consistent with an α-phase half-life of about 5 min following intravenous injection of procaine HCl (2.5 mg/kg). The β-phase of the elimination curve following intravenous administration showed a half-life of 45 min (Tobin *et al.*, 1977).

In pharmacokinetic and forensic studies, procaine hydrolysis in the blood samples collected must be prevented to quantify accurately the blood concentration present at the time of collection. Esterases may be inhibited by adding sodium arsenite or physostigmine to the blood collection tubes before collection. Cooling the blood tubes (to 0°C) also reduces the rate of procaine hydrolysis (Tobin *et al.*, 1976b).

Following intra-articular, subcutaneous and intramuscular injections of procaine HCl (0.33, 3.3 and 10 mg/kg respectively), plasma concentrations decreased with half-lives of about 97, 65 and 125 min respectively. The apparent half-life of procaine in joint fluid was estimated to be 48 min (Wintzer *et al.*, 1981).

Pharmacokinetics

After intramuscular injection of procaine penicillin (33,000 IU/kg), plasma concentrations decreased with a half-life of about 600 min (Tobin *et al.*, 1977). In another study, different procaine penicillin preparations were administered with procaine dosages varying from 0.83 to 2.48 g. Peak plasma procaine concentrations occurred at 10 min for Azimycin® (Schering Canada, Pointe-Claire, Quebec, Canada) and 3 h for Cillimycin® (Austin Labs, Joliette, Quebec, Canada). Plasma procaine was detected for only 3 h after Azimycin® administration but for 20 h following Penamycin® (Sterivet Labs, Mississauga, Ontario, Canada) and Cillimycin® administration. Urinary procaine concentration peaked at 0.5–1.5 h post dosing, and procaine was detectable for 144 h after Azimycin® and 78 h after Cillimycin® and Penamycin® administration (Stevenson *et al.*, 1992).

Saturation of plasma esterases occurs at a procaine concentration of about 5 μg/mL. Since procaine toxicity occurs at a plasma procaine concentration of about 600 ng/mL in the horse, plasma esterase saturation would not be expected *in vivo*. Therefore, the rate of procaine hydrolysis depends directly on the plasma concentration of procaine.

The esterase activity of synovial fluid is only 20% of that of plasma (Tobin *et al.*, 1976b). However, it would appear that synovial esterase saturation does not occur *in vivo* since the half-lives of procaine in plasma (45 min) and synovial fluid (48 min) are similar.

Following intramuscular injection of procaine (4 g), peak plasma concentrations (600 ng/mL) were reached 20 min post dosing. Excitation of the central nervous system (CNS) was observed in one-third of the horses attaining this plasma concentration of procaine (Tobin *et al.*, 1977).

Peak plasma procaine concentration (20 ng/mL) was reached 30 min after intraarticular injection (160 mg), and procaine was no longer detectable 5 h after dosing. In contrast, urinary concentration of procaine peaked (300 ng/mL) at 6 h after dosing and procaine was no longer detectable 30 h post injection (Tobin & Blake, 1977).

In a Canadian study (Stevenson *et al.*, 1992), peak plasma concentration was reached 20–40 min after subcutaneous injection of procaine regardless of dose (80–1600 mg). However, detection time was dose-dependent, with procaine being detectable for 1 and 6 h after 80 and 1600 mg doses respectively. Similarly, peak urinary concentration was attained 1.5–3.0 h post dosing regardless of dose, and detection time was dose-dependent, with the 80–200 mg doses persisting for 23 h and the 1600 mg dose persisting for 30–54 h.

After intravenous injection of procaine (2.5 mg/kg), the estimated peak plasma concentration was 1200 ng/mL. This decreased to 600 ng/mL at the first sampling time (10 min post injection; Tobin *et al.*, 1977). Plasma procaine was no longer detectable 2 h post dosing. However, urinary procaine concentrations peaked at 4 h and were detectable up to 24 h post dosing (Tobin & Blake, 1977).

One unusual aspect of the kinetics of procaine in horses is the high and prolonged urinary concentrations of the drug. Even when procaine is administered intravenously (when delayed absorption is not a factor), substantial concentrations of the drug are present

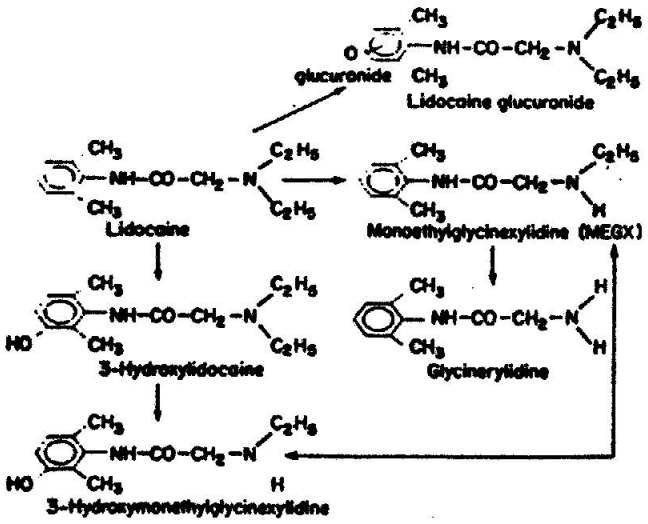


Fig. 3. Structure of lidocaine and its major metabolites.

in urine long after it is no longer detectable in plasma. In one study (Stevenson *et al.*, 1992) in which a topical procaine preparation was applied, procaine could not be detected in plasma but was measured in urine up to 30 h post dosing. These findings demonstrate that urine is the most appropriate fluid for highly sensitive detection of procaine, regardless of the route of administration (Stevenson *et al.*, 1992).

Most of the research to date on procaine in equine urine deals primarily with parent procaine and not with its metabolites. One of the authors (R.A.S.) has observed significant concentrations of procaine glucuronide in refereed samples containing low concentrations of procaine and subjected to enzymatic hydrolysis. This suggests that procaine glucuronide may be found in equine urine in significant quantities, especially when the concentration of procaine in the sample is low. The persistent presence of procaine glucuronide suggests that enzymatic hydrolysis of procaine samples would significantly increase the procaine concentrations. Since the concentrations of procaine glucuronide are much less likely to be influenced by urinary pH than parent procaine, procaine glucuronide may have potential for use in determining a urinary threshold concentration for procaine.

Toxicity

Historically, adverse reactions in horses following procaine penicillin administration have been attributed to penicillin anaphylaxis (Green *et al.*, 1974). However, recent reviews have implicated procaine toxicity as the major cause of adverse reactions in horses (Nielsen *et al.*, 1988; Chapman *et al.*, 1992).

In humans, procaine toxicity is characterised by one or all of the following: fearfulness, restlessness, dementia, muscle tremors, change in respiratory pattern, continuous running, ataxia, lateral recumbency and death (Tobin & Blake, 1976; Nielsen *et al.*, 1988; Chapman *et al.*, 1992). Following intravenous infusion of procaine HCl, horses show CNS excitation at plasma concentrations of about 600 ng/mL and become uncontrollable at plasma concentrations of about 1,500 ng/mL (Tobin & Blake, 1976). Procaine stimulation of the CNS in horses occurs at only one-twentieth the dose rate associated with CNS excitation in humans (Tobin & Blake, 1976). However, procaine toxicity is rare in horses owing to the relatively low dose required for local anaesthesia.

Pretreatment with diazepam 2 h before administering a dose of procaine adequate to stimulate the CNS eliminates the behavioural and locomotor effects. However, diazepam treatment 20 s after procaine administration does not ameliorate the signs of procaine toxicity (Chapman *et al.*, 1992).

One study (Chapman *et al.*, 1992) revealed that procaine penicillin preparations for veterinary use contain a higher concentration of soluble procaine than preparations intended for humans. Furthermore, storage at 50°C for 1–7 days (to replicate storage conditions in a veterinarian's car trunk) significantly increased soluble procaine concentrations in all veterinary, but not human, preparations. It was concluded that a horse treated with a recommended dose of 20 mL of procaine penicillin (after heating to 50°C) could receive 1–1.6 g of soluble procaine (range of 2–3.2 mg/kg for a 500-kg horse). Tobin *et al.* (1977) reported that i.v. administration of 2.5 mg/kg procaine produced CNS signs within 30–40 s. Therefore, inadvertent intravenous administration of procaine penicillin could cause procaine toxicity. To prevent inadvertent i.v. administration, at least one manufacturer of procaine penicillin supplies a needle with a clear hub. Since the opaque white suspension may hinder the visualization of blood in the syringe barrel, blood can be more easily seen through a clear needle hub.

Regulatory detection

Procaine is detectable by thin-layer chromatography (TLC) analysis and enzyme-linked immunosorbent assays (ELISAs), with at least two different ELISA tests for procaine commercially available. Procaine is detectable at extremely low concentrations, 1 and 5 ng/mL by ELISA and TLC analyses respectively. Because of the prolonged detection of procaine in urine following procaine penicillin administration in horses, recent research has determined forensic threshold concentrations for procaine in plasma. Harkins *et al.* 1995) determined that a dose of only 5.0 mg of procaine HCl produced significant anaesthesia. As noted earlier, procaine can be detected in urine for at least 18 days after the last dose of procaine penicillin.

LIDOCAINE

Disposition and metabolism

The first step in the metabolism of lidocaine in rats and rabbits is *N*-dealkylation of the tertiary amine to form the secondary amine, monoethylglycinexylidine (MEGX), which is much more susceptible to amide hydrolysis (Fig. 3). Only 6% of a dose of lidocaine is excreted unchanged in man during the first 12 h after injection (Hollunger, 1960).

Pharmacokinetics and pharmacodynamics

Following unilateral and bilateral cervicothoracic ganglion blockade in horses, onset of sedation occurred within 10–30 min and persisted for 60–120 min. Maximal mean venous plasma concentration of lidocaine after unilateral and bilateral blockade were 0.86 and 1.14 μg/mL respectively and occurred 26 and 31 min respectively, post dosing (Skarda *et al.*, 1987). Following subcutaneous infiltration of the plantar nerves, peak plasma lidocaine (0.2 μg/mL) occurred at 1 h post dosing (Courtot, 1979). Following a 'line block' in a horse at a dose of 10 mg/kg, a peak plasma lidocaine concentration of approximately 3.4 μg/mL was detected 15 min post dosing (Heavner, 1981). Lidocaine has a short half-life of about 30 min in the rat (Keenaghan & Boyes, 1972), 45–60 min in the dog (Boyes *et al.*, 1970; Wilke *et al.*, 1983) and 90 min in human beings (Boyes *et al.*, 1971) following i.v. administration.

Toxicity

In man, overdose of lidocaine causes atrial fibrillation. Side-effects include sleepiness, dizziness, paraesthesia, altered mental status and seizures (Ritchie & Greene, 1990). Toxic concentrations of lidocaine in man, dogs and sheep occur at 4–10 μg/mL (Skarda *et al.*, 1987). Several studies have measured plasma lidocaine concentrations after ganglion blockade (Skarda *et al.*, 1987) and subcutaneous infiltration (Courtot, 1979; Heavner, 1981). Plasma concentrations of lidocaine were minimal following parenteral injection and unilateral or bilateral cervicothoracic ganglion blockade. Maximal plasma lidocaine concentrations measured in horses were < 2.5 μg/mL, and cardiovascular measurements showed no evidence of toxicity at that concentration (Skarda *et al.*, 1987).

Regulatory detection

In a study by Short *et al.* (1988a), very little parent lidocaine was detected in samples not subjected to enzymatic hydrolysis. The concentration of MEGX in urine is high 3–5 h after lidocaine administration; therefore, detection of MEGX is suggestive of administration of its precursor, lidocaine.

Following infiltration of 120 mg of lidocaine, the drug was detectable in urine for 24 h by gas chromatography (GC) (Short *et al.*, 1988b). Like procaine, lidocaine is detectable in urine long after the pharmacological effects have disappeared. Lidocaine is detectable by mass spectroscopy, GC and fluorescence polarization immunoassay (FPIA) (Barker *et al.*, 1992). Chalmers *et al.* (1987) detected lidocaine in urine for 60 h following a 200-mg subcutaneous dose to yield the longest clearance time reported for this drug (Chalmers *et al.* 1987).

MEPIVACAINE

Disposition and metabolism

In rats, the metabolism of mepivacaine includes *N*-demethylation to yield the less toxic metabolite pipecolylxylidine (PPX) and *para*-hydroxylation of the xylidine ring. Ten per cent of a dose of mepivacaine was excreted unchanged in the urine of rats (Hansson *et al.*, 1965).

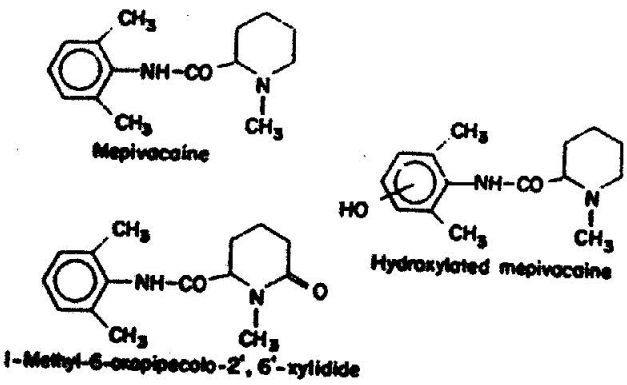


Fig. 4. Structure of mepivacaine and its metabolites 1-methyl-6-oxopipecolo-2',6'-xylidide and hydroxylated mepivacaine.

In humans, a significantly greater amount of mepivacaine (16%) is excreted unchanged when compared with bupivacaine (6%). Both bupivacaine and mepivacaine are *N*-dealkylated to yield PPX. The process of *N*-dealkylation is less important in the metabolism of bupivacaine and mepivacaine than for lidocaine since only 5% and 1.2%, respectively, of those drugs are excreted as PPX (Reynolds, 1971). The principal products of mepivacaine metabolism in horses are 1-methyl-6-oxopipecolo-2',6'-xylidide and hydroxylated mepivacaine (Fig. 4).

Pharmacokinetics and pharmacodynamics

In humans, the plasma concentration of bupivacaine declines more rapidly than does mepivacaine during the first 2 h after i.v. injection. Thereafter, disappearance rates are similar up to 8 h post injection, at which time plasma concentrations of the drugs are too low for accurate measurement using GC. Reynolds (1971) postulated that the faster excretion rate of bupivacaine was due to more extensive protein binding and higher lipid solubility of bupivacaine compared with mepivacaine.

Following subcutaneous injections in the rat and monkey, tissue concentrations of mepivacaine peaked at 15–60 min post dosage. In an equine study assessing the analgesic effectiveness of mepivacaine following epidural (dose = 60–100 mg) and subarachnoid (dose = 20–30 mg) injections, peak plasma mepivacaine concentrations for both routes of administration were reached about 50 min post dosing. Peak plasma concentrations were similar for both routes of administration (0.05 and 0.047 μg/mL, respectively) notwithstanding the 3.5-fold difference in dosage (Skarda *et al.*, 1984).

For subarachnoid and epidural injections in horses, onset (8.3 and 21.4 min respectively) and duration (67.4 and 80.0 min respectively) of caudal analgesia were significantly different between routes of administration. Mean plasma mepivacaine concentrations were 0.035 and 0.02 μg/mL at termination of analgesia following epidural and subarachnoid injections respectively. The authors concluded that the rate of absorption of mepi-

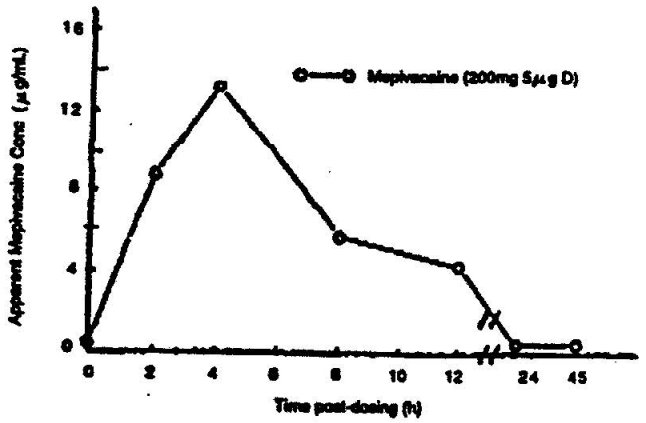


Fig. 5. Mepivacaine detection in equine urine following subcutaneous administration (200 mg).

vacaine from the epidural space was significantly faster than from the subarachnoid space. Mepivacaine was detected in plasma as early as 15 min after epidural injection, which was before the peak analgesic effect. In contrast, plasma mepivacaine was not detectable 15 min after subarachnoid injection when analgesia was complete. The varied rates of absorption were attributed to anatomical vascular differences at the injection sites and different routes of administration (Skarda *et al.*, 1984).

In a subsequent study of subarachnoid analgesia in horses (Skarda *et al.*, 1985), the critical cerebrospinal fluid (CSF) mepivacaine concentration averaged 204.4 μg/mL after injection through a catheter into the subarachnoid space; however, there was wide variation between horses (range = 86.5–331.3 μg/mL). *In vitro* studies indicated that mepivacaine is not significantly hydrolysed in CSF of horses. Rather, the decline of analgesia is due to diffusion of mepivacaine within CSF and absorption of the drug into the bloodstream.

Toxicity

Toxic signs have not been observed following epidural and subarachnoid analgesia in horses (Skarda *et al.*, 1984). Muscular twitching and hypotension have been reported in humans following epidural analgesia with mepivacaine HCl. A mean blood mepivacaine concentration of 6.27 μg/mL was obtained (Skarda *et al.*, 1984).

Regulatory detection

The major metabolites of mepivacaine (1-methyl-6-oxopipecolo-2′,6′-xylidide and hydroxylated mepivacaine) are used in the regulatory detection of the drug. Screening with an ELISA technologies test for mepivacaine, one of the authors (R.A.S.) detected a 200-mg dose of mepivacaine for up to 12 h after a single dose of the drug (Fig. 5). In contrast, Canadian researchers report a 48-h clearance time for mepivacaine (Agriculture Canada, 1991).

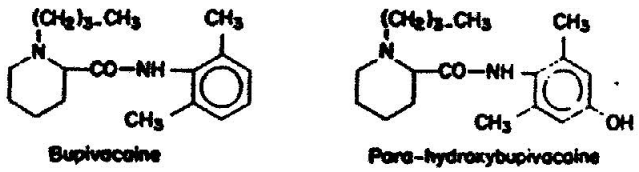


Fig. 6. Structure of bupivacaine and its metabolite *para*-hydroxylated bupivacaine.

BUPIVACAINE

Disposition and metabolism

The metabolism of bupivacaine is similar to that of mepivacaine. As discussed earlier, less bupivacaine is excreted unchanged than mepivacaine, and more PPX is excreted after bupivacaine than mepivacaine treatment. Bupivacaine is more extensively bound to plasma proteins than mepivacaine (Reynolds, 1971). Amide-type LAs (lidocaine, mepivacaine and bupivacaine) are metabolised predominately in the liver. Decreased metabolism can occur in horses with impaired liver function (Day & Skarda, 1991).

Pharmacokinetics and pharmacodynamics

In a study using tritiated bupivacaine (Goehl *et al.*, 1973), maximum tissue concentrations were found 15 min post injection. However, absorption of the drug was slow, with 53% of the dose still present at the injection site 30 min post dosing. Slow absorption is desirable in a LA.

Toxicity

Bupivacaine has a potency and toxicity four times that of mepivacaine (Goehl *et al.*, 1973). According to a study of bupivacaine enantiomers in sheep (Mather, 1991), there is a significant difference in the CNS toxicity of the stereoisomeric forms of bupivacaine. Specifically, administration of 40 mg of D-bupivacaine to 43-kg ewes consistently induced convulsions, whereas an equal dose of L-bupivacaine caused no seizures in the same animals.

Additionally, it has been suggested that neonatal jaundice in humans following maternal anaesthesia with bupivacaine may be related to bupivacaine crossing the placenta, binding to fetal red blood cells and shortening red bloodcell survival (Clark & Landaw, 1985).

Regulatory detection

The major metabolite of bupivacaine is *para*-hydroxylated bupivacaine (Fig. 6), and this is the substance most commonly detected in equine urine following a bupivacaine administration. Harkins *et al.* (1995) determined that significant anaesthesia was produced by a dose of only 0.5 mg of bupivacaine HCl, a surprisingly small dose of drug. The best estimate available for a clearance time is 24 h (Agriculture Canada, 1991).

BENZOCAINE

Metabolism and disposition

Benzocaine (ethyl *para*-aminobenzoate) metabolism has been studied in various species other than the horse. Rainbow trout eliminate benzocaine and its major metabolites [acetylbenzocaine, *para*-aminobenzoic acid (PABA), and acetyl-PABA] primarily in the effluent water and, to a lesser degree, in the urine and bile following intra-aortic injection of benzocaine. The predominance of acetylated by-products indicates that acetylation is the primary pathway of metabolism (Meinertz *et al.*, 1991). In a metabolism study of benzocaine following cutaneous application to guinea pig and human skin (Nathan *et al.*, 1990), acetylation (to *N*-acetylbenzocaine) was again the primary method of biotransformation. Following cutaneous application to rats, benzocaine was metabolised mainly to PABA, which was further metabolised. Following topical administration in horses, benzocaine was rapidly absorbed and reached peak concentration in the urine between 1 and 3 h post dosing (Annan *et al.*, 1983).

Pharmacokinetics and pharmacodynamics

Following cutaneous application to guinea pig and human skin (Nathan *et al.* 1990), benzocaine was absorbed primarily during the first 6 h. Furthermore, 77% and 50% of the applied benzocaine was absorbed within 48 h of application to guinea pig and human skin respectively.

In horses, benzocaine (737 mg) was applied topically to the front cannon bone areas. Urinary concentrations of benzocaine were 50–100 and 5–20 ng/mL at 1–3 and 8–24 h post dosing, respectively (Annan *et al.*, 1983).

Toxicity

Although benzocaine is comparatively non-irritating and non-toxic at concentrations normally used (2–10%), several reports have implicated benzocaine as the cause of methaemoglobinaemia in sheep (Guertler *et al.*, 1992; Lagutchik *et al.*, 1992), cats (Wilkie & Kirby, 1988), dogs (Harvey *et al.*, 1979), rats (Englebach & Harp, 1986), and humans (Seibert & Seibert, 1984; Bhutani *et al.*, 1992). Methaemoglobin is formed when the iron atoms are oxidised from the ferrous (Fe^{2+}) to the ferric (Fe^{3+}) state. Methaemoglobinaemia decreases the oxygen content of blood by shifting the oxygen dissociation curve to the left (Smith, 1991), which results in tissue hypoxia. The degree of hypoxia is severity on the proportion of methaemoglobinaemia. Although there are no reports of this condition in horses following benzocaine therapy, subclinical methaemoglobinaemia could significantly decrease performance in racing horses. Intravenous methylene blue is the treatment of choice for methaemoglobinaemia and produces rapid and dramatic reversal of this condition.

Regulatory detection

Benzocaine is detectable by TLC, mass spectroscopy and high-pressure liquid chromatography (HPLC) (Valente & Psaltidi, 1987). However, Harkins *et al.* (1995) determined that no dose of topical benzocaine produced significant anaesthesia in horses. Estimated clearance times for benzocaine are longer than 48 h (Short *et al.*, 1988a).

REGULATORY CONTROL OF LOCAL ANAESTHETICS IN RACING

For the purpose of racing regulations, most LAs are categorised as class 2 drugs in the Association of Racing Commissioners International (RCI) drug classification system (Short *et al.*, 1993). Class 2 drugs have a 'high potential for affecting the outcome of a race' and also manifest a high potential for abuse, although the potential for abuse is significantly less than for class 1 drugs. Because of their nerve-blocking capability, which can enable a lame horse to run sound, LAs have substantial abuse potential. However, the loss of proprioceptive feedback from a blocked joint or limb may increase the likelihood of a misstep and a catastrophic breakdown (Tobin, 1981). While the use of LAs is often permissible in human athletes, these drugs have been illegal in horse racing for at least 30 years.

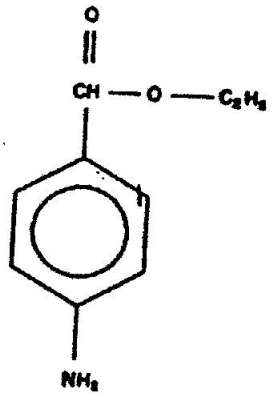
Historically, detection of LAs in blood or urine primarily depended on GC or TLC analyses. With the introduction of ELISA testing, the detection of these agents has significantly improved. Currently ELISAs are available for procaine, lidocaine and mepivacaine. It is probable that ELISAs will be developed for all the major LAs, which will further increase the efficacy of detection.

Effective detection of LAs is suggested by review of RCI drug ruling files, which record 73 procaine positives, seven benzocaine positives, four mepivacaine positives, two lidocaine positives and one bupivacaine positive from January 1990 to June 1993. (Dr Robert Gowen, Racing Commissioners International, Lexington, KY, USA, personal communication.) With apparently limited clinical use of procaine as a LA, the finding of 73 procaine positives suggests a high incidence of inadvertent positives for this drug.

The belief that most procaine positives are inadvertent and due to procaine penicillin administration is reflected in the listing of procaine as a class 3 drug. Additionally, procaine is considerably less potent and shorter acting than the more modern LA agents, and, as such, has lower abuse potential than other LAs.

Because most procaine positives are probably inadvertent, it is important to interpret correctly the forensic significance of low procaine concentrations in post-race urine samples. The goal of this research is to reduce the number of inadvertent positives caused by traces of procaine administered as procaine penicillin.

Additionally, it is clear from this review that, except in the case of procaine, there is little pharmacokinetic and clearance time information available on the clinically used LAs in horses. Reasonable descriptions of the pharmacokinetics and urinary clearance times for benzocaine, lidocaine, mepivacaine and bupivacaine in the horse would allow racing industry professionals to interpret confidently the regulatory significance of forensic data, and this need is especially pressing in the case of procaine.



Benzocaine

Fig. 7. Structure of benzocaine.

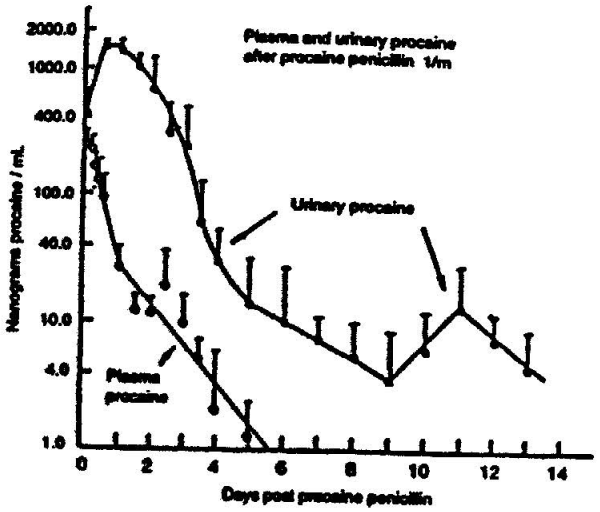


Fig. 8. Plasma and urinary procaine concentrations following intramuscular injections of procaine penicillin. Reproduced with permission from Tobin *et al.* (1977) *Journal of Equine Medicine and Surgery*, 1, 191.

DISTINCTION BETWEEN PROCAINE ADMINISTERED AS PROCAINE PENICILLIN AND PROCAINE ADMINISTERED AS LOCAL ANAESTHETIC

A recent study of procaine metabolism (Stevenson *et al.*, 1992) emphasized the relatively large amounts of procaine (0.83–2.48 g) present in various penicillin-containing preparations. Since a regimen of procaine penicillin can easily contain 5–10 g of procaine, it is not surprising that procaine from procaine penicillin is easily detected in equine urine for very long periods.

Twenty years ago, it was believed that procaine became undetectable in urine after 72 h when administered as procaine penicillin. In 1977, Tobin & Blake demonstrated that procaine was detectable for 13 days after procaine penicillin administration. In a more recent study, the period in which procaine was detectable in urine was extended to 18 days (Stevenson *et al.*, 1992).

Because experiments on procaine disposition have generally been performed in small numbers of research horses, it is likely that substantially longer clearance times will be found under field conditions (e.g. in large numbers of exercising horses producing urine of lower pH). Under these conditions, it is not unreasonable to expect procaine 'clearance times' of substantially longer than 20 days. Consistent with this view, reports from forensic laboratories suggest that procaine can be detectable for up to 30 days after administration of procaine penicillin (Dr Scott Stanley, Truesdail Laboratories, Tustin, CA, USA, personal communication).

Procaine is readily detectable in the urine of horses, where it is found at much higher concentrations and for much longer durations than in plasma. As illustrated in Fig. 8 (Tobin & Blake, 1977), procaine plasma concentration drops below 4 ng/mL by 4 days after dosing. In contrast, urinary concentrations of the drug were substantially higher and declined much more slowly over a period of 13 days.

Furthermore, there is an unexplained tendency for urinary procaine concentrations to unexpectedly increase (spike) several days after treatment, as shown in Fig. 8. This finding has also been reported by Stephenson *et al.* (1992). The unexplained spikes of urinary procaine are another possible cause of urinary positives long after plasma concentrations of the drug have declined below detectable concentrations.

One approach to the problem of inadvertent urinary positives for procaine is to determine a plasma threshold concentration for the therapeutic (local anaesthetic) effect of the drug. For example, if procaine does not exhibit a LA effect below a plasma concentration of *X* ng/mL, that value could be declared a threshold concentration for the drug. In this way, a procaine plasma concentration above *X* ng/mL would be ruled 'positive', whereas a concentration below *X* ng/mL would be an incidental finding, regardless of the urinary procaine concentration.

This approach has been introduced in Canada, where a 25-p.p.m. plasma threshold concentration of procaine has been instituted. Since a urinary procaine concentration below the threshold concentration would not be expected to cause a pharmacological or performance-altering effect, such an approach in the US should eliminate a large number of inadvertent urinary 'positives'.

Currently, the Canadian plasma threshold for procaine is the only threshold for any LA. Despite the widespread use of LAs in equine medicine and surgery and the clear therapeutic indications for these drugs in horses close to post time, horsemen in the US are not provided with guidelines for withdrawal times of these agents. In contrast, horsemen in Canada are provided with withdrawal times for these agents.

A future goal for research in this area is to develop plasma or urinary threshold concentrations and estimated clearance times for clinically-used LAs. Clearance times would enable clinicians to use LAs close to post time with more confidence. Availability of regulatory thresholds would provide industry professionals with clear guidelines on which concentrations of drugs or their metabolites in plasma or urine are likely to constitute evidence of illegal use of LAs.

CONCLUSION

Local anaesthetics (LAs) block the local perception of pain and are widely used in equine diagnostics and therapeutics. The LAs can enable a lame horse to run sound and, therefore, have substantial abuse potential. Racing Commissioners International classifies LAs as class 2 drugs (i.e. drugs with the second highest potential for abuse). Procaine, however, is a class 3 drug, less potent than other LAs and commonly administered as procaine penicillin.

Because LAs have legitimate therapeutic uses in racing horses, there is a need for information on the 'clearance times' of these agents in racing horses. With the recent development of highly sensitive enzyme-linked immunosorbent assays (ELISAs), this need has become acute. In this communication, we review the detection, actions, effects and uses of LAs in the horse with particular regard to their regulation in racing.

Over a 3.5-year period (January 1990 to June 1993), at least 73 procaine positives have been confirmed in North American racing. Although procaine may be administered as a LA, it is also present in procaine penicillin to prolong the duration of penicillin in the plasma. Procaine has been detected in equine urine for as long as 18 days after the last dose of procaine penicillin. Procaine hypersensitivity, which can cause acute death after administration of procaine penicillin, is also a significant clinical problem.

Benzocaine is a topical agent widely used in racing horses; however, the drug's putative anaesthetic effect is doubtful. Seven positives have been confirmed for benzocaine in North American racing during the 3.5-year period. Benzocaine is not available in injectable form, and topical application is the only route of administration. Little information is available on the disposition, pharmacodynamics, or 'clearance times' of benzocaine, although clearance times of 24–48 h have been reported.

Four mepivacaine positives have been reported in North American racing over the 3.5-year period. Mepivacaine has a rapid onset and more prolonged duration of action, which makes it a much more effective LA than procaine. Peak plasma concentrations occur about 50 min post dosing, and reports from Canada suggest a 48 h 'clearance time' for this drug in horses.

Two lidocaine positives have been reported in North American racing over the 3.5-year period. Little information is available on the disposition or pharmacodynamics of lidocaine in horses. However, one study suggests a 60 h 'clearance time' for this drug.

One bupivacaine positive has been confirmed in North American racing in the 3.5 years. Bupivacaine is eight times more potent and more toxic than mepivacaine. Limited pharmacodynamic and 'clearance time' data for bupivacaine in the horse are available, with Canadian data suggesting a 24 h 'clearance time'.

ACKNOWLEDGMENTS

This work was supported by grants entitled 'development of a test for procaine in horses' funded by The Equine Drug Council and The Kentucky Racing Commission and 'Research on endotoxin shock in horses' funded by Centaur Pharmaceuticals, San Francisco, CA, and support from Mrs John Hay Whitney.

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