DETERMINATION OF THE LOCAL ANAESTHETIC EFFICACY OF PROCAINE, COCAINE, BUPIVACAINE AND BENZOCAINE

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ABSTRACT

The degree of anaesthesia following administration of incremental doses of local anaesthetics (procaine, cocaine, bupivacaine and benzocaine) were determined using the heat lamp/hoof withdrawal model of Kamerling *et al.* (1985b) and the abaxial sesamoid block model of local anaesthesia. Effective local anaesthetic (LA) blockade prevented heat sensation in treated legs. Thermal stimulus experiments were terminated after 10 s to prevent undue tissue damage.

Following an abaxial sesamoid block with bupivacaine, anaesthesia was evident following a dose of 0.5 mg. Increasing the dose to 2 mg/site apparently produced complete and prolonged LA blockade.

Analogous work showed that a dose of about 5.0 mg/site of procaine produced measurable anaesthesia. Similarly, the dose response curve for procaine was parallel with that of bupivacaine but was shifted 10-fold to the right. The duration of the LA response following procaine injection was less than for bupivacaine, with the response following 40 mg/site lasting less than 90 min.

Cocaine was less potent than procaine, showing a shallower dose response curve and a shorter duration of action. A dose of 45 mg/site was required for reliable local anaesthesia. Because this dose of cocaine is highly detectable, cocaine is unlikely to escape detection if used improperly as a local anaesthetic in racing horses.

Benzocaine had no significant LA action when 800 mg was applied topically as a 5% preparation.

INTRODUCTION

The ability of analysts to detect traces of illegal and therapeutic drugs in post race samples has improved greatly during the past 10 years. Many positives appear to be inadvertent, resulting from administration of legal medications.

Local anaesthetics that may yield long lasting residual concentrations include procaine, when used as a component of a long-acting antibiotic; benzocaine, a topical LA found in leg braces and liniments; cocaine, which has both LA (Lumb and Jones 1984) and stimulatory actions (McKeever *et al.* 1993); and bupivacaine, a high-potency LA widely used in veterinary practice. All of these agents have been detected in serum or urine of racing horses, and the significance of trace or residual concentrations of these agents has been debated. The objective of this study was to determine the anaesthetic efficacy of different doses of LA.

MATERIALS AND METHODS

Horses

Thoroughbred mares weighing 413–602 kg were used for this study. All horses were kept in their stalls for 24 h prior to experimentation. Because of the critical role of skin temperature in these experiments, no LA quantification experiments were performed when ambient temperature was less than 10°C. At least 4, and more commonly 7, days elapsed between individual LA dose response curve experiments.

Site preparation

Before each experiment in which a LA (procaine, cocaine, bupivacaine) was injected, the hair on the front and lateral sides of the foreleg pasterns was clipped and blackened with stamp pad ink (Dennison Manufacturing Co, Massachusetts, USA) to ensure equal and consistent heat absorption for all horses. Before each topical anaesthetic (benzocaine) experiment, the hair on the front and

TABLE 1: Peak local anaesthetic response (% of control latency) for incremental doses of procaine

Procaine dose (mg)	Peak response (% control latency)
2.5	111.5
5.0	130.5
10.0	196.8
20.0	200.4
40.0	198.4

TABLE 2: Peak local anaesthetic response (% of control latency) for incremental doses of cocaine

Cocaine dose (mg)	Peak response (% control latency)
1.5	100.0
5.0	127.5
15.0	146.5
45.0	240.0

lateral sides of the cannon and pastern bones was clipped and blackened with stamp pad ink. Contralateral legs were also clipped, blackened, and tested to assess any systemic effect of the LAs.

Drug administration

All injectable drugs were administered subcutaneously in a standard volume of 2.0 ml with matching doses of 2.0 ml of saline administered to the contralateral leg. The site of injection was into the area of the lateral volar nerve where it passes medial to the lateral sesamoid bone. This block is referred to in clinical practice as an abaxial sesamoid block.

Randomly selected doses of 2% procaine HCl (2.5, 5.0, 10.0, 20.0 and 40.0 mg; Abbott Laboratories, Illinois, USA), 0.5% bupivacaine HCl (0.25, 0.5, 1.0, 2.0 and 10.0 mg; Abbott Laboratories) and cocaine HCL (1.5, 5.0, 15.0 and 45.0 mg; Sigma Chemical Company, Missouri, USA) were injected at the test site. Topical benzocaine (800 mg; EPF-5, Summit Hill Laboratories, New Jersey, USA) was applied to the front and lateral side of the cannon bone between the knee and fetlock joint. Care was taken to ensure no benzocaine contacted the pastern area. Saline (2 ml) and bupivacaine HCl (10 mg/2 ml) were injected as negative and positive controls, respectively.

Dose and time response relationships for procaine, cocaine, benzocaine and bupivacaine were determined with a heat projection lamp adapted from that described by Kamerling *et al.* (1983; 1985a, b). In the anaesthetised leg, the duration of light exposure was limited to 10 s to prevent undue damage to the skin. A secondary unfocused light beam ('sham' light) was used to confound the horse, reducing the possibility that the flexion-withdrawal reflex was to visual rather than thermal perception of the focused light beam.

Dose and time response relationships

The hoof withdrawal reflex latency (HWRL) was measured at 30 and 15 min and immediately before injection or topical application of the LA. These 3 HWRL times were used to establish a control value for HWRL in each horse. The HWRL was also measured at 7.5, 15, 30, 45, 60, 75, 90, 120, 150 and 180 min after administration of the different doses of LA. Using this model, full dose response curves for the LA actions of procaine, cocaine and bupivacaine were developed (Tables 1–3).

RESULTS

Dose and time response curves to procaine

There was no significant anaesthetic effect following injections of 2.5 and 5.0 mg procaine HCl. After administration of 10.0, 20.0 and 40.0 mg procaine HCl, there was a significant difference between control and procaine values up to 30 min after injection of the anaesthetic. Peak anaesthesia occurred 15–30 min after injection. Administration of 2 ml normal saline to the contralateral limb produced no significant changes in HWRL (Table 1).

Dose and time response curves to cocaine

There were no significant anaesthetic effects following injections of 1.5, 5.0 and 15.0 mg cocaine HCl. After administration of 45.0 mg cocaine HCl, there was a significant difference between saline controls and cocaine values at 15, 30, 45 and 60 min after injection of the anaesthetic. Peak anaesthesia occurred 30 min after injection. Administration of 2 ml normal saline to the contralateral limb produced no significant changes in HWRL (Table 2).

Dose and time response curves to benzocaine

There was no significant difference between control and benzocaine-treated cannon or pastern values at any point during the test. There was a significant difference between negative (saline) and positive (bupivacaine, 10 mg) control values at every time point after the anaesthetic was injected. Furthermore, there was no anaesthetic effect in the contralateral leg.

TABLE 3: Peak local anaesthetic response (% of control latency) for incremental doses of bupivacaine

Bupivacaine dose (mg)	Peak response (% control latency)
0.25	112.4
0.50	179.8
1.0	204.8
2.0	250
10.0	250

Dose and time response curves to bupivacaine

After administration of 10.0 mg bupivacaine HCl, there were significant differences between saline controls and bupivacaine values at every time point after anaesthetic injection. For doses of 2.0, 1.0 and 0.5 mg bupivacaine HCl, there were significant differences between saline controls and bupivacaine values from 15–90, 30–75 and at 30 min post injection, respectively. For doses of 0.25 mg, there was no significant difference between saline controls and bupivacaine values at any time post injection. Peak anaesthesia occurred 15–60 min after injection. There was no apparent anaesthetic effect in the contralateral leg at any time point after administration of bupivacaine at any dosage rate, suggesting no central nervous effect of the administered bupivacaine (Table 3).

Tables 1-3 show the peak HWRL expressed as a percent of control latency for each drug tested.

DISCUSSION

A clinical model of local anaesthesia was used to assess the peak HWLR following incremental doses of various LAs. The clinical model selected was an abaxial sesamoid block, in which the dose of the local anaesthetic to be tested was administered in a 2 ml volume.

Bupivacaine is a highly effective LA, and doses of only 2 mg/site produce complete local anaesthesia. Furthermore, the dose must be reduced about 10-fold to reach a non-effective dose. The significant local anaesthesia seen at doses of only 0.5 mg/site illustrates the efficacy of modern LA agents.

Inadvertent detection of procaine in post race urine samples is a major problem for equine veterinarians, horsemen and regulatory officials, arising from the improved ability of chemists to detect small traces of therapeutic medications in post race samples. The LA effect of procaine is considerably less potent than that of bupivacaine. No discernible local anaesthesia was produced with a dose of 2.5 mg/site. A procaine dose of 5 mg/site produced a discernible, although statistically non-significant, effect and a dose of 10 mg/site produced virtually full, though transient, local anaesthesia.

Cocaine is a major drug of abuse in man and is available widely among certain groups. Furthermore, cocaine is well absorbed across mucous membranes (Jaffe 1990), and little skill is required to apply the drug to mouth, nose or genitalia of a horse. Such applications may be intentional or inadvertent. A recent study (McKeever *et al.* 1993) showed that the pharmacological effects of cocaine are short lived, suggesting limited usefulness for cocaine as a stimulant medication in racing horses.

Cocaine was a relatively less effective LA than bupivacaine or procaine, with a very shallow dose response curve. To produce a 'full' local anaesthetic response comparable to that seen with procaine or bupivacaine, a 45 mg/site dose of cocaine was required. This is a significant total dose of cocaine, and it raises the possibility that central effects of this drug might be significant. However, the lack of any increase in HWRL for the contralateral leg, suggests that this dose of cocaine produced no systemic effects detectable in the contralateral leg. Decreasing the injected dose to 15 mg/site substantially reduced the LA response, and decreasing the dose to 5 mg reduced the local response even further. Because this dose of cocaine is highly detectable, cocaine is unlikely to escape detection if used improperly as a local anaesthetic in racing horses.

Benzocaine is a widely used topical LA and is a common additive in leg braces and liniments used in racing horses. The drug is absorbed rapidly and reaches peak concentration in the urine 1–3 h post dosing (Annan *et al.* 1983). Because benzocaine is classified as a LA, its detection in post race samples has resulted in 7 positive calls in North American racing during the past 2.5 years (R. Gowen, personal communication). Topical application of benzocaine to the cannon bones had no effect on the heat-lamp response times, in the area of local application (cannon bones) or in areas distal to the local application (pasterns). The total dose of benzocaine applied at each test site was 800 mg, and the absence of any LA effect suggests that the LA efficacy of benzocaine at the concentrations used in these tests is essentially negligible.

For all LAs tested, the absence of a LA effect in the contralateral leg suggested there was no central nervous effect. This was not surprising for procaine, bupivacaine and benzocaine. However, following the 45 mg injection of cocaine, there was a non-

significant increase in HWRL for the contralateral leg at 30 min post injection. In 2 of the horses, there was a dramatic increase in HWRL in the contralateral leg, but the other 2 horses demonstrated no increased effect. This suggests there may be individual differences in the sensitivity of horses to relatively low concentrations of cocaine as suggested by Shults *et al.* (1982).

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