Determination of Highest No-Effect Doses (HNED's) for Local Anesthetic Responses to Procaine, Cocaine, Bupivacaine, and Benzocaine in Thoroughbred Mares

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Bupivacaine is a highly effective local anesthetic with a low HNED of 0.25 mg. Procaine is considerably less potent than bupivacaine with a HNED of 2.5 mg, cocaine was less effective than bupivacaine or procaine as a local anesthetic, and benzocaine provided no discernible local anesthesia to treated areas. Authors' addresses: Maxwell H. Gluck Equine Research Center and the Dept. of Veterinary Science, University of Kentucky, Lexington, KY 40506 (Harkins, Woods, Rees, Thompson, and Tobin); The Kentucky Racing Commission, Lexington, KY 40511 (Mundy); and Truesdail Laboratories, Tustin, CA, 92680 (Stanley).

1. Introduction

The sensitivity of equine drug testing has increased dramatically, allowing chemists to detect small traces of therapeutic medications in postrace samples. Currently, many racing jurisdictions use arbitrary thresholds that are based on the experiences, skills, and analytical capabilities of their analysts rather than scientifically established thresholds. One approach to interpreting the significance of trace concentrations of therapeutic medications is to determine the highest no-effect dose (HNED), defined as "the highest dose of a drug at which there is no possibility of the horse having been pharmacologically influenced during a race."[1] Once the HNED is established, the highest plasma or urinary concentration or highest no-effect threshold (NET) can be determined, defined as "the highest concentration of a drug or metabolite following HNED administration." In this report we describe the establishment of HNED's for four local anesthetics, or LA's (procaine, cocaine, bupivacaine, and benzocaine) that account for a high percentage of positive calls in racing horses.

2. Materials and Methods

Injectable LA's (procaine,[a] bupivacaine,[b] and cocaine[c]) were administered as abaxial sesamoid blocks, and topical benzocaine[d] was applied to the metacarpus in six Thoroughbred mares (see Table 1). Dose and time responses were determined with a heat projection lamp,[2,3] which directed light and heat onto the pastern of a horse to elicit the classic flexion withdrawal reflex. Hoof withdrawal reflex latency

NOTES

Table 1. Percent Change in HWRL after Injection of Local Anesthetics

	Cocaine		Procaine					Bupivacaine			
Minutes	5 mg	15 mg	45 mg	2.5 mg	5 mg	10 mg	20 mg	0.25 mg	0.5 mg	1 mg	2 mg
0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
7.5	90.1	98.4	128.4					103.0	122.3	108.6	205.8
15	131.9	118.9	179.8	106.2	130.5	193.2	200.3	109.5	139.5	117.1	250.0
30	108.4	127.6	240.0	100.0	119.6	196.8	176.8	102.8	179.8	193.0	250.0
45	98.8	115.6	201.0	97.1	116.9	147.9	134.3	111.5	162.5	204.8	250.0
60	115.0	116.4	204.0		80.2	154.1	127.8	104.1	162.8	204.8	250.0
75	72.0	76.3	194.3			116.3	121.1	106.5	150.4	196.3	232.3
90	108.9	104.4	160.0			93.9	121.4	112.4	158.0	178.3	200.0
105			100.8					105.1	126.1	167.3	151.6
120									106.8	155.8	111.2
135										101.6	98.9

(HWRL) is defined as the time between lamp illumination and withdrawal of hoof. An infrared scanner was used to measure the superficial skin temperature of treated horses. Paired *t* tests were used to compare HWRL saline and treatment values for LA's at each measuring time ($p < 0.05$).

3. Results

A. Skin-Temperature Measurements

The superficial skin temperature of unanesthetized limbs increased to ~95°C. Following the administration of 10 mg of bupivacaine, mean superficial skin temperatures of anesthetized limbs reached ~120°C after a 10-s exposure.

B. Dose and Time Response Curves of Local Anesthetics

After the administration of 10.0, 20.0, and 40.0 mg of procaine HCl, there was a significant difference between control and procaine values up to 30 min after injection of the anesthetic. Although there was a slight increase in HWRL 15 min following injection of 5.0 mg of the drug, there was no statistically significant LA effect following injections of 2.5 and 5.0 mg of procaine HCl.

After the administration of 45.0 mg of cocaine HCl, there were significant differences between saline controls and cocaine values at 15, 30, 45, and 60 min after injection of the anesthetic. There were no significant LA effects following injections of 1.5 and 15.0 mg cocaine HCl; however, there was a significant LA effect at 15 min after injection of 45.0 mg of cocaine HCl.

After the administration of 10.0 mg of bupivacaine HCl, there were significant differences between saline controls and bupivacaine values at every time point after anesthetic injection. For doses of 2.0, 1.0, and 0.5 mg of bupivacaine HCl, there were significant differences between saline controls and bupivacaine values from 15–90, 30–75, and at 30 min postinjection, respectively. For doses of 0.25 mg, there was no significant difference between saline controls and bupivacaine values at any time postinjection.

Following the application of benzocaine, there was no significant anesthetic effect at any point during the test.

4. Discussion

Bupivacaine is a highly effective LA, and doses of only 2 mg/site produce complete local anesthesia.[4] Furthermore, the dose must be reduced approximately tenfold to eliminate a significant anesthetic effect. From this data, it appears that the HNED for bupivacaine is ~0.25 mg/site, which is a surprisingly small quantity of drug.

The LA effect of procaine is considerably less potent than that of bupivacaine. The data show that no discernable local anesthesia was produced with a dose of 2.5 mg/site, the apparent HNED, which again is a very small quantity of drug. A procaine dose of 5 mg/site produced a discernible, although statistically nonsignificant, effect, and a dose of 10 mg/site produced virtually full, though transient, local anesthesia. The dose response curve for procaine was parallel in slope but elevenfold less potent than that observed for bupivacaine.

Cocaine was relatively less effective than bupivacaine or procaine as a LA. The production of a full LA response comparable with that seen with procaine or bupivacaine required a 45 mg dose of cocaine, which is a significant total dose of drug.

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References and Footnotes

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[a]Procaine HCl 2% (2.5, 5.0, 10.0, 20.0, and 40.0 mg), Abbott Laboratories, North Chicago, IL 60064.

[b]Bupivacaine HCl Inj. 0.5% (0.25, 0.5, 1.0, 2.0, and 10.0 mg), Abbott Laboratories, North Chicago, IL 60064.

[c]Cocaine HCl (1.5, 5.0, 15.0, and 45.0 mg), Sigma Chemical Company, St. Louis, MO 63178.

[d]Benzocaine (800 mg), EPF-5, Summit Hill Laboratories, Navesink, NJ 07752.