

## Character and Duration of Pharmacological Effects of Intravenous Ioxsuprine

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All measured pharmacological effects of intravenous Ioxsuprine returned to control values within 4 h after administration. In light of the extended detection time of 30 days following the last administration of the agent, threshold levels have to be established to allow racing horses the benefit of this medication. Authors' address: Maxwell H. Gluck Equine Research Center and the Dept. of Veterinary Science, University of Kentucky, Lexington, KY 40506 (Harkins, Woods, and Tobin); The Kentucky Racing Commission, Lexington, KY 40511 (Mundy); Trusdell Laboratories, Tustin, CA, 92680 (Stanley); Analytical Toxicology Laboratory, Ohio State University, Columbus, OH (Sams); and Dept. of Physiology and Biophysics, University of Kentucky, Lexington, KY 40506 (Richardson).

### 1. Introduction

Ioxsuprine is an effective treatment for navicular disease<sup>1</sup> and is one of the most frequently detected therapeutic agents in racing horses.<sup>2</sup> Prolonged administration (weeks) can result in drug sequestration in body fat, and the sensitive enzyme-linked immunosorbent assay (ELISA) test can detect low nanogram concentrations of Ioxsuprine or its metabolites in equine urine up to 30 days after the administration of the last dose.

In contrast with its prolonged detection time, Ioxsuprine appears to have a relatively short duration of pharmacological action. Ross et al.<sup>3</sup> showed little effect on blood-chemistry parameters, heart rate, blood pressure, respiratory rate, and body temperature after administration of the agent. In similar research,<sup>4</sup> significant increases in lower limb temperatures were measured by thermography for only 6 h after oral administration. Furthermore, the recom-

mended treatment frequency of Ioxsuprine is twice daily, suggesting a duration of action of less than 12 h. Therefore, previous research suggests that Ioxsuprine is unlikely to exert any significant pharmacological effect for longer than a period of 12 h after administration, and that there is little regulatory need for the prolonged (> 14 days) detection times provided by ELISA testing. The overall goal of this research project is to develop practical analytical guidelines on the detection of Ioxsuprine in horses. In this communication we establish the character and duration of the pharmacological effects of acute intravenous Ioxsuprine to establish a no-effect threshold (NET) for the agent.

### 2. Materials and Methods

In a cross-over study, six mature Thoroughbreds were administered Ioxsuprine HCP in 50 ml of sterile water and 25 ml of 95% ethanol. Control

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### NOTES

## PHARMACOLOGY AND TOXICOLOGY

horses were injected with 50 ml of sterile water and 25 ml of 96% ethanol. Several variables were measured following treatments: skin and rectal (core) temperatures; respiratory, heart, and intestinal motility rates; sweat production; skin thermographic temperature; cutaneous blood flow (by the use of a laser Doppler flow meter); and anal smooth muscle tone (by the use of a bulb dynamometer).

Paired *t* tests were used to compare control and isoxsuprine values for each physiologic variable (except sweat production) at each measuring time. Because of the large individual variability in sweat production, the sign test was used to compare the effects of control and isoxsuprine treatments ( $p < 0.05$ ).

### 3. Results

Heart rate increased dramatically following isoxsuprine administration and was significantly greater than control values 5–150 min after treatment. Thermographic temperature of front legs decreased for 30–180 min, and the lowest mean temperature (27.0°C) was measured 60 min after treatment.

Anal muscle tone gradually decreased in control horses then returned to near-baseline values. Anal muscle tone of isoxsuprine-treated horses decreased immediately and at a greater rate and was significantly less than control 10–180 min following treatment. Core temperature was significantly reduced 30–120 min after isoxsuprine treatment. Skin temperature was significantly elevated following both control and isoxsuprine treatments but was significantly decreased 45–120 min after isoxsuprine treatment.

All horses produced sweat following isoxsuprine injection, and peak production varied from 1 to 49 ml/5 min. Although not statistically significant, blood flow to the pastern appeared to increase and then decrease during the first 60 min following isoxsuprine administration. There were no significant effects on respiratory and intestinal motility rates.

### 4. Discussion

Peak heart rate was 340% of control values and had declined to control value by 180 min after drug administration, which was consistent with Matthews et al.<sup>4</sup> The onset of increased skin temperature was as rapid as the increased heart rate, and the peak was 6% greater than control values. Sweat production followed closely behind the increased skin temperatures and peaked 20 min after injection.

Decreased anal tone for control horses (and to the same extent, for isoxsuprine-treated horses) can be attributed to an accommodation for the bulb dynamometer in the anal canal.

Although the wide variation in blood flow to the

pastern prevented a significant difference between treatments, the apparent increased blood flow paralleled the increased skin temperature and sweat production. The production of sweat suggested that a greater amount of heat was being emitted by isoxsuprine-treated horses. This was verified by decreased core temperature (2%), skin temperature (10%), and skin thermographic temperature (9%) of isoxsuprine-treated horses. All three values reached a peak reduction 50–80 min after injection.

Deumer<sup>3</sup> and Rose<sup>2</sup> gave isoxsuprine orally and showed increased front leg temperatures 1.5–8 h after administration. The decreased thermographic measurements 30–180 min following isoxsuprine treatment in our study can be explained by the different route of administration and the rapid onset and brief duration of intravenous injections. Surface thermistors recorded significant increases in skin temperature 5–25 min following isoxsuprine treatment, and then significant decreases 45–120 min after treatment.

In conclusion, all measured pharmacological effects of intravenous isoxsuprine returned to control values within 4 h after administration. Other researchers have reported less dramatic pharmacological effects following oral administration, and the effects may persist for a longer duration than that seen following intravenous administration. However, in light of the extended detection time following the last administration (30 days), threshold levels for this agent have to be established to allow racing horses the benefit of this medication.

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### References and Footnotes

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<sup>a</sup>Dr. Robert Gowen, Racing Commissioners International, Lexington, KY 40511 (personal communication), 1995.  
<sup>b</sup>2.0 mg/kg; Sigma Chemical Co., St. Louis, MO 63178.