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Lack of local anaesthetic efficacy of Sarapin® in the abaxial sesamoid block model

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Sarapin® is a distillate of the pitcher plant that has long been used in human and veterinary medicine for 'regional analgesia'. The mechanism of the reported analgesic response is unknown; however, the agent is purported to provide more effective analgesia for slow, chronic pain than for sharp, acute pain. Reportedly, Sarapin® is also widely used as an analgesic agent in the horse, generally in combination with corticosteroids and other agents. To determine its local anaesthetic efficacy in the horse, we tested Sarapin® in a unilateral abaxial sesamoid block model at two dose levels, 2 mL and 10 mL per site, respectively. Cutaneous pain was induced with a light/heat lamp, and analgesia was assessed by measuring the hoof-withdrawal reflex latency period. Neither dose of Sarapin® altered hoof-withdrawal reflex latency in this experimental model tested over a two-week period. Based on the demonstrated efficacy of this local anaesthetic model, it seems clear that Sarapin® has no significant classical local anaesthetic actions in the horse, and probably not in other species either.

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INTRODUCTION

Sarapin® is a natural product distilled from the pitcher plant (*Sarraceniaceae*) that has been used as a regional analgesic agent for control of pain of neuralgic origin. Reportedly, pitcher plant extract has been used for over 200 years for analgesia, and Sarapin® was introduced into current medical practice in the early 1930's by Dr Judovich of the University of Pennsylvania Graduate Hospital. Sarapin® has been used for over 50 years (Plumb, 1995) in human patients to treat neuromuscular pain. Much of the literature on Sarapin® dates from early in this period and consists largely of reports of clinical experiences with this agent. Sarapin® is still used in human medicine, although most commonly in combination with other agents and generally as a site-directed injection (Namey, 1985). The manufacturer recommends Sarapin® to treat sciatic pain, intercostal neuralgia, alcoholic neuritis, occipital neuralgia, brachial plexus neuralgia, meralgia paresthetica, lumbar neuralgia, and trigeminal neuralgia.

Unlike local anaesthetics with relatively short durations of activity, Sarapin® has been reported to give relief from pain for over six months after injection (Rask, 1984). The relatively sparse literature on the mechanism of action of Sarapin® suggests that it does not act like a classic local anaesthetic (i.e. an agent that blocks all sensations such as pain, cold, heat, pressure, and proprioception). Local anaesthetic drugs also produce measurable changes in the temperature and blood flow of an area in which they are injected. In contrast, Sarapin® is purported to produce pain relief 'without the unwanted side-effects of local anaesthetics' (Bates & Judovich, 1942).

The exact nature and mechanism of the pain-relieving properties of Sarapin® are unknown; however, the agent is reported to affect sensory nerves with little or no effect on motor nerves (Plumb, 1995). Bates and Judovich (1942) reported there was no motor weakness nor loss of touch, pressure, pinprick, or temperature sensation following Sarapin® injection. There also seems to be some concern about the actions of ammonium ion and the relationship between ammonium ions and the actions of Sarapin®. Specifically, it has been hypothesized that the pitcher plant distillate contains an unidentified biological antagonist that potentiates the actions of ammonium ions (Steward *et al.*, 1940).

Anecdotal reports of Sarapin®'s effectiveness in relief of pain in racing horses prompted this investigation. The agent is routinely injected at nerve-block sites for a long-term nerve block, at acupuncture points for analgesia, and into the lumbar muscles of racing horses that exhibit back soreness. The response to these treatments is apparently favourable in at least some horses (Kellon & Tobin, 1995).

In previous studies of local anaesthetics (Harkins *et al.*, 1994; Harkins *et al.*, 1996a), we have used an abaxial sesamoid block/radiant heat/hoof withdrawal model as described by Kamerling *et al.* (1988) and Harkins *et al.* (1996a) to analyse the effects of

these agents in horses. This model is highly sensitive and readily detects the local anaesthetic effects of sub-milligram doses of potent local anaesthetics. In this communication, we report the results of experimental evaluations of the local anaesthetic effects of Sarapin® using this model.

MATERIALS AND METHODS

Horses

The horses and ponies used for these studies were stabled as groups in separate one-acre paddocks with access to shade. The animals were maintained on grass hay and feed (12% protein), which is a 50:50 mixture of oats and an alfalfa-based protein pellet. They were vaccinated annually for tetanus and were dewormed quarterly with Ivermectin. A routine clinical exam was performed prior to entry into these experiments to ensure that the animals were healthy and sound.

Experimental design

Two separate tests of the Sarapin® (High Chemical Company, Levittown, PA) injection were performed. In the first experiment, five female ponies weighing 63–130 kg were injected with 2.0 mL of Sarapin® in an abaxial sesamoid block model, with matching doses of 2.0 mL of saline administered to the contralateral leg. In the second experiment, four mixed-breed horses weighing 355–420 kg were injected with 10 mL of Sarapin® with matching doses of saline administered to the contralateral leg. The experimental protocol was approved by the Institutional Animal Care and Use Committee at the University of Kentucky.

Abaxial sesamoid block model

The site of injection for all experiments was the area where the lateral palmar nerve passes lateral (abaxial) to the lateral proximal sesamoid bone. This block is referred to in clinical practice as an abaxial sesamoid block (Stashak, 1987). The hair over the lateral sesamoid bone was clipped, and the skin was cleansed with alcohol. Sarapin® and control (saline) treatments were injected through a 25 ga. needle.

In addition to the negative control provided by saline, historic data from a previous experiment (Harkins *et al.*, 1996b) is presented as a positive control to show the duration of local anaesthesia from bupivacaine injection (10 mg). In our experiments, the maximal hoof withdrawal reflex latency (HWRL) was limited to 10 s to prevent undue damage to the skin.

Site preparation

Before each experiment, the hair on the dorsal and lateral sides of the fore leg pasterns was clipped, and the pastern was blackened with stamp pad ink (Dennison Manufacturing Co, Framingham, MA) to ensure equal and consistent heat application for all horses. Contralateral legs were also clipped, blackened, and tested for control values.

Determination of local anaesthetic effect

Dose and time response relationships for the agent were determined with a heat projection lamp described previously (Harkins *et al.*, 1996a). Briefly, focused radiant light/heat was used as a noxious stimulus and was directed onto the pastern of a horse to elicit the classic flexion-withdrawal reflex. HWRL was defined as the time between lamp illumination and withdrawal of the hoof. In general, the intensity of the light beam was adjusted with a rheostat so that HWRL period was about 4–6 s in a non-anaesthetized leg, with the actual HWRL recorded on an electronic timer built into the lamp. A secondary unfocused light beam (sham light) was used to confuse 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

In the first experiment, HWRL was measured at -20 and -10 min and immediately before Sarapin® injection. These three HWRL times were used to establish a baseline value for HWRL in each horse. HWRL was also measured at 1 and 2 h after injection and on day 1, 2, 3, 5, 6, 7, 8, 9, and 13 after injection. In the second experiment, HWRL was measured at -20 and -10 min and immediately before Sarapin® injection, and these three HWRL values were used to establish a baseline value for each horse. HWRL was also measured on day 1, 2, 3, 6, 7, 10, and 12 after injection.

HWRL was not measured between 2 and 24 h in the first experiment, nor between 0 and 24 h in the second experiment for two reasons. In a preliminary experiment with two horses, there was no change in HWRL during the first six hours after injection, and we were more concerned with duration of effect rather than time of onset.

Statistical analysis

Data are presented as means ± SEM. Analysis of variance with repeated measures was used to compare control and Sarapin® values at each measuring time. Significance was set at $P < 0.05$.

RESULTS

Neither the high nor low dose of Sarapin® produced local anaesthesia following injection (Fig. 1). There were day-to-day variations in the HWRL; however, the variations were consistent in both the negative control and Sarapin®-treated legs. For a positive control, previous data from an evaluation of the local anaesthetic effect of bupivacaine has been added to both figures to present a typical local anaesthetic response as measured by this model.

DISCUSSION

Anecdotal reports in the racing community and from equine practitioners suggest that Sarapin® is used as a local anaes-

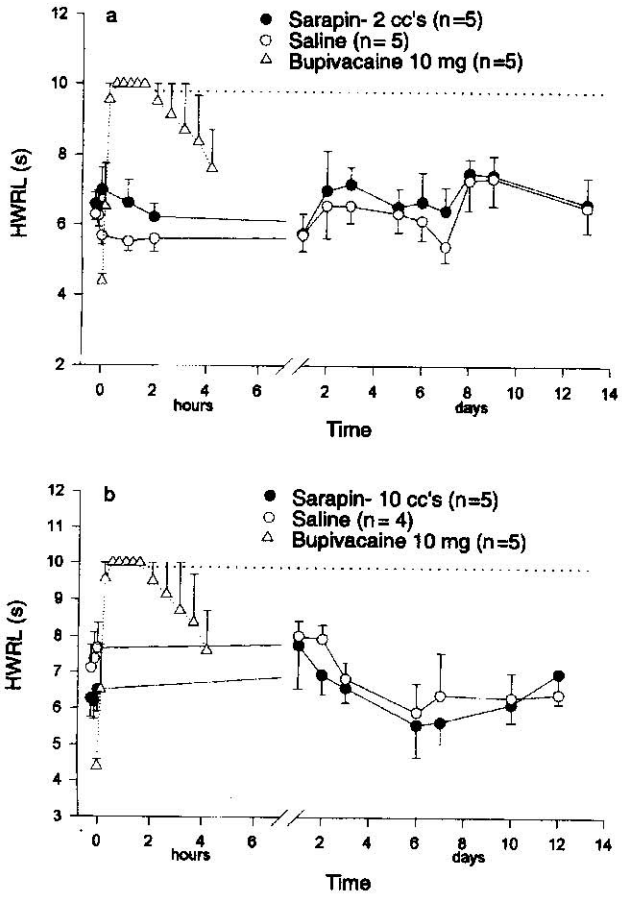

Fig. 1. HWRL (±SEM) of control and Sarapin®-treated legs following injection of (a) 2 cc's and (b) 10 cc's of Sarapin®. Open triangles (Bupivacaine-10 mg) represent historic data used as a positive control (Mean±SEM). Dashed line illustrates maximum HWRL (10 sec).

thetic/nerve blocking agent, either as an individual agent or, more commonly, in association with other agents such as corticosteroids, other analgesics, or anti-inflammatory agents (E.M. Kellon, pers. comm). The potential for abuse of Sarapin® in this way raises questions as to the efficacy of regulatory control of this agent, which is challenging because the active principle in the pitcher plant extract has never been identified. Therefore, before investigating the chemistry of this agent, we elected to evaluate its therapeutic efficacy in the horse. We tested Sarapin® because of anecdotal reports of the efficacy of this agent as a nerve block and its ability to reduce pain perception following site-directed injections of localized areas. Because our local anaesthetic model is validated for assessing local anaesthetic activity in the horse (Harkins *et al.*, 1994), we injected Sarapin® in an abaxial sesamoid block model.

Based on our experience with other local anaesthetics, the dose selected for the first experiment was 2.0 mL/site. The agent was administered according to a standard protocol for local anaesthetics (Harkins *et al.*, 1996a), which has been shown to be a very sensitive test of local anaesthetic responses. Based on prior experience with local anaesthetics, we expected to see some signs of local anaesthesia within minutes to hours after a 2.0 mL dose. When no such effect was observed, we extended the observational period for two weeks, based on reports of the long duration of action of Sarapin®. However, no signs of a longer duration or of a slowly developing effect of Sarapin® were detected in these experiments.

After discussions with colleagues and consideration of their experiences and suggestions, we raised the dose of Sarapin® five-fold and repeated the experiment. Again, Sarapin® failed to produce any local anaesthetic effects.

Since the mechanism by which Sarapin® purportedly provides analgesia is unknown, it is difficult to speculate about the failure of Sarapin® to provide analgesia in these experiments. In the early forties, investigators suspended the saphenous nerve from a cat in a solution of Sarapin® (Steward *et al.*, 1940). After about 5 min, oscillographic recordings of A fibres showed only a slight reduction of the maximal action potential while the action potentials of C fibres were completely obliterated. C fibres are small, unmyelinated nerves with slow conduction velocities that carry dull, aching pain impulses. In contrast, thinly myelinated A afferent fibres carry fast, sharp, shooting pain sensations, which is the type of pain produced by acute thermal stimulation (Guyton, 1986). The study by Steward *et al.* (1940) is the only objective study we know of suggesting classical local anaesthetic efficacy for Sarapin®.

It was important for us to test the pharmacological effects of local administration of Sarapin® rigorously in horses. The local anaesthetics are agents that are considered to have very high potential to influence the performance of horses. Skillfully used, a local anaesthetic can block a nerve or joint and render an impaired horse racing sound. Although local anaesthetics block pain perception, they also impair proprioception, which inhibits a horse's ability to determine the location and the orientation of the blocked area (Tobin, 1981). Loss of proprioception can presumably increase the likelihood of injury, and for this reason it is prohibited for a racing horse to run with a detectable concentration of a local anaesthetic in its system. The perception that local anaesthetics have the potential to influence performance and to cause death or injury to horses and jockeys has resulted in local anaesthetics being classified by the Association of Racing Commissioners International (ARCI) as class 2 agents, the second highest category of prohibited medications.

Based on the findings reported here, it is clear that Sarapin® is unlikely to have significant local anaesthetic effects in the horse. Based on review of the literature, it is also clear that evidence for significant pharmacologic or therapeutic efficacy of this agent in the horse or any other species is limited. In previous reports, Sarapin® was almost always administered in conjunction with other therapeutic agents or modalities such as acupuncture. These patterns of use of Sarapin® do not provide a clear-cut picture of the therapeutic efficacy of this agent. The most generous interpretation is that any analgesic effects on pain from Sarapin® injection may be limited to chronic, aching pain rather than sharp, acute pain.

In conclusion, Sarapin® did not alter the perception of pain with the heat-lamp model used for evaluation of local anaesthetics in horses. Therefore, the agent is not a classic local anaesthetic and should not be classified as such.

Review of the literature on Sarapin® has produced no clear-cut scientific evidence demonstrating pharmacologic or therapeutic efficacy for this agent. This picture of marginal clinical efficacy should be borne in mind when establishing priorities for research on the detection or control of Sarapin® use in horses. However, it is important to remember that the efficacy of analgesics may vary depending on the model being used for evaluation. Although Sarapin® did not increase pain tolerance with the heat-lamp model, other models may better demonstrate Sarapin's® analgesic property. For example, administration of Sarapin® may yield beneficial results in a trial with chronically lame horses. Therefore, the question of the analgesic efficacy of Sarapin® is still open, and there is sufficient reason to pursue its detection and control in racing horses.

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