Lack of local anaesthetic efficacy of fentanyl in the abaxial sesamoid block model

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Fentanyl and other opioid drugs have their effect in the central nervous system; however, activity at peripheral sites has also been demonstrated. Pain-suppression activity at peripheral sites raises the possibility of skilled individuals producing local anaesthetic effects with small doses of opioid drugs that would be difficult to detect forensically and could be used to affect the outcome of a race. Therefore, the local pain-suppression effect (peripheral nerve inhibition) of fentanyl was tested using an abaxial sesamoid block/hoof withdrawal model. With this model, fentanyl did not produce significant anaesthesia when tested in eight Thoroughbred horses. This suggests that fentanyl at this or lower doses is unlikely to reduce pain perception when applied directly to sensory neurons. However, the effect of fentanyl and other opioids on joint pain perception of horses, especially inflamed joints, is unknown.

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INTRODUCTION

Opioid drugs are some of the oldest and most widely used agents in therapeutics. Historically, opioid drugs have been considered to act in the central nervous system (CNS). However, recent studies have characterized potent and receptor-specific opioid activity at peripheral sites which was reversed by local administration of naloxone (Stein *et al.*, 1991). All three opioid receptor types (mu, delta, kappa) appear to be functionally active in peripheral tissues (Stein, 1993).

Although opioids have a depressant effect in humans, horses are behaviourally aroused following administration of most opioids (Tobin *et al.*, 1979). Fentanyl is a potent opioid analgesic with rapid onset and short duration of action. Its pharmacological activity is similar to that of morphine, except that it does not cause emesis or histamine release. Furthermore, it is about 150 times more potent than morphine. As fentanyl is a potent opioid analgesic, the identification of opioid activity at peripheral sites raises the possibility that a nerve or joint block could be performed with a small concentration of the drug, and the drug might then be undetected with the postrace screening methods currently used. Fentanyl is readily detectable at doses that produce a systemic effect; however, local administration of a smaller dose as a nerve or joint block could produce pain suppressing effects, and the smaller dose could be difficult to detect by current forensic techniques (Woods *et al.*, 1986; Tobin *et al.*, 1989).

In previous studies of local anaesthetics (Harkins *et al.*, 1994, 1996), we have used an abaxial sesamoid block/radiant heat/hoof withdrawal model as described by Kamerling *et al.* (1988) and Harkins *et al.* (1996) to analyse the effects of analgesic agents in horses. This model is highly sensitive and readily detects the local anaesthetic effects of submilligram doses of potent local anaesthetics. In this communication, we report the results of experimental evaluations of the effects of fentanyl administered as a local anaesthetic using this model.

METHODS AND MATERIALS

Horses

Eight mature Thoroughbred mares weighing 468–501 kg were used for this study. The animals were maintained on grass hay

and feed (12% protein), which was a 50: 50 mixture of oats and an alfalfa-based protein pellet. Horses were fed twice a day. The animals were vaccinated annually for tetanus and were dewormed quarterly with ivermectin (MSD Agvet, Rahway, NJ). A routine clinical examination was performed before each experiment to ensure that the animals were healthy and sound. Because of the critical role of superficial skin temperature in these experiments, no local anaesthetic (LA) quantification experiments were performed when the ambient temperature was less than 10°C. Animals used in these experiments were managed according to the rules and regulations of the University of Kentucky Institutional Animal Care Use Committee, which also approved the experimental protocol.

Experimental design

Horses received subcutaneous injections in the front legs on three different occasions. One injection was with 300 μg of fentanyl (50 μg/mL, total volume = 6 mL) in one leg and an equal volume of saline in the contralateral leg, which was tested in parallel with the fentanyl-treated leg to assess any central analgesic effect of the narcotic. This dose was selected because the authors believed it was sufficiently high (twice the recommended dose for a 70-kg human), and the dose seemed a reasonable test for direct deposition at high concentration on a peripheral nerve. In previous work by this laboratory, 500 μg was the highest no-effect dose in a behavioural study (Combie *et al.*, 1979). At higher doses, locomotor stimulation was evident, and this is a serious problem when using the heat lamp model in the horse (Kamerling *et al.*, 1985). Furthermore, this dose is readily detectable in equine urine. Therefore, if this detectable dose did not have a local, pain-suppressing effect, then neither would lower, difficult-to-detect doses (Woods *et al.*, 1986; Tobin *et al.*, 1989).

On a second occasion, saline (2 mL) was injected into both legs as a negative control to control for possible effects of pressure or volume. Bupivacaine HCl (10 mg in 2 mL; Abbott Labs Chicago, IL) was injected on another occasion as a positive control.

The site of injection was the lateral volar nerve where it passes lateral (abaxial) to the lateral sesamoid bone. In clinical practice, this block is known as an abaxial sesamoid block. Before each experiment, the hair on the front 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 absorption independent of skin and hair colour. Contralateral legs were also clipped, blackened and tested to assess any systemic effect of this dose of fentanyl.

The time response for this dose of fentanyl was determined with a heat projection lamp described previously (Harkins *et al.*, 1996). Briefly, focused radiant light/heat was used as a noxious stimulus and was directed onto the pastern of the horse to elicit the classic flexion-withdrawal reflex. Hoof withdrawal reflex latency (HWRL) was defined as the time between lamp illumination and withdrawal of the hoof. These times were adjusted by varying the intensity of the heat output with a rheostat so that the HWRL period was about 3–4 s in the control legs, with the actual HWRL recorded on an electronic timer built into the lamp. In the anaesthetized leg, the duration of light exposure was limited to 10 s to prevent 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.

The HWRL was measured at–30 and–15 min and immediately before injection of fentanyl. These three HWRL times (–30,–15, and 0 min) were used to establish a baseline value for HWRL in each horse. The HWRL was also measured at 7.5, 15, 30, 45, 60, 90 and 120 min after fentanyl administration. The HWRL was expressed as a percentage of baseline values.

Statistical analysis

Data are presented as means ± SEM. Analysis of variance with repeated measures (SAS Institute Inc., 1985) was used to compare values for control and fentanyl treatments at each measuring time. Significance was set at $P < 0.05$.

RESULTS

There was no significant effect in HWRL following fentanyl injection (Fig. 1a). There was a significant difference between negative (saline) and positive (bupivacaine, 10 mg) control values at every time point after anaesthetic injection. Additionally, there was no LA effect in the contralateral leg (Fig. 1b), suggesting an absence of any systemic effect.

DISCUSSION

Opioid receptors are located at the tips of afferent nerve terminals, and opioid drugs are effective analgesics when applied directly to the nerve terminals. There is also evidence of opioid receptors along peripheral sensory and autonomic nerve axons (Stein, 1993); however, opioid drugs are generally ineffective when injected perineurally, such as in a nerve block (Mather, 1995). One study of pain relief after knee surgery in humans showed that intra-articular morphine had greater efficacy than intravenous morphine during the early postoperative period (Stein *et al.*, 1991). However, a recent review of studies that used opioid agents (morphine, fentanyl, alfentanil, buprenorphine and butorphanol) at peripheral sites, excluding intra-articular, concluded that those agents were not clinically relevant (Picard *et al.*, 1997).

The lack of analgesic effect appears to be due to tight intercellular contacts at the innermost layer of the perineurium that maintain homeostasis of the tissue surrounding peripheral neurons. The layer serves as a diffusion barrier for high molecular weight compounds, hydrophilic substances, and also for lipophilic compounds such as fentanyl and sufentanil (Gissen *et al.*, 1987). This barrier is continuous to the peripheral endings of nerve fibres. However, the barrier can be disrupted by

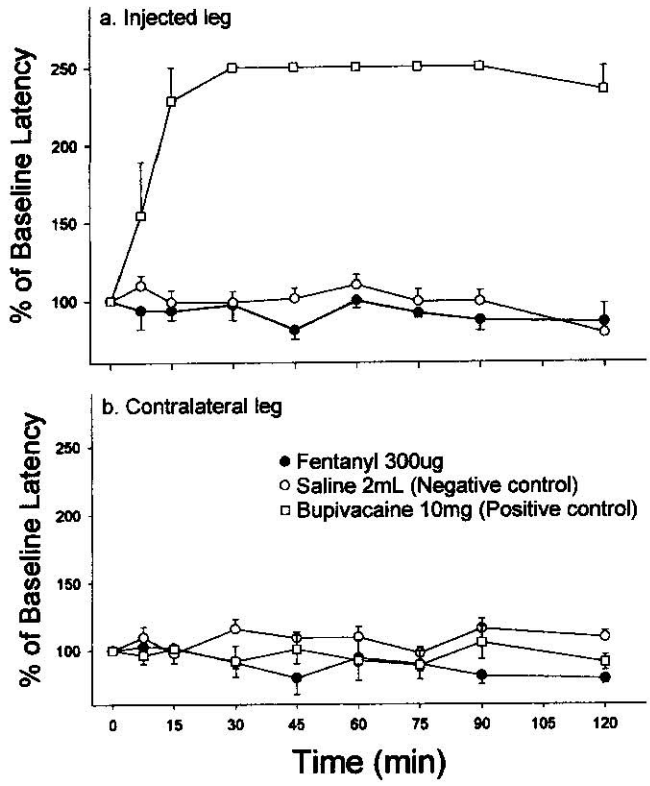

Fig. 1. (a) % of baseline HWRL (±SEM) following injections of fentanyl (300 μg) in treated leg; and (b) HWRL (±SEM) in contralateral leg after saline injection. Time = 0 is an average of the HWRL at–30,–15 and 0 min. Injections were made as abaxial sesamoid blocks.

inflammation or by artificial disruption of the blood–nerve barrier with application of hyperosmolar solutions to the tissue around the nerve. The latter approach has been accomplished with hypertonic (20%) saline and mannitol (Antonijevic *et al.*, 1995). Although fentanyl did not provide analgesia when injected as a nerve block in healthy tissue, the possibility remains that combining fentanyl with hypertonic saline could sufficiently disrupt the blood–nerve barrier to allow the opioid to penetrate to the receptor sites in the axons and cause an analgesic effect.

The local anaesthetics are agents that are considered to have very high potential to influence the performance of horses. Skilfully 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 the ability of a horse 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. Because of the perception that local anaesthetics have the potential to influence performance and to cause death or injury to horses and jockeys, it is important to regulate the use of these agents in racing horses.

In conclusion, fentanyl injected as an abaxial sesamoid block did not alter the perception of pain with the heat-lamp model used for evaluation of local anaesthetics in horses. The data suggest that fentanyl is unlikely to reduce pain perception when applied directly to sensory neurons. However, the effect of fentanyl and other opioids on joint pain perception of horses, especially inflamed joints, is unknown. In studies of human patients recovering from arthroscopic surgery, fentanyl was less effective in reducing postoperative pain than was morphine (Uysalel *et al.*, 1995) and alfentanyl (Gupta *et al.*, 1994).

In summary, the objective of this study was to determine if a small dose of fentanyl could produce a pain-suppressing effect, yet be undetectable by routine screening methods. The relatively high dose of 300 μg of fentanyl applied directly to the lateral volar nerve did not alter pain perception. As this dose is readily detectable by routine analytical methods, it is unlikely that fentanyl could be used as an effective local analgesic at undetectable doses.

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