TITLE: Study on Tolerance Development after Daily Epidural Injection of Sufentanil in Dogs

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Introduction: Administration of epidural opioids is an accepted method for the management of post-operative pain. Sufentanil, with its high lipid solubility and high receptor affinity should have three advantages: a rapid onset of the analgesic effect, potentially a longer duration than other anilinopiperidines and limited cephalad spread. This was already partially shown in other acute animal and clinical studies (1-3). Extensive clinical use of this agent should, however, be preceded by its systematic characterization in an animal model. In the present studies we have sought to examine the antinociceptive effects of three concentrations of sufentanil given daily for 15 days in chronically prepared dogs.

Methods: Dogs (beagles between 8-12 kg), under halothane anesthesia with aseptic procedures, were implanted in the epidural space with a catheter (PE_{50}-tubing) inserted at L_7/S_1 interspace and passed to the level of $L_3/4$. The catheter was tunneled subcutaneously to exit at the nape of the neck. After three days of recovery, daily injections were initiated of sufentanil in the epidural space for 15 days. Dogs were randomly assigned to receive saline or sufentanil in 1 of 3 doses (10 µg, 50 µg or 100 µg) in a volume of 2 ml. Each group consisted of 6 dogs. Daily, before and following each injection, neurological characteristics (placing/stepping, motor strength) and nociception were assessed periodically at intervals out to 5 hrs. The nociceptive response was quantified by measuring the response latency of the thermally evoked skin twitch produced by applying a thermal probe to the flanks. At the end of the 15-day period, the dogs were sacrificed by pentobarbital overdose, and spinal cords were exposed following vascular perfusion of saline followed by formalin. Care was taken upon exposure to assess the disposition of the catheter in the epidural space.

Results: On day 1, there was an immediate (<5 min), dose-dependent (100 µg = 50 µg > 10 µg > sal = 0) increase in the skin twitch response latency. The time for the effect to return to 50% of maximum was 140 min (10 µg); 275 min (50 µg) and 290 min (100 µg). By day 15, there was a small decrease in the maximum response, but all doses displayed a significant reduction in duration. thus, the time for return to 50% of maximum was 65 min (10 µg); 75 min (50 µg) and 140 min (100 µg). Computation each day of the percent of the maximum possible area under the time-effect curve (percent AUC) emphasized the significant reduction in duration of anti-nociceptive actions over the 15 days of treatment (see Figure 1). Behaviorally, on day 1, all of the dogs receiving 100 µg and 50 µg showed behavioral depression. No depression was observed in the 10 µg dogs. Respiratory depression, as measured by rate, bradycardia and defecation was observed within 10-15 min of the epidural injection of 50 and 100 µg of sufentanil. Feeding behavior, body weight and demeanor were essentially unchanged over the 15-day injection period. Upon sacrifice, examination of the spinal cord revealed that all catheters, including those obtained from saline-treated animals, showed significant investment by tissue that appears to be organization of the local epidural fat. No evidence of hemorrhage or an inflammatory reaction was noted.

Discussion: In this study, daily doses of even high concentrations (50 µg/ml) of epidural sufentanil gave no evidence of a lasting toxicological effect. Behaviorally, the early behavior depression observed is consistent with a rapid vascular redistribution, a finding consistent with the drug's lipid partition coefficient. The loss of response observed with repeated administration may well reflect underlying processes related to tolerance commonly observed after long term treatment. On the other hand, the prominent organization of the epidural fat around the catheter may result in a kinetically relevant change in the properties of drug distribution after epidural administration through chronically implanted epidural catheters.

References:

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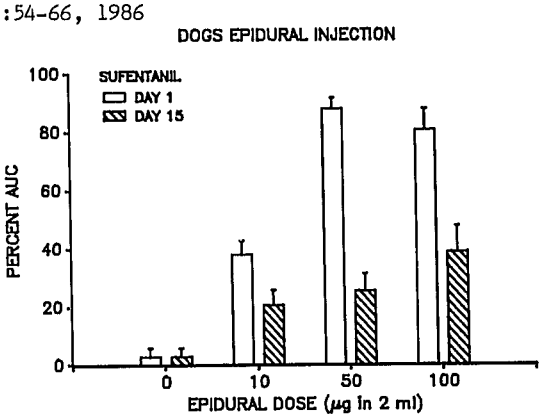

Histogram showing the µ ± S.E. of the percent of maximum possible "area under the curve" measured on on day 1 and day 15 in dogs receiving saline or sufentanil (10 µg, 50 µg or 100 µg) daily for 15 days. N=6 in each group.

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