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TITLE: SYSTEMATIC STUDIES ON THE USE OF HYDROXY-PROPYL-ß-CYCLODEXTRIN AS A SPINAL DRUG DELIVERY VEHICLE: OPIOID ANALGESIA IN RATS

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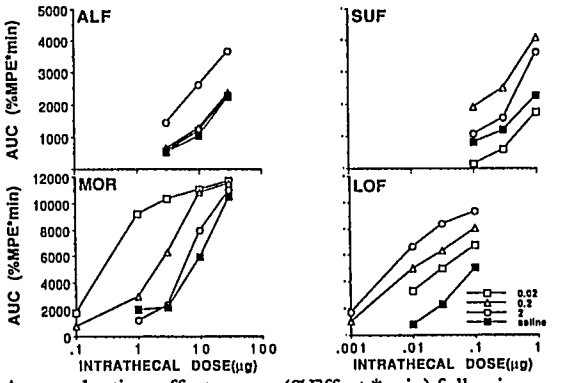
Introduction: Hydroxy-propyl-ß-cyclodextrin (CDEX), a crown ether, forms reversible inclusion complexes in its hydrophobic cavity with the lipophilic portion of drug molecule by a non-covalent bond. This property can increase the water solubility of hydrophobic molecules for spinal and parenteral delivery[1]. Such a vehicle can also serve to sequester lipophillic agents, reducing the concentration gradient across lipid membranes and thereby reduce the rate of movement of the free drug and reduce the vascular redistribution of lipophillic agents after spinal administration. In this fashion, CDEX could prolong the analgesic action of spinal drugs and reduce their supraspinal redistribution to diminish their supraspinal actions. This hypothesis was assessed in the present experiments.

Methods: Following institutionally approved protocols, male Sprague Dawley rats were prepared with chronic lumbar intrathecal (IT) catheters. Dose response curves were carried out on the 52.5 °C hot plate (HP) test using the opioids morphine, lofentanil, alfentanil and sufentanil dissolved in saline or in CDEX (2%, 0.2%, and 0.02% in sterile water). To define the IT drug effect, area under the curve (AUC: response latency in % effect x min) was calculated for each animal. Supraspinal effects were determined by the assessment of catalepsy (immobility for periods >10 sec).

Results: As shown in the figure, CDEX prolonged the duration of analgesia on the HP produced by IT opioids. The magnitude of the facilitatory effect was dependent upon CDEX concentration and a different optimal concentration was noted for each agent. For each of the four agents, the highest dose examined produced a significant catalepsy (morphine: 100ug; sufentanil: 0.3ug; alfentanil: 100ug and lofentanil: 0.3ug) when admininstered in saline vehicle. Following admininstration of these doses in the respective optimal CDEX concentration for each agent, no catalepsy was observed. No toxicity was observed at the highest CDEX (40%) concentration examined. The T1/2 of IT 2% CDEX-C^{14} in rat spinal CSF was 0.49 hr. The T1/2 of IT Inulin-C^{14} was 0.45 hr. These data suggest that CDEX is cleared as a large water soluble molecule in the CSF by bulk flow. Jointly, these observations suggest that CDEX may be a useful spinal vehicle for rapidly diffusible drugs.



Area under time effect curves (%Effect * min) following intrathecal injection of alfentanil, sufentanil, morphine, and lofentanil in saline or CDEX (0.02, 0.2, 2%).N=5-8 rats/point

[1] Yaksh, et al, Life Science 48:623-633, 1991. (Supported by University of California, Board of Regents; TLY).

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Title: **EFFECTS OF HALOTHANE ON RETINAL BLOOD FLOW IN CATS**

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General anesthesia is frequently chosen for retinal surgery, but little data are available about its effects on the ocular circulation. We previously demonstrated a dose-dependent increase in preretinal oxygen tension, known to reflect retinal blood flow and oxygen availability, during enflurane anesthesia.[1] In this study, we tested the hypothesis that retinal blood flow is increased during general anesthesia with another inhalational anesthetic, halothane.

Eight adult cats weighing 2.5-3.5 kg were studied after approval of our Animal Care Committee. The animals were anesthetized with halothane and air-oxygen. The lungs were mechanically ventilated to maintain arterial PCO_2 at 28-30 mm Hg and PO_2 above 100 mmHg. A left atrial (LA) catheter was placed via thoracotomy, and a femoral artery was cannulated for withdrawal of arterial blood samples. We continuously recorded mean arterial pressure (MAP); left atrial, intraocular (IOP), and airway opening pressures. IOP was measured as we previously described.[1] End-tidal halothane and CO_2 were monitored with calibrated gas analyzers. Blood flows were measured by injection of radioactively labelled microspheres of Sn 113, Ce 141, and Nb 95 into the LA using the reference blood sample method.[2] Measurements were made at 0.5, 1.0, and 1.5 MAC halothane in a random sequence. At the conclusion of the experiment, the animals were killed; the eyes were enucleated and carefully dissected in order to remove the retina. Results were analyzed using repeated measures of ANOVA and Bonferroni correction with $p < .02$ considered statistically significant.

Ocular perfusion pressure (OPP = MAP-IOP) decreased significantly during halothane anesthesia. Despite the decline in perfusion pressure (Table), there was a significant dose-dependent increase in retinal blood flow (RetBF).

These results indicate that increasing anesthetic depth results in vasodilatation in the retina. Since retinal blood flow is critical for the blood supply to the inner retina, these data indicate that halothane could safely be used where viability of the retina may be endangered perioperatively.

References: 1. Invest Ophthalmol Vis Sci 29: S179, 1988
2. Prog Cardiovasc Dis 20:55-78, 1977

Supported in part by FAER.

	Halothane Concentration (MAC)		
	0.5	1.0	1.5
OPP (mmHg)	128 ± 14	101 ± 13	82 ± 12 * †
Ret BF (ml/100gm/min)	36 ± 3	52 ± 9	61 ± 5*

* $p < .02$ vs 0.5 MAC
† $p < .02$ vs 1.0 MAC

Values are mean ± SEM