Title: A CHRONIC MODEL FOR VISCERAL PAIN ASSESSMENT IN THE RAT

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Introduction. A new model was designed to induce a mechanical visceral stimulus which is reproducible, reversible, and results in a graded discomfort adequate for the assessment of analgesic agents. Unlike visceral chemical models which rely on the inflammatory effects of noxious chemical agents[1], this approach utilizes a duodenal distention generated through the inflation of a surgically placed balloon catheter. This visceral distention model allows for the repeated testing necessary for determining, within a given animal, the development of tolerance or cross tolerance to various analgesics.[2]

Methods. Under halothane anesthesia, 225 gram male Sprague Dawley rats are surgically implanted with a specially designed balloon catheter (VPM catheter-Plane III, Inc., Dover, Delaware). This is accomplished by performing a gastrostomy and inserting the catheter into the stomach, then passing through the pylorous 3 cm into the duodenum. The catheter is secured to the stomach wall with suture, brought through the muscle layer and tunneled subcutaneously to exit at the neck dorsally. Catheter placement takes approximately 20 minutes and postoperative complications are rare (95% survival). The rat is allowed at least 72 hours to recover prior to testing.

Nociceptive testing is accomplished by initially defining a minimum threshold volume (MTV) which elicits a behavioral change (e.g. shake) without destroying the integrity of the gut. The animal is then given 5 pulses of the balloon at the MTV and observed for 10 minutes. The animal is returned to its cage for at least 24 hours prior to retesting at the same minimum threshold volume. Catheters remain functional indefinately and generally do not interfere with normal behavior or digestive function. Finally, the rats are sacrificed and confirmation of catheter placement and function is made under direct visualization during post mortem.

Results. Preliminary results of baseline nociceptive testing demonstrated an acute writing response in 70% of the animals. The response was characterized by an initial shake, followed by a profound contraction of the abdominal musculature and a stretch. A preliminary study with morphine sulfate administered either subcutaneously or intrathecally showed complete inhibition of the distention induced writhing response. Morphine sulfate was injected subcutaneously (1 mg/kg at 1 mg/ml in saline) into the dorsal neck region, or infused intrathecally (2 ug in 10 ul with 10 ul saline flush) through a spinal catheter[3], in both cases 20 minutes prior to testing.

MECHANICALLY INDUCED WRITHING REACTIVITY

	Control(n=12)	Morphine,s.c.(n=8)	Morphine,i.t.(n=3)
Baseline Test (No drug)	9/12 (75%)	6/8 (75%)	2/3 (67%)
Post Treatment Test	7/12 (58%)	0/8 (0%)	0/3 (0%)

Discussion. Preliminary studies show that this surgical approach is well tolerated and can be used in conjunction with a chronically placed intrathecal catheter. The writhing response can routinely be elicited in greater than 70% of the animals. This is comparable with the frequency of writhing following chemical peritoneal injection, but the latter is associated with inflammatory injury. Application of this model in the assessment of analgesic agents appears feasible. The above data indicate that the writhing response can be inhibited by the administration of narcotic agents via either a subcutaneous or intrathecal route. Further work is in progress to define both the utility of this model in the assessment of opiate receptor agonists given via multiple routes and the rate of tolerance development of agents directed against chronic visceral pain.

References.

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