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Differential effects on gastrointestinal activity after intrathecal morphine, sufentanil and alfentanil in rats

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ABSTRACT This paper reports on investigations of the effects on gastrointestinal (gi) transit of subcutaneous (sc) or intrathecal (i.t.) administration of the opiates morphine, alfentanil and sufentanil. Prior sc of all 3 drugs produced a significant dose-dependent decrease in transit of a charcoal test meal.

Morphine i.t. to rats with catheters chronically implanted in the subarachnoid space did not decrease gi transit. This was in contrast to the effects of i.t. alfentanil and sufentanil, which caused marked dose-dependent slowing of the passage of the meal. Prior sc of the opiate antagonist nalaxone completely blocked the depression of gi transit caused by high doses of i.t. sufentanil. The different responses to i.t. morphine and sufentanil or alfentanil may be due to the different mu receptor affinities of the drugs to spinal receptors, or to the slower passage of morphine into the intravascular compartment and hence a slower effect on supraspinal structures. Alternatively the results may be interpreted as indicating the presence of multiple subtypes of mu receptors in spinal cord.

KEY WORDS gastrointestinal motility; intrathecal injections; subcutaneous injections; endorphin receptors; morphine; sufentanil; alfentanil; inbred WF rats

Injection of narcotic analgesics into the subarachnoid space has been introduced into clinical anaesthesia[1]. Many side effects after i.t. morphine have been reported[2]. Some of these effects, for instance respiratory depression, are mediated by mu receptor stimulation[3]. Gastrointestinal motility is also depressed by mu receptor stimulation[4]. But no reports have dealt with constipation following i.t. morphine.

Alfentanil and sufentanil are powerfnl synthetic narcotic analgesics applied in clinical anaesthesia. Sufentanil, in particular, has an extremely high affinity for mu receptors[4]. We are interested to know if the decrease of gi transit would be produced by i.t. administration of these drugs.

MATERIALS AND METHODS

Inbred Wistar rats of either sex (305 ± SD 16 g) underwent catheterisation of subarachnoid space[5]. A polyethylene catheter (external diameter 0.61 mm) was introduced via the cisterna magna into the subarachnoid space and advanced 8 cm so that the tip lay in the lumbar region. The total length of the catheter was 16 cm and its volume 10 μl. The catheter, protruding from the nucha, was filled with saline and the end was sealed by heat. The rats were housed in individual cages. Experiments were performed 5-7 d later. Only those rats showing no neurological impairment were included in the experiment.

By using a Hamilton microlitre syringe, drugs were injected in a volume of 5-10 μl followed by flushing with 10 μl saline. Gastrointestinal transit was determined by charcoal meal test[6], in which 2 ml of a mixture of charcoal, flour and water

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(1:2:6) was fed by gavage.

Groups of overnight-fasted rats received either drug or saline i.t. followed by a charcoal meal. After 20 min the rats were killed. The point in the small intestine where the charcoal had reached was identified and the distance travelled was expressed as % of the total length of the intestine between pyloric sphincter and ileocecal junction. Groups of rats received morphine 50 μg, alfentanil 2.5 μg, 5 μg and sufentanil 0.25 μg, 0.5 μg respectively and were compared with the group of rats receiving i.t. saline. Because the transit for saline varied from day to day, a new saline control group was established on each day.

Four groups of rats (without intrathecal catheters) received sc morphine 1,3, 10 and 30 mg/kg, respectively. Four groups received alfentanil 50, 125, 250 and 500 μg/kg, respectively. Three groups were given sufentanil 5, 15 and 50 μg/kg, respectively.

A charcoal meal was given 25 min after morphine, but only 10 min after alfentanil and sufentanil because of their short duration of action. All rats receiving sc narcotics were killed after 20 min.

In order to demonstrate that the observed decreases in gi transit were indeed caused by opiate receptor activation, the opiate antagonist naloxone (2 mg/kg) was injected sc to a group of rats 10 min prior to 0.5 μg sufentanil followed by a charcoal meal.

Difference in transit between saline groups and narcotic groups were assessed by paired *t* test.

RESULTS

The distance travelled by the charcoal meal in the saline groups varied from day to day. The transit distance after i.t. or sc narcotics were therefore expressed as % of the mean saline transit on the day of the experiment. The effects of i.t. narcotics and sc naloxone in combination with sufentanil 0.5 μg are presented in Fig 1 A.

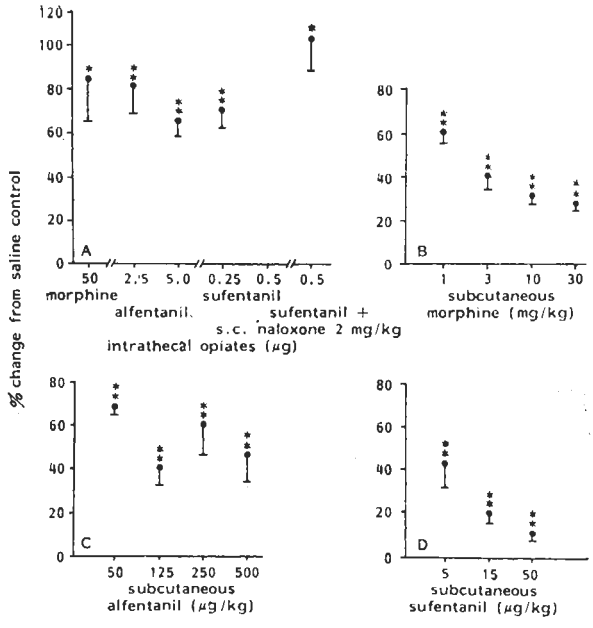

Fig 1. Gastrointestinal transit in rats. (A)Effects of intrathecal morphine, alfentanil, sufentanil and antagonism by subcutaneous naloxone. Effects of subcutaneous morphine (B), alfentanil (C) and sufentanil (D). *p>0.05, **p<0.05, ***p<0.01

A relatively large dose of i.t. morphine (50 μg) produced no significant decrease in gi transit, but alfentanil and sufentanil produced a dose dependent decrease. This was particularly evident in the case of sufentanil 0.5 μg. This effect was completely blocked by sc naloxone 2 mg/kg.

The effects of the above drugs on gi motility when given sc are shown in Fig 1 B–D. Both morphine and sufentanil yielded a clear dose-related slowing of the passage of the charcoal meal, again the greatest suppression of activity was caused by the largest dose of sufentanil. The results after different doses of alfentanil were more variable, though significant decreases in transit were seen at all doses. Within 1 min after i.t. sufentanil and alfentanil they caused muscular rigidities of neck and chest of the rats but never after i.t. morphine. The rats

always assumed a characteristic hunched posture. They did not move spontaneously except when disturbed. This effect was not seen after i.t. sufentanil if the rats had been pretreated with sc naloxone.

DISCUSSION

It was demonstrated that decreased transit after i.t. morphine 1–10 μg was antagonized by sc naloxone 2 mg/kg. The degree of inhibition of gi activity by narcotics appeared to be species dependent. IT morphine 10–30 μg, a dose 10–30 times that of the analgesic dose, did not produce any decrease in gi motility[7]. We have confirmed these findings and have shown that an even higher dose of i.t. morphine (50 μg) was similarly ineffective in producing constipation. On the other hand, i.t. sufentanil and alfentanil, which have high affinity for mu receptors, produced a dose-dependent decrease in gi transit. The fact that, the constipation caused by sufentanil was antagonised by pretreatment with sc naloxone strongly, suggests the presence of mu receptors controlling gi motility.

The question arises as to why morphine has no effect on GI transit whereas a considerable depression in motility is seen after alfentanil and sufentanil. One possibility is that the spinal action of morphine is somehow altered by indwelling catheters. Alfentanil and sufentanil are more lipid soluble and their spinal actions are not affected.

Another possibility may be that sufentanil and alfentanil, which have very high solubilities, are rapidly absorbed into the blood stream and gain access to supraspinal structures. Morphine, on the other hand, has a much lower lipid solubility and hence could not reach the higher centres so rapidly. Thus, muscular rigidity of neck and chest was induced by i.t. sufentanil and alfentanil but not by i.t. morphine. This explanation may not be true because morphine depresses gi motility in mice after section of cervical spinal cord[8].

En résumé, i.t. morphine was, during the first 20 min, ineffective in suppressing gi motility in rats. This was in contrast to IT alfentanil and sufentanil which had a marked dose-dependent effect on gi transit. When the 3 drugs were given sc, they produced similar degrees of inhibition of gi motility at equipotent doses.

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注射吗啡、阿芬太尼及舒芬太尼对大鼠胃肠道食物移行的影响

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提要　本文研究在含炭末食物gi移行试验中，sc吗啡阿芬太尼、舒芬太尼，在等效剂量范围内它们均可产生显著的、程度相仿且依赖于剂量的食物在gi中移行减缓的作用。在大鼠小脑延髓池事先埋植聚乙烯慢性套管，通过此管鞘内注射(i.t.)上述三药。吗啡并不起减缓作用，但阿芬太尼及舒芬太尼却可产生明显的依赖于剂量的gi中食物移行减缓作用。为了证明这一作用确系阿片受体被激动所引起，大鼠被预先sc阿片受体特异性拮抗剂纳洛酮2 mg/kg，10 min后再i.t.舒芬太尼0.5 μg，结果其减缓食物在gi中移行作用被完全阻断，从而说明这一作用与脊髓中阿片μ受体功能有关。

吗啡、阿芬太尼、舒芬太尼i.t.对gi中食物移行所产生的作用不同，可能由于它们对脊髓中阿片μ受体的亲和力不同或由于吗啡的脂溶性小于其它两药，进入血管腔隙较迟缓，从而作用于脊髓上部结构及高级中枢也慢之故。此外，这一结果也提示脊髓中可能存在多种μ受体亚型。

关键词　胃肠活动；鞘内注射；皮下注射；内啡肽受体；吗啡；舒芬太尼；阿芬太尼；近交系WF大鼠

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