Opioid-induced Delay in Gastric Emptying
A Peripheral Mechanism in Humans


Background: Opioids delay gastric emptying, which in turn may increase the risk of vomiting and pulmonary aspiration. Naloxone reverses this opiate action on gastric emptying, but it is not known whether this effect in humans is mediated by central or peripheral opiate antagonism. The importance of peripheral opioid receptor antagonism in modulating opioid-induced delay in gastric emptying was evaluated using methylnaltrexone, a quaternary derivative of the opiate antagonist naltrexone, which does not cross the blood–brain barrier.

Methods: In a randomized, double-blind, crossover placebo-controlled study, 11 healthy volunteers were given either placebo (saline), 0.09 mg/kg morphine, or 0.09 mg/kg morphine plus 0.3 mg/kg methylnaltrexone on three separate occasions before ingesting 500 ml deionized water. The rate of gastric emptying was measured by two methods: a noninvasive epigastric bioimpedance technique and the acetalminophen absorption test.

Results: The epigastric bioimpedance technique was sufficiently sensitive to detect opioid-induced changes in the rate of gastric emptying. The mean ± SD time taken for the gastric volume to decrease to 50% (t0.5) after placebo was 5.5 ± 2.1 min. Morphine prolonged gastric emptying to (t0.5) of 21 ± 9.0 min (P < 0.03). Methylnaltrexone given concomitantly with morphine reversed the morphine-induced delay in gastric emptying to a t0.5 of 7.4 ± 3.0 (P < 0.04). Maximum concentrations and area under the concentration curve from 0 to 90 min of serum acetalminophen concentrations after morphine were significantly different from placebo and morphine administered concomitantly with methylnaltrexone (P < 0.05). No difference in maximum concentration or area under the concentration curve from 0 to 90 min was noted between placebo and methylnaltrexone coadministered with morphine.

Conclusions: The attenuation of morphine-induced delay in gastric emptying by methylnaltrexone suggests that the opioid effect is mediated outside the central nervous system. Methylnaltrexone may have the potential to decrease the side effects of opioid medications, which are mediated peripherally, while maintaining the central analgesia effect of the opioid. (Key words: Gastric emptying, Opioid, Methylnaltrexone. Electrical bioimpedance. Acetalminophen absorption test.)

DELAYED gastric emptying may alter the rate of absorption of orally administered drugs, increase the risk of pulmonary aspiration, and is associated with nausea and vomiting.1 One cause of delayed gastric emptying and drug absorption in the perioperative period is administration of opioid analgesic drugs.2–4 Opioid inhibition of gastrointestinal transit may be mediated by both central and peripheral mechanisms.5 In animal studies, morphine has been reported to act at supraspinal,6 spinal,7 and peripheral8,9 opioid receptors to inhibit gastrointestinal transit. A study by Shook10 suggested that peripheral opioid μ receptors are involved independently of central μ receptors in the inhibition of gastrointestinal transit in mice.

In humans, opioid-induced delay in gastric emptying was reversed by naloxone.11 Whether this effect was mediated by antagonism of the central nervous system or peripheral opioid receptors remains unknown. Accordingly, our aim in this study was to evaluate the contribution of peripheral opioid receptor activation in the modulation of opioid-induced delay in gastric emptying in humans. To this end we examined the extent to which methylnaltrexone, a novel quaternary derivative of the opioid antagonist naltrexone, which

* Research Registrar in Pharmacology and Therapeutics, University College Cork.
† Head, Guildford Clinical Pharmacology Unit, University of Surrey.
‡ Professor of Clinical Pharmacology, Western General Hospital.
§ Professor of Clinical Pharmacology, University College Cork.

Received from the Cork University Hospital, Wilton, Cork City, Ireland; University of Surrey, Surrey, and Western General Hospital, Edinburgh, United Kingdom; and University College Cork, Cork, Ireland. Submitted for publication October 11, 1996. Accepted for publication May 13, 1997.

Address reprint requests to Dr. D. B. Murphy: Department of Pharmacology and Therapeutics, Clinical Sciences Building, Cork University Hospital, Wilton, Cork City, Ireland.

Anesthesiology, V 87, No 4, Oct 1997
does not cross the blood–brain barrier, might blunt morphine-induced delay in gastric emptying.

Methods

Eleven healthy volunteers (six men and five women) gave informed consent for the study, which was approved by the Clinical Research Ethics Committee of the Cork Teaching Hospitals and by the Irish National Drugs Advisory Board. All volunteers denied a history of gastrointestinal disease or drug hypersensitivity and were taking no medications. They fasted for a minimum of 8 h before all study sessions and abstained from alcohol for 24 h before dosing. Studies were performed between 9:00 AM and 12:00 PM.

At intervals of at least 7 days, volunteers were given placebo (saline), 0.09 mg/kg morphine, or 0.3 mg/kg methylaltrexone and 0.09 mg/kg morphine concomitantly in a random-order, double-blind crossover design. Drugs were administered as an intravenous infusion during a 10-min period. The rate of gastric emptying was evaluated directly by a noninvasive electrical bioimpedance method¹² and indirectly by the acetaminophen absorption technique.¹³

Electrical Bioimpedance Technique

The basis of the bioimpedance technique is that after the ingestion of fluids with a different conductivity from body tissues, the impedance to an electrical current through the upper abdomen changes. Impedance increases as the stomach fills and decreases as it empties. The slope of the plot of impedance versus time allows us to calculate the time for emptying half the meal (t₅₀; fig. 1).

Twenty minutes before drugs were administered, three silver/silver chloride electrodes were placed on the abdomen, one at the left subcostal margin in the midclavicular line, the second 1 cm medial, and the third 1 cm lateral to the central electrode along the subcostal border. Three electrodes were placed on the back in a parallel, reciprocal position. A constant 4-mA 100-kHz AC current was applied through the abdomen, and the voltage variations were recorded. Low-pass filtering excluded cardiac but not respiratory signal interference, and an offset voltage control allowed for differences in basal body impedance. Participants lay still and semirecumbent at 45°, and heart rate, blood pressure, and respiratory rate were recorded throughout. Baseline impedance recordings were established before drug infusion. At exactly 10 min after completion of drug infusion, each volunteer ingested 1.5 g acetaminophen in 500 ml deionized water at room temperature.

The resultant increase in impedance produced a deflection on the epigastrograph corresponding to gastric filling, which was measured in millimeters from baseline and designated 100%. The time taken to decrease to 50% of the original value was calculated (fig. 1), giving a value for impedance half-life (t₅₀).

Acetaminophen Absorption Test

The appearance of acetaminophen in the systemic circulation is an indirect method of determining the rate of gastric emptying. Accordingly, the area under the serum concentration curve (AUC) of acetaminophen after oral administration is determined by the rate of gastric emptying, because acetaminophen is not absorbed from the stomach but is rapidly absorbed from the small intestine.¹⁵

Venous blood samples were obtained immediately before ingestion of the acetaminophen and thereafter at 10, 20, 30, 40, 50, 60, 70, and 90 min. The samples were centrifuged, separated immediately, and the serum frozen at −60°C until analyzed blindly for acetaminophen concentrations by high-performance liquid chro-
matography. The mean coefficient of variation for five replicate analyses of spiked plasma standards containing 5 mg/l and 25 mg/l acetaminophen was less than 2.5%. The limit of detection for acetaminophen was less than 1 µg/ml, and there was no interference from the other drugs. Differences in the rate of acetaminophen absorption were estimated by determining the area under the serum concentration curve for 0 to 90 min (AUC0–90) using the trapezoidal rule and the peak concentration.

At 10-min intervals, nausea (from 1 = no nausea to 10 = worst possible nausea) was evaluated using a subjective verbal score rating scale.

Statistical Analysis

The BMDP statistical software (University College Cork) was used to analyze differences in t0.5 values, serum acetaminophen concentrations, AUC0–90, peak concentration, nausea scores, heart rate, blood pressure, and respiratory rate between treatments, applying the methods for three-period crossover designs using analysis of variance and covariance. Pairwise comparisons using t tests of the data (t0.5, AUC 0–90, and so on) were done only when the overall comparison of the treatments proved significant at the 5% level.

Results

Results are expressed as mean ± SD unless otherwise stated. The mean age of the 11 volunteers was 26 ± 4.4 yr, and their body weight and height were 64 ± 8.3 kg and 168 ± 10.4 cm, respectively. One participant failed to complete the study, because she vomited after morphine. Heart rate, blood pressure, and respiratory rate did not differ between treatments.

The average time to empty half the stomach contents (t0.5) after placebo measured by bioimpedance was 5.5 ± 1.9 min. Morphine delayed gastric emptying and quadrupled the t0.5 to 21.5 ± 9.0 min (P < 0.03), whereas adding the antagonist methylaltrexone reversed this effect almost fully (t0.5 of 7.4 ± 3.0 min [P < 0.04]; table 1 and fig. 2).

Figure 3 shows the acetaminophen concentrations during the three sessions. Acetaminophen was absorbed rapidly after placebo. Morphine delayed absorption of acetaminophen, resulting in peak concentration values that were significantly lower (P < 0.05) than placebo. There were no statistical differences in serum acetaminophen concentrations at 30, 40, 50, and 60 min between placebo and methylaltrexone administered with morphine. The AUC0–90 was significantly decreased after morphine when compared with placebo.

![Figure 2](image-url)

Fig. 2. Epigastric impedance recordings. The y axis represents the overall impedance (measured in ohms). Time 0 is the point of maximum impedance increase due to the ingestion of 500 ml deionized water. Trace A records a normal gastric emptying half-time (t0.5) of 4–6 min. Trace B shows no immediate tendency to return to baseline when the participant received 0.09 mg/kg morphine and a subsequent prolongation in t0.5 to 30 min. In trace C, there is return to normal gastric emptying t0.5 (5–8 min) value when 0.3 mg/kg methylaltrexone was given concomitantly with 0.09 mg/kg morphine.
(P < 0.05) or when methylaltrexone was coadministered with morphine (P < 0.05). No significant difference was noted in the AUC_{0–90} between placebo and morphine plus methylaltrexone. There was no significant difference in peak concentration values between placebo and methylaltrexone plus morphine (table 2).

The highest nausea scores were recorded after morphine alone, and there was a significant difference compared with saline 50 min after drug infusion (P < 0.014). When compared with morphine, there was a lower nausea score when morphine was given with methylaltrexone, but this was not significant (fig. 4). Three volunteers vomited after morphine, and one also vomited when he received methylaltrexone with morphine. Vomiting occurred more than 60 min after drug infusion, and thus sufficient epigastric impedance recordings were completed to allow calculation of the t_{max} in all cases. No participant experienced nausea or vomiting with saline.

**Discussion**

In this study, methylaltrexone attenuated morphine-induced delay in gastric emptying, measured by the epigastric bioimpedance technique or the acetaminophen absorption test.

Methylaltrexone is a quaternary opioid receptor antagonist. The highly ionized quaternary methyl group limits the transfer of methylaltrexone across the blood–brain barrier. Methylaltrexone is active at peripheral rather than central opioid sites, as demonstrated by its failure in high doses to penetrate the central nervous system sufficiently to promote withdrawal in morphine-dependent dogs (50 mg/kg given subcutaneously) and monkeys (32 mg/kg given subcutaneously), in contrast to naltrexone, which did so at 0.3

---

**Table 2. Acetaminophen Absorption Test**

<table>
<thead>
<tr>
<th></th>
<th>Saline</th>
<th>Morphine</th>
<th>Morphine + Methylaltrexone</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{0–90} mg/l/h</td>
<td>1078 ± 295</td>
<td>502 ± 395*</td>
<td>798 ± 481†</td>
</tr>
<tr>
<td>C_{max} mg/l</td>
<td>18.39 ± 4.6</td>
<td>8.1 ± 5.3*</td>
<td>13.33 ± 7.9†</td>
</tr>
</tbody>
</table>

Results expressed as mean ± SD.

Area under the plasma concentration curve (AUC) and peak plasma concentration of acetaminophen (C Max). *P < 0.05 compared to saline. †P < 0.05 when morphine was compared with methylaltrexone + morphine.

Anesthesiology, V 87, No 4, Oct 1997
mg/kg and 0.004 mg/kg subcutaneous doses, respectively. An \textit{in vitro} study showed that methylnaltrexone at 100 nm blocked morphine-induced (100 nm) inhibition of smooth muscle contraction elicited by electrical stimulation in guinea pig ileum and human small intestine. The selection of the dose of methylnaltrexone (0.3 mg/kg) in this study was based on animal studies in which the ratio of methylnaltrexone to morphine (3:1) was shown to be effective, and freedom from side effects observed in previous human studies.

Opioid peptides and their receptors are found throughout the gastrointestinal system with particularly high concentrations in the gastric antrum and proximal duodenum. The mechanisms of inhibition of gastric emptying by exogenous and endogenous opiates are unclear, and although central and peripheral mechanisms may be involved, their relative contributions are uncertain. A central mechanism of opioid-induced delay in gastrointestinal transit was postulated because administration of morphine-like drugs directly into the central nervous system delayed gastrointestinal transit. Intracerebroventricular injection of morphine in the rat inhibits gastrointestinal propulsion, and this effect is reversed by intracerebroventricular injection of opioid antagonists and vagotomy. In contrast, a peripheral site of action was demonstrated by the finding that local intra-arterial infusion of morphine to the pylorus of the cat induced gastric relaxation, which was antagonized by naloxone.

Several other studies suggest that the delay in gastric emptying caused by analgesic doses of opioids is mediated at receptors outside the central nervous system. Central and peripheral \( \mu \) receptors can regulate gastric emptying, and peripheral \( \mu \) receptors were involved independently of central \( \mu \) receptors in the inhibition of gastrointestinal transit in mice. Manara \textit{et al.} inferred that inhibition of gastrointestinal transit in the rat was mediated \textit{via} peripheral opioid receptors because the inhibitory effects of subcutaneous, intraperitoneal, and intravenous morphine were antagonized by the quaternary antagonist N-methyl-naloxone.

Opioid-induced delay in gastric emptying in humans was reversed by naloxone, but whether this effect was mediated centrally or peripherally could not be determined because the antagonist acts on both sites simultaneously. It has been reported, in healthy persons, that methylnaltrexone prevented morphine-induced delay in oral-cecal transit time, as assessed by the pulmonary hydrogen measurement technique, without affecting analgesia. However, different physiologic mechanisms are involved in regulating gastric emptying and intestinal transit. The demonstration in the present study that methylnaltrexone attenuates morphine-induced changes in the rate of gastric emptying indicates that peripheral opioid antagonism modulates opiate-induced delay of gastric emptying in humans. Morphine may delay gastric emptying in humans primarily \textit{via} a peripheral mechanism because methylnaltrexone significantly attenuated the effects of intravenous morphine.

It might be argued that demethylation of methylnaltrexone with subsequent central nervous system penetration of naltrexone could confound interpretation of our results. However, methylnaltrexone is not demethylated in humans.

Methylnaltrexone reduced morphine-induced emesis in dogs, and in the present study it had a similar effect in reducing the nausea score produced by morphine. This attenuation of morphine-induced nausea may be due to antagonism of morphine at the chemoreceptor trigger zone (which is physiologically located outside the blood-brain barrier) or through limitation of the delay in gastric emptying, which in itself may cause nausea. The epigastric impedance tracings showed delayed gastric emptying before the onset of nausea, suggesting that nausea itself did not delay gastric emptying.

Many techniques have been developed to assess gastric emptying in humans, and they all have disadvantages. The epigastric impedance method was pioneered by McClelland and Sutton, and it gives similar estimates of gastric emptying rates as scintigraphy, the dye dilution technique, and the acetaminophen absorption test. The principal benefit of the bioimpedance method is that it is noninvasive and avoids gastric intubation or exposure to radioactivity. A limitation is that the participant must not move the torso, because major alterations in body posture may alter baseline impedance readings and thus invalidate the recording. Another possible source of error is that gastric secretions might reduce the conductivity of gastric contents, thus reducing total surface impedance, and produce inaccurate emptying rates. For this reason we chose deionized water as our “test meal” because it does not appear to provoke sufficient gastric secretions to alter impedance and it reduced the time needed for participants to remain still. We also note that there was agreement between our two methods.

Do the findings in this study have clinical implications? The adverse effects of many opiates, including nausea, vomiting, constipation, and biliary spasm, may
be mediated by receptors outside the functional blood-brain barrier. Based on our findings, methylaltrexone has the potential to reverse morphine-induced delay in gastric emptying without decreasing its centrally mediated analgesia effects. This property, coupled with its antiemetic potential, suggests that the coadministration of methylaltrexone with opiates may be of benefit to patients in the perioperative period.

The authors thank Professor M. F. Roizen and Dr. J. Foss, Department of Anaesthesia and Critical Care, University of Chicago, for providing methylaltrexone.

References