Effects of nalbuphine, pentazocine and U50488H on gastric emptying and gastrointestinal transit in the rat†

T. ASAI, W. W. MAPLESON, I. POWER

Summary
We studied the effect of mixed agonist-antagonist opioids (nalbuphine and pentazocine) and a kappa opioid agonist (U50488H) on gastric emptying and gastrointestinal transit, and their interactions with morphine in rats. In each group, nalbuphine (0.01–30 mg kg⁻¹), pentazocine (1–30 mg kg⁻¹), U50488H (1–100 mg kg⁻¹) or saline was injected i.p. at 0 min. Another four groups of rats received morphine 13.4 mg kg⁻¹ (ED75) and one of the following substances: saline, nalbuphine, pentazocine or U50488H. In both groups, at 30 min, radiolabelled saline 1 ml was infused into the stomach; at 1 h, gastric emptying and gastrointestinal transit were calculated by measuring the radioactivity in the gastrointestinal tract. Slopes for dose–response curves were determined. Nalbuphine significantly, but only weakly, delayed gastric emptying (P<0.0005) and gastrointestinal transit (P<0.01). Pentazocine markedly inhibited both, whereas U50488H did not significantly inhibit either. The slopes of the dose–response curves for nalbuphine, but not for pentazocine, on both gastric emptying and gastrointestinal transit were significantly less steep than those for morphine. Nalbuphine significantly antagonized the inhibitory effect of morphine on gastric emptying (P=0.005) and gastrointestinal transit (P=0.02), whereas pentazocine and U50488H did not. Nalbuphine and pentazocine delay gastric emptying and gastrointestinal transit, possibly by different mechanisms. (Br. J. Anaesth. 1998; 80: 814–819)

Keywords: interactions (drug) opioids; gastrointestinal tract gastric emptying; complications gastric stasis; rat

Opioids may bind to more than one receptor, and the intrinsic activity for each receptor may differ. Some of them have no or weak intrinsic activities to produce agonist effects at one receptor (competitive or partial agonists). When a partial agonist and a full agonist are given concurrently, binding of the full agonist will be partially prevented by binding of the partial agonist, and thus the effect of the full agonist will be reduced. For example, the opioid nalbuphine antagonizes the antinociceptive effect of mu opioid receptor agonists. Such opioids are called mixed agonist–antagonist opioids, and include nalbuphine, nalorphine and pentazocine.

Mu opioid receptor agonists, such as morphine, delay gastric emptying and intestinal transit. In contrast, kappa receptor opioid agonists have weak or no inhibitory effects. Little is known about the effects and mechanisms of mixed agonist–antagonist opioids on gastric emptying and intestinal transit. In mice, nalbuphine, nalorphine and pentazocine delayed gastrointestinal transit, but the inhibitory effect was weak. We found only one report in which the effect of the mixed agonist–antagonist on gastric emptying was studied in animals. In that study, the residual volume of gastric contents was examined 30 min after infusion of dyed antacid into the stomach and injection of either pentazocine or saline in rats. The residual volume was greater in the pentazocine group than the saline group; however, the residual volume in the pentazocine group was greater than the volume of initial infusion of dyed antacid. Antacid itself delays gastric emptying and increases gastric acid secretion; therefore, the effects of pentazocine are not clear.

More than one opioid, such as nalbuphine and morphine, may be given concurrently during surgery. The interactive effects of these drugs and the effect on gastrointestinal motility are not known.

We decided to study the effects of a mu agonist (morphine), mixed agonist–antagonists (nalbuphine and pentazocine) and a highly selective kappa agonist (U50488H) on gastric emptying and gastrointestinal transit; we also studied the interactive effects of these opioids.

Materials and methods
The study was conducted under the Animal (Scientific Procedures) Act 1986 (Home Office Licence: PPL 40/954, PPL 40/1397). Male Wistar rats, each weighing 200–250 g, were housed under standard controlled environmental conditions, with a 12 h light–dark cycle. The animals were fasted for 24 h, but allowed free access to water until 20–30 min before the start of the experiment. They were kept in individual wire-mesh cages to prevent coprophagy

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Effects of opioids on gastrointestinal transit during fasting. All experiments were started between 10:00 and 11:00. Nalbuphine, pentazocine (Sigma Chemical Co., UK) and U50488H (Upjohn Company, USA) were prepared freshly on each day of the experiment.

A group of six rats was allocated for each set of circumstances. If more than one rat was excluded, another group of six rats was used until a group was completed in which no more than one rat was excluded. Data from the non-excluded rats from all groups for each study (5–10 rats) were used.

Gastric emptying and gastrointestinal transit were studied, as described previously. In brief, at 0 min, a substance or a combination of substances (see below), in a volume of 1.0 ml kg\(^{-1}\) for each substance was given i.p. At 30 min, 1.0 ml of saline containing radiolabelled sodium chromate was infused into the stomach. At 60 min, the rats were killed. The stomach and small intestine were removed, and the small intestine divided into 10 equal segments. The radioactivity in the stomach and each segment of the intestine was counted. If there was chyme in the stomach or small intestine, the data were not used.

Gastric emptying and gastrointestinal transit (expressed in terms of the geometric centre) in each rat and the percentage inhibition of gastric emptying or gastrointestinal transit for each test drug were calculated.

### EFFECTS OF INDIVIDUAL OPIOID AGONIST

We studied the effects on gastrointestinal motility of three different types of opioid receptor agonist: a mu opioid receptor agonist (morphine, 0.1–30 mg kg\(^{-1}\)); a

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Gastric emptying</th>
<th>Gastrointestinal transit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine (n=52)*</td>
<td>2.8 (2.1, 3.8)</td>
<td>1.2 (0.87, 1.71)</td>
</tr>
<tr>
<td>Nalbuphine (n=36)</td>
<td>— (28.1, —)</td>
<td>— (369, —)</td>
</tr>
<tr>
<td>Pentazocine (n=29)</td>
<td>12.8 (8.2, 24.7)</td>
<td>39.8 (16.0, —)</td>
</tr>
<tr>
<td>U50488H (n=28)</td>
<td>—†</td>
<td>—†</td>
</tr>
</tbody>
</table>

Table 2 Slopes (logit (% gastric emptying) or logit (% geometric centre) per unit log dose) and differences in slopes of the logit curves (with 95% confidence limits (CL)) for the effect of opioids on gastric emptying and gastrointestinal transit of saline

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Slopes (95% CL)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric emptying</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine (n=52)</td>
<td>—1.38 (−1.48, −1.29)</td>
<td></td>
</tr>
<tr>
<td>Nalbuphine (n=36)</td>
<td>—0.48 (−0.55, −0.40)</td>
<td></td>
</tr>
<tr>
<td>Pentazocine (n=29)</td>
<td>−1.67 (−1.8, −1.5)</td>
<td></td>
</tr>
<tr>
<td>Differences between drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine — nalbuphine</td>
<td>—0.91 (−1.27, −0.55) ≤0.001</td>
<td></td>
</tr>
<tr>
<td>Morphine — pentazocine</td>
<td>0.29 (−0.28, 0.86) 0.32</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal transit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine (n=52)</td>
<td>—0.97 (−1.05, −0.89)</td>
<td></td>
</tr>
<tr>
<td>Nalbuphine (n=36)</td>
<td>—0.23 (−0.30, −0.16)</td>
<td></td>
</tr>
<tr>
<td>Pentazocine (n=29)</td>
<td>−1.03 (−1.18, −0.88)</td>
<td></td>
</tr>
<tr>
<td>Differences between drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine — nalbuphine</td>
<td>—0.74 (−1.05, −0.44) ≤0.001</td>
<td></td>
</tr>
<tr>
<td>Morphine — pentazocine</td>
<td>0.06 (−0.43, 0.54) 0.82</td>
<td></td>
</tr>
</tbody>
</table>

*Data for morphine are from a previous report. †U50488H up to 100 mg kg\(^{-1}\) did not significantly delay gastric emptying and gastrointestinal transit.
Table 3  Effect of nalbuphine, pentazocine or U50488H on the inhibitory effect of morphine on gastric emptying and gastrointestinal transit of saline (median). Non-parametric one-way analysis of variance (Kruskal–Wallis test) showed a significant difference in gastric emptying (P<0.05) and gastrointestinal transit (P=0.01) between groups; the Minitab version of Mann–Whitney U test was used to obtain P values and 95% confidence limits of the difference between rats that received morphine with saline and those that received a combination of morphine and an agonist. Six to seven rats were used for each group.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Gastric emptying (%)</th>
<th>Difference from morphine group</th>
<th>Gastrointestinal transit</th>
<th>Difference from morphine group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>95% CI</td>
<td>Confidence limits</td>
<td>95% CI</td>
<td>Confidence limits</td>
</tr>
<tr>
<td>Morphin 13.4 mg kg⁻¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ saline</td>
<td>20.0</td>
<td>(4.0, 32.2)</td>
<td>0.02</td>
<td>(0.4, 2.1)</td>
</tr>
<tr>
<td>+ nalbuphine 1.0 mg kg⁻¹</td>
<td>41.0</td>
<td>(−8.0, 11.0)</td>
<td>0.41</td>
<td>(−0.4, 0.9)</td>
</tr>
<tr>
<td>+ pentazocine 1.0 mg kg⁻¹</td>
<td>22.5</td>
<td>(−9.8, 19.3)</td>
<td>1.6</td>
<td>(−0.4, 0.8)</td>
</tr>
<tr>
<td>+ U50488H 1.0 mg kg⁻¹</td>
<td>22.1</td>
<td>(−9.8, 19.3)</td>
<td>1.6</td>
<td>(−0.4, 0.8)</td>
</tr>
</tbody>
</table>

kappa opioid receptor agonist (U50488H, 1–100 mg kg⁻¹)16; and a mixed agonist–antagonist opioid (nalbuphine, 0.01–30 mg kg⁻¹, and pentazocine, 1–30 mg kg⁻¹). However, only four rats were used for 100 mg kg⁻¹ U50488H, because of limited availability of the drug. Data for morphine have been reported already,13 but were not used in any hypothesis tests. The experiments with the other three opioids were all conducted within the period over which the measurements with morphine were made.

INTERACTIONS OF TWO OPIOID AGONISTS

Another four groups of rats received morphine 13.4 mg kg⁻¹ (ED₅₀) and one of the following substances: saline, nalbuphine, pentazocine or U50488H (the last three at 1.0 mg kg⁻¹).

STATISTICAL ANALYSIS

The variation of percentage inhibition with the dose of each agent was modelled, except for results for U50488H, by fitting a sigmoid logit curve to fractional inhibition against log dose, to calculate ED₅₀ and ED₇₅ and, by means of the Fieller equation, the 95% confidence interval (CI) of those doses.15

When the logit curve showed that the test drug did not inhibit gastric emptying or gastrointestinal transit by more than 50%, the Mann–Whitney U test was used to compare gastric emptying and gastrointestinal transit between the drug and saline groups of rats; the values for all doses of the test drug were pooled for this analysis. P<0.05 was considered significant.

For U50488H, it was not legitimate to fit a logit curve because of many negative values for percentage inhibition. Therefore, to see if there was any tendency for inhibition to increase with increasing dose, a linear and a quadratic equation were fitted to the data and tested for significant negative slope and negative curvature, respectively.

The 95% confidence intervals for median difference between saline and drug groups were calculated using the SINTERVAL command (sign test) in Minitab Release 8.2 (running on a Macintosh LC computer), which shows exact intervals for a stated confidence level close to 95%.

The slope of each logit curve and the difference between the slopes for two drugs (e.g. morphine and nalbuphine), and the standard errors, emerge from the GLIM analysis. The 95% confidence intervals for the slopes and differences of slopes were calculated as described by Gardner and Altman.17

To study the interactive effects of morphine and an agonist (nalbuphine, pentazocine or U50488H), non-parametric one-way analysis of variance (Kruskal–Wallis test) was used to compare gastric emptying and gastrointestinal transit between the four groups. If this proved significant, the Mann–Whitney U test was used to compare gastric emptying and gastrointestinal transit between rats that were subjected to morphine (and saline), and those that received a combination of morphine and another agonist (nalbuphine, pentazocine or U50488H).

Results

EFFECTS OF INDIVIDUAL OPIOID AGONIST

Nalbuphine significantly delayed gastric emptying (P < 0.0005 by Mann–Whitney U test), but its inhibitory effect was weak (95% CI for the difference from saline: 15.1–35.9% at the maximum dose of nalbuphine, 30 mg kg⁻¹) (fig.1; table 1). It also significantly decreased gastrointestinal transit (P<0.01), but its inhibitory effect was weak (95% CI for difference from saline: − 0.5 − 2.2% at the maximum dose, 30 mg kg⁻¹) (fig.1).

Pentazocine significantly delayed both gastric emptying and gastrointestinal transit (fig.1; table 1). U50488H did not significantly inhibit either gastric emptying or gastrointestinal transit. The Mann–Whitney U test showed no significant difference in either gastric emptying and gastrointestinal transit between U50488H and saline groups (table 1), and neither the slope of a fitted straight line nor the curvature of a fitted parabola was significant (fig.1).

The slopes of the dose–response curves for nalbuphine on both gastric emptying and gastrointestinal transit were significantly less steep than those for morphine (P << 0.001) (table 2). In contrast, the slopes for pentazocine were similar to those for morphine (table 2).

INTERACTIVE EFFECTS OF TWO OPIOID AGONISTS

One-way analysis of variance showed that the values were significantly different between the four groups, for gastric emptying (P<0.05) and gastrointestinal transit (P=0.01) (table 3). Nalbuphine significantly antagonized the inhibitory effect of morphine on...
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gastric emptying \((p<0.02)\) and gastrointestinal transit \((p<0.005)\), whereas pentazocine and U50488H did not (table 3).

Discussion

Nalbuphine and pentazocine significantly inhibited gastric emptying and gastrointestinal transit of saline, but the effects were weak for nalbuphine. These findings are consistent with previous reports, which have shown that nalbuphine and pentazocine have weak inhibitory effects on transit in the small intestine in mice.\(^7\)\(^9\) In contrast, in accordance with previous reports in rats and mice,\(^13\) U50488H, a highly selective kappa opioid receptor agonist,\(^16\) did not significantly alter gastric emptying or gastrointestinal transit.

When the fitted curves for the effect of each drug on gastric emptying and gastrointestinal transit are plotted in terms of percentage of control values (fig. 2), it is apparent that morphine nearly maximally inhibited both gastric emptying and gastrointestinal transit, whereas nalbuphine did not produce maximum inhibitory effects.

For each opioid the inhibitory effect on gastric emptying was similar to that on gastrointestinal transit. These results are in contrast to the effects of alpha2 adrenoceptor agonists, which strongly inhibited transit in the small intestine, but only weakly inhibited gastric emptying.\(^15\) Altogether, it is likely that the opioid receptor is involved in controlling both gastric emptying and intestinal transit, whereas the alpha2 adrenoceptor is involved mainly in controlling intestinal transit.

OPIOID RECEPTOR TYPES FOR THE INHIBITORY EFFECT OF NALBUPHINE AND PENTAZOCINE

A partial agonist will show the following three features\(^1\): (1) the slope of the dose–response curve of a partial agonist is less steep than that of a full agonist; (2) there is a ceiling to its effect; and (3) a partial agonist will partially antagonize the effects of large doses of a full agonist.

The slope of the dose–response curve for nalbuphine was significantly less than that of morphine (table 2); there was a ceiling to its effect (fig. 2); and nalbuphine antagonized the inhibitory effect of morphine (table 3). These results are consistent with the characteristics of a partial agonist — in this case, a partial mu agonist.\(^1\)

In contrast, for pentazocine, the slope of the dose–response curve did not differ significantly from that for morphine; there was no clear ceiling to its effect at the doses used; pentazocine did not significantly affect the inhibitory action of morphine. Therefore, it is likely that pentazocine delayed gastric emptying and gastrointestinal transit, not as a partial mu agonist, but possibly as a full mu opioid receptor agonist or a non-mu, non-kappa receptor agonist. The effect could be through the sigma receptor, as pentazocine has agonist activity at this receptor.\(^18\)\(^19\)

Previous studies have shown that in some situations, nalbuphine acts as a partial mu agonist, whereas pentazocine cannot.\(^2\)\(^20\)\(^31\) For example, nalbuphine antagonizes the antinociceptive effect of mu opioid receptor agonists.\(^2\) It also antagonizes the inhibitory effect of mu opioid receptor agonists on respiration,\(^20\)\(^21\) and decreases the incidence of nausea, vomiting and pruritus after injection of a mu receptor agonist.\(^22\) In contrast, pentazocine does not generally antagonize the antinociceptive effect of morphine.\(^24\)\(^26\) Although a few studies\(^19\)\(^25\)\(^27\) showed that pentazocine antagonized the antinociceptive effect of morphine, this effect was considered to be mediated by the sigma receptor and the effect was not stereospecific.\(^19\)\(^27\) In the isolated guinea-pig ileum, nalbuphine inhibited field-stimulation-induced contraction of the ileum through the mu opioid receptor, whereas pentazocine did so mainly through the kappa receptor.\(^30\)\(^31\)

Figure 2  Gastric emptying and gastrointestinal transit as percentages of the control values for (A) morphine, (B)nalbuphine and (C) pentazocine. The extrapolated part of the curve for pentazocine is shown by a broken line. ED\(_{50}\) values and 95% confidence intervals are also shown. Data for morphine are from a previous study.\(^8\)
Clinical Implications

In humans, both nalbuphine and pentazocine significantly inhibited gastric emptying of liquids. This is consistent with the results obtained in the present study in rats. However, it is not known whether there is a ceiling to the inhibitory effect of these drugs in humans, and whether they interact with morphine (or other strong mu receptor agonists) in a similar manner to that in rats.

The current and previous studies suggest that nalbuphine reduces the inhibitory effect of morphine on gastric emptying and intestinal transit, but it also reduces the antinociceptive effects. In contrast, pentazocine does not affect the antinociceptive effect of morphine or alter the inhibitory effect of morphine on gastric emptying and intestinal transit. Therefore, concurrent injection of nalbuphine and morphine or pentazocine and morphine, in theory, will not provide a potent analgesia with a relatively weak inhibitory effect on gastric emptying and intestinal transit. However, this theory needs to be tested in humans, because the pharmacological effects may differ between species.

In conclusion, we have found that, in the rat, a mu agonist (morphine), but not a kappa agonist (U50488H), delayed gastric emptying and gastrointestinal transit. Nalbuphine and pentazocine delayed these, possibly by different mechanisms; nalbuphine, but not pentazocine, acted as a partial mu opioid receptor agonist.

Acknowledgements

We thank Mr C. Juniper, HNC, for skilful technical assistance, Dr W. D. Evans, Department of Medical Physics and Bioengineering, for advice and help in use of the gamma counter, and Mrs P. de Souza, Department of Haematology, for providing the radio-labelled liquid. We also thank the Upjohn Company, Michigan, USA, for the gift of U50488H.

References


