Differential effects of clonidine and dexmedetomidine on gastric emptying and gastrointestinal transit in the rat†

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

Summary
We have studied the effect of clonidine, dexmedetomidine and morphine on gastric emptying and gastrointestinal transit in the rat. In one group, each agonist was injected i.p. in 6–12 male Wistar rats. In another group of rats, yohimbine, naloxone or saline was injected with an agonist. At 30 min, radio-labelled 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. We found that clonidine and dexmedetomidine strongly inhibited gastrointestinal transit (ED50 0.08 and 0.04 mg kg−1, respectively). They also significantly inhibited gastric emptying (P<0.05), but the effect was weak (95% confidence intervals for difference from saline 8.2–34.9% with clonidine 1 mg kg−1 and 3.4–15.4% with dexmedetomidine 0.03 mg kg−1). Morphine strongly inhibited both gastric emptying and gastrointestinal transit (ED50 2.8 and 1.2 mg kg−1, respectively). Yohimbine significantly antagonized the inhibitory effects of clonidine and dexmedetomidine (P<0.05), whereas naloxone, which significantly antagonized the effect of morphine (P<0.01), did not antagonize the effect of either of the other agonists. (Br. J. Anaesth. 1997; 78: 301–307).

Key words
Gastrointestinal system, gastric emptying. Sympathetic nervous system, adrenergic agonists.

Delayed gastric emptying may induce several complications during the perioperative period. In critically ill patients, gastric emptying and intestinal transit are often delayed and this delay may cause pulmonary infection and bacterial overgrowth in the gastrointestinal tract.1 Opioids have been used widely in the perioperative period and in intensive care units, but they markedly delay both gastric emptying and intestinal transit.2 3 However, we have been unable to trace any report of the ED50 of morphine in inhibiting gastric emptying; therefore, the relative potency of opioids on gastric emptying and intestinal transit is not known.

Alpha2 adrenoceptor agonists, such as clonidine or dexmedetomidine, reduce anxiety, induce sedation and produce analgesia.4 5 They also decrease the amount of opioid and inhalation agent needed for induction and maintenance of anaesthesia while providing haemodynamic stability.4 5 Alpha2 agonists produce less respiratory depression, nausea and vomiting or pruritus than opioids.4 5 For these reasons, the use of alpha2 adrenoceptor agonists as adjuncts to anaesthetics has received much attention recently.4 5

There have been several reports on the effects of alpha2 adrenoceptor agonists on gastric emptying, but the results are inconclusive. In some studies, peripherally injected alpha2 adrenoceptor agonists did not delay gastric emptying in rodents.5 6 In other studies they delayed gastric emptying of liquids in the rat7 and that of both solids and liquids in the dog.8 In humans, oral clonidine did not significantly delay gastric emptying of either a solid meal9 or liquids, whereas lidamidine, which also has an alpha2 adrenoceptor agonist effect, weakly delayed gastric emptying.10 These differences might have been caused by selectivity of these drugs to receptors other than the alpha2 adrenoceptor.

Dexmedetomidine, the dextro-stereoisomer of medetomidine, is a highly selective alpha2 adrenoceptor agonist.11 Binding studies have shown that the selectivity of medetomidine to the alpha2 adrenoceptor over the alpha1 adrenoceptor is 5–10 times greater than that of other alpha2 adrenoceptor agonists, such as clonidine and detomidine.12

The first aim of this study was to examine the effect of clonidine, dexmedetomidine and morphine on gastric emptying and gastrointestinal transit of liquids in the rat. The second aim was to determine the receptor type involved in the effects of these agonists.

Materials and methods
We used male Wistar rats, weighing 200–250 g. The study was conducted under the Animal (Scientific

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Procedures) Act 1986 (Home Office Licence PPL 40/954, PPL 40/1397). Before the experiment, rats were housed under standard controlled environmental conditions, with a 12-h light–dark cycle. The animals were fasted for 24 h, but they were allowed free access to water until 20–30 min before the start of the experiment. Each animal was kept individually in a wire-mesh cage to prevent coprophagy during fasting. All experiments were started between 10:00 and 11:00. Dexmedetomidine (Orion-Famos Pharmaceuticals, Finland), clonidine, morphine and yohimbine (Sigma Chemical Co., UK) were prepared freshly on each day of experiment.

A group of six rats was allocated for each set of circumstances. If more than one rat was excluded (see below), 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 set of circumstances (the number of rats ranged from 5 to 12) were used. However, we stopped after studying three rats for the highest doses of morphine and dexmedetomidine because of apparent complications (see results).

Gastric emptying and gastrointestinal transit were studied using radiolabelled sodium chromate,16-17 which is minimally absorbed when infused into the stomach.17 Clonidine 0.001–1.0 mg kg\textsuperscript{-1}, dexmedetomidine 0.0001–0.1 mg kg\textsuperscript{-1}, morphine 0.1–30 mg kg\textsuperscript{-1} or saline, in a volume of 1.0 ml kg\textsuperscript{-1}, was given i.p. These doses were chosen on the basis of the reported ED\textsubscript{50} values for the antinociceptive effect of each drug (see discussion).

Thirty minutes later the rats were anaesthetized lightly with halothane. When the rat had become unconscious, saline 1.0 ml containing a radioactive marker (0.5 μCi (18.5 kBq) of chromium as the sodium salt (\textsuperscript{51}Cr as Na\textsubscript{2}CrO\textsubscript{4})) was given via a metal cannula into the stomach. The rat was allowed to recover from anaesthesia, which usually occurred within a few minutes.

Another 30 min later the rats were killed, the oesophagus just proximal to the gastric fundus and the duodenum just distal to the pylorus were cross-clamped, and the stomach and small intestine were removed. Twelve clamps were applied to the small intestine during gentle removal of the intestine to minimize the movement of contents. The intestine was placed on a ruled template and divided into 10 equal segments. The stomach and segments of intestine were placed into individual counting tubes.

Radioactivity in each segment was measured using an automatic gamma sample counter and counts per minute (cpm) obtained. Each sample was counted twice and mean cpm obtained. To obtain the control total count, 1.0 ml of radiolabelled saline was placed into a tube and the radioactivity counted. If there was chyme in either the stomach or small intestine, data were not used.

Gastric emptying of liquids was calculated as the percentage of radioactivity (cpm) which had entered the small intestine:

\[
\%\text{gastric emptying} = \frac{[(\text{total cpm} - \text{stomach cpm})/(\text{total cpm})] \times 100}{(\text{total cpm} - \text{stomach cpm})/(\text{total cpm})} \times 100
\]

From these values, percentage inhibition of gastric emptying was calculated from:

\[
\%\text{inhibition of GE} = 100 \times \left(\frac{(\text{control } \%\text{GE} - \text{test } \%\text{GE})}{\text{control } \%\text{GE}}\right)
\]

where control \%GE = mean \%GE in the rats that received saline, and test \%GE = \%GE in each rat that received the test drug.

Gastrointestinal transit was assessed using the “geometric centre” (the centre of gravity) (\textsuperscript{5}G/Ci, where \textit{Ci} = count in segment \textit{Si}):

\[
\text{geometric centre (GC)} = \frac{\Sigma (\text{Ci} \text{Si})}{\Sigma \text{Ci}}
\]

where \text{Ci} = count in segment \text{Si}.

Percentage inhibition of gastrointestinal transit, expressed as the geometric centre (%GC), was calculated from:

\[
\%\text{inhibition of gastrointestinal transit} = 100 \times \left(\frac{(\text{control GC} - \text{test GC})}{\text{control GC}}\right)
\]

In the second part of the experiment, the receptor type involved in the inhibitory effect of the agonists was studied using yohimbine (an \alpha\textsubscript{2} antagonist) and naloxone. The initial plan was to inject yohimbine, naloxone or saline with the ED\textsubscript{75} (see below) of each agonist. However, neither clonidine nor dexmedetomidine inhibited gastric emptying by greater than 50% (see results). Therefore, for clonidine, the ED\textsubscript{50} for antinociceptive effect (0.15 mg kg\textsuperscript{-1})\textsuperscript{18} was used; for dexmedetomidine, the second highest dose (0.03 mg kg\textsuperscript{-1}) was used as the ED\textsubscript{50} for antinociceptive effect in rats was not available. In another group of rats, gastric emptying and gastrointestinal transit after injection of either yohimbine or naloxone alone were studied.

**STATISTICAL ANALYSIS**

The Mann–Whitney U test was used to compare gastric emptying and gastrointestinal transit between groups of rats which were subjected to different agonists or agonist–antagonist combinations. The values for all doses of clonidine or dexmedetomidine were pooled for this analysis. Either a Wilcoxon-type test for trend\textsuperscript{19} (when two doses of an antagonist were used) or the Mann–Whitney U test (when one dose of an antagonist was used) was used to examine the effect of either yohimbine or naloxone on the inhibitory effect of agonist. \(P<0.05\) was considered significant. The confidence intervals for medians
Effects of alpha₂ agonists on gastric emptying

were calculated using the SINTERVAL command (sign test) in Minitab Release 8.2 (running on Macintosh LC computer), which shows exact intervals for a stated confidence level close to 95%. Confidence intervals (CI) for the difference in gastric emptying between saline and an alpha₂ agonist were also calculated.

The variation in percentage inhibition with the dose of each agent was modelled by fitting a sigmoid logit curve to fractional inhibition against log dose. This was done (see appendix) using the statistical package GLIM (Generalized Linear Interactive

<table>
<thead>
<tr>
<th></th>
<th>Gastric emptying</th>
<th>Gastrointestinal transit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonidine</td>
<td>—</td>
<td>0.080</td>
</tr>
<tr>
<td>((n=41))</td>
<td>(4.6, —)</td>
<td>(0.049, 0.13)</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>—</td>
<td>0.039</td>
</tr>
<tr>
<td>((n=30))</td>
<td>(4.3, —)</td>
<td>(0.027, 0.065)</td>
</tr>
<tr>
<td>Morphine</td>
<td>2.8</td>
<td>1.2</td>
</tr>
<tr>
<td>((n=52))</td>
<td>(2.1, 3.8)</td>
<td>(0.87, 1.7)</td>
</tr>
</tbody>
</table>

Figure 2  Effect of clonidine (top), dexmedetomidine (middle) and morphine (bottom) on gastrointestinal transit. Saline 1 ml, containing a radiolabelled marker \(^{51}\text{Cr}\), was given 30 min after i.p. injection of drug. Gastrointestinal transit was examined 30 min later. A fitted logit dose–response curve is shown together with the value obtained from each rat (○). Symbols were displaced slightly on the X axis if there were similar values for any given dose. Values at zero dose are for the saline control.

Figure 3  Effect of clonidine (top), dexmedetomidine (middle) and morphine (bottom) on gastric emptying of a liquid. Saline 1 ml, containing a radiolabelled marker \(^{51}\text{Cr}\), was given 30 min after i.p. injection of drug. Gastric emptying was examined 30 min later. A fitted logit dose–response curve is shown together with the value obtained from each rat (○). Symbols were displaced slightly on the X axis if there were similar values for any given dose. The extrapolated parts of the curves for clonidine and dexmedetomidine are shown by a broken line. Values at zero dose are for the saline control.

Table 1  ED\(_{50}\) (mg kg\(^{-1}\)) of clonidine, dexmedetomidine and morphine on gastric emptying and gastrointestinal transit (with 95% confidence limits). The ED\(_{50}\) and upper 95% confidence limit were omitted when they were outside the range of doses used.
Table 2: Effect of yohimbine or naloxone on the inhibitory effect of clonidine, dexmedetomidine or morphine on gastric emptying and gastrointestinal transit of saline (median). $P$ values were calculated using either the Wilcoxon-type test for trend\(^{20}\) (when two doses of antagonist were used) or the Mann-Whitney U test (when one dose of antagonist was used), and 95% confidence limits (CL) of the difference between rats which received saline and those which received an antagonist are shown. Six to 12 rats were used for each group. *Antagonist effect; $^\dagger$additive effect

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Gastric emptying</th>
<th>Gastrointestinal transit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Empting (%)</td>
<td>Difference from saline group</td>
</tr>
<tr>
<td></td>
<td>(0 dose of an antagonist)</td>
<td>Geometric centre</td>
</tr>
<tr>
<td>Clonidine 0.15 mg kg(^{-1})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ Saline</td>
<td>70.9</td>
<td>2.0</td>
</tr>
<tr>
<td>+ Yohimbine 1.0 mg kg(^{-1})</td>
<td>73.7</td>
<td>[−3.3, 16.1]</td>
</tr>
<tr>
<td>+ Yohimbine 3.0 mg kg(^{-1})</td>
<td>83.0</td>
<td>[1.6, 24.1]</td>
</tr>
<tr>
<td>+ Naloxone 1.0 mg kg(^{-1})</td>
<td>63.1</td>
<td>[−16.8, 3.6]</td>
</tr>
<tr>
<td>+ Naloxone 3.0 mg kg(^{-1})</td>
<td>51.5</td>
<td>[−30.3, 0.9]</td>
</tr>
<tr>
<td>Dexmedetomidine 0.03 mg kg(^{-1})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ Saline</td>
<td>78.0</td>
<td>2.5</td>
</tr>
<tr>
<td>+ Yohimbine 1.0 mg kg(^{-1})</td>
<td>84.9</td>
<td>[0.1, 10.7]</td>
</tr>
<tr>
<td>+ Yohimbine 3.0 mg kg(^{-1})</td>
<td>83.1</td>
<td>[1.4, 9.1]</td>
</tr>
<tr>
<td>+ Naloxone 1.0 mg kg(^{-1})</td>
<td>64.2</td>
<td>[−21.3, 3.2]</td>
</tr>
<tr>
<td>Morphine 13.4 mg kg(^{-1})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ Saline</td>
<td>23.0</td>
<td>1.9</td>
</tr>
<tr>
<td>+ Naloxone 1.0 mg kg(^{-1})</td>
<td>64.2</td>
<td>[26.2, 51.7]</td>
</tr>
<tr>
<td>+ Yohimbine 1.0 mg kg(^{-1})</td>
<td>34.8</td>
<td>[−12.3, 28.1]</td>
</tr>
<tr>
<td>+ Yohimbine 3.0 mg kg(^{-1})</td>
<td>16.8</td>
<td>[−19.8, 3.5]</td>
</tr>
<tr>
<td>Saline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ Saline</td>
<td>88.2</td>
<td>4.9</td>
</tr>
<tr>
<td>+ Yohimbine 1.0 mg kg(^{-1})</td>
<td>86.0</td>
<td>[−12.7, 6.4]</td>
</tr>
<tr>
<td>+ Yohimbine 3.0 mg kg(^{-1})</td>
<td>82.8</td>
<td>[−53.7, 8.2]</td>
</tr>
<tr>
<td>+ Naloxone 1.0 mg kg(^{-1})</td>
<td>71.7</td>
<td>[−23.6, 8.4]</td>
</tr>
<tr>
<td>+ Naloxone 3.0 mg kg(^{-1})</td>
<td>72.2</td>
<td>[−30.0, −2.5]</td>
</tr>
</tbody>
</table>

Results

Morphine 30 mg kg\(^{-1}\) caused muscle rigidity; therefore, we stopped after studying three rats at this dose. Dexmedetomidine 0.1 mg kg\(^{-1}\) caused strong sedation and apparent respiratory depression; therefore, we stopped after studying three rats. Clonidine 1.0 mg kg\(^{-1}\) and dexmedetomidine 0.03 mg kg\(^{-1}\) caused obvious sedation in all rats.

GASTROINTESTINAL TRANSIT

Clonidine, dexmedetomidine and morphine inhibited gastrointestinal transit in a dose-dependent manner (fig. 2, table 1).

GASTRIC EMPTYING

Morphine inhibited gastric emptying in a dose-dependent manner (fig. 3, table 1). In contrast, although clonidine significantly inhibited gastric emptying ($P$=0.001), the inhibitory effect was weak (95% CI for difference from saline 8.2–34.9% at the maximum dose of clonidine, 1 mg kg\(^{-1}\)) (fig. 3). Dexmedetomidine also weakly, but significantly, inhibited emptying ($P$<0.05; 95% CI for difference from saline 3.4–15.4% at the next-to-maximum dose, 0.03 mg kg\(^{-1}\)) (fig. 3).

RECEPTOR TYPE

Yohimbine, an alpha\(_2\) adrenoceptor antagonist,\(^{22}\) significantly antagonized the inhibitory effect of clonidine and dexmedetomidine, but not that of morphine (table 2). Yohimbine itself at the doses used did not significantly affect either gastric emptying or gastrointestinal transit, although the rate of gastric emptying varied considerably after injection of yohimbine 3.0 mg kg\(^{-1}\).

Naloxone itself significantly delayed gastric emptying, but not gastrointestinal transit (table 2). Despite its inhibitory effect, naloxone significantly antagonized the inhibitory effect of morphine (table 2). Naloxone did not significantly antagonize the effect of clonidine or dexmedetomidine; in fact, naloxone delayed gastric emptying further (table 2).

Discussion

DIFFERENCE IN THE EFFECTS BETWEEN ALPHA\(_2\) AGONISTS AND MORPHINE

When the fitted curves for the effect of each drug on gastric emptying and gastrointestinal transit were plotted in terms of percentage of control values (fig. 4), it was apparent that morphine inhibited gastric emptying and gastrointestinal transit to a similar degree, whereas with clonidine and dexmedetomidine, inhibition of gastric emptying was much weaker than that of gastrointestinal transit. The ratio of the ED\(_{50}\) values for gastrointestinal transit and
gastric emptying was 2.3 for morphine but (by extrapolation) 365 for clonidine and infinity for dexmedetomidine.

The range of the reported ED50 for the antinociceptive effect of morphine (table 3) includes the present ED50 for gastric emptying (2.8 mg kg\textsuperscript{-1}). For clonidine and dexmedetomidine, however, the ED50 values for antinociceptive effect (table 3) are very much less than the present ones for gastric emptying (lower limit of 95% CI: 4.6 mg kg\textsuperscript{-1} for clonidine and 4.3 mg kg\textsuperscript{-1} for dexmedetomidine). Therefore, it is unlikely that clonidine and dexmedetomidine at antinociceptive doses strongly inhibit gastric emptying, whereas it is likely for morphine.

There are several differences between alpha\textsubscript{2} adrenoceptor agonists and opioids in the mechanisms of their effects on gastric motility. First, alpha\textsubscript{2} adrenoceptor agonists inhibit the contraction of the stomach caused by stimulation of cholinergic neurones,\textsuperscript{28–30} but not that induced by exogenous acetylcholine,\textsuperscript{28 29} and these agonists may not lower the basal tone of the stomach.\textsuperscript{28 30} In contrast, opioids strongly inhibit both basal and stimulated gastric motility.\textsuperscript{31 32}

Second, opioids increase pyloric pressure\textsuperscript{33 34} leading to delay in gastric emptying. In contrast, alpha\textsubscript{2} adrenoceptor agonists either have no effect or relax the pylorus\textsuperscript{35–37} and thus the pylorus does not impede emptying of gastric contents. However, a dilated pylorus may increase duodenogastric reflux,\textsuperscript{37} and if so, net gastric emptying may be delayed. This may explain why there was a mild delay in gastric emptying after injection of clonidine and of dexmedetomidine in our study.

**POSSIBLE REASONS FOR DISCREPANCIES BETWEEN STUDIES**

There have been two reports in which the effects of clonidine on gastric emptying of liquids were studied in the rat. Cooper and McRitchie found that clonidine 0.003–1.0 mg kg\textsuperscript{-1} strongly inhibited gastric emptying of 5 ml of test liquid.\textsuperscript{9} In contrast, Ruwart, Klepper and Rush found that clonidine up to 1.0 mg kg\textsuperscript{-1} did not inhibit gastric emptying of 0.25 ml of test liquid, but strongly inhibited small intestinal transit.\textsuperscript{6} The results of the Ruwart, Klepper and Rush study are similar to ours for clonidine using 1.0 ml of test liquid.

The reasons for the discrepancies between studies are not clear, but one possible cause is the difference in the volume of test liquids used. Because clonidine strongly inhibits intestinal transit, it is likely that the greater the volume of a test liquid infused into the stomach, the greater the pooling of the liquid in the duodenum. Distending the duodenum stimulates reflex relaxation of the stomach,\textsuperscript{38–40} In the rat, distension of the duodenum by direct infusion with as little as 0.05 ml of saline relaxes the stomach, and the degree of gastric relaxation depends on the degree of distension of the duodenum.\textsuperscript{38} Gastric emptying is delayed when the stomach is relaxed, because emptying is influenced by a pressure gradient between the stomach and the duodenum.\textsuperscript{39} Cooper and McRitchie\textsuperscript{9} infused a large volume of liquid (5 ml) into the stomach, whereas Ruwart, Klepper and

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**Table 3** The reported ED\textsubscript{50} (mg kg\textsuperscript{-1}) for the antinociceptive effect of clonidine, dexmedetomidine and morphine injected either i.p. or s.c. in rats (unless specified). *The 0.05 mg kg\textsuperscript{-1} produced 70% inhibition. "This value was obtained in mice; no data were available for rats.

<table>
<thead>
<tr>
<th>Type of nociceptive stimuli</th>
<th>ED\textsubscript{50} (mg kg\textsuperscript{-1})</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonidine</td>
<td>Thermal</td>
<td>0.1–2.7</td>
</tr>
<tr>
<td></td>
<td>Chemical</td>
<td>0.08–0.15</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>Thermal</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td></td>
<td>Chemical</td>
<td>0.01*</td>
</tr>
<tr>
<td>Morphine</td>
<td>Thermal</td>
<td>0.6–8</td>
</tr>
<tr>
<td></td>
<td>Chemical</td>
<td>0.4–0.8</td>
</tr>
</tbody>
</table>
Rush\(^9\) used a much smaller volume (0.25 ml); therefore, it is likely that the degree of distension of the duodenum and thus the degree of relaxation of the stomach would have been the greatest in the Cooper and McRitchie study\(^9\) and least in the Ruwart, Kлепер and Rush study.\(^6\) Therefore, this may explain the marked delay in gastric emptying found in the study of Cooper and McRitchie\(^9\) and the absence of delay in the Ruwart, Kлепер and Rush study.\(^6\)

The marked inhibition of gastric emptying in the study of Cooper and McRitchie\(^9\), however, may not be physiological. We found that, when 5 ml of liquid were infused into isolated rat stomachs, there was marked distension and thinning of the gastric wall (unpublished observation). Thus the stomach was likely to be over distended in their study. In addition, increase in gastric volume relaxes the gastric tone\(^40\)\(^41\) by stimulating the non-adrenergic, non-cholinergic vagal nerve.\(^42\) These differences in the conditions of the stomach may also contribute to an explanation of the discrepancy.

POSSIBLE CONFOUNDING FACTORS

We gave halothane to rats to insert an orogastric cannula. This might have affected the data. However, it is unlikely that halothane caused the difference in the transit between groups in our study, because halothane was used in both control and test groups, and also because the effect of clonidine and morphine was antagonized by yohimbine and naloxone, respectively.

It is also not clear if the inhibitory effect of clonidine and dexmedetomidine on gastric emptying and gastrointestinal transit is a direct effect or a secondary effect derived from other factors, such as decreased arterial pressure, heart rate or body temperature.

GASTRIC EMPTYING AND GASTROINTESTINAL TRANSIT

In this study, clonidine and dexmedetomidine strongly inhibited transit in the small intestine, but only weakly inhibited gastric emptying. In contrast, atropine does not affect transit of liquids in the small intestine at doses that delay gastric emptying.\(^43\) Caerulein, a cholecystokinin-like peptide, enhances intestinal transit but it either has no effect or even delays gastric emptying.\(^44\) Furthermore, acoustic stress to mice accelerates gastric emptying without affecting gastrointestinal transit.\(^45\) Thus it is likely that some of the mechanisms influencing gastric emptying are different from those influencing transit in the intestine.

CLINICAL IMPLICATIONS

There are similarities between humans and rats in terms of the presence of opioid and alpha\(_2\) adrenoceptor receptors in the gastrointestinal tract and in terms of behavioural effects (such as the antinociceptive effect) of opioids and alpha\(_2\) agonists. Therefore, although the present ED\(_{50}\) values cannot be transferred to humans, it is likely that, at antinociceptive doses, clonidine and dexmedetomidine would produce less inhibition of gastric emptying (relative to that on gastrointestinal transit) than does morphine.

In summary, we have shown that, in the rat, morphine inhibited both gastric emptying and gastrointestinal transit via opioid receptors to a similar degree, whereas clonidine and dexmedetomidine did so via alpha\(_2\) adrenoceptors with only a weak inhibitory effect on gastric emptying, even at the maximum tolerable dose.

Appendix

The method provided by the GLIM package, of fitting a sigmoid logit curve directly to the fractional inhibition, is usually used when each datum is in the form of r responders of a total of n subjects. The procedure assumes that the residuals conform to the binomial distribution in which the variance is a function of the fitted value of the proportion of individuals responding (\(\hat{p}\)). Applying the process to fitting fractional inhibition in each rat resulted in residuals approximately 10 times greater on average than those of the binomial distribution; but this was compensated by using a scaling factor to correct for “over dispersion” as explained in the GLIM manual.\(^9\) This implies the assumption that the variance of the residuals depended on the fitted proportion in the same way as in the binomial distribution—apart from the scaling factor. In other words, that the residuals were distributed in a manner proportional to the binomial distribution.

To test this assumption, the variance of the observed values from the fitted value was calculated for each dose of each agent, for both gastric emptying and gastrointestinal transit, including data from studies of two other agents, nalbuphine and pentazocine. This provided a total of 64 variances. The ratios of these variances to the corresponding binomial variances ranged from approximately 0.4 to 1.3 times the mean ratio—a range of approximately 3:1.

The data were also analysed using the conventional method of fitting a straight line to the logit of the fractional inhibition and assuming that the residuals were normally distributed. This implies that the variances were the same for all levels of inhibition; in fact they varied from 0.15 to 1.5 times the mean variance—a range of approximately 10:1.

Therefore, although the assumptions of the method we used were not entirely met, they were considerably more closely met, for our data set, than the assumptions involved in the conventional approach. It is also important to note that the ED\(_{50}\) values from the conventional approach were all well within the 95% confidence limits of those obtained by the adopted method.

Acknowledgement

We thank Mr C. Juniper, HNC, for his skilful technical assistance, Dr W. D. Evans, Department of Medical Physics and Bioengineering, for his advice and help in the use of the gamma counter, and Mrs P. de Souza, Department of Haematology, for providing the radiolabelled liquid. We also thank Orion-Famos Pharmaceuticals, Turku, Finland, for the generous gift of dexmedetomidine.

References

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