Effect of clonidine on gastric emptying of liquids

T. ASAI, C. MCBETH, J. I. M. STEWART, J. WILLIAMS, R. S. VAUGHAN AND I. POWER*

Summary
We have investigated the effects of clonidine on gastric emptying of liquids in 30 patients. In a double-blind, randomized design, clonidine 150 μg, morphine 10 mg or saline in 1 ml was given i.m. One hour later, the patient drank a paracetamol solution (1.5 g in 50 ml water). Venous blood samples were obtained every 15 min for 90 min thereafter. Plasma paracetamol concentrations were measured using high-pressure liquid chromatography and the area under the concentration-time curve was calculated. The degree of sedation and complications were recorded. The area under the curve for 0–60 min was significantly smaller in the morphine group than in the saline group (P = 0.002; 95% confidence interval (CI) for difference –1237 to –502 μg min ml−1), whereas it was greater in the clonidine group compared with the saline group, although this was not significant (95% CI for difference −423 to 1264 μg min ml−1). Arterial pressure was significantly lower in the clonidine group compared with the saline group. Both clonidine and morphine appeared to cause mild sedation. We conclude that clonidine 150 μg i.m. does not delay gastric emptying of liquids in a similar manner to morphine. (Br. J. Anaesth. 1997; 78: 28–33)

Key words
Gastrointestinal tract, emptying. Sympathetic nervous system, clonidine. Pharmacology, clonidine.

Delay in gastric emptying may induce nausea and vomiting which may increase the risk of pulmonary aspiration of gastric contents during the perioperative period. It may also delay absorption of orally administered drugs. In critically ill patients whose lungs are ventilated mechanically, delay in gastric emptying causes bacterial overgrowth in the gastrointestinal tract and increases the incidence of pulmonary infection.1 Opioids, which have been used widely for premedication, markedly delay the rate of gastric emptying.2–4

Alpha2 adrenoceptor agonists, such as clonidine, reduce anxiety, induce sedation and possibly produce analgesia.5 6 They decrease the requirements for opioid and inhalation agents during induction and maintenance of anaesthesia and provide haemodynamic stability.5 6 Alpha2 agonists also produce less respiratory depression, nausea and vomiting, or pruritus than opioids.5 6 Thus the, use of α2 adrenoceptor agonists as adjunctive agents has received considerable attention.

The effects of α2 agonists on gastric emptying have been studied, but the results are inconclusive.7–11 In some studies in rodents, α2 adrenoceptor agonists injected subcutaneously did not delay gastric emptying of liquids,7–9 whereas in other studies the agonists delayed emptying.10 11 In humans, oral clonidine did not significantly delay gastric emptying of radiolabelled solid food,12 whereas lidamidine, which is also considered as an α2 adrenoceptor agonist, delayed gastric emptying of solid food.13

The rate and mechanism of gastric emptying differ considerably for liquids and digestible solids.14 15 The effect of α2 adrenoceptor agonists on gastric emptying of liquids in humans has not been studied. The main aim of this study therefore was to examine the effect of clonidine on gastric emptying of liquids in humans.

Patients and methods
In a double-blind, randomized design, before induction of anaesthesia, we studied 30 patients (ASA I or II) undergoing routine gynaecological surgery. Patients with a history of gastrointestinal, heart, hepatic and renal disease were excluded. Patients in whom systolic arterial pressure was either greater than 160 mm Hg or less than 100 mm Hg, or had a heart rate less than 60 beat min−1, and those receiving any other medications or with a history of allergic reaction to any drug were excluded. The local research Ethics Committee approved the study and written informed consent was obtained from all patients.

Patients were asked not to eat solid food for at least 5 h and not to drink liquids for 2 h before the start of the study. No premedication was given. Approximately 3 h before induction of anaesthesia,

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the patient was transferred to a quiet area in the recovery room. An electrocardiograph and non-invasive arterial pressure monitor were attached to the patient. A large-gauge i.v. cannula was inserted under local anaesthesia into the antecubital fossa for blood sampling. Patients were asked to stay in a semi-recumbent position throughout the study. They were also asked to refrain from drinking, eating and smoking.

Patients were allocated randomly to one of three groups. Block randomization (in blocks of 12) was used for allocation and cards indicating allocations were placed in serially numbered, sealed opaque envelopes: clonidine group, clonidine 150 μg in a volume of 1 ml; morphine group, morphine 10 mg in a volume of 1 ml; saline group, saline 1 ml.

One anaesthetist prepared the study drug shortly before the start of the study. The second anaesthetist injected the test drug into the anterolateral aspect of the thigh muscle. Both the second anaesthetist and patients were unaware of the randomization.

Gastric emptying was assessed by measuring the plasma concentrations of paracetamol after oral ingestion. One hour after injection of the test drug, 50 ml of water containing paracetamol 1.5 g were given orally. We decided that the time from injection of the test drug to ingestion of paracetamol solution should be 1 h, because both the plasma concentration and analgesic effect of i.m. clonidine were maximal at about 1 h. Venous blood (10 ml) was obtained every 15 min for 90 min after injection. Each blood sample was placed immediately in an individual tube containing heparin. Plasma was obtained using a centrifuge (CS-15R Centrifuge, Beckman) with a speed of 3000 min⁻¹ for 10 min; temperature in the centrifuge was set as 4 °C. Plasma was stored at −20 °C until paracetamol concentrations were measured.

Plasma paracetamol concentration was measured using high-pressure liquid chromatography. The sensitivity of the chromatographic method was 0.1 μg ml⁻¹ of plasma paracetamol. The intra-assay coefficient of variation, that is the precision of the assay for quality control samples prepared at 5, 10 and 50 μg ml⁻¹, was less than 3%. The inter-assay coefficient of variation, that is the accuracy of the assay for the same quality control samples, was less than 5%.

The degree of sedation was examined before, and at 1 and 2.5 h after administration of the test drug. The degree of sedation was scored as follows: 1 = awake, 2 = drowsy or sleeping, easy to arouse by verbal contact, 3 = asleep, difficult to arouse, 4 = asleep, not arousable. Any incidence of vomiting, pruritus or dryness of mouth was also recorded.

Arterial pressure and heart rate were monitored throughout. If systolic arterial pressure decreased by more than 30% of the pre-injection value, crystalloid fluid in a volume up to 500 ml was given. Fluid was infused through another i.v. cannula which was inserted into the other arm to avoid possible dilution of the blood sample for paracetamol assay. If arterial pressure was still low, incremental doses of ephedrine 3 mg i.v. were given. If heart rate decreased to less than 45 beat min⁻¹, atropine 0.6 mg was given. If either ephedrine or atropine, or both, were given, patients were withdrawn from the study.

STATISTICAL ANALYSIS

Median maximum plasma paracetamol concentration (\(C_{\text{p max}}\)), time to maximum concentration (\(t_{\text{C p max}}\)), area under the concentration–time curve (AUC) and 95% confidence interval (CI) for each value were calculated. The area was calculated based on the trapezoidal rule.

Hypothesis tests were used only for AUC. Normal plots (plots of normal scores) and Shapiro–Francia W² test showed that the data were normally distributed; however, the F test showed that the variability between the three groups was significantly different. Therefore, the Kruskal–Wallis test was used to compare AUC values between groups. If this proved significant, the Mann–Whitney U test was used to compare AUC between the clonidine and saline groups, and between the morphine and saline groups. \(P\) values were adjusted for ties. \(P<0.05\) was considered significant.

Differences between two groups in AUC, \(C_{\text{p max}}\) and \(t_{\text{C p max}}\) were described by medians and 95% confidence intervals (CI). CI values for medians were calculated using the Sinterval command (sign test) in Minitab Release 8.2, which shows a confidence level close to 95%.

Mean arterial pressure and heart rate at 1 and 2.5 h after administration of the test drug were expressed as difference from pre-injection values. The maximum difference was also obtained. The 95% CI for differences between two groups were calculated.

There is no apparent criterion to decide the clinically relevant difference in AUC between the control and test groups. In one study, in which the same dose of paracetamol in the same volume of water was used as in this study (1.5 g in 50 ml), morphine 10 mg i.m. decreased AUC0–90 min by 59%. We considered that a reduction in AUC by a test drug of 50% would be a clinically relevant difference. To detect this reduction, with a power of 0.9 and \(P=0.05\), approximately eight patients in each group were required. We considered that smaller changes in AUC could be assessed using 95% CI. Therefore, we decided to study 30 patients, expecting withdrawal of a few patients from the test groups because of possible complications.

Results

Ten patients were allocated to the saline group, 11 to the morphine group and nine to the clonidine group. One patient, in whom morphine had been given, vomited shortly after ingestion of the paracetamol solution. Data from this patient were not used for analysis. In two patients in the clonidine group, it was not possible to obtain the blood sample at 90 min because the patient was transferred to the anaesthetic room. Age, weight and height of the patients were similar in the three groups (table 1).

Morphine 10 mg i.m. significantly delayed gastric emptying, whereas clonidine 150 μg i.m. did not.
infusion of crystalloid fluid 500 ml. Changes in however, returned to baseline values shortly after decreased by more than 30%. Arterial pressure, clonidine had been given, arterial pressure after saline (table 3). In one patient in whom the groups after injection of the test drug and was similar in the three groups (table 3). Arterial pressure decreased in all injection of the test drug were similar in the three 30

showed that the AUC value was significantly differ-
pared with the saline group (table 3). Non-parametric one-way analysis of variance (Kruskal–Wallis test) showed a significant difference between groups (P<0.001); the Mann–Whitney U test was used to compare morphine and saline groups and clonidine and saline groups.

Both arterial pressure and heart rate before administration of the test drug, and minimum values (mean (SD) [95% confidence intervals]). Differences between groups (clonidine – saline or morphine – saline groups) are also shown. The test drug was injected i.m. immediately after i.m. injection of the test drug (saline, clonidine 150 µg or morphine 10 mg in 1 ml). Hypothesis tests were used only for AUC0–60min. (AUC0–60min), maximum plasma paracetamol concentration (Cmax) and time to maximum concentration (tmax) for each group and the differences between groups (median (95% confidence limits)). Paracetamol was given 60 min after (fig. 1, table 2). One-way analysis of variance showed that the AUC value was significantly different between the three groups (P<0.001); it was significantly smaller in the morphine group compared with the saline group (P=0.002; 95% CI for difference −1237 to −489 µg min ml−1). In contrast, although AUC was greater in the clonidine group than in the saline group, this was not statistically significant (95% CI for difference −423 to 1264 µg min ml−1). Both arterial pressure and heart rate before injection of the test drug were similar in the three groups (table 3). Arterial pressure decreased in all the groups after injection of the test drug and was significantly lower after injection of clonidine than after saline (table 3). In one patient in whom clonidine had been given, arterial pressure decreased by more than 30%. Arterial pressure, however, returned to baseline values shortly after infusion of crystalloid fluid 500 ml. Changes in heart rate were not clinically significant (table 3).

Both clonidine and morphine appeared to have sedative effects. The degree of sedation, when present, was always mild (score 2: see text) *Data at 150 min were from seven patients.

### Table 1
Patient characteristics (mean (SD) [range])

<table>
<thead>
<tr>
<th></th>
<th>Saline group (n=10)</th>
<th>Clonidine group (n=9)</th>
<th>Morphine group (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>66 (13.5) [52–90]</td>
<td>65 (13.4) [51–85]</td>
<td>73 (10.9) [55–90]</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>161 (3.9) [155–168]</td>
<td>158 (5.0) [150–168]</td>
<td>162 (6.0) [147–170]</td>
</tr>
</tbody>
</table>

### Table 2
Area under the concentration-time curve for 0–60 min after ingestion of the paracetamol solution (AUC0–60min), maximum plasma paracetamol concentration (Cmax) and time to maximum concentration (tmax) for each group and the differences between groups (median (95% confidence limits)). Differences between groups for changes from baseline (median (95% confidence limits)). Paracetamol was given 60 min after i.m. injection of the test drug (saline, clonidine 150 µg or morphine 10 mg in 1 ml). Hypothesis tests were used only for AUC0–60min. Non-parametric one-way analysis of variance (Kruskal–Wallis test) showed a significant difference in AUC0–60min between groups (P<0.001); the Mann–Whitney U test was used to compare morphine and saline groups and clonidine and saline groups.

<table>
<thead>
<tr>
<th></th>
<th>AUC0–60min (µg min ml−1)</th>
<th>P</th>
<th>Cmax (µg ml−1)</th>
<th>tmax (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline group (n=10)</td>
<td>1371 [873, 1695]</td>
<td>—</td>
<td>30.0 [24.2, 38.0]</td>
<td>15.0 [15.0, 50.1]</td>
</tr>
<tr>
<td>Clonidine group (n=9)</td>
<td>1840 [914, 2716]</td>
<td>—</td>
<td>35.7 [22.3, 57.4]</td>
<td>30.0 [18.2, 41.6]</td>
</tr>
<tr>
<td>Morphine group (n=10)</td>
<td>427 [311, 550]</td>
<td>—</td>
<td>15.2 [9.8, 16.9]</td>
<td>75.0 [39.9, 90.0]</td>
</tr>
</tbody>
</table>

### Table 3
Baseline systolic arterial pressure and heart rate, change from baseline values at 60 and 150 min after administration of the test drug. The degree of sedation, if present, was always mild (score 2: see text) *Data at 150 min were from seven patients.

<table>
<thead>
<tr>
<th></th>
<th>Baseline (0 min)</th>
<th>Change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>60 min – 0 min</td>
<td>150 min – 0 min</td>
</tr>
<tr>
<td><strong>Systolic arterial pressure (mm Hg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Differences between groups for changes from baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonidine – saline</td>
<td>−6 [−18, 6]</td>
<td>−12 [−20, −3]</td>
</tr>
<tr>
<td>Morphine – saline</td>
<td>7 [−3, 18]</td>
<td>2 [−7, 10]</td>
</tr>
<tr>
<td><strong>Heart rate (beat min−1)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Differences between groups for changes from baseline</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 4
Number of patients who were sedated before, and 60 and 150 min after administration of the test drug. The degree of sedation, if present, was always mild (score 2: see text) *Data at 150 min were from seven patients.

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>60 min</th>
<th>150 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline group (n=10)</td>
<td>0</td>
<td>1 (10%)</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Clonidine group (n=9*)</td>
<td>0</td>
<td>5 (56%)</td>
<td>4 (57%)</td>
</tr>
<tr>
<td>Morphine group (n=10)</td>
<td>0</td>
<td>3 (30%)</td>
<td>7 (70%)</td>
</tr>
</tbody>
</table>
Discussion

We have shown that clonidine 150 μg i.m. did not delay gastric emptying of liquids as did morphine. The median plasma paracetamol concentration in the clonidine group was greater than the upper 95% confidence limit of the median concentration in the saline group (fig. 1, table 2).

It was somewhat surprising to see higher plasma concentrations in some patients who had received clonidine. Alpha2 adrenoceptor agonists inhibit contraction of the stomach caused by stimulation of cholinergic neurones, although they do not inhibit contraction induced by exogenous acetylcholine. However, they either have no effect or may have a stimulatory effect on the basal tone of the stomach. In addition, α2 adrenoceptor agonists inhibit contraction of the pylorus. In contrast, opioids increase pyloric pressure which impedes emptying of gastric contents into the intestine. Therefore, it might be possible that clonidine increased gastric emptying whereas morphine delayed it.

Paracetamol is not absorbed from the stomach but is well absorbed from the upper small intestine. It has been shown that there is a good correlation between the rate of absorption of paracetamol given orally and gastric emptying of liquids measured by a radio-isotope method. Thus the rate of absorption of paracetamol indicates the rate of gastric emptying. However, several factors, other than the rate of gastric emptying, may affect plasma paracetamol concentration.

First, if absorption of liquids from the small intestine is increased, the increase in plasma paracetamol concentration may be enhanced. In the isolated membrane of either the ileum or colon, α2 adrenoceptor agonists increase net transport of both fluid and electrolytes from the mucosal to the serosal side. In intact animals, when secretion from the intestine is stimulated by chemical stimulation, α2 adrenoceptor agonists inhibit hypersecretion. However, it is not clear if these drugs increase absorption of liquids, electrolytes and drugs from the small intestine during the unstimulated state in intact animals. In addition, opioids also increase absorption of liquids from the small intestine.

Second, several factors affect hepatic enzyme activity and influence elimination of paracetamol that is metabolized by the liver: sex differences, ethnic differences, anticonvulsants, antituberculosis drugs, contraceptive pills and pregnancy. It is not known if clonidine affects elimination of paracetamol. However, clonidine, about 50% of which is metabolized by the liver, decreases elimination of sulphobromophthalein or bupivacaine from the liver and increases plasma concentrations. Therefore, it is possible that clonidine interferes with elimination of paracetamol.

The decrease in arterial pressure after administration of clonidine might also have directly affected gastric emptying, or alternatively, might have decreased elimination of paracetamol by decreasing hepatic blood flow, leading to higher plasma paracetamol concentrations. In this study, the mean decrease in arterial pressure in the clonidine group was less than 20% compared with the saline group (table 3); in one patient in the clonidine group, arterial pressure decreased by more than 30%, but the duration of the decrease was short. In addition, calcium-channel blocking agents, at doses which would decrease arterial pressure, did not affect gastric emptying in humans, although arterial pressure was not measured in any study cited. Therefore, the effect of this factor is likely to be minimum.

It seems reasonable to conclude that although the increase in plasma paracetamol concentration after administration of clonidine could have been caused by factors other than increased gastric emptying, it is unlikely that clonidine markedly delayed gastric emptying.

Figure 1 Individual plots of plasma paracetamol concentration vs time after ingestion of paracetamol 1.5 g in 50 ml of water in the saline (top), clonidine (middle) and morphine (bottom) groups.
emptying. Nevertheless, caution is required when the effect of either a test drug or conditions on gastric emptying is interpreted by differences in plasma paracetamol concentrations between groups, in particular when the difference is small.

Clonidine and morphine appeared to provide mild sedation. After administration of clonidine, patients became calmer, suggesting a possible anxiolytic effect of the drug. Morphine caused the well-known undesirable effects, such as vomiting, dryness of mouth and pruritus. In contrast, the incidence of these complications after clonidine was either less or none.

One of the concerns of the use of α2 adrenoceptor agonists as premedication or analgesia is hypotension. Arterial pressure decreased significantly after administration of clonidine but generally the decrease was either mild or moderate. The reference intervals represent the estimated range of values that include a certain percentage of the values among the population.21 The 95% reference interval (mean±1.96) for the minimum arterial pressure after clonidine was 95–110 mm Hg. Although arterial pressure decreased by more than 30% in one of nine patients in our study, infusion of crystalloid fluid restored the pressure to baseline. Arterial pressure was within the normal range in this study; it is not known if clonidine markedly decreases arterial pressure more frequently in patients with hypertension or hypotension.

References