EFFECT OF PREMEDICATION ON DRUG ABSORPTION AND GASTRIC EMPTYING

J. G. TODD AND W. S. NIMMO

SUMMARY

The rate of paracetamol absorption after oral administration was used as a model of drug absorption and as an indirect measure of the rate of gastric emptying in 37 patients awaiting elective general surgery after different premedications. After saline (control) and diazepam, paracetamol absorption was normal but after morphine or nefopam, absorption was delayed markedly, presumably as a result of delayed gastric emptying. After naloxone there was a small but insignificant delay.

Opioid analgesic drugs are known to delay gastric emptying and the absorption of drugs administered by mouth (Nimmo, Wilson and Prescott, 1975), factors which may be disadvantageous when these drugs are used in premedication. In addition, pain and anxiety are thought to delay gastric emptying and may increase the risk of regurgitation at the time of induction of anaesthesia (Kaufman, 1980).

This study was undertaken to investigate the effects of a narcotic (morphine), a non-opioid analgesic (nefopam) and an anxiolytic (diazepam) on gastric emptying. Naloxone was included as a test drug as it had been shown to reverse partially the delay in gastric emptying produced by narcotics (Nimmo et al., 1979). Patients receiving saline formed a control group.

Paracetamol has been used as a model drug for gastric emptying studies (Nimmo, Wilson and Prescott, 1975; Goldstraw and Bach, 1981). Since paracetamol is not absorbed from the stomach but is rapidly absorbed from the upper small bowel, its rate of absorption after oral administration is an indirect measure of the rate of gastric emptying (Clements et al., 1978). This correlates well with direct measures of gastric emptying (Heading et al., 1973). Rapid paracetamol absorption indicates rapid gastric emptying, while delayed absorption is assumed to reflect delayed gastric emptying.

PATIENTS AND METHODS

Thirty-seven patients without clinical evidence of gastrointestinal disease and awaiting elective general surgery were allocated randomly to receive one of the following premedications i.m. 2–3 h before the induction of anaesthesia: saline 1 ml, morphine 10 mg, nefopam 20 mg, diazepam 10 mg or naloxone 1.2 mg. All injections were given to the buttock using 21-SWG needles. Neither patient nor anaesthetist was aware of which drug had been given. Diazepam was given i.m. so that the patients did not know which premedication was given. Although oral administration produces better absorption than the i.m. route, this dose i.m. would be expected to give mean peak diazepam concentrations of $100 \pm 5.1 \mu g \text{ ml}^{-1}$ at 90 min (Gamble, Dundee and Assaf, 1975).

Approval for the study was obtained from the Hospital Ethics Advisory Committee and all patients gave informed verbal consent. The majority of patients underwent surgery for varicose veins, inguinal hernia and minor gynaecological procedures.

Following an overnight fast, and 20 min after the i.m. injection of the premedicant drug, each patient received paracetamol 1.5 g as three Panadol tablets with water 50 ml. Blood samples were withdrawn at 0, 15, 30, 45, 60, 75 and 90 min for the measurement of plasma paracetamol concentrations by high pressure liquid chromatography (Howie, Adriaenssens and Prescott, 1977).

Paracetamol absorption was assessed by the plasma concentrations at each time point, the times to reach peak concentrations and the areas under the plasma concentration time curves (AUC) at 45 and 90 min. Statistical analyses were carried out using the Wilcoxon test.

RESULTS

There were no significant differences between the five premedication groups with respect to age,
weight or sex (table I). The patients who received saline tended to be older, particularly when compared with the diazepam group. However, previous studies on the effect of age on drug absorption have demonstrated that, after oral administration, absorption was not altered appreciably (Stevenson et al., 1979). The anaesthetist, who was unaware of which premedication had been given, found it hard to tell, before the induction of anaesthesia, which of the five agents the patient had received. This probably resulted from the delay between the time of premedication and induction of anaesthesia, with little difference in clinical effects detectable at 2–3 h. However, in the period immediately after operation, the patients who had received saline or naloxone tended to be more restless.

Control group

In the seven patients who had received saline, paracetamol absorption was rapid (table II, fig. 1). The mean (± SEM) peak paracetamol concentration was 22.9 ± 2.2 μg ml⁻¹ occurring 60 min after ingestion.

Diazepam

Paracetamol absorption was rapid in the seven patients who had received diazepam (table II). The mean peak paracetamol concentration was 21.7 ± 4.5 μg ml⁻¹ at 60 min. At no time did the plasma paracetamol concentrations or the AUC (table III) differ significantly from those in the control group.

Morphine and nefopam

Following morphine, or nefopam, there was a significant delay in paracetamol absorption. The mean concentrations at 90 min were 11.9 ± 2.4 μg ml⁻¹ and 11.0 ± 2.4 μg ml⁻¹, respectively (table II, fig. 1) and concentrations were still increasing. No peak concentrations were seen. In all eight patients, after nefopam, no paracetamol could be detected at 15 min. In both groups plasma concentrations at 30, 45, 60 and 75 min were significantly smaller than in the saline group (P < 0.05). The AUC from 0 to 45 min and from 0 to 90 min were significantly smaller than in the control group (table III).

### Table I. Comparison of patient data

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of patients</th>
<th>Mean age (yr) (range)</th>
<th>Mean wt (kg) (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>7 (4M)</td>
<td>59.1 (38–74)</td>
<td>67.1 (57–75)</td>
</tr>
<tr>
<td>Diazepam</td>
<td>7 (2M)</td>
<td>41 (33–60)</td>
<td>60.3 (50–80)</td>
</tr>
<tr>
<td>Morphine</td>
<td>7 (4M)</td>
<td>49.5 (18–68)</td>
<td>65.4 (54–74)</td>
</tr>
<tr>
<td>Nefopam</td>
<td>8 (5M)</td>
<td>48.6 (32–62)</td>
<td>72.2 (59–90)</td>
</tr>
<tr>
<td>Naloxone</td>
<td>8 (3M)</td>
<td>45.6 (29–78)</td>
<td>67.3 (51–105)</td>
</tr>
</tbody>
</table>

### Table II. Mean plasma paracetamol concentrations (± SEM) after different premedications. Patients received paracetamol 1.5 g by mouth with water 50 ml. *P < 0.05 compared with saline (Wilcoxon test)

<table>
<thead>
<tr>
<th>Group</th>
<th>15 min</th>
<th>30 min</th>
<th>45 min</th>
<th>60 min</th>
<th>75 min</th>
<th>90 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline (n = 7)</td>
<td>12.0</td>
<td>21.6</td>
<td>22.6</td>
<td>22.9</td>
<td>21.1</td>
<td>20.0</td>
</tr>
<tr>
<td>± 7.2</td>
<td>± 5.5</td>
<td>± 2.4</td>
<td>± 2.2</td>
<td>± 2.2</td>
<td>± 1.8</td>
<td></td>
</tr>
<tr>
<td>Diazepam (n = 7)</td>
<td>14.8</td>
<td>16.4</td>
<td>17.9</td>
<td>21.7</td>
<td>21.7</td>
<td>17.8</td>
</tr>
<tr>
<td>± 6.0</td>
<td>± 4.9</td>
<td>± 3.4</td>
<td>± 4.5</td>
<td>± 4.2</td>
<td>± 3.7</td>
<td></td>
</tr>
<tr>
<td>Morphine (n = 7)</td>
<td>4.0</td>
<td>6.8*</td>
<td>7.8*</td>
<td>10.8*</td>
<td>10.2*</td>
<td>11.9</td>
</tr>
<tr>
<td>± 1.9</td>
<td>± 2.7</td>
<td>± 2.1</td>
<td>± 3.2</td>
<td>± 2.2</td>
<td>± 2.4</td>
<td></td>
</tr>
<tr>
<td>Nefopam (n = 8)</td>
<td>0</td>
<td>0.9*</td>
<td>2.8*</td>
<td>7.3*</td>
<td>10.8*</td>
<td>11.0</td>
</tr>
<tr>
<td>± 0.5</td>
<td>± 0.8</td>
<td>± 2.1</td>
<td>± 2.7</td>
<td>± 2.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naloxone (n = 8)</td>
<td>4.9</td>
<td>11.4</td>
<td>14.2</td>
<td>15.3</td>
<td>15.7</td>
<td>16.6</td>
</tr>
<tr>
<td>± 3.9</td>
<td>± 4.8</td>
<td>± 4.4</td>
<td>± 3.4</td>
<td>± 3.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### TABLE III.

Mean areas under the plasma paracetamol concentration time curves (AUC) after different premedications (± SD). Compared with saline (Student's t test): *P < 0.05; **P < 0.01; ***P < 0.001

<table>
<thead>
<tr>
<th>Group</th>
<th>AUC (μg h(^{-1}) ml(^{-1}))</th>
<th>0–45 min</th>
<th>0–90 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline (n = 7)</td>
<td>11.3 ± 7.3</td>
<td>27.6 ± 8.5</td>
<td></td>
</tr>
<tr>
<td>Diazepam (n = 7)</td>
<td>10.0 ± 7.9</td>
<td>26.4 ± 13.9</td>
<td></td>
</tr>
<tr>
<td>Morphine (n = 7)</td>
<td>3.6* ± 2.9</td>
<td>11.4** ± 6.1</td>
<td></td>
</tr>
<tr>
<td>Nefopam (n = 8)</td>
<td>0.6** ± 0.5</td>
<td>6.9*** ± 4.4</td>
<td></td>
</tr>
<tr>
<td>Naloxone (n' = 8)</td>
<td>5.9 ± 8.1</td>
<td>16.9 ± 16.8</td>
<td></td>
</tr>
</tbody>
</table>

### Naloxone

In the eight patients who received naloxone, paracetamol absorption varied considerably. Three patients showed a marked delay in absorption with no paracetamol detected at 45 min and in a fourth patient no paracetamol was found at 30 min. In the remaining four patients absorption was normal in three and very rapid in one.

However, at no time did the naloxone group differ significantly from the controls, although there was a trend towards lower concentrations throughout. When compared with morphine, again there was no significant difference (table II, fig. 2). No obvious peak concentration was seen after naloxone. The AUC up to 45 and 90 min did not differ significantly from saline or morphine.

### DISCUSSION

Paracetamol absorption in patients receiving saline or diazepam was rapid. Paracetamol concentrations at all time points were almost identical to those obtained in eight healthy volunteers after the same dose of paracetamol (Nimmo and Prescott, 1978).

![Fig. 1. Mean plasma paracetamol concentrations (±SEM) after saline, morphine and nefopam. Patients received paracetamol 1.5 g by mouth with 50 ml water.](image1)

![Fig. 2. Mean plasma paracetamol concentrations (±SEM) after saline, morphine and naloxone. Patients received paracetamol 1.5 g by mouth with 50 ml water.](image2)
Normal paracetamol absorption implies normal gastric emptying.

However, paracetamol absorption was markedly delayed after morphine and nefopam. This confirms previous studies for morphine, which is known to decrease gastric motility and delay the passage of gastric contents through the duodenum (Jaffe and Martin, 1980). Morphine 10 mg i.m. has been shown to delay significantly the absorption of oral diazepam (Gamble et al., 1976) and a similar, although less marked, effect was seen following parenteral atropine 0.6 mg.

Nefopam is chemically related to diphenhydramine and is totally distinct from the centrally acting narcotic analgesics. It lacks significant opiate receptor binding affinity in vitro (Tresnak-Rustad and Wood, 1981) and probably causes the delay in gastric emptying by a combination of anticholinergic and sympathomimetic actions. Other autonomic side-effects are reported to include nausea, nervousness, blurred vision and dry mouth, although none of the patients complained of these during this study.

Naloxone 1.2 mg i.v. has been shown to reverse partially the delaying effects of pentazocine on gastric emptying and drug absorption in healthy volunteers (Nimmo et al., 1979). The authors suggest that this may have been a result of incomplete reversal of the effects of pentazocine by naloxone or the shorter duration of action of naloxone compared with that of pentazocine. Recently, however, Champion and colleagues (1982) have shown, using a radioisotope test meal in healthy volunteers, that naloxone 2 mg i.v. inhibits the gastric emptying of solids. They suggest that naloxone itself may act as an opiate agonist. Although inconclusive, the results from our study also suggest that naloxone may have a delaying action in some patients. The large variability in response to this drug may be a result of differences in absorption from the i.m. site of a preparation designed primarily for i.v. use, combined with individual variations in the serum half-life. Ngai and co-workers (1976) found the serum half-life ranged from 30 to 81 min (mean 64 ± 12 min) in nine volunteers.

The numbers in each group in the study were small, but were sufficient to show a striking difference for morphine and nefopam. Since consecutive patients were studied and were randomly allocated to the five groups there was a marked variation in ages and weights within each group. However, none of the premedications tested are routinely prescribed on an mg kg⁻¹ basis, nor indeed is paracetamol. In particular, studies of paracetamol absorption in obese patients have shown this to be no different from normal healthy volunteers (Lee, Kramer and Granville, 1980).

It seems likely that the major cause of any delay in gastric emptying and drug absorption before surgery is the analgesic drug. Diazepam 10 mg i.m. had no effect. Naloxone may delay gastric emptying under certain circumstances and only further study following administration i.v. will clarify the situation.

ACKNOWLEDGEMENTS

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REFERENCES


Nimmo, W. S., Heading, R. C., Wilson, J., and Prescott, L. F.
PREMEDICATION AND GASTRIC FUNCTION


EFFET DE LA PREMEDICATION SUR L'ABSORPTION DES MEDICAMENTS ET LA VIDANGE GASTRIQUE

RESUME
Nous avons utilisé la vitesse d'absorption du paracétamol après administration per-os comme modèle d'absorption médicamenteuse et comme mesure indirecte de la vitesse de vidange gastrique chez 37 patients attendant de subir des actes de chirurgie générale réglée après avoir reçu différentes prémédications. Après administration de chlorure de sodium (témoins) et de diazépam, l'absorption du paracétamol était normale, mais après administration de morphine ou de nefopam, l'absorption était nettement retardée, probablement à cause d'un ralentissement de la vidange gastrique. Après administration de naloxone, il y avait un léger retard non significatif.

WIRKUNG DER PRÄMEDIKATION AUF MEDIKAMENTENABSORPTION UND MAGENENTLEERUNG

ZUSAMMENFASSUNG

EL EFECTO DE LA PREMEDICACION SOBRE LA ABSORCION DE DROGAS Y VACIAMIENTO GASTRICO

SUMARIO
Se uso el ritmo de absorción de paracetamol después de la administración oral como modelo de la absorción de drogas y como medida indirecta del ritmo de vaciamiento gástrico en 37 pacientes en espera de una cirugía general electiva después de varias premedicaciones. Después de una solución salina (control) y del diazepan, la absorción de paracetamol fue normal pero después de la morfina o del nefopán, la absorción fue bastante atrasada, probablemente a raíz del vaciamiento gástrico diferido. Después de la naxolona, hubo un atraso pequeño pero insignificante.