PREGNANCY DELAYS PARACETAMOL ABSORPTION AND GASTRIC EMPTYING IN PATIENTS UNDERGOING SURGERY

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Nausea, vomiting and heartburn occur during early pregnancy, and may indicate abnormal gastrointestinal function at this time. An increase in the release of progesterone from the corpus luteum and placenta causes relaxation of gastrointestinal smooth muscle and this may result in a decrease in the motility of the stomach [1]. Gastric emptying may also be impeded mechanically during pregnancy if the stomach is pushed into a more horizontal position and the pylorus is displaced upwards and posteriorly [2].

Previous studies of gastric emptying during pregnancy have produced conflicting results. In 1937, Hansen [3] found that the emptying time of a radio-opaque test meal was increased by 30–90 min during pregnancy. However Boyden and Rigler [4], using fluoroscopic examination, found little alteration in gastric emptying during the second and third trimester of pregnancy, but suggested that peristalsis may have been slower. Hunt and Murray [5] used dye dilution to measure the rate of emptying of 750 ml of fluid in five pregnant women and showed that it did not differ from that found in the same patients 40 weeks after delivery. In 1970, Davison, Davison and Hay [6] measured gastric emptying using a double sampling dye-dilution technique in 11 non-pregnant women and 11 women of at least 34 weeks gestation. The mean total emptying time of a water test meal was increased in pregnant patients, but there was no difference in the volume of the stomach contents after 30 min.

These conflicting results may reflect differences in the measurement techniques. It is difficult to quantitate gastric emptying radiologically. Gastric aspiration methods correct for the volume of gastric secretion during the study period, but only allow one single measurement of emptying. Solute absorption has been used widely to measure stomach emptying before surgery, as it is non-invasive and does not require the ingestion of large amounts of fluid [7]. In the present study the rate of paracetamol absorption was used to measure gastric emptying rate during pregnancy and in non-pregnant control subjects.

PATIENTS AND METHODS

Twenty-eight women undergoing termination of pregnancy and 14 non-pregnant women having minor gynaecological surgery were studied. All patients were healthy and none was taking any drugs, including oral contraceptives, which might alter gastric motility. Before surgery the gestation of the pregnant patients was assessed by a consultant gynaecologist, and they were grouped
Gastric emptying was measured using a paracetamol absorption technique similar to that described by Heading and colleagues [8]. After a fast of at least 4 h each patient took paracetamol tablets 1.5 g (Winthrop Laboratories) with 150 ml of water. Patients remained supine for 2 h whilst blood was sampled at intervals, through an i.v. cannula; blood sampling was completed before the induction of anaesthesia. Plasma samples were frozen at −20 °C and paracetamol concentrations were measured using an enzymatic assay method, specific for the parent compound, which did not detect paracetamol metabolites (Cambridge Life Sciences). The enzyme aryl acylamide amido-hydrolase was used to split the amide bond of paracetamol, producing acetate and p-amino-phenol. The latter reacted with o-cresol to form a stable blue compound which was measured using a spectrophotometer capable of reading at 615 nm.

The procedure was automated to improve the performance of the assay at the low concentrations of paracetamol expected. The system used was a hybrid Technicon AAII/Fisons Vitatron with a Hook and Tucker sampler adapted for the procedure. The external quality control was a commercial kit (American Hospital Supplies), used routinely for measuring therapeutic concentrations of paracetamol in plasma. The coefficients of variation were 0.96% (within batch) and 2.24% (between batch). The assays of 72 patients were reanalysed on a different day and gave a coefficient of variation of 2.35%.

Fig. 1. Mean plasma paracetamol concentrations (± SEM) after paracetamol 1.5 g by mouth with 150 ml of water. Women 12–14 weeks pregnant had significantly lower concentrations at 30, 45 (P < 0.05), 60 (P < 0.01) and 75 (P < 0.05) min compared with controls.

**Table I. Age and weight of patients and duration of fasting (mean (SD))**

<table>
<thead>
<tr>
<th>Gestation</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Starved (h)</th>
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</thead>
<tbody>
<tr>
<td>Control (n = 14)</td>
<td>31.8 (7.5)</td>
<td>59.6 (9.6)</td>
<td>8.0 (4.5)</td>
</tr>
<tr>
<td>8–11 weeks (n = 16)</td>
<td>25.6 (8.0)</td>
<td>60.3 (11.5)</td>
<td>6.8 (4.1)</td>
</tr>
<tr>
<td>12–14 weeks (n = 12)</td>
<td>24.8 (8.6)</td>
<td>57.8 (7.3)</td>
<td>5.7 (2.9)</td>
</tr>
</tbody>
</table>
The area under the plasma paracetamol concentration–time curve was calculated using the trapezoidal rule. Data were analysed using one-way analysis of variance for independent samples, followed by Scheffé's test where appropriate.

RESULTS

There was no significant difference in age, weight or duration of fasting between the pregnant and control groups (table I).

Plasma paracetamol concentrations were significantly lower at 30, 45 (P < 0.05), 60 (P < 0.01) and 75 (P < 0.05) min in patients who were 12–14 weeks pregnant compared with control subjects. Paracetamol concentrations in the 8–11 weeks pregnant group were between, but were not significantly different from either of, the other two groups (fig. 1). The 12–14 weeks pregnant group had lower peak paracetamol concentrations compared with controls (P < 0.05), and showed a delay in the time taken to reach a peak compared with controls and 8–11 weeks pregnant women (P < 0.05) (table II).

The areas under the plasma paracetamol concentration–time curve (AUC) at 1 and 2 h were less in 12–14 weeks pregnant patients compared with controls (P < 0.05). The AUC in the 8–11 weeks pregnant group were not significantly different from either of the other groups (fig. 2).

DISCUSSION

As paracetamol is not absorbed in the stomach, but is readily absorbed in the upper small bowel, the rate of absorption depends on the rate of gastric emptying. Heading and colleagues [8] demonstrated a significant correlation between the half-time of gastric emptying, measured by sequential gamma scintiscanning of the stomach, and plasma paracetamol concentrations. Therefore, the reduction in mean plasma paracetamol concentrations in the 12–14 weeks pregnant patients, in the present study, represented a delay in gastric emptying. The smaller area under the
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plasma paracetamol concentration–time curve in these subjects reflected a reduction in paracetamol absorption [9]. Although no statistically significant difference was demonstrated between the control and the 8–11 weeks pregnant patients, the values for the latter group were between the 12–14 weeks and the non-pregnant values.

Inhalation of gastric contents remains an important cause of anaesthetic mortality and morbidity [10]. Many studies have demonstrated large volumes of acid stomach contents in patients prepared for surgery. Hester and Heath [11] reported that, after prolonged fasting, more than 40 ml of fluid was recovered from the stomach of one in eight patients presenting for elective surgery, and over half the patients had gastric contents with a pH of less than 2.5. More than 25 ml of acidic stomach fluid was aspirated from 66% of patients presenting for minor outpatient operations [12]. As many patients undergo surgery during early pregnancy, it may be important to determine whether significant gastric stasis is present at this time. Although the present study demonstrated delayed stomach emptying during pregnancy, it did not show whether this increased the risk of aspiration of gastric contents.

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REFERENCES