EFFECT OF ORAL OMEPRAZOLE ON INTRAGASTRIC pH AND VOLUME IN WOMEN UNDERGOING ELECTIVE CAESAREAN SECTION

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SUMMARY
We have studied in obstetric patients the efficacy of omeprazole in increasing intragastric pH to more than 2.5 and reducing volume to less than 25 ml. Omeprazole 40 mg was given orally the night before and again on the morning of surgery to 30 Asian women scheduled to undergo elective Caesarean section. After induction of anaesthesia, a gastric tube was inserted and intragastric contents aspirated. Volume and pH were recorded and measurements were repeated on completion of surgery. The median (range) volume was 2 (1-13) ml before surgery and 4 (0-14) ml at the end of surgery. There was insufficient volume to measure pH in all patients. The median (range) pH was 6.7 (4.6-7.4) before surgery in 20 patients and 6.6 (4.6-7.8) at the end of surgery in 28 patients. No adverse drug reactions were noted in mothers or neonates. Omeprazole 40 mg orally twice before elective Caesarean section appeared to be effective in reducing intragastric volume and acidity to acceptable values.

KEY WORDS

Pulmonary aspiration of acidic gastric contents remains an important contributor to obstetric mortality [1]. In patients requiring general anaesthesia, prophylaxis includes reduction of intragastric volume and acidity with various combinations of histamine type 2 (H₂) receptor antagonists, antacids and metoclopramide. No ideal therapy has been defined and many different regimens are followed [2]. An intragastric pH less than 2.5 and volume greater than 0.4 ml kg⁻¹ (approximately 25 ml) have been suggested as being particularly dangerous [3], although this has been questioned [4]. Studies of pulmonary aspiration in rats have shown that pH is a more important factor than volume in determining lung injury [5] and mortality [6].

Omeprazole is a specific inhibitor of the enzyme H⁺K⁺ATPase, which acts at the final step in the acid secreting pathway and is found only in the parietal cell [7]. Suppression of gastric acid secretion is more prolonged by omeprazole than by H₂ receptor antagonists, without an increase in side effects. Omeprazole is effective in treatment of acid-related gastrointestinal diseases [7]. Omeprazole was suggested for obstetric anaesthesia many years ago [8], but a single 80-mg dose the night before surgery was associated with an intragastric pH < 2.5 in three of 20 obstetric patients [9]. Repeated administration of omeprazole has a cumulative effect on acid inhibition [7] and should be more effective in increasing intragastric pH than a single dose.

We undertook a non-comparative study to assess the efficacy of two doses of omeprazole 40 mg in reducing gastric acidity and volume in women undergoing elective Caesarean section.

PATIENTS AND METHODS

The study was approved by the Research Ethics Committee of the Chinese University Faculty of
Medicine. Written informed consent was obtained from all patients.

We studied healthy Asian women with uncomplicated pregnancies of at least 36 weeks duration undergoing elective Caesarean section before midday. Patients were excluded if they had symptoms of acid-related gastrointestinal disease, previous gastric surgery, known drug allergy or abuse, or ingestion within the past 4 days of drugs known to affect gastric motility and secretion. Laboratory investigations included routine haematological, biochemical and liver function tests.

Omeprazole was provided as enteric coated granules in hard gelatin capsules, each containing 20 mg. Omeprazole 40 mg, with 50 ml water, was given orally at 20:00 the night before surgery and again at 06:00 on the morning of surgery. Patients were fasted from midnight.

All women were transported to the operating theatre in the lateral position. Before induction of anaesthesia patients were questioned directly for unusual symptoms which might indicate adverse drug reactions with omeprazole. Patients were maintained in the left lateral tilt position and monitored with the electrocardiograph and an automated non-invasive arterial pressure device.

After preoxygenation for at least 3 min, rapid sequence induction of anaesthesia was performed with thiopentone 4 mg kg$^{-1}$ while cricoid pressure was applied. Suxamethonium 1.5 mg kg$^{-1}$ was given i.v. to facilitate tracheal intubation and neuromuscular block maintained with atracurium 0.5 mg kg$^{-1}$. Ventilation of the lungs was controlled to maintain an end-tidal carbon dioxide concentration of 4.0–4.5 %. Anaesthesia was maintained with 50 % nitrous oxide and 1 % enfurane in oxygen until delivery, after which nitrous oxide was increased to 70 % and enfurane decreased to 0.5 %. At delivery, oxytocin 10 u. and morphine 0.2 mg kg$^{-1}$ were given i.v. Enflurane was discontinued at commencement of skin closure and 100 % oxygen administered at the end of surgery. Atropine 1.2 mg and neostigmine 2.5 mg were given to all patients to antagonize residual neuromuscular block.

Intragastric pH and volume were measured after induction of anaesthesia and again on completion of surgery. A 16-French gauge Salem Sump tube was inserted orally and correct position in the stomach checked by auscultation of injected air. We attempted to maximize returned volume by repeated aspiration with the tube rotated and withdrawn 10 cm and readvanced. The volume of aspirate was recorded and pH measured within 1 h with a Corning 240 pH meter calibrated daily at pH 4, 7 and 10.

At delivery, samples of maternal venous (MV), umbilical arterial (UA) and umbilical venous (UV) blood were obtained in most patients. Plasma was separated and stored at $-20 \degree$C for subsequent assay for omeprazole.

Plasma analysis for omeprazole was performed by the Department of Bioanalytical Chemistry, AB Hässle, Sweden. The method used high pressure liquid chromatography on a silica gel with mobile phase of methylenehydroxide in methanol. The flow rate was 1.5 ml min$^{-1}$ and the eluent was monitored by u.v. detection at 302 nm. The minimum determinable concentration of omeprazole was 20 nmol litre$^{-1}$ in plasma and the relative sd was 10–15%.

Neonatal Apgar scores at 1 and 5 min were recorded. Weight gain and suckling ability were reviewed daily until discharge.

Patients were questioned again after operation for unusual symptoms and the preoperative laboratory investigations were repeated before discharge.

Simple linear regression was used to evaluate associations among pH and volume data, omeprazole concentrations and the time from the last dose of omeprazole. The Wilcoxon rank sum test was used to compare UA with UV concentrations of omeprazole and the initial with the final aspirate pH and volume data. $P < 0.05$ was considered significant.

RESULTS

Although 33 women were entered into the trial, three were withdrawn. One patient required emergency Caesarean section and surgery was deferred in the other two. Thirty women, aged 23–38 yr, weighing 50–81 kg and of 37–39 weeks gestation completed the study.

The duration of surgery ranged from 30 to 80 min. The time from the last dose of omeprazole to intragastric pH and volume measurements ranged from 3.0 to 6.4 h.

The median (range) gastric volume was 2 (1–13) ml before surgery and 4 (0–14) ml at the end of surgery (fig. 1). There was insufficient volume to measure intragastric pH in 10 patients before surgery and two patients at the end of surgery. The median (range) pH was 6.7 (4.6–7.4) before surgery and 6.6 (4.6–7.8) at the end of surgery.
Two pH measurements were possible in 19 patients with the final pH often slightly greater than the initial pH \((P < 0.01)\). Volume and pH were not related to time since the last omeprazole dose.

Maternal and umbilical blood samples were obtained 3.0–5.5 h after the last dose of omeprazole and omeprazole was detectable in all samples (table I). UA and UV concentrations of omeprazole were similar in the same neonate and always less than the corresponding MV sample. There was good correlation between omeprazole concentrations in MV and UV \((r = 0.96)\) and MV and UA \((r = 0.95)\). Values were not related to gastric pH or the time after the last dose of omeprazole.

Apgar scores were satisfactory. Two neonates were admitted to the intensive care unit. One neonate was of low birth weight (2.2 kg) and developed a respiratory infection, while the other was admitted on the 3rd day for phototherapy of physiological jaundice. All neonates had satisfactory weight gain and suckling ability, except for the low birth weight neonate in intensive care.

No adverse symptoms were elicited from the mothers and the postoperative laboratory investigations showed no abnormal variation from preoperative values.

### DISCUSSION

Omeprazole 40 mg orally the night before and again on the morning of surgery appeared to be effective in increasing gastric pH to more than 2.5 while keeping intragastric volume less than 25 ml.

The technique of blind gastric aspiration underestimates intragastric volume [10], but it is a simple method which has been used commonly in similar trials. Dye dilution measurement of gastric volume may not be superior in anaesthetized patients [11] and extra complexity is added to the procedure. Even if one considers that the postoperative aspirate may have been present at the beginning of surgery, the addition of the two volumes was still low (range 2–20 ml). Omeprazole has been found to reduce the volume of gastric juice secretion [12].

The pH of gastric aspirate may be more important than volume in determining pulmonary damage [5, 6]. Although pH was not measurable in 10 patients initially, subsequent pH measurements at the end of surgery were obtained in nine and all were satisfactory.

Our results are better than the previous study of a single 80-mg dose in obstetric patients in which six of 20 patients failed either volume or pH criteria [9]. This is probably because of the additive effect of the two omeprazole doses on acid inhibition, although patient and procedural differences cannot be discounted. The time from drug administration to induction of anaesthesia was shorter in our study than the 11.8–16.3 h investigated previously [9].

### TABLE I. Omeprazole concentration data from maternal vein (MV) \((n = 25)\), umbilical vein (UV) \((n = 29)\) and umbilical artery (UA) \((n = 20)\). CI = Confidence interval

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
<th>95 % CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>MV ((\mu\text{mol litre}^{-1}))</td>
<td>1.64</td>
<td>1.12</td>
<td>0.37–4.83</td>
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<tr>
<td>UV ((\mu\text{mol litre}^{-1}))</td>
<td>0.88</td>
<td>0.52</td>
<td>0.17–2.00</td>
<td></td>
</tr>
<tr>
<td>UA ((\mu\text{mol litre}^{-1}))</td>
<td>0.94</td>
<td>0.49</td>
<td>0.20–1.95</td>
<td></td>
</tr>
<tr>
<td>UV/MV ((n = 25))</td>
<td>0.54</td>
<td>0.10</td>
<td>0.31–0.71</td>
<td>0.49–0.58</td>
</tr>
<tr>
<td>UA/UV ((n = 20))</td>
<td>1.02</td>
<td>0.16</td>
<td>0.81–1.58</td>
<td>0.95–1.10</td>
</tr>
</tbody>
</table>
The safety of all new drugs in obstetric anaesthetic practice must be considered. Omeprazole is a pro-drug which is activated only at pH less than 4. It has no effect on other H+ secreting cells in the body. After activation, the specific target of the drug is the enzyme H+K+ATPase, causing a non-competitive, long lasting inhibition of hydrochloric acid secretion. Omeprazole is eliminated rapidly, with an elimination half-life of 0.5–1.5 h, but the effect on acid secretion does not correlate with plasma concentrations [7]. Omeprazole is metabolized in the liver via the cytochrome P450 system and therefore alterations in disposition of other drugs metabolized through that system can be surmised. Omeprazole has been shown in healthy subjects to decrease the clearance of phenytoin and diazepam [7].

Placental transfer of omeprazole has been measured in sheep [13] and humans [9]. In the latter study, neonatal intragastric pH was almost neutral after delivery, but subsequent changes in acidity were not evaluated. However, the normal neonatal intragastric pH at birth is almost neutral [14] and omeprazole would not be activated in these conditions. The umbilical concentrations of omeprazole in our study were greater than those reported previously [9] because of the shorter dose to sampling interval. There are no data on the neonatal metabolism of omeprazole.

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REFERENCES


