Secretion of intravenously administered antibiotics in gastric juice: Implications for management of Helicobacter pylori

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Abstract
Aims: To study whether differences in eradication rates of antibiotics may be explained by differences in secretion of antibiotics in gastric juice.

Methods: A single intravenous dose of either ampicillin 500 mg, erythromycin 500 mg, or metronidazole 500 mg was administered to four healthy Helicobacter pylori negative volunteers on different days. Antibiotic concentrations were measured in gastric juice before and every 10 minutes after administration of the drug for two hours and after one hour in serum.

Results: No ampicillin was detected in gastric juice. Erythromycin concentrations in gastric juice showed considerable individual variation and reached maximum concentrations of 2-2-4-8 mcg/ml between 30 and 80 minutes after dosing. Metronidazole concentrations in gastric juice showed much less individual variation and maximum concentrations of 5-6 mcg/ml were reached within 30 minutes and remained high during the study period.

Conclusion: Metronidazole and erythromycin are secreted across the gastric mucosa, but ampicillin is not.

The discovery of Helicobacter pylori and its close association with chronic active gastritis and peptic ulcer disease has led to an active interest in trials of antibiotic treatment to eradicate the organism. It is clear that eradication is difficult to achieve,1 2 that recrudescence of the organism will occur if suppression rather than eradication is achieved,3 and that antibiotic monotherapy is not very effective.4 Furthermore, the in vitro susceptibility of a therapeutic agent does not necessarily predict its in vivo effectiveness.5 For example, although erythromycin has low minimum inhibitory concentrations MIC50 and MIC90 values and is effective in combination with other compounds, it was not effective as a single agent in eradicating H pylori.6 It has been suggested that the inability of antimicrobial agents to achieve sufficiently high concentrations in the gastric pits contributes to poor eradication rates.7 We studied the secretion in gastric juice of intravenously administered ampicillin, erythromycin, and metronidazole in healthy volunteers to investigate whether differences in the ability to secrete these compounds could help explain the clinical findings.

Methods
Four healthy volunteers (age 21–25 years) participated in the study. They all underwent an upper gastrointestinal endoscopy and were H pylori negative by histological examination and culture of antral biopsy specimens. Participants were studied on three different days, one for each of the three drugs which were administered in random order. There were at least two washout days between study days. On the morning of each study day, after an overnight fast, a nasogastric tube was passed into the stomach and left in place for the three hours of the protocol. Initial gastric contents were aspirated and discarded. Gastric juice was aspirated for 30 minutes before infusion of the antibiotic, at the time of infusion, and then every 10 minutes for another two hours. Gastric juice pH concentrations were determined for each sample throughout the study.

The following drugs were given intravenously as a single bolus of 250 cc, in random order, on each of the three study days: ampicillin 500 mg; erythromycin 500 mg; and metronidazole 500 mg. Serum concentrations of these drugs were measured one hour after infusion of each drug. Aliquots of gastric juice and serum were stored in ice and measurements were done in triplicate. Bioassay methods were used for measuring drug concentrations of ampicillin8 and erythromycin5; metronidazole measurements were performed using an HPLC (high power liquid chromatography) (Beckman) technique.10 11 In one patient erythromycin concentrations were uninterpretable because gastric juice was mixed with macroscopically visible bile. Results remained uninterpretable when the bioassay was repeated with Streptococcus faecalis, which is resistant to bile, instead of Micrococcus luteus which is normally used for the assay.

The research protocol was approved by the ethics committee at McMaster University Medical Centre and informed written consent was obtained from each volunteer.
Results
Upper gastrointestinal endoscopies in all four subjects were normal and no H pylori organisms were identified on histology or by culture. All subjects had normal basal acid profiles with a fasting gastric juice pH ranging from 1.47 to 2.15.

Ampicillin: In none of the four subjects was any ampicillin detected in gastric juice during the two hours following administration of the drug. Serum ampicillin concentrations one hour after intravenous administration were 4.8, 4.9, 4.9 and 5.1 mcg/ml, respectively.

Erythromycin: Figure 1 shows the results of erythromycin measurements in gastric juice in three subjects. Erythromycin concentrations were uninterpretable in one patient because gastric juice was mixed with macroscopically visible bile. Results remained uninterpretable when the bioassay was repeated with S faecalis, which is resistant to bile, instead of M luteus which is normally used for the assay. There were considerable individual variations in the results and erythromycin appeared in gastric juice soon after intravenous infusion in two, and at 30 minutes in the third subject. Peak concentrations were reached between 30 and 80 minutes. The concentration of erythromycin in gastric juice started to fall during the second hour in each subject. Serum erythromycin concentrations one hour after intravenous administration were 2.2, 2.8, and 4.8 mcg/ml.

Metronidazole: Figure 2 shows the results of metronidazole secretion in gastric juice. Metronidazole appeared at 10 minutes and peak gastric juice concentrations were obtained at 30–50 minutes and only declined slightly during the two hours of the study. Serum concentrations were 5.2, 5.5, 6.4 and 6.6 μg/ml at one hour after dosing.

Discussion
Our results show that after intravenous administration erythromycin and metronidazole are secreted in gastric juice. Despite adequate serum ampicillin concentrations it was not detected in the gastric juice. We are unaware of any other study that has shown active secretion of erythromycin or metronidazole in the human stomach. We were surprised not to find any ampicillin in the gastric juice because it is generally stable in the presence of gastric acid. Up to 55% of an oral dose of ampicillin is absorbed, indicating that it can pass intact through the stomach. It is therefore unlikely that ampicillin was broken down by gastric acid and that this was the reason it could not be detected by the bioassay. Ampicillin may not be secreted by or pass through the gastric mucosa because of certain pharmacokinetic properties, but this was not assessed in our study.

McNulty et al found inhibitory concentrations of activity against H pylori following an oral dose of amoxycillin 500 mg in endoscopic biopsy specimens from the gastric antrum, but it is unclear whether the tissue concentrations were achieved by local absorption from the gastric lumen or by active secretion through the gastric mucosa.

In one subject there was interference with the measurement of erythromycin concentrations caused by the presence of bile, which is a recognised problem. Although erythromycin and metronidazole were both secreted in the gastric juice, there were differences between the two compounds. Erythromycin showed more individual variation; the average peak concentration was reached later than metronidazole and gastric juice concentrations fell in the second hour of the study in contrast to metronidazole where concentrations tended to be maintained. Considerable variations in mucosal concentrations of erythromycin were also found in McNulty’s study, but metronidazole was not investigated.

Clinical experience has shown that ampicillin as a single agent can eradicate H pylori in about 25% of cases whereas metronidazole and erythromycin can not. McNulty et al have shown that the influence of pH on antimicrobial activity may have an important role: the MIC of ampicillin increased from 0.06 at pH 7.5 to 0.5 at pH 5.5. For erythromycin these values were 0.06 at pH 7.5 and 8.0 at pH 5.5. The values for metronidazole, which has weak in vitro inhibitory activity with an MIC of 0.5–1.0 and MIC4–8.0, did not show any change and remained stable at 2.0. Although the effects of further lowering the pH were not studied, as H pylori does not grow well at lower pH, it is certainly possible that the MIC may increase further at the more acid pH concentrations of 1.0–2.0 that were present in our study and are commonly found in the stomach.
Secretion of intravenously administered antibiotics in gastric juice in *H pylori* infection

explanations for the differences between in vitro and in vivo behaviour of antibiotic agents against *H pylori* are changes in structure of the compound by acid, poor mucus penetration, and differences in absorption or secretion in the stomach. 2

Our study was limited by examining only the effect of a single intravenous dose of each agent in healthy volunteers. It is possible that the topical effect or local absorption of these compounds is important for clinical efficacy. Our results would support a topical effect or absorption in the stomach as possible reasons for the clinical effect of ampicillin rather than secretion across the mucosa. Whether the presence of inflammation in patients with gastritis influences the secretion and absorption of antibiotics in the stomach is not known.

In conclusion, we have shown that in healthy volunteers the intravenous administration of metronidazole and erythromycin results in secretion of these compounds in high concentrations in gastric juice whereas for ampicillin this does not seem to be the case.

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doi: 10.1136/jcp.45.3.225

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