Effect of gastric bypass surgery on azithromycin oral bioavailability

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Objectives: Azithromycin is used widely for community-acquired infections. The timely administration of azithromycin in adequate doses minimizes treatment failure. Gastric bypass, a procedure that circumvents the upper gut, may compromise azithromycin plasma levels. We hypothesized that azithromycin concentrations would be reduced following gastric bypass.

Methods: A single-dose pharmacokinetic study in 14 female post-gastric bypass patients and 14 sex- and body mass index (BMI)-matched controls (mean age 44 years and BMI 36.4 kg/m2) was performed. Subjects were administered two 250 mg azithromycin tablets at time 0 and plasma azithromycin levels were sampled at 0.5, 1, 1.5, 2, 3, 5, 7 and 24 h. The AUC of the plasma azithromycin concentrations from time 0 to 24 h (AUC0–24) was the primary outcome.

Results: Azithromycin concentrations were lower in gastric bypass patients compared with controls throughout the entire duration of sampling. Compared with controls, the AUC0–24 was reduced in gastric bypass subjects by 32% [1.41 (SD 0.51) versus 2.07 (0.75) mg .h/L; P=0.008], and dose-normalized AUC0–24 was reduced by 33% [0.27 (0.12) versus 0.40 (0.13) kg .h/L; P=0.009]. Peak azithromycin concentrations were 0.260 (0.115) in bypass subjects versus 0.363 (0.200) mg/L in controls (P=0.08), and were reached at 2.14 (0.99) h in gastric bypass subjects and 2.36 (1.17) h in controls (P=0.75).

Conclusions: Azithromycin AUC was reduced by one-third in gastric bypass subjects compared with controls. The potential for early treatment failure exists, and dose modification and/or closer clinical monitoring of gastric bypass patients receiving azithromycin should be considered.

Keywords: obesity, bariatric surgery, drug absorption

Introduction

Azithromycin is a macrolide antibiotic commonly prescribed for community-acquired pneumonia (CAP) and other infections.1 Each year, CAP and influenza together account for over 4 million cases and 600 000 hospital admissions in the USA and comprise the sixth leading cause of death.2 Azithromycin monotherapy is currently recommended as a first-line outpatient treatment for milder CAP, and azithromycin in combination with a β-lactam drug is recommended for sicker CAP cases. As 50% of CAP is managed on an outpatient basis,3 many patients are not directly monitored in hospital. In addition, early antibiotic dosing is vital because mortality is lower when patients with CAP receive antimicrobials within 4–8 h of assessment.4 Thus, early (within 24 h) drug administration in adequate doses is essential to optimize therapeutic success.

Roux-en-Y gastric bypass surgery (RYGB), which is performed in 140 000 extremely obese patients annually, reduces gastric capacity by 95% and bypasses the proximal small intestine.5 RYGB causes nutrient malabsorption and potentially reduces drug absorption, but controlled trials are lacking.6 A higher likelihood of post-gastric-bypass absorptive compromise exists for drugs that are absorbed in the proximal gut and for drugs that are intrinsically poorly absorbed.6 Both of these properties apply to azithromycin, which has an oral bioavailability of only 37%.1 We sought to determine whether the single-dose 24 h plasma concentrations of azithromycin were altered in RYGB patients compared with controls, and thereby clarify whether an increased potential for treatment failure exists in post-RYGB patients treated with this agent.
Methods

Study population
We recruited 14 post-gastrectomy bypass patients and 14 sex- and body mass index (BMI)-matched (within 5 kg/m²) controls aged 18–60 years through local advertisements and from the Edmonton Weight Wise regional bariatric programme. The University of Alberta Research Ethics Board granted ethical approval. Informed consent was obtained from all subjects. Enrolment was limited to surgical patients ≥3 months post-op who had no history of major post-operative gastrointestinal complications (e.g. anastomotic leak, outlet obstruction). Patients currently receiving azithromycin or with contraindications to azithromycin treatment were excluded.

Endpoints
The primary endpoint was the AUC of the plasma azithromycin concentration from time 0 to 24 h (AUC₀₋₂₄). Secondary outcomes included the time to peak drug concentration (Tₘ₉₉₉) and the peak plasma drug concentration (Cₘ₉₉₉).

Pharmacokinetic and pharmacodynamic testing
Subjects were admitted to the unit on the morning of testing after fasting overnight and following documentation of a negative pregnancy test. Weight was measured to the nearest 0.1 kg using a calibrated scale with the subject wearing indoor clothing and no shoes. At time 0, subjects then ingested two 250 mg azithromycin tablets. Plasma azithromycin sampling was performed 0.5, 1, 1.5, 2, 3, 5, 7 and 24 h after azithromycin ingestion. Standardized meals (1000 calories in total, 60% carbohydrates) were administered 2 and 6 h post-drug-administration, and a standardized snack was administered 4 h post-drug-administration. The patients were discharged from the unit after 8 h, and they returned the following morning for 24 h blood sampling.

Sample processing and azithromycin assay
Immediately following collection, samples were centrifuged and stored at −70 °C. Azithromycin concentrations were determined by using liquid chromatography–mass spectrometry. An internal standard (imipramine) and liquid–liquid extraction based on 0.5 mL of human plasma was used, with separation performed on a C18 column. The assay was validated and liquid–liquid extraction based on 0.5 mL of human plasma was used, chromatography–mass spectrometry. An internal standard (imipramine) was used if between-group variances were unequal. Mann–Whitney U-tests were used if t-test assumptions were not satisfied. Fisher’s exact tests were used for binary variables. Two-tailed P values were considered significant below a threshold of 0.05.

Results

Baseline characteristics
Baseline characteristics are detailed in Table 1. Aside from lipid levels, which were significantly lower in the bypass group, other baseline variables and comorbidities did not differ between groups (Table 1).

Azithromycin pharmacokinetics
Azithromycin mean concentrations were lower in gastric bypass patients compared with controls throughout the entire duration of sampling (Figure 1). In 11 of 14 comparisons, bypass subjects had lower azithromycin concentrations than control subjects.

Compared with controls, AUC₀₋₂₄ was reduced in gastric bypass subjects by 32% [1.41 (SD 0.51) versus 2.07 (0.75) mg·h/L; P=0.008]. Dose-normalized AUC₀₋₂₄ was likewise reduced by 33% [0.27 (0.12) versus 0.40 (0.13) kg·h/L; P=0.009]. Azithromycin Cₘ₉₉₉ values were non-significantly lower (28%) in bypass subjects compared with controls [0.260 (0.115) versus 0.363 (0.200) mg/L, P=0.08], and were reached at 2.14 (0.99) h for bypass subjects and 2.36 (1.17) h for controls (P=0.75).

Discussion
In summary, 24 h azithromycin plasma AUC in gastric bypass subjects were reduced by 32% compared with matched controls. To our knowledge, this is the first controlled study that has examined antibiotic levels post-gastric-bypass.

Azithromycin works intracellularly by inhibiting protein synthesis and has a low bioavailability, a large volume of distribution and long terminal phase half-life.1 Typical azithromycin pharmacokinetic parameters in plasma following a daily oral dose of 500 mg are: Cₘ₉₉₉ 0.40–0.45 mg/L, Tₘ₉₉₉ 2.5–2.6 h, half-life up to 57 h and AUC₀₋₂₄ 3.39 mg·h/L.7 These properties enable once-daily dosing and shorter durations of treatment relative to other antibiotics (e.g. 3–5 rather than 7–10 day treatment courses for pneumonia).1 Azithromycin is primarily eliminated unchanged faecally and has a large volume of distribution (23–31 L/kg), reflecting extensive uptake into cells and tissues.7 Thus, cell and tissue concentrations are often much higher than plasma levels, especially in phagocytes and in lung, tonsillar, urological and gynaecological tissues.1

Given that our subjects were matched for BMI, it seems unlikely that they differed in their plasma or tissue unbound fractions of azithromycin; consequently, lower plasma concentrations in the surgical patients would imply corresponding decreases in tissue concentrations. Whether this would have any impact on clinical efficacy is dependent on numerous factors including pathogen and site of infection. Even with a reduced oral bioavailability, tissue levels adequate for successfully clearing infection might be achieved. For Streptococcus pneumoniae, the commonest cause of CAP, the azithromycin MIC is ≤2 mg/L. The peak tissue concentrations achieved after ingestion of a 500 mg azithromycin dose range between
2–10 mg/L; therefore, tissue drug concentrations appear adequate for antibacterial activity. However, higher MIC levels (up to 16–32 mg/L) may be required if antibiotic resistance is present. Pneumococcal resistance to azithromycin is now highly prevalent in the USA (found in 35% of isolates). Resistance often results from the presence of efflux pumps in the bacterial membrane that limit intracellular entry, and this problem may theoretically be overcome by higher drug doses. Therefore, the possibility of treatment failure, especially with more resistant bacterial strains, and the importance of higher drug levels cannot be dismissed. In addition, azithromycin antibacterial action is optimal when plasma concentrations are maximized above MIC thresholds (high AUC/MIC ratio); plasma concentrations, AUC/MIC ratios, and lung tissue levels all increase in proportion to the initial dose. The lower single-dose 24 h trough concentrations in bypass patients (Figure 1) are predictive of reduced steady-state concentrations with repeat doses. Additional studies examining rates of treatment failure in gastric bypass patients requiring azithromycin are required to address the clinical relevance of our findings.

The prevalence of azithromycin use in RYGB patients for CAP or other indications is unknown. Furthermore, due to the 24 h sampling period, which is short relative to the half-life of azithromycin (72–96 h), we could not accurately measure the terminal phase half-life or calculate oral clearance. We were primarily interested in assessing 24 h azithromycin concentrations, because early and adequate antibiotic dosing is crucial to avoid treatment failure.

Gastric bypass circumvents the upper gut, which is the site of maximal absorption for azithromycin. This is the most plausible explanation for reduced azithromycin bioavailability post-bypass, rather than an increase in drug clearance. Azithromycin is, however, also a known target for multiple membrane transporters and little is known about the expression of these transporters following gastric bypass. It is possible that this procedure may alter drug pharmacokinetics by altering transporter expression.

In conclusion, azithromycin concentrations were substantially reduced in gastric bypass subjects compared with controls. Although the clinical relevance is currently uncertain, dose modification and/or closer clinical monitoring for treatment failure

### Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Bypass, N=14</th>
<th>Controls, N=14</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>44.1 (7.7)</td>
<td>44.5 (14.3)</td>
<td>0.93</td>
</tr>
<tr>
<td>Gender, female/male</td>
<td>14/0</td>
<td>14/0</td>
<td>—</td>
</tr>
<tr>
<td>BMI (kg/m²), mean (SD)</td>
<td>36.8 (6.2)</td>
<td>35.9 (6.3)</td>
<td>0.98</td>
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<td>Weight (kg), mean (SD)</td>
<td>95.5 (18.9)</td>
<td>99.0 (16.9)</td>
<td>0.70</td>
</tr>
<tr>
<td>Preoperative weight (kg), mean (SD)</td>
<td>135.1 (26.1)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Months post-bypass, mean (SD)</td>
<td>24.6 (13.3)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Roux limb length (cm), mean (SD)</td>
<td>102.5 (7.5)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Creatinine (mmol/L), mean (SD)</td>
<td>62.3 (7.3)</td>
<td>65.3 (8.8)</td>
<td>0.51</td>
</tr>
<tr>
<td>ALT (U/L), mean (SD)</td>
<td>22.3 (9.7)</td>
<td>24.9 (7.7)</td>
<td>0.41</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L), mean (SD)</td>
<td>3.7 (0.4)</td>
<td>4.7 (1.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Triglyceride (mmol/L), mean (SD)</td>
<td>0.9 (0.3)</td>
<td>1.4 (0.7)</td>
<td>0.008</td>
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<tr>
<td>HDL cholesterol (mmol/L), mean (SD)</td>
<td>1.4 (0.3)</td>
<td>1.2 (0.2)</td>
<td>0.25</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L), mean (SD)</td>
<td>1.9 (0.4)</td>
<td>2.8 (1.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>5 (36)</td>
<td>2 (14)</td>
<td>0.40</td>
</tr>
<tr>
<td>Type 2 diabetes, n (%)</td>
<td>1 (7)</td>
<td>3 (21)</td>
<td>0.60</td>
</tr>
<tr>
<td>Dyslipidaemia, n (%)</td>
<td>0 (0)</td>
<td>5 (36)</td>
<td>0.04</td>
</tr>
<tr>
<td>Depression, n (%)</td>
<td>5 (36)</td>
<td>6 (43)</td>
<td>1.0</td>
</tr>
<tr>
<td>Sleep apnoea, n (%)</td>
<td>3 (21)</td>
<td>2 (14)</td>
<td>1.0</td>
</tr>
<tr>
<td>Gastrintestinal reflux, n (%)</td>
<td>1 (7)</td>
<td>3 (21)</td>
<td>0.60</td>
</tr>
</tbody>
</table>

HDL, high-density lipoprotein; LDL, low-density lipoprotein; ALT, alanine aminotransferase. Subjects were sex-matched.

**Figure 1.** Mean (SEM) plasma azithromycin concentration versus time profiles. *Significant differences between bariatric surgery and control obese subjects. Student’s unpaired t-test (α=0.05).
may be required. Further study is required to verify these findings and delineate mechanisms for the reduced plasma AUC after RYGB.

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**Transparency declarations**
None to declare.

**References**