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Does sex matter? The influence of gender on gastrointestinal physiology and drug delivery.

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Abstract

We all respond differently to drugs. Personalised medicine aims to improve efficacy and reduce side effects, and efforts are being made to understand the physiological differences that underlie responses to drugs. Genetics, diet and disease state can be key; however, gender also plays an important role in pharmacokinetics, pharmacodynamics and drug toxicity. Differences in metabolism and clearance of drugs as a consequence of distinct hepatic and renal processes in males and females are now much better understood but little is known about gender differences in the gastrointestinal tract. As the recipient of all orally administered medications, differences at this level can have a major impact on drug delivery and bioavailability; yet these continue to be ignored and insufficiently studied in the context of drug disposition. The aim of this review is to highlight the known gender differences in gut physiology. Clinical case studies are presented, where possible, to illustrate the influence of these differences on drug disposition and gaps in current knowledge are highlighted to encourage further research in this area.

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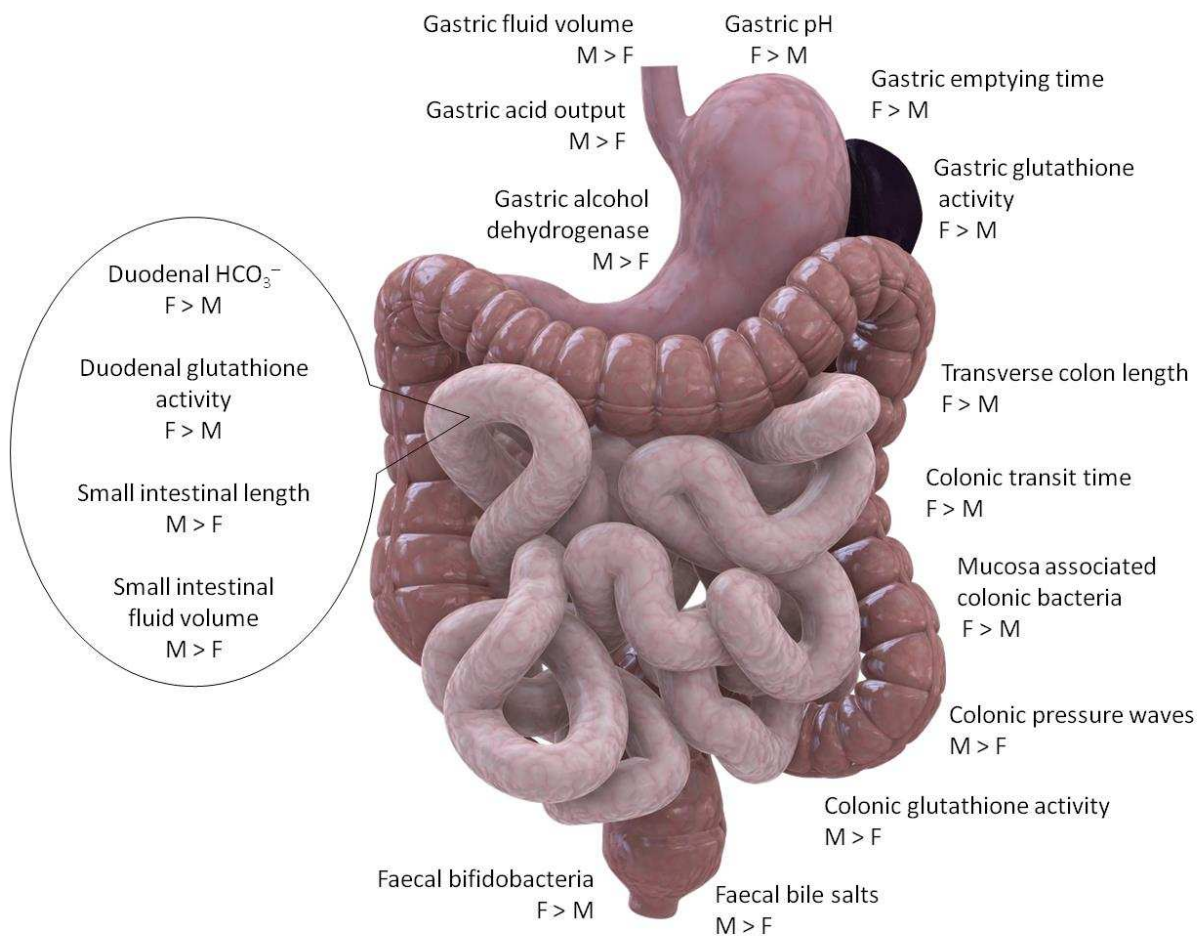Telephone: +44 207 753 5865   +44 1484 472387

Fax: +44 207 753 5865   +44 1484 472182

FIGURES

Gastric fluid volume
M > F

Gastric pH
F > M

Gastric emptying time
F > M

Gastric acid output
M > F

Gastric glutathione activity
F > M

Gastric alcohol dehydrogenase
M > F

Duodenal HCO$_3^-$
F > M

Duodenal glutathione activity
F > M

Small intestinal length
M > F

Small intestinal fluid volume
M > F

Transverse colon length
F > M

Colonic transit time
F > M

Mucosa associated colonic bacteria
F > M

Colonic pressure waves
M > F

Colonic glutathione activity
M > F

Faecal bifidobacteria
F > M

Faecal bile salts
M > F

Figure 1. Key gender differences at the level of gastrointestinal tract affecting oral drug delivery and bioavailability, refer to Table 1 for details.
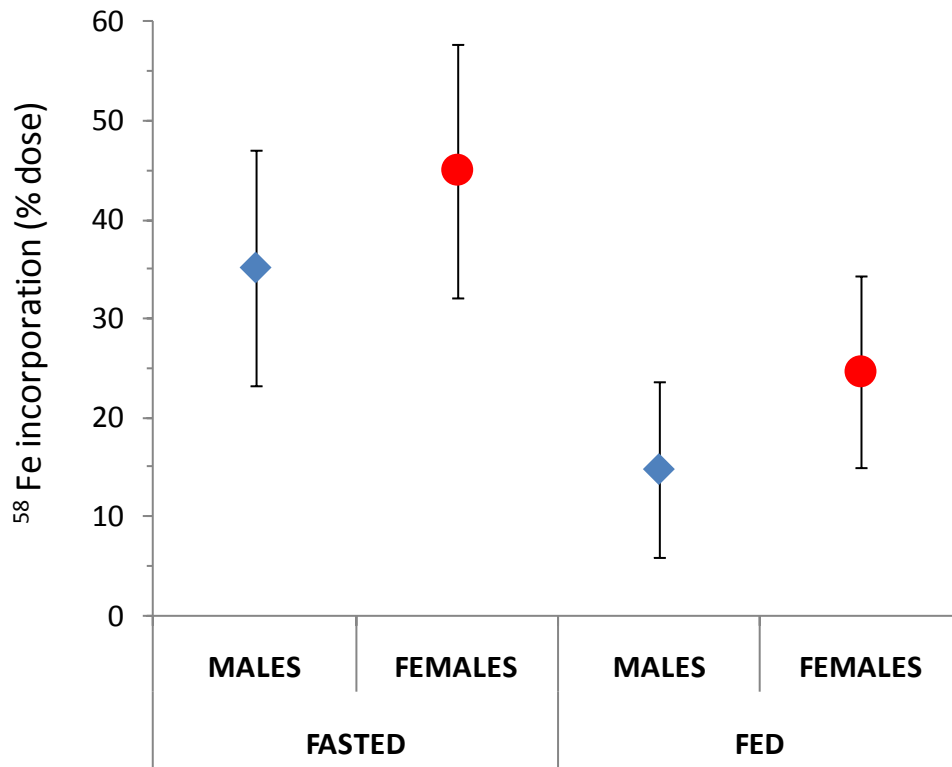
Figure 2. Gender differences in iron absorption (^{58}Fe erythrocyte incorporation) in preadolescent subjects (n=15 each) presented as geometric mean $\pm$ SD of the group. Figure drawn using data from Woodhead et al., 1991.
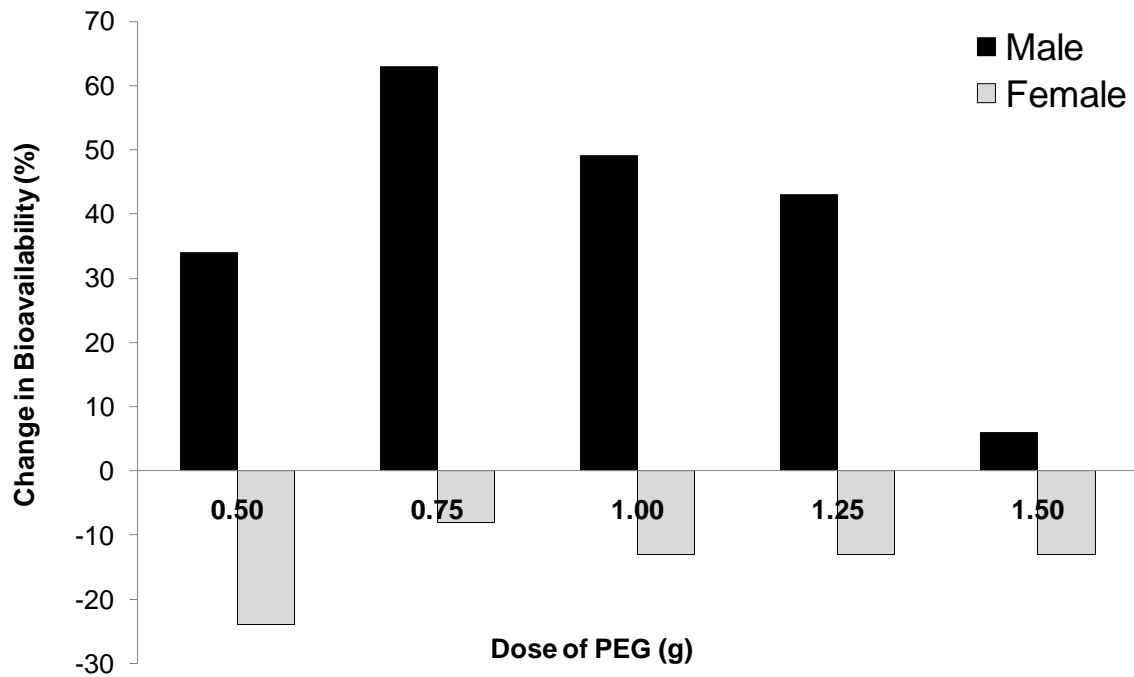

Figure 3. Percentage change in ranitidine bioavailability (excreted in urine over 24 h) in male and female volunteers (n=6 each). Figure drawn using data from Ashiru et al., 2008.
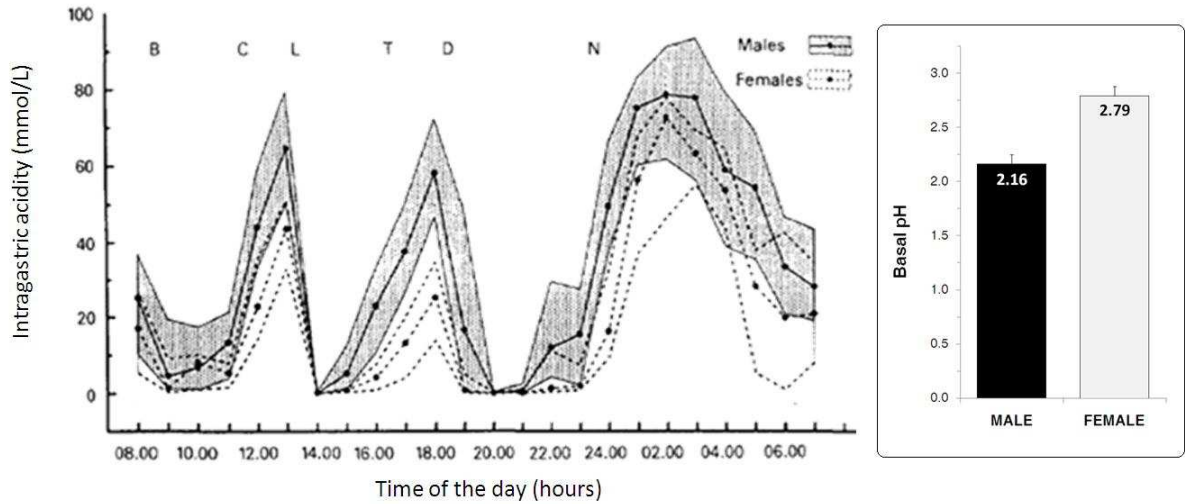
Figure 4. Median hourly intragastric acidity in 35 healthy females and 36 healthy male subjects. In the figure, **B**- Breakfast, **C**-coffee, **L**-lunch, **T**-tea, **D**-dinner, **N**-nightcap. Reproduced from Prewett *et al.,* 1991. Bar chart on the right represents Mean ($\pm$ SE) basal pH in healthy subjects (252 men, 113 women). Figure drawn using data from Feldman and Barnett 1991.
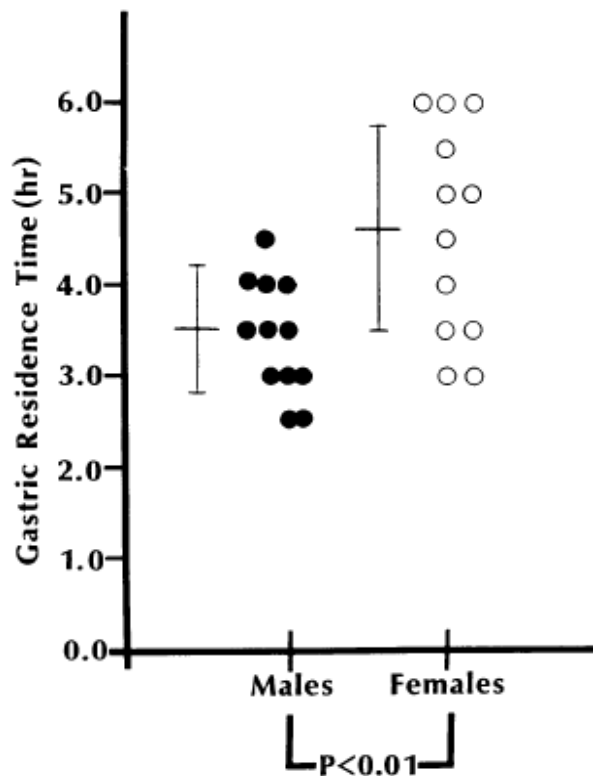

Figure 5. Individual and mean ($\pm$SD) gastric residence time of Heidelberg capsule of 12 healthy male and 12 aged and race-matched female counterparts. Figure reproduced from Mojaverian *et al.,* 1988.
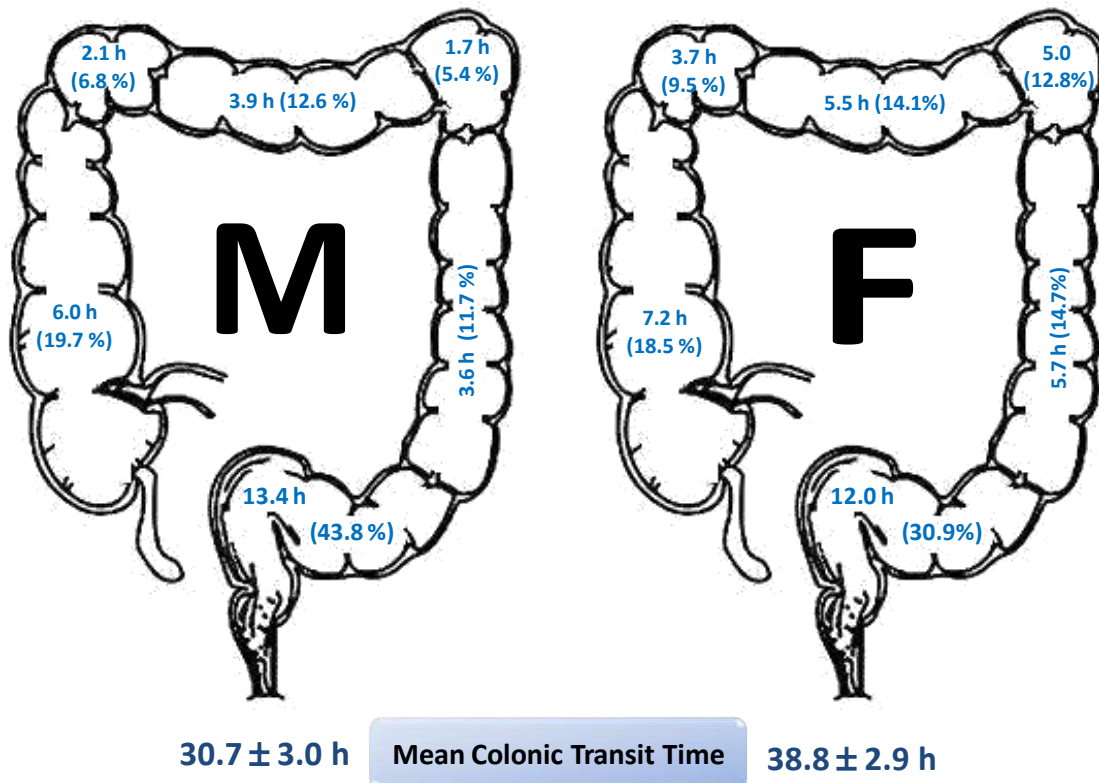
Figure 6. Proportion of total colonic transit time spent in different segments of the colon in 73 normal subjects (M = Male, F = Female). Figure redrawn from Metcalf *et al.,* 1987.
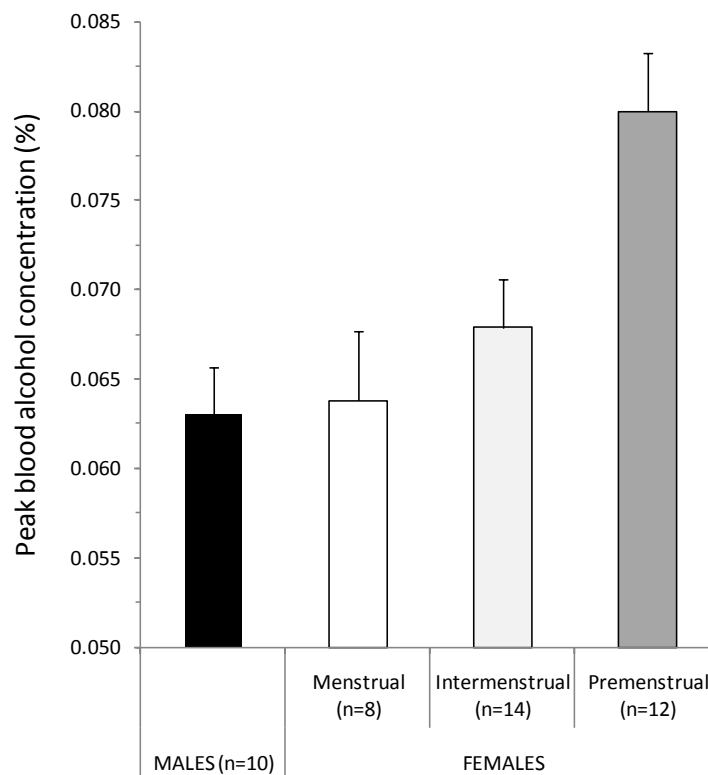

Figure 7. Mean (±SE) peak blood alcohol levels for males and females tested at different times in the menstrual cycle. Figure redrawn from Jones and Jones 1976.
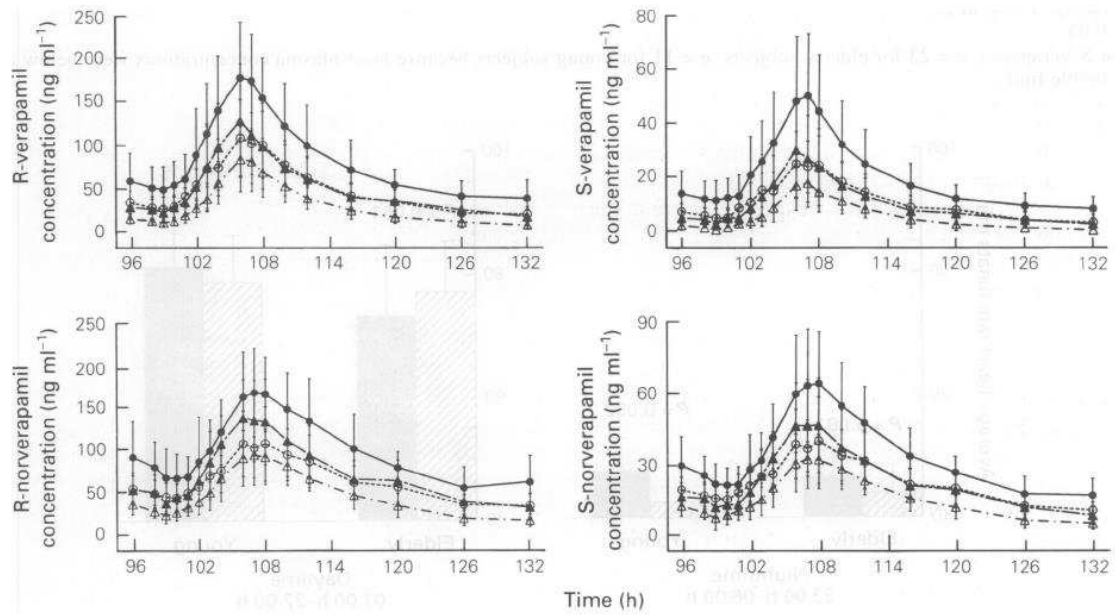
Figure 8. Mean plasma R-verapamil, S-verapamil, R-norverapamil, S-norverapamil concentration-time profiles at steady state in young and elderly subjects (men and women) following osmotically-controlled extended release verapamil (180 mg) formulation.
△ young male, ○ elderly male, ▲ young female, ● elderly female.
Figure reproduced from Gupta et al 1995.
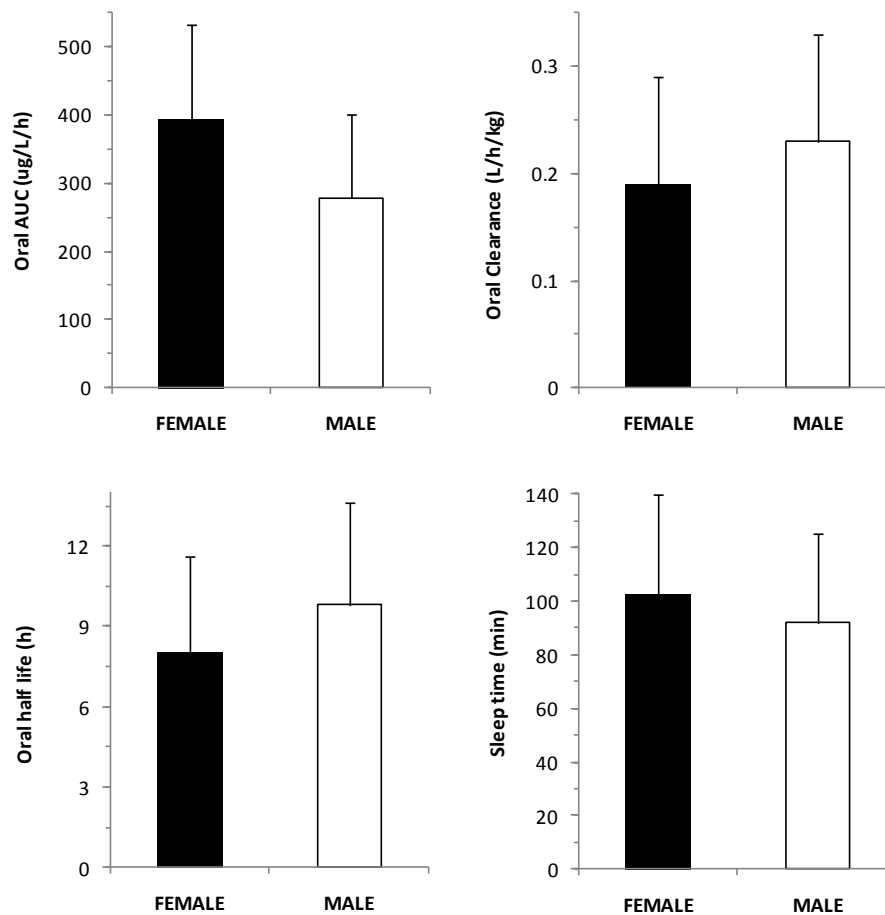
Figure 9. Midazolam pharmacokinetics parameters (mean ± SD) after oral administration in male and female healthy volunteers (n=8 each) after clarithromycin administration (500 mg twice a day for 7 days). Figure drawn using data from Gorski et al 1998.

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