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Review

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.

Contents

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1. Introduction

It is often said that "men are from Mars and women are from Venus". This may be tongue-in-cheek, but it is true that there are significant physiological differences between men and women and these can be implicated in a differing response to medication. There are many reports of gender differences in therapeutic outcomes in the clinic; of sixty-seven new molecular entities approved by the FDA during 2000–2002, twenty-five were found to have sex differences in pharmacokinetics, efficacy or adverse events (Yang et al., 2008) and it has been established that women are at a greater risk (50–70% higher) of experiencing drug related side effects than men (Rademaker, 2001).

The variability in pharmacokinetic and pharmacodynamics is the result of a complex interplay between many factors (genetics, disease state, dietary habits, physicochemical properties of the drug and formulation characteristics) (Jamei et al., 2009) but sex is also a relevant marker of inter-individual variability. This is being increasingly recognised and in 1993, the FDA overturned a previous regulation, which excluded women from early stage studies, and issued new guidelines in favour of equal representation of males and females in clinical trials. Progress in achieving this has, however, been very slow (Jagsi et al., 2009). In particular, there may still be ethical and safety concerns to include women of child-bearing age in trials. Women continue to be under-represented in clinical research of some drug classes and sex-based analysis of clinical data is still lacking. In 2001, the Institute of Medicine stressed that "Barriers to the advancement of knowledge about sex differences in health and illness exist and must be eliminated" (Wizemann and Pardue, 2001). The under-representation of women in clinical trials means that women may not be getting fair access to experimental medication and that less is known about efficacy and safety in women. Gender differences are particularly evident in cardiovascular pharmacology (Oertelt-Prigione and Regitz-Zagrosek, 2009), pain management (Fillingim et al., 2009), pharmacokinetics and safety of antidepressants (Bigos et al., 2009), and H1 antihistamines (Nicolas et al., 2009). One of the most cited examples of a sex-specific adverse drug reaction is the drug-induced form of the anti-arrhythmic syndrome, Torsade de Pointes. This syndrome is characterised by an extended QT interval on the echocardiogram, which can result in syncope, cardiac arrest or sudden death. The risk of developing this syndrome is considerably higher in females, with almost 70% of all cases occurring in this gender (Makkar et al., 1993). This sex-specific adverse reaction has resulted in the withdrawal of a few drugs from the market, such as terfenadine, astemizole and cisapride (Heinrich, 2001). Interestingly, the QT interval is particularly lengthened during the first half of the menstrual cycle (Rodriguez et al., 2001) hinting at a role of hormones in pharmacokinetics and pharmacodynamics. There are efficacy issues to address as well. The anti-cancer drug erlotinib (Tarceva) has been found to work better in women than in men (Faehling et al., 2010), and the converse may be true for some medications. For example, when ciclosporine A (Neoimmun) was taken after a fat-rich breakfast, the peak drug concentration (C_{max}) was increased in males but not in females, an observation which was not evident under fasting conditions (Kees et al., 2007).

The effects of gender variation in drug response are clear, but what are the reasons? We need to consider the processes occurring in drug administration: absorption, distribution, metabolism and elimination. Considering first distribution: apart from body weight, there are many other prominent biological differences between women and men, which can influence the clinical response to drugs. Women have a higher percentage of body fat, lower average plasma volume, increased organ blood flow, and an altered drug/plasma protein binding profile (Nicolson et al., 2010). Plasma volume and organ flow also vary during the menstrual cycle and pregnancy (Spaanderman et al., 2000). Next, metabolism: for hepatic processes, drugs metabolized by phase I, phase II (conjugative) and by combined oxidative and conjugation processes are usually cleared faster in men compared to women (Schwartz, 2003, 2007). Elimination: renal clearance (glomerular filtration, tubular reabsorption, and secretion) is lower in women than in men at all ages (Schwartz, 2003). Finally, absorption: this is governed by processes occurring in the gastrointestinal tract which, despite being the omnipresent factor when considering oral drug delivery, has been largely neglected in the context of gender.

There are some known gender based differences in gastrointestinal physiology. Table 1 and Fig. 1 illustrate the current knowledge, and lack thereof, of gender differences in the gastrointestinal tract. What is striking about Table 1, are the many instances where no information is available on gender differences. Understanding drug and dosage form behaviour has been shown to be subject to much more than gross physiological differences and is highly dependent on many critical aspects of the intestinal environment (McConnell et al., 2008). A more in-depth understanding of the gut environment in both sexes and its implications for therapeutic responses is clearly needed. The implications of the role of the gut environment are illustrated by differences in absorption of some molecules. It has been reported that absorption of copper is higher in females than in males aged 20–59 years (Johnson et al., 1992). Another study reported similar findings for iron, with a greater extent of absorption in preadolescent females than in males (Fig. 2), which explains the higher prevalence of iron-deficiency anaemia in males than in females during 11–15 years of age (Woodhead et al., 1991). A final introductory example of absorption differences was observed with ranitidine. While the pharmacokinetics and pharmacodymamics of ranitidine are similar between men and women, an unexpected gender difference was reported in the pharmacokinetics of ranitidine in the presence of the "inert" pharmaceutical excipient polyethylene glycol 400 (Ashiru et al., 2008), with bioavailability increased by up to 63% in males but no increase was observed in females (Fig. 3). This has been partially attributed to the role of polyethylene glycol 400 on absorption and efflux mechanisms in the gut wall, highlighting the complexity of these gender issues.

This review aims to highlight the current knowledge around gender differences in the gastrointestinal tract and the interplay with the drug molecule and the engineered formulations, which can influence therapeutic efficacy and clinical response. In the sections below, we have attempted to present gender based gastrointestinal features in relation to clinical therapeutics; the gaps in current knowledge are also highlighted to encourage further research in this direction.

2. Gender and the gastrointestinal lumen

Several important pre-absorption processes (e.g. disintegration, dispersion and dissolution) occur when a dosage form comes into contact with the luminal environment of the gastrointestinal tract. The composition of the gastrointestinal luminal fluids is dynamic and complex, encompassing food remains, secretory enzymes, bile salts and several electrolytes in an aqueous environment. The fate of the drug in the gastrointestinal tract depends on its interaction with these components but also on the pH and volume of fluids available in the gut.

2.1. Luminal pH

pH is implicated in drug dissolution (and hence absorption) and dosage form behaviour, in particular for modified release systems e.g. enteric coatings (Ibekwe et al., 2008). In a study involving 113

Table 1
Anatomical and physiological features of the human gastrointestinal tract in males (M) and the females (F), values represent mean ± SD or SEM.

GI characteristics		Stomach	Small intestine			Large intestine		
			Duodenum	Jejunum	Ileum	Ascending colon	Transverse colon	Descending colon
Length (cm)	M	–	27.8 ± 6.8[(PM),[1], n = 100]	643.9 ± 110.8[(PM),[1],n = 100,a]		23 (15–38)[2],n = 100	40 (20–67)[2],n = 100	25 (8–36)[2],n = 100
	F	–	25.2 ± 5.4[(PM),[1],n = 100]	573.8 ± 97.1[(PM),[1],n = 100,a]		23 (11–41)[2],n = 104	48 (19–38)[2],n = 104	23 (11–43)[2],n = 104
pH	M	2.16 ± 0.09[3],n = 252	6.75 ± 0.63[4],n = 2	7.2 ± 0.56[5],n = 22	–	–	–	7.18 ± 0.08[6],n = 11,b
	F	2.79 ± 0.18[3],n = 113	7.16 ± 0.29[4],n = 5	7.1 ± 0.68[5],n = 15	–	–	–	6.51 ± 0.07[6],n = 15,b
Basal acid output (mmol/h)	M	4.0 ± 0.2[3],n = 252	–	–	–	–	–	–
	F	2.1 ± 0.2[3],n = 113	–	–	–	–	–	–
Bicarbonate secretion, basal (μmol/cm h)								
20–29 years	M	–	120.7 ± 16.2[7],n = 9	–	–	–	–	–
	F	–	189.5 ± 23.5[7],n = 9	–	–	–	–	–
60–69 years	M	–	109.8 ± 16.2[7],n = 9	–	–	–	–	–
	F	–	123.1 ± 17.8[7],n = 9	–	–	–	–	–
Motility (contractions/min or waves/h)	M	3.06 ± 0.06[8],n = 12,c	4.4 ± 0.2[9],n = 17,c	3.7 ± 0.2[9],n = 17,c	–	–	141.5 ± 21.4[10],n = 13,d	
	F	3.07 ± 0.04[8],n = 20,c	4.5 ± 0.3[9],n = 13,c	4.5 ± 0.4[9],n = 13,c	–	–	103.4 ± 24.0[10],n = 12,d	
Transit time (min/h)								
Solids	M	59.8 ± 3.7 min[11],n = 15,e	181 ± 19 min[12],n = 20,~,f			8.9 ± 1.1 h[13],n = 34,g	8.7 ± 1.5 h[13],n = 34,g	13.0 ± 1.7 h[13],n = 34,g
	F	92.4 ± 7.5 min[11],n = 15,e	196 ± 22 min[12],n = 12,~,f			13.3 ± 1.6 h[13],n = 39,g	13.7 ± 2.1 h[13],n = 39,g	11.8 ± 1.6 h[13],n = 39,g
Liquid	M	30.3 ± 2.3 min[11],n = 15,e	–	–	–	–	–	–
	F	53.8 ± 4.9 min[11],n = 15,e	–	–	–	–	–	–
Fluid volume								
mL/kg	M	2.3 ± 1.5[14],n = 8,(PM)	4.2 ± 1.6[14],n = 8,(PM),–			1.3 ± 2.1[14],n = 8,(PM)	–	–
	F	1.4 ± 1.4[14],n = 5,(PM)	2.2 ± 1.3[14],n = 5,(PM),–			1.4 ± 1.3[14],n = 5,(PM)	–	–
mL	M	135 ± 79[14],n = 8,(PM)	259 ± 105[14],n = 8,(PM),–			84 ± 144[14],n = 8,(PM)	–	–
	F	90 ± 89[14],n = 5,(PM)	138 ± 75[14],n = 5,(PM),–			83 ± 69[14],n = 5,(PM)	–	–
Bile salts								
Total (mM)	M	0.2 ± 0.41[5],n = 19	–	2.6 ± 2.25[5],n = 22	–	–	–	21.69 ± 2.39[15],n = 18,b
	F	0.3 ± 0.62[5],n = 17	–	3.2 ± 3.79[5],n = 15	–	–	–	17.58 ± 2.63[15],n = 16,b
Cholic acid (μM)	M	–	7.6 ± 1.1[4],n = 2	9.8 ± 6.2 [4],n = 2	–	–	–	0.20 ± 0.15[15],n = 18,b
	F	–	8.2 ± 1.5[4],n = 5	15.3 ± 16.6[4],n = 4	–	–	–	0.15 ± 0.08[15],n = 16,b
Lithocholic acid (μM)	M	–	–	–	–	–	–	10.09 ± 1.15[15],n = 18,b
	F	–	–	–	–	–	–	7.66 ± 1.13[15],n = 16,b
Deoxycholic acid (μM)	M	–	2.9 ± 1.4[4],n = 2	2.4 ± 1.8[4],n = 2	–	–	–	9.47 ± 1.21[15],n = 18,b
	F	–	5.2 ± 3.0[4],n = 5	3.0 ± 1.7[4],n = 4	–	–	–	7.56 ± 1.48[15],n = 16,b
Chenodeoxycholic acid (μM)	M	–	4.3 ± 3.5[4],n = 2	4.6 ± 4.9[4],n = 2	–	–	–	0.87 ± 0.16[15],n = 18,b
	F	–	3.3 ± 0.4[4],n = 5	3.3 ± 2.9[4],n = 5	–	–	–	0.81 ± 0.15[15],n = 16,b

Table 1 (*Continued*)

GI characteristics		Stomach	Small intestine			Large intestine		
			Duodenum	Jejunum	Ileum	Ascending colon	Transverse colon	Descending colon
Microbiota								
Total count (cfu mg^{-1})	M	–	–	–	–	$4.1 \times 10^5 \pm 3.3 \times 10^{5[16],n=2,h}$	$3.8 \times 10^5 \pm 3.7 \times 10^{5[16],n=2,h}$	$7.5 \times 10^5 \pm 7.8 \times 10^{5[16],n=2,h}$
	F	–	–	–	–	$4.0 \times 10^5 \pm 2.6 \times 10^{5[16],n=4,h}$	$24 \times 10^5 \pm 29 \times 10^{5[16],n=5,h}$	$9.4 \times 10^5 \pm 9.8 \times 10^{5[16],n=5,h}$
Bifidobacteria ($\log_{10} g^{-1}$)	M	–	–	–	–	–	–	$8.6 \pm 1.1^{[17],n=14,b}$
	F	–	–	–	–	–	–	$9.2 \pm 0.7^{[17],n=33,b}$
Clostridium coccoides (relative abundance)	M	–	–	–	–	–	–	$0.479 \pm 0.0182^{[18],n=50,b}$
	F	–	–	–	–	–	–	$0.453 \pm 0.0176^{[18],n=50,b}$
Bacteroides spp. (relative abundance)	M	–	–	–	–	–	–	$0.282 \pm 0.0179^{[18],n=50,b}$
	F	–	–	–	–	–	–	$0.327 \pm 0.0180^{[18],n=50,b}$
Clostridium leptum spp. (relative abundance)	M	–	–	–	–	–	–	$0.239 \pm 0.0178^{[18],n=50,b}$
	F	–	–	–	–	–	–	$0.243 \pm 0.0163^{[18],n=50,b}$
Mucosal enzymes								
Gluthathione (GST) (nmoles mg^{-1} protein)	M	$21.2 \pm 0.8^{[19],n=104,i}$	$34.2 \pm 1.4^{[19],n=104,i}$	–	–	–	$32 \pm 8^{[20],n=102,j}$	$30 \pm 10^{[20],n=102,j}$
	F	$24.8 \pm 1.0^{[19],n=98,i}$	$36.2 \pm 1.2^{[19],n=98,i}$	–	–	–	$33 \pm 8^{[20],n=106,j}$	$31 \pm 10^{[20],n=106,j}$
GST enzyme activity (mmoles min^{-1} mg^{-1} protein)	M	$576 \pm 21^{[19],n=104,i}$	$813 \pm 30^{[19],n=104,i}$	–	–	–	$261 \pm 59^{[20],n=31,j}$	$253 \pm 81^{[20],n=31,j}$
	F	$679 \pm 32^{[19],n=98,i}$	$851 \pm 33^{[19],n=98,i}$	–	–	–	$228 \pm 84^{[20],n=19,j}$	$203 \pm 62^{[20],n=19,j}$
Alcohol dehydrogenase (mmoles min^{-1} mg^{-1} protein)[k]	M	$0.046 \pm 0.005^{[21],n=11}$	–	–	–	–	–	–
	F	$0.025 \pm 0.003^{[21],n=17}$	–	–	–	–	–	–

–Indicates gender-based information not found.
~Indicates that the value represents the whole small intestine.
(PM)Indicates measurement performed *post-mortem*.
[1]Hounnou et al. (2002); [2]Saunders et al. (1996); [3]Feldman and Barnett (1991); [4]De la Cruz Moreno et al. (2006); [5]Lindhal et al. (1997); [6]Stephen et al. (1986); [7]Tuo et al. (2008); [8]Bennink et al. (1998); [9]Soffer et al. (1998); [10]Rao et al. (2001); [11]Datz et al. (1987); [12]Degen and Phillips (1996); [13]Metcalf et al. (1987); [14]Gotch et al. (1957); [15]Lampe et al. (1993); [16]Zoetendal et al. (2002); [17]Whelan et al. (2009); [18]Li et al. (2009); [19]Hoensch et al. (2002); [20]Hoensch et al. (2006); [21]Frezza et al. (1990).

[a] Indicates jejunum + ileum.
[b] Measured in faeces.
[c] Contractions per minute under *fed* (stomach) and *fasting* (small intestine).
[d] Number of pressure waves per hour in transverse + descending colon.
[e] Half emptying time (min).
[f] Small intestinal transit of radiolabelled food.
[g] Transit measured using three types of radiopaque markers (2×6, 6×6 and 1×6 mm).
[h] Mucosa-associated bacteria analysed from colonic biopsy samples.
[i] Represents data from 202 individuals, 16–92 years age (mean 62 years).
[j] Values represents individuals <50 years.
[k] The data represents subjects with 22–53 years of age from Frezza et al. (1990). Refer Fig. 7 for enzyme activity in young, middle, and old aged males and females (Parlesak et al., 2002).

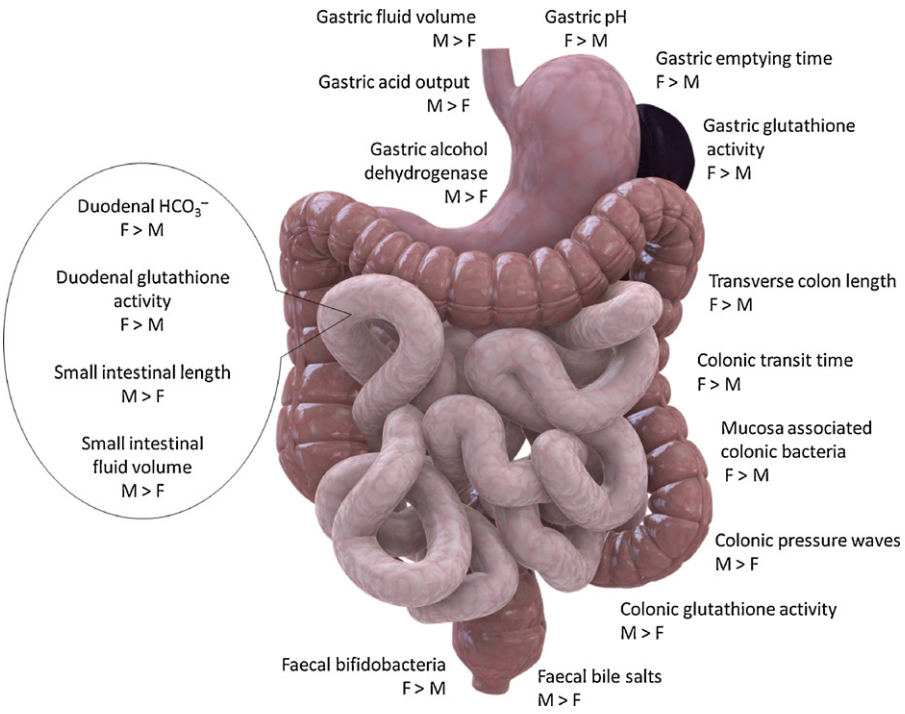

Fig. 1. Key gender differences at the level of gastrointestinal tract affecting oral drug delivery and bioavailability (M = Male, F = Female), refer to Table 1 for details.

women and 252 men, fasting gastric pH was higher in women than in men (2.79 ± 0.18 and 2.16 ± 0.09, respectively) (Feldman and Barnett, 1991) and this has been linked to reduced acid secretion in women (Dotevall, 1961; Feldman and Barnett, 1991; Goldschmiedt et al., 1991; Prewett et al., 1991). The basal acid output, in the fasted state, was almost twice as high in men than in women (4.0 ± 0.2 and 2.1 ± 0.2 mmol/h, respectively (Feldman and Barnett, 1991). In response to a meal, the secretion of acid is also significantly higher in men than in women (Fig. 4) (Prewett et al., 1991). Surprisingly the basal serum gastrin concentration and meal-stimulated serum gastrin is significantly higher in women than in men (Feldman et al., 1983). The reasons for this gender-difference in acid secretion have not yet been fully clarified however many theories have been put forward, including stomach size and hormones. *Post-mortem* measurements of the mucosal surface area of the stomach from 222 individuals revealed that women have smaller size stomachs than men (783 vs. 850 cm^2). This difference could not be correlated to age or body size (Cox, 1952). The fundus region of the gastric compartment in women, which contains most of the secretory cells, was smaller in size in relation to the antrum. This has led to the assumption that women have decreased parietal cell mass. Another study suggested an influence of female sex hormones on acid secretion and reported minimum acid secretion levels during ovulation (Macdonald, 1956). However, studies conducted in pregnant women produced confounding results and failed to find any correlation between the circulating levels of these hormones and the secretion of acid in the stomach (Chang, 2004). Lastly, there is some evidence that the sensitivity of the parietal cells to gastrin is decreased in women when compared with men (Feldman et al., 1983).

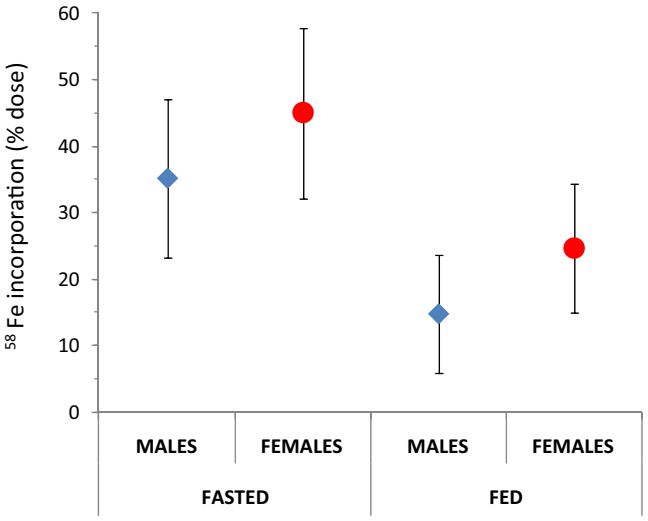

Fig. 2. Gender differences in iron absorption (^{58}Fe erythrocyte incorporation) in preadolescent subjects (n = 15 each) presented as geometric mean ± SD of the group. Figure drawn using data from Woodhead et al. (1991).

A recent investigation into the basal secretion of mucosal bicarbonate in the duodenum revealed that in pre-menopausal women (but not in post-menopausal) the secretion of bicarbonate is significantly higher than in age-matched men (189.5 ± 23.5 vs. 120.7 ± 16.2 μmol/cm h, respectively) (Tuo et al., 2008). The secretion of bicarbonate was increased following luminal perfusion of 17-β-estradiol, in both pre- and post-menopausal subjects, leading to the conclusion that female sex hormones may play a role in regulating the secretion of bicarbonate. Two studies performed in a small number of subjects, found no gender variations in the pH of the duodenum and jejunum by gender (Lindhal et al., 1997; De la Cruz Moreno et al., 2006) (Table 1). However, the prevalence of duodenal ulcers is reported to be higher in males than in females, which may be due to the lower bicarbonate secretion in the duodenum and higher acidity of the stomach contents in men (Johnsen et al., 1992; Pratha, 2004).

Little emphasis has been placed on investigating gender differences in the pH of the colon and although this is often measured in male and female subjects, pH values are rarely separated by gender. Colonic mucosal pH has previously been shown not to vary by

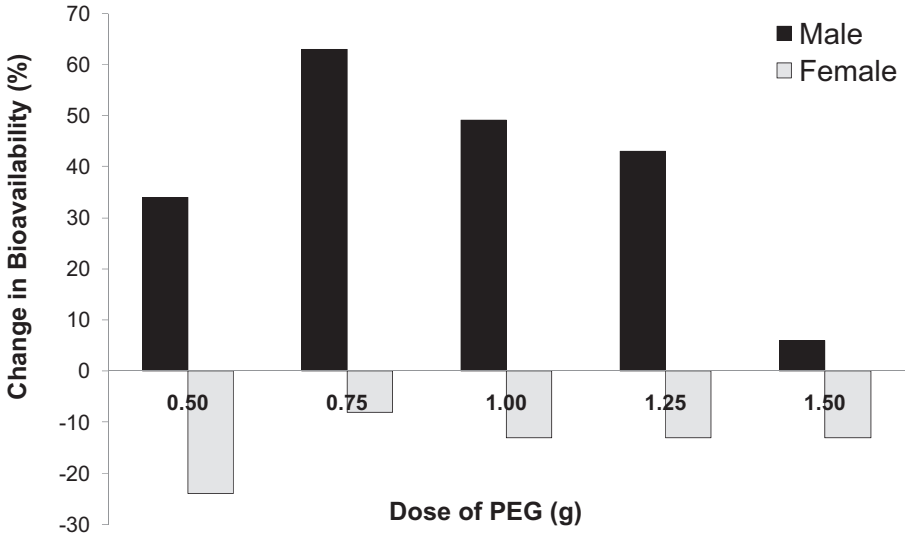

Fig. 3. Change in ranitidine bioavailability in the presence of different doses of polyethylene glycol 400 (PEG 400) in male and female volunteers ($n = 6$ each). Figure drawn using data from Ashiru et al. (2008).

gender (McDougall et al., 1993). However, it must be stressed that mucosal pH is only a direct measure of bicarbonate mucosal secretion and does not account for other host factors such as diet and bacterial fermentation in the colon. A study in 26 subjects (15 men and 11 women) under a controlled diet reported sex-related differences in faecal pH (Stephen et al., 1986). Women had significantly higher faecal pH than men (7.18 ± 0.08 and 6.51 ± 0.07) and this was correlated to the production of methane by the female subjects. Although very few studies have dealt with the influence of sex on the production of methane by the colonic microbiota, we found one study (Pitt et al., 1980) that reported a higher incidence of methane producing bacteria in females (49%) than in males (33%). This difference was particularly evident between Caucasian individuals, with 58% of all female Caucasians excreting methane compared to only 35% of males. A possible explanation for the higher faecal pH in methane producers is that the absorption of short chain fatty acids from the colon is more efficient in these subjects than in non-producers (Flick and Perman, 1989).

2.2. Fluid volumes

Drug dissolution is often the rate limiting step in drug absorption. Consequently, fluid levels in the gut are critical. It is reported that postprandial changes in gastric volumes are higher in males than females (Bouras et al., 2002). Interestingly, in this study, age and body mass index were found to have no influence on both fasting and post-prandial gastric volumes. Gotch et al. (1957) measured *post-mortem* fluid volumes in the stomach, small intestine and the proximal colon from 8 males and 5 females. After reanalyzing the data based on gender, it was found that the volume of fluids in the stomach and small intestine were higher in men than in women (Table 1). This difference was still apparent when the data was normalized for body weight. However, there was no significant difference in fluid volume in the proximal colon between genders. Although the full length of the colon was not studied, the inference was not different from another study considering the complete large bowel (Cummings, 1990, 2010).

2.3. Composition of luminal fluids

In recent years, considerable attention has been paid to the characterisation of the gastrointestinal milieu (Kalantzi et al., 2006; Clarysse et al., 2009). One of the best studied human fluids is the saliva, perhaps because of the ease with which it can be collected and examined. The composition of saliva has been shown to vary between men and women (Bales et al., 1990; Laine et al., 1991). Female sex hormones might be responsible for such differences as the salivary composition has been shown to fluctuate during pregnancy (Laine et al., 1988) and in women taking oral contraceptives (Laine et al., 1991).

There have been limited studies that have characterised the composition of the gastric and intestinal fluids by gender, but it follows that the hormonal effects in saliva may continue to other secretions in the gastrointestinal tract. However, according to some early studies conducted *post-mortem* in a small number of subjects, the concentration of electrolytes (Na^+, K^+, Ca^{++}, and Cl^-) in the stomach, small intestine and proximal colon appear not to be subject to gender variations (Edelman and Sweet, 1956; Nadell et al., 1956; Sweet et al., 1957). The osmolality and ionic strength of the luminal fluids aspirated from the stomach and jejunum were also shown not to differ by gender (Lindhal et al., 1997). One gender variation, which is relatively well documented is the difference in bile acid composition and secretion between women and men. The ratio of primary to secondary bile acids in the gallbladder is lower in young adult women than in men (Fisher and Yousef, 1973). The composition of the bile also appears to change during the menstrual cycle and pregnancy (McMichael and Potter, 1980). Although being compositionally different between men and women, the relative concentrations between genders are unknown with only combined values for bile salts in the small intestinal fluids in male and female reported in the literature. Interestingly, the faecal excretion of bile acids has been shown to vary by gender. In a diet controlled study, the concentration of faecal bile acid was significantly higher in men than in women even after adjusting for energy and fat intake. The difference was particularly evident for the secondary bile acids, lithocolic and deoxycholic acid (Table 1) (Lampe et al., 1993). Another study noted that in response to several diets with different contents of fibre, the faecal excretion of neutral steroids and bile acids differed considerably by gender. In fact, males and females responded to the diets in opposite ways, an effect, which was not explained (Stasse-Wolthuis et al., 1980).

Faecal material, being a relatively easy source of quantifiable gastrointestinal matter, has been the subject of several studies in which gender was studied. In the simplest measurement, stool

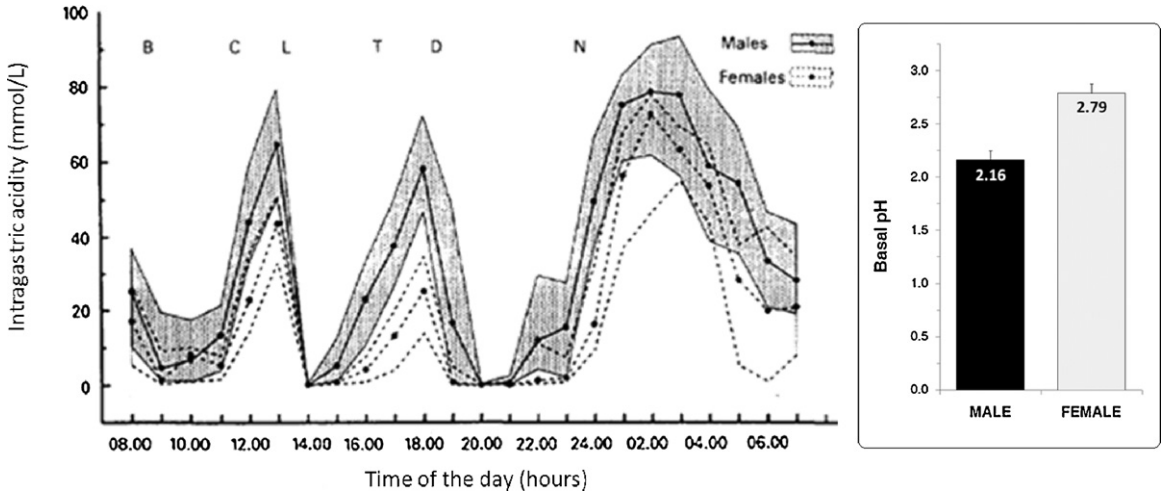

Fig. 4. Median hourly intragastric acidity in 35 healthy females and 36 healthy male subjects. In the figure, B – Breakfast, C – coffee, L – lunch, T – tea, D – dinner, N – nightcap. Reproduced from Prewett et al. (1991). Bar chart on the right represents Mean (±SE) basal pH in healthy subjects (252 men, 113 women). Figure drawn using data from Feldman and Barnett (1991).

weight can be studied, and when given the same diet, adjusted for daily energy requirements, this weight was higher in men than in women (Stephen et al., 1986). Although differences can be a result of a higher energy intake by men, an effect of female sex hormones should not be excluded as stool weight in women has been shown to vary during the menstrual cycle in women consuming a low-fibre western diet (McBurney, 1991). A significant decrease in stool weight was observed during the luteal phase of the menstrual cycle, when the levels of progesterone peak. Another study noted that the moisture content of faeces was not changed by gender (Lampe et al., 1993) and concluded that the higher faecal bulking in men was only attributed to increased faecal dry matter. This result is puzzling and suggests that colonic function is subject to gender differences. One such difference is the well-documented longer colonic transit time in women (Stephen et al., 1986). However, little is known about other gender differences in the colon, in particular, variations at the level of the faecal bacterial population. There is a dearth of studies specifically designed to explore the gender specific prevalence of the gut microbiota. The few studies that have investigated the gut microbiota in males and female subjects found interesting gender variations in some bacterial groups. For example, women appear to have significantly higher levels of faecal bifidobacteria than men (Whelan et al., 2009) whereas the faecal concentration of *Bacteroides prevotella* is significantly higher in males than in female subjects (Mueller et al., 2006). However, another study found no gender differences in the relative abundance of three predominant bacterial groups in faeces (*Clostridium coccoides*, *Bacteroides* and related genera and *Clostridium leptum* group) (Li et al., 2009). The implications of these differences are still unknown however, recently it has been reported that the probiotic treatment (*Lactobacillus fermentum VRI-003*) reduced the severity of chest infections, illness load and use of medications associated with respiratory infections in well-trained male athletes but not in females (West et al., 2009). The underlying mechanisms and reasons for such differences are not yet understood but it may be linked to gender differences in the gut microbiota.

3. Gender and gastrointestinal motility

The physiological considerations of gastrointestinal motility are complex. In a highly coordinated manner, the brain (via the autonomic nervous system) and several endocrine substances, of which some are known to be gastrointestinal hormones, dictate the rate at which food or any other material travel through the gastrointestinal tract (Hellström et al., 2006; Herbert and Holzer, 2008). The exact role of female sex hormones (progesterone and estrogen) in this process is still unknown. In animals, female steroidal hormones were shown to promote intestinal hypomotility (Scott and Deflora, 1983) and inhibit gastric emptying (Coşkun et al., 1995; Liu et al., 2002) by acting as a smooth muscle relaxant. Another means by which progesterone may decrease gastrointestinal motility is through an inhibitory effect on motilin (Christofides et al., 1982; Qiu, 1993), a hormone that stimulates motility. Whether this hormonal mediated relaxation effect occurs in humans is still highly debatable. Recently, it was found that constipated females had an over-expression of progesterone receptors in the colon (Cheng et al., 2010).

Many studies have highlighted inter-gender differences in gastrointestinal motility patterns and transit time. Gender differences have been reported in the duration and velocity of contractions above the lower esophageal sphincter. These may not have a direct clinical significance, however, may be an important aspect in interpreting oesophageal motility tests (Dantas et al., 1998). Differences of clinical significance also exist, for example, the prevalence of gastroparesis is higher in females (Soykan et al., 1998) and several women experience dyspeptic symptoms during the menstrual cycle (Heitkemper and Jarrett, 1992). Women are more often constipated than men (Connell et al., 1965). In terms of total gut transit, women have higher total gastrointestinal transit times than men (91.7 ± 12.8 h vs. 44.8 ± 4.3 h, Stephen et al., 1986), with clear differences seen mainly in the gastric emptying time and colonic transit time. These differences will be discussed in detail hereafter.

3.1. Gastric emptying

Pre-menopausal women have significantly longer gastric emptying times than men, for both solids and calorific liquids (Datz et al., 1987; Mojaverian et al., 1988; Hermansson and Sivertsson, 1996; Knight et al., 1997; Bennink et al., 1998; Sadik et al., 2003). This difference is not explained by the frequency of contractions in the stomach, which is comparable between men and women (see Table 1) (Bennink et al., 1998), but is, according to Knight et al. (1997) the result of the lower strength of contractions in the antral region of the stomach in women. Interestingly, no gender related difference is seen with non-calorific liquids (Bennink et al., 1998). Baschetti (1997, 1999) proposes that this difference between calorific and non-calorific liquids is due to gastric emptying being

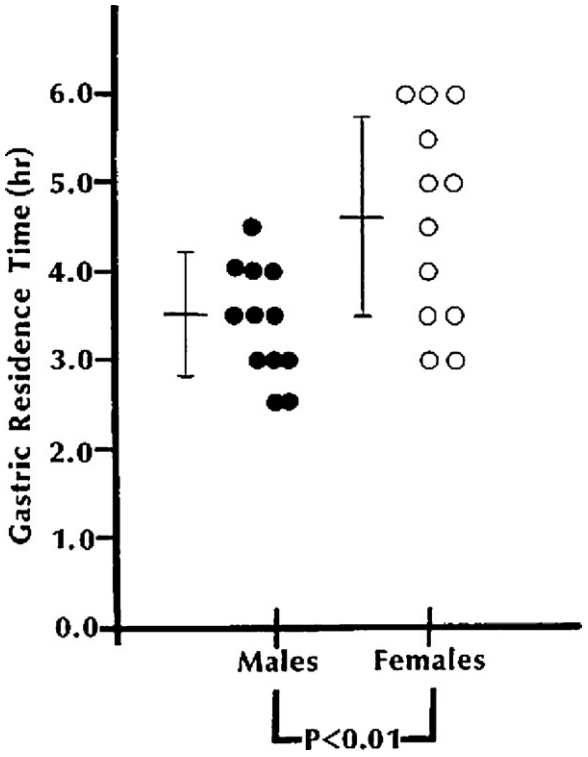

Fig. 5. Individual and mean (±SD) gastric residence time of Heidelberg capsule of 12 healthy male and 12 aged-and race-matched female counterparts. Figure reproduced from Mojaverian et al. (1988).

a function of the role of exogenous glucose oxidation for calorific meals. Hypo- and hyper- glycaemia are also related to accelerated and slowed gastric emptying, respectively (Datz et al., 1987; Schvarcz et al., 1997). Baschetti argues that since glucose requirements are dictated by muscle mass primarily, thus explaining the apparent gender specific differences and proposes that gastric emptying in muscular females will be faster than that in less muscular women and thin males.

Further to these proposed glucose mediated effects, there is a role of female steroidal hormones on gastric motility, which is still not fully understood. It appears that gastric emptying changes during the final stages of pregnancy (Simpson et al., 1988) and varies considerably during the menstrual cycle (Wald et al., 1981), adding strength to the hypothesis that the circulating levels of these hormones are able to modulate the stomach's motility and its emptying pattern. Differences were also encountered between fertile and post-menopausal women (Hutson et al., 1989). In post-menopausal women, the gastric emptying time decreases and becomes similar to that in men. However, despite abundant evidence implicating the role of hormonal steroids, this subject remains highly controversial and in other investigations (Horowitz et al., 1985; Mones et al., 1993) no correlation was found between the levels of steroidal hormones and gastric motility.

Data on gastric emptying of actual dosage forms in the two genders is lacking. A small number of studies have reported a significantly longer gastric emptying time of a Heidelberg capsule (7 mm × 20 mm) in the fed state in females than in age-and race-matched males (Fig. 5) (Mojaverian et al., 1987; Mojaverian et al., 1988). These differences in dosage form transit time can be linked to drug absorption. For example, one study showed a shorter absorption lag time of an enteric coated aspirin tablet in males than in females under fed conditions, and attributed this to inter-gender differences in the gastric emptying time (Mojaverian et al., 1988). Gender differences in the absorption kinetics of orally administered sodium salicylate (9 mg/kg dissolved in 200 mL water) have also been reported in the fasted state (Miaskiewicz et al., 1982). A significantly longer t_{max} was reported in females than in males (54 ± 7 vs. 32 ± 3 min). The study was repeated on 5 different occasions during the female menstrual cycle (days 2, 7, 14, 20 and 25); t_{max} was more variable, whereas C_{max} remained unchanged during the menstrual cycle. No sex differences were reported in the apparent volume of distribution, plasma salicylate clearance and area under the concentration-time curve, suggesting that the observed gender differences are a result of gender-based differences in gastric emptying.

3.2. Transit through the small and large intestines

Given the variability in small intestinal transit (Fadda et al., 2009), it is not surprising that gender effects on small intestinal transit time have not been clearly elucidated. Some studies reported no gender differences in this parameter (Masden, 1992; Degen and Phillips, 1996), whereas others showed a significantly slower small intestinal transit in females (Graff et al., 2001; Sadik et al., 2003). Comparison of the motility patterns of the small intestine between genders also produced conflicting data and gave no definitive answer as to whether transit in the small intestine can be affected by gender (Soffer et al., 1998; Aytug et al., 2001).

Transit through the colon is significantly longer in women than in men (Metcalf et al., 1987; Degen and Phillips, 1996; Jung et al., 2003; Sadik et al., 2003). These inter-gender differences were shown to be accentuated during the luteal phase of the menstrual cycle, when the levels of progesterone are higher (Jung et al., 2003). Transit was also reported to be longer in fertile women compared with post-menopausal women (Sadik et al., 2003). However, caution must be exercised when analysing results from both studies as there was no appropriate control of diet and smoking habits, factors which are well known to change the transit though the colon. When these factors were controlled for, there was no effect of the menstrual cycle phase on colonic transit (Degen and Phillips, 1996).

Values for transit in men and women in the right, left and sigmoidal colon were given by Metcalf et al. (1987). Transit through the right and left colon of women was longer than in men (Fig. 6). These findings concur with those of Rao et al. (2001), which reported a lower pressure activity (as seen by the lower incidence of pressure waves) in women, and this difference was particularly significant in the transverse and descending colon. Moreover, women have a longer transverse colon (48 cm vs. 40 cm, in women and men, respectively), which tends to coil. This anatomical feature may hinder transit through the transverse colon, delaying it significantly (Saunders et al., 1996).

The significantly increased total gut transit time in women may have important implications in the oral bioavailability of drugs, in particular for modified-release formulations. For example, colon-specific drug delivery systems can be affected by the transit time as shown in one study in which a rapid gut transit led to negligible bioavailability (Tuleu et al., 2002). An extended release diltiazem formulation administered once daily has also been previously shown to be sensitive to variations in transit time (Zimmermann et al., 1999).

A sex-specific effect was also found in a bioequivalence study of two different oral extended release formulations (Williams et al., 2002). Mean plasma levels of drug following administration of the formulation 'A' were significantly higher in women than in men; however, plasma levels from formulation 'B' were comparable between sexes. The two formulations differed in their in vitro drug release profiles. For formulation 'A' release was faster at pH 6.8 (release occurring in the distal small intestine and colon) whereas for formulation 'B' most drug was released at pH 4.5 (released in the

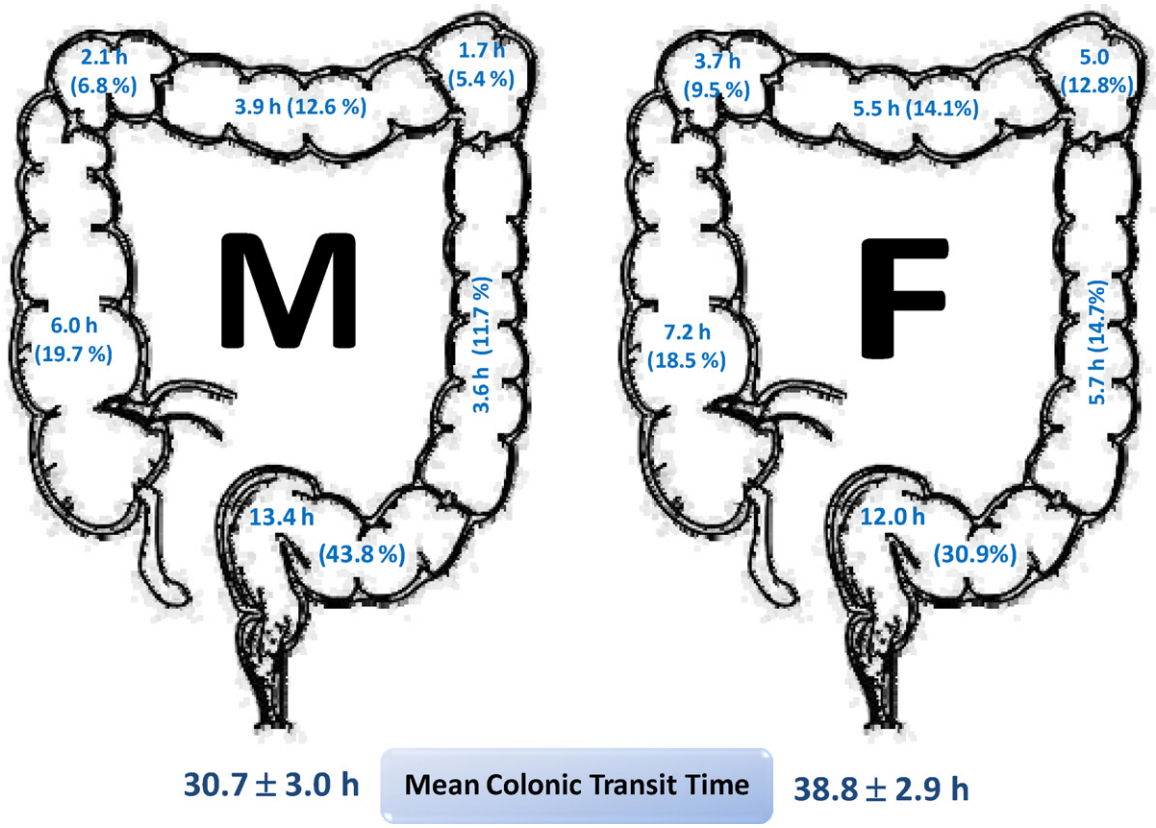

Fig. 6. Proportion of total colonic transit time spent in different segments of the colon in 34 male and 39 female subjects (M = male, F = female). Figure redrawn from Metcalf et al. (1987).

small intestine). The authors hypothesized that this could be linked to the longer transit time in the colon of females in addition to the potential differences in metabolizing enzymes and transporters in the colon as this drug is a known substrate for both CYP3A4 and P-gp (Chen, 2005).

4. Gender and the gastrointestinal mucosa

Dissolution is often considered the first barrier to oral absorption, but equally important is that the drug molecule has to pass through the mucosal membrane. Transport across the mucosa is, in part, regulated by mucosal enzymes and transporters. Inter-gender variation at the mucosa may, therefore, lead to variations in drug transport and gut-wall metabolism, which may ultimately translate into significant differences in the systemic availability of drugs.

4.1. Gastric alcohol dehydrogenase

Significant sex-related differences have been noted in the expression of a gastric mucosal enzyme, alcohol dehydrogenase (ADH), which is responsible for the biotransformation of alcohol (Table 1). Gastric ADH activity is lower in women than in men (Frezza et al., 1990) and this is particularly evident in younger subjects (20–40 years). An opposite situation is found in middle age (41–60 years), where females show higher gastric ADH activity than males. This gender difference then diminishes in old age subjects (61–80 years) (Parlesak et al., 2002). Gender differences were also found in postprandial gastric emptying of alcohol, which was longer in women than in men (74 vs. 52 min, (Baraona et al., 2001). The difference in ADH activity is thought to be responsible for the lower alcohol first pass metabolism in females, resulting in considerably higher blood alcohol levels in women compared with men (Fig. 7). Interestingly, this gender difference was more noticeable during the pre-menstrual period (days 21–28) than during the menstrual (days 1–3) and inter-menstrual (days 13–18) periods (Jones and Jones, 1976).

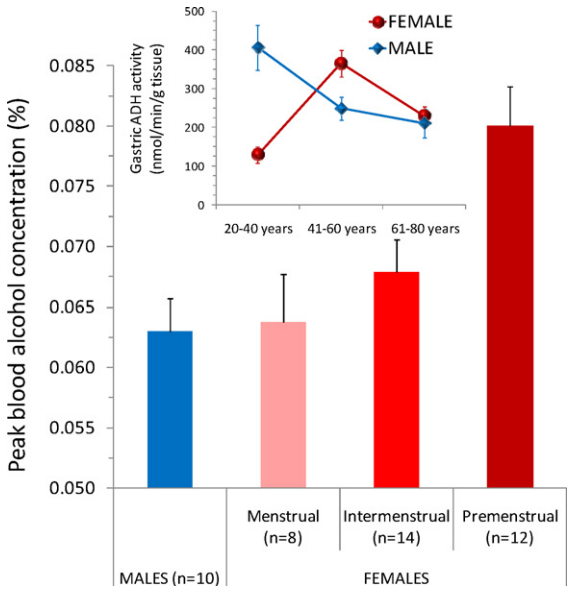

Fig. 7. Mean (±SE) peak blood alcohol levels for males and females tested at different times in the menstrual cycle. Figure redrawn from Jones and Jones (1976). The inset shows the gastric alcohol dehydrogenase enzyme activity (Mean ± SD) in gastric biopsies from 111 subjects (Figure redrawn from Parlesak et al., 2002).

4.2. Glutathione enzyme system

Glutathione-S-transferase (GST) families constitute a superfamily of ubiquitous, multifunctional enzymes which play a key role in cellular detoxification, protecting macromolecules from attack by reactive electrophiles, including environmental carcinogens, reactive oxygen species and chemotherapeutic agents (Di Pietro et al., 2010). GSTs are regulated by a large number of structurally diverse xenobiotics, anticancer drugs, and high intake of vegetables and fruits (Hayes and Pulford, 1995; Hoensch et al., 2002; Di Pietro et al., 2010). Genetic variations and polymorphisms (Di Pietro et al., 2010), and gender differences (Hoensch et al., 2002; Hoensch et al., 2006) further complicate the situation.

The expression of glutathione in gastric and duodenal tissues is higher in females than in males at all age groups, resulting in an increased GST enzyme activity in females (Hoensch et al., 2002). However, in the colon, the situation is complex and varies among different age groups. For example, in subjects <50 years of age, the overall glutathione expression in the colon is similar between genders, however, the expression of GST pi-1 and mu-1 (sub classes of GST) were higher in males than in females leading to a higher GST enzyme activity in the colon of males. In the older age groups (50–70 years and >70 years) no gender differences were found in the colon, which was due to an increase in enzyme activity with age in the females. This increased enzyme activity was diminished when tested in older women (>50 years) taking oral hormonal replacement therapy (Hoensch et al., 2006), which advocates the influence of female sex hormones in the regulation of the GST enzyme system.

Besides the colon, the enhanced GST expressions in females have also been reported in hepatic (Mulder et al., 1999), renal cortex and lung tissues (Temellini et al., 1995). It was also reported that in patients with a recurrence of colorectal cancer, GST enzyme activities and glutathione content in the distal colon were lower compared to patients without tumour recurrence (Hoensch et al., 2006). The up regulation of GST enzyme activity in older females suggests that females may be better protected from colon neoplasia than males above 50 years of age. An inverse correlation has been reported between GST enzyme activity in the mucosa along the gastrointestinal tract, and the incidence of tumours (Peters et al., 1993). Tumour-acquired drug resistance due to GST over-expression in cancer tissues has also been a problem (Hayes and Pulford, 1995) but the emergence of GST-activated cytotoxic prodrugs (such as canfosfamide) has shown promising results in clinical trials (Di Pietro et al., 2010). Hence gender specific GST expression may have important clinical implications and might trigger another avenue for personalised medicine.

4.3. Cytochrome P450 (CYP450) and transporters

CYP P450 enzymes are responsible for the metabolism of many drug substrates. Among the CYP family of metabolic enzymes, 2C and 3A are the most common isoforms found in the small intestine (Lindell et al., 2003). A review by McConnell et al. (2009) summarised the relative levels of many metabolic enzymes found in the small intestine and colon. CYP3A4 and P-gp have a common tissue distribution (Matheny et al., 2001) and there is a striking overlap in drugs that are metabolized by CYP3A4 and those that are substrates or inhibitors of P-gp (Wacher et al., 1995). In the liver, it is known that males have 2-fold higher P-gp expression than females (Schuetz et al., 1995) and that CYP3A activity in males is half of that in females (Hunt et al., 1992; Wolbold et al., 2003). Females of childbearing age have a slightly higher CYP2D6 activity compared with males, but no difference in CYP2C19 activity (Hagg et al., 2001).

Gender differences in the expression of CYP and P-gp in the gastrointestinal mucosa, however, are still not fully elucidated. The expression of intestinal P-gp was previously shown to vary by race (Kim et al., 2001). In some studies, there has been an indication of gender differences but the number of subjects in these studies is very low to draw any meaningful conclusions (Mouly and Paine, 2003; Canaparo et al., 2007a,b). Paine et al. (2005) conducted a larger study and found no gender differences in the expression of P-gp, CYP3A4 and CYP3A5. However, this study was performed on duodenal samples only and the tissues were previously exposed to some xenobiotics and foods, which may have masked the gender effects. There is, however, some strong evidence that female sex hormones may modulate the levels of these enzymes. For example, a significantly reduced activity of CYP3A4 was noted in post-menopausal women (20% less than pre-menopausal) (Paine et al., 2005) and female sex hormones were shown to induce the expression of P-gp many fold, both at the protein and mRNA levels, on MDR1-transfected MDCK cell lines (Nakayama et al., 1999; Kim and Benet, 2004). Another study suggests the inhibitory effects of synthetic progestins on P-gp in vitro (L-MDR1, P388/dx cells) and *ex vivo* (human peripheral blood mononuclear cells), which may have clinical implications on treatments with P-gp substrates (Frohlich et al., 2004). Clark and colleagues established that this hormonal interaction with P-gp was important for the prognosis of HIV in post-menopausal women who fared better on hormone replacement therapy (Clark and Bessinger, 1997). Likewise hormones and P-gp have been implicated in the higher number of deaths from digoxin toxicity in women (Rathore et al., 2002). Clearly there is a high clinical need for the awareness of these types of hormone related transporter effects in drug delivery.

There are also clinical examples of CYP gender effects. For instance, the plasma concentration and bioavailability of verapamil (a putative CYP3A substrate) from a sustained-release (SR) formulation was higher in healthy females than in males (Fig. 8) (Gupta et al., 1995; Krecic-Shepard et al., 2000). Similar gender effects were also reported with an immediate release (IR) form of verapamil, and a faster oral clearance was observed in men than in women (Krecic-Shepard et al., 2000). An attempt has been made to determine the intestinal contribution to such gender differences by measuring area under the curve (AUC) ratios of norverapamil (N-demethylated metabolite) to verapamil after administration of IR and SR verapamil to the same volunteers on different occasions. In both men and women, bioavailability was lower with the SR verapamil compared to the IR form of verapamil without changes in the AUC ratios of norverapamil to verapamil, suggesting an intestinal mechanism (Krecic-Shepard et al., 2000). Another study explored gender effects at the intestinal level by comparing the effects of clarithromycin (a CYP450 inhibitor) on intestinal clearance of midazolam (a CYP450 substrate). Midazolam is widely used therapeutically as a sedative-hypnotic in surgical procedures whereas clarithromycin is a commonly used macrolide antibiotic in the clinic. When these drugs were administered concomitantly, the pharmacokinetics of midazolam was significantly altered, producing an 86% reduction in oral clearance and resulted in doubling the midazolam-induced sleep time (Gorski et al., 1998). This delay in sleep-time will have severe implications for therapeutic use of midazolam as sedative-hypnotic during surgical interventions. Interestingly, this effect of clarithromycin on midazolam pharmacokinetics was more pronounced in women than in men (Fig. 9) (Gorski et al., 1998).

4.4. Effect of food and excipients

Complicating the issues of transporter and efflux mechanisms, interactions with '*inert*' formulation excipients and food components may exacerbate gender effects. The interactions with dietary components such as grapefruit juice (Lown et al., 1997; Tapaninen et al., 2010), char-grilled meat (Fontana et al., 1999) and nutritional

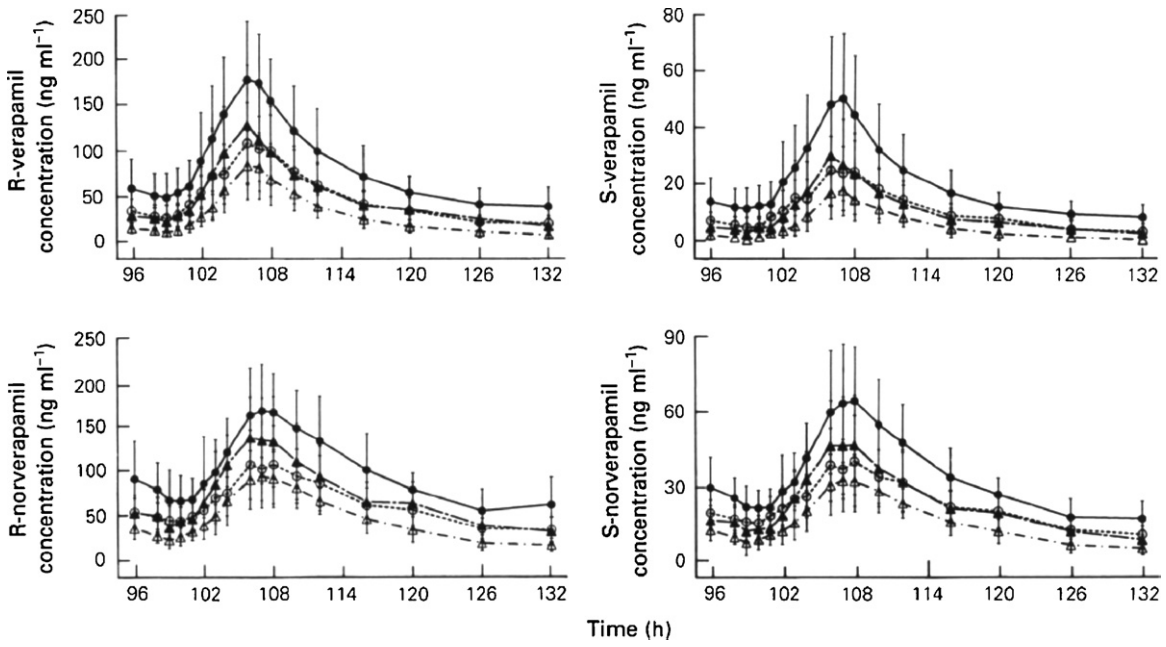

Fig. 8. Mean plasma R-verapamil, S-verapamil, R-norverapamil, S-norverapamil concentration–time profiles at steady state in young and elderly subjects (men and women) following osmotically controlled extended release verapamil (180 mg) formulation. Δ – young male, o – elderly male, ▲ – young female, • – elderly female. Figure reproduced from Gupta et al. (1995).

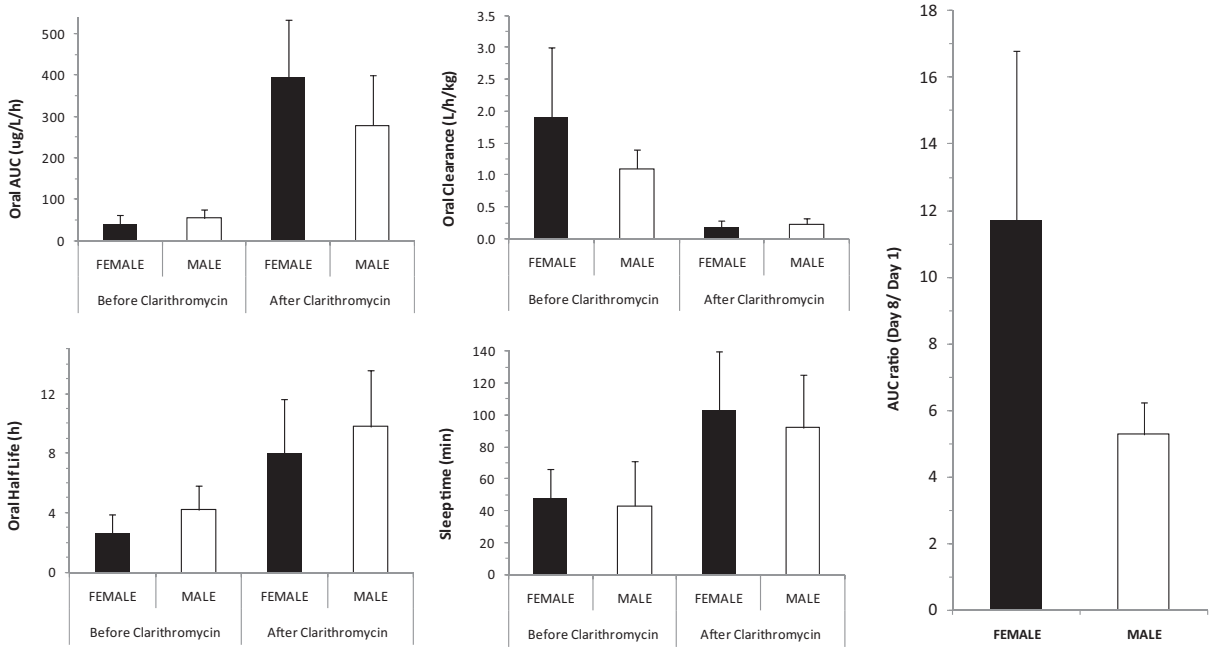

Fig. 9. Midazolam pharmacokinetics parameters (mean ± SD) after oral administration in male and female healthy volunteers ($n = 8$ each) after clarithromycin administration (500 mg twice a day for 7 days). Significant difference ($p < 0.05$) in the relative change in the AUC ratio between male and female subjects after clarithromycin treatment. Figure drawn using data from Gorski et al. (1998).

supplements (Krecic-Shepard et al., 2000) are of notable significance, however, sex-based analysis of such effects is essentially missing in these studies leaving this important parameter unexplored.

Formulation excipients such as polyethylene glycols (PEG 300, 400, 1000, 2000, 20,000 and vitamin E TPGS) have been shown to inhibit P-gp efflux in rat intestinal tissues or in vitro cell cultures (Hugger et al., 2002; Johnson et al., 2002; Cornaire et al., 2004; Shen et al., 2006; Collnot et al., 2007; Zhang et al., 2008; Mokhtar et al., 2009). An interesting drug-excipient interaction has been reported with ranitidine and polyethylene glycol 400 (PEG 400) in a human study. Ranitidine, which is widely used as an antisecretory therapy for peptic and duodenal ulcers, is a class III compound (high solubility, poor permeability) according to the Biopharmaceutics Classification System (BCS). Typically, ranitidine has a low bioavailability (~50%) (Roberts, 1984; Basit et al., 2004) and has no sex differences in its pharmacokinetics (Abad-Santos et al., 1996). However, in the presence of PEG 400, the bioavailability of ranitidine

was enhanced by 63% in males but no bioavailability enhancement was noted in the females (Fig. 3) (Ashiru et al., 2008). More recently, a similar observation was found with cimetidine–another BCS III drug (Ashiru et al., 2009). The reasons for such gender differences are not clear however underlying mucosal metabolism and efflux transport can be the most logical explanation.

5. Conclusion

The physiology of the gut is becoming better understood and yet inter-gender differences continue to be neglected. The literature in this area is sparse but in this review we have attempted to collate the differences in gastrointestinal motility, luminal and mucosal features, ranging from simple anatomical features to complex molecular expressions in the gastrointestinal tract of males and females. For instance, gastrointestinal transit tends to be slower in women, and is subject to hormonal influences. Gastric acid output also differs by gender, leading to significant differences in the pH of the stomach with men having more acidic conditions. This can manifest in changes in drug dissolution or enteric dosage form performance, but also medically as demonstrated by the greater prevalence of ulcers in men. From the macro to micro scale, mucosal enzymes and transporters show clear hormonal dependence or gender effects. This can greatly influence bioavailability and toxicity.

This review has highlighted not only the current literature on gastrointestinal gender differences, but also the lack of literature on many aspects. For example, true differences in terms of intestinal secretions remain largely unknown. The net effect of such differences on the oral bioavailability of drugs is complex and often difficult to envisage. However, based on the evidence presented, it is clear that there remains a need for specialised gender based studies to understand the underlying gastrointestinal mechanisms. Even within gender there is huge variability: among women, differences (e.g. motility pattern and mucosal enzyme activity) during pre- and post-menopause, with and without hormonal treatments, and during menstrual cycle need to be properly assessed. With this review we hope to encourage further studies to understand the gender-differences in the gut and its implications for oral delivery of drugs.

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