Variability in Human Drug Response
G.T. Tucker, Editor

Gender as a source of variability in human pharmacokinetics and pharmacodynamics.

Paul Rolan and Lynn McKeown

Medeval Ltd, Skelton House, Manchester, U.K.

ABSTRACT

The issue of gender as a clinically important source of variability has only received attention relatively recently. Most literature relates to possible pharmacokinetic differences. Where pharmacokinetic differences do occur, they are generally small and are unlikely to be clinically important. Gender-related dose-response differences are frequently reported for CNS-acting compounds but have also been reported for other classes such as corticosteroids. Whether such differences have a pharmacokinetic or pharmacodynamic basis is not clear but further investigation is warranted as the magnitude of some of the reported differences is clinically important. In women, the effects of phase of menstrual cycle, hormonal contraception, pregnancy and the interaction with age are additional potentially significant sources of variability and need to be considered in assessing gender differences in drug response.

Key words: gender, variability, pharmacodynamics, pharmacokinetics.

Correspondence: Paul Rolan, MD, Medeval Ltd, Skelton House, Lloyd Street North, Manchester M15 6SH, UK, Tel: +44-161-226-6525, Fax: +44-161-226-8936, Email: p.rolan@medeval.com

1. INTRODUCTION

The issue of gender differences between men and women has only been a significant component of clinical pharmacology literature in relatively recent years, approximately the last decade. Drugs were developed mainly using male subjects, because of the concern about potential effects of a new chemical entity on the embryo or foetus and fertility if given to women of child-bearing potential. This traditional view was challenged by women's rights groups because this approach had lead to women of child bearing potential being disadvantaged in not being offered early access to novel potential therapies. Partly in response to these concerns, the US FDA issued advice to pharmaceutical companies in 1993 [1], encouraging them to include women in early clinical studies but also encouraged the early exploration of gender-related and hormonal-treatment- related effects on drug handling and

response. This advice led to a major increase in the literature on gender-drug interactions and related issues, such as interactions between drugs and hormonal treatment and contraception. In this article, we have reviewed and summarised such literature and assessed the likely contribution of such factors to variability in drug response.

2. GENDER DIFFERENCES IN PHARMACOKINETICS

2.1. Absorption/ bioavailability

Although there is evidence that gastric emptying and intestinal transport may be slower in women than men, evidence that this causes differences in drug absorption is lacking. Indeed, Aarons *et al.* [2] found that absorption of orally administered aspirin was faster in women than men, without a change in extent of absorption. Some studies have found an apparent slower absorption of "intramuscularly" administered drug to be slower in women, but the potential confounder of the administration actually being subcutaneous (due to the greater depth of adipose tissue) needs so be considered in interpreting such claims [2]. For drugs delivered by the inhaled pulmonary route, Knight *et al.* [3] found less respiratory tract deposition of aerosolised ribavirin in women compared to men. In contrast, Bennett [4] found a 30% greater deposition of 2 m particles of carnauba wax in women. The difference has been attributed to breathing patterns but the clinical significance is not clear.

In contrast to the inconsistent gender differences in drug absorption, significant differences in bioavailability with drug subject to first-pass extraction have been reported, mainly due to differences in hepatic enzyme activity (see section 2.3). Part of the gender difference in alcohol pharmacokinetics is attributed to lower gastric and/or hepatic alcohol dehydrogenase activity in women [5].

2.2. Distribution

Compared to men, women have a lower body weight and a higher percentage of body weight being adipose tissue. Higher body-weight adjusted distribution volumes have been reported in women for lipophilic drugs such as trazodone, diazepam and sufentanil [6] but a significantly lower volume of distribution for ethanol [5].

Although gender-related differences in plasma protein binding have been reported, the extent appears to be small and not of clinical relevance [7].

2.3. Metabolism

Most of the literature on gender-related differences in pharmacokinetics has reported differences in drug metabolism. This has recently been extensively reviewed by Harris *et al.* [7]. The available data have been summarised by individual metabolic pathways as there are no consistent trends for gender-related differences common to all pathways. The same lack of consistent trend can be said for drug classes: for examples, with benzodiazepines, some are cleared more quickly in men, some more quickly in women, and for some there is no gender difference.

When considering potential gender-related differences in drug metabolism, it is important to separate differences due to gender from those related to body weight, and so weight-adjusted clearances should be examined.

2.3.1. Hepatic cytochrome P450s

2.3.1.1. CYP 3A4

CYP 3A4 is the enzyme responsible for the metabolism of most therapeutic drugs. There is a consistent body of evidence that young women have a 20-40% higher clearance of CYP 3A4 substrates than young men. This has been shown for erythromycin, methylprednisolone, verapamil, diazepam, midazolam. Although there are some negative studies, small sample size and subject heterogeneity may have made the gender effect difficult to detect.

2.3.1.2. CYP 2D6

After CYP 3A4, CYP 2D6 is the next most important enzyme for metabolism of therapeutic drugs. Its activity shows a genetic polymorphism which is not influenced by gender. In contrast to CYP 3A4, the available data suggest that clearance by CYP 2D6-dependent pathways is higher in men than women. Higher rates have been found for clearance of desipramine, *(R)*-propranolol, and clomipramine hydroxylation.

2.3.1.3. CYP 2C19

CYP 2C19 is another important drug metabolising enzyme that displays genetic polymorphism, but which is independent of gender. Consistent effects of gender on clearance of CYP 2C19 substrates are lacking, but the trend is for faster clearance rates in men.

2.3.1.4. CYP 1A2

The available data on gender differences in clearance of CYP 1A2 substrates is lacking, with faster rates reported for men for caffeine and thiothixene but faster rates for women for theophylline. Smoking appears to induce CYP 1A2 to a greater extent in men than women.

2.3.2. Conjugation

Where gender-related differences in clearance by conjugation have been observed, the trend is for it to be faster in men than women by approximately 20-30%. Examples of drugs with faster clearance in men include temazepam, oxazepam, paracetamol and diflunisal. In contrast, no gender-related differences were detected for clofibric acid or ibuprofen, with conflicting data for salicylic acid conjugation with glycine.

2.3.3. Dihydrouracil dehydrogenase

The hepatic enzyme responsible for the metabolism of the anticancer drug fluorouracil is dihydrouracil dehydrogenase. Given its narrow therapeutic index and Michaelis-Menten kinetics at therapeutic concentrations, the markedly lower clearance in women is likely to be clinically important [7,8].

2.4. Elimination

Elimination of drugs by renal filtration is unlikely to be gender-dependent as GFR is comparable in men and women after adjustment for body weight. There are little data examining possible gender affects on tubular secretion or reabsorption, although differences have been found for the renal clearance of the diastereomeric cations quinine and quinidine which undergo significant tubular secretion [9].

3. GENDER DIFFERENCES IN PHARMACODYNAMICS

Many of the studies that report a possible gender-related difference in pharmacodynamics do not exclude pharmacokinetic differences or possible prescription and reporting bias as the explanation for the difference. However, as the differences may be clinically important, we attempt to summarise the available literature.

3.1. Psychotropic medication

The most compelling gender differences in pharmacodynamics appear to stem from psychiatric disease processes and their treatment [7,10,11]

3.1.1. Antipsychotics

When treated with the antipsychotic chlorpromazine, young women show a greater magnitude of response with more severe side effects [10,12]. In a study by Chouinard *et al.*, women are also prescribed approximately half the dose of the antipsychotic fluspirilene for men for the treatment of schizophrenia despite similarities in age and weight [13]. However, Simpson *et al.* [14] implied that the required therapeutic dose of fluphenazine was not significantly different between males and females. The differences in the dose-response relationship of antipsychotics may be a mirror of the pharmacokinetics as suggested by higher thiothixene clearance in males or higher plasma levels of chlorpromazine in women [13,15], but it is not known if other variables were taken into consideration e.g. menstrual cycle, smoking and oral contraception, during these trials.

A possible explanation for pharmacodynamic differences is the hypothesis that oestrogen can act as a dopamine antagonist, accentuating the effects of the antipsychotics [7,10] whilst the metabolites of progesterone may act on GABA receptors as agonists or antagonists, also inducing behavioural changes.

Tardive dyskinesia is an adverse effect of neuroleptics. Chouinard *et al.* [16] suggested that males had more severe forms and were more susceptible to the disorder. Conflicting data from Smith *et al.* stated that there was a higher prevalence in treated females [17]. In reviewing both sets of data, Smith concluded that age and gender should always be considered concurrently since the over 67s' age group appeared to have a significant gender difference and women over the age of 67 had much higher incidences of tardive dyskinesia [17]. This is thought to be due to dopaminergic denervation supersensitivity therefore if oestrogen were acting at dopamine receptors it would be consistent with a protective effect for premenopausal

females not post menopausal. There are other factors that could complicate these effects and no studies have yet confirmed any hypothesis.

Oestrogen has not been studied for antipsychotic activity in humans only in animal models and the fluctuations of the menstrual cycle have not been examined for female intra-individuality. The extent to which schizophrenia and its treatment are affected by gender is still being studied.

3.1.2. Antidepressants

In the treatment of depression with panic attacks it has been suggested that men have a better response to the tricyclic antidepressants like imiprimine whilst young women have better responses to the monoamine oxidase inhibitors (MAOIs), e.g. phenelzine [7,10]. Raskin *et al.* [18] implied that older women (over 40) also responded well to imiprimine and therefore age must be considered together with gender.
Some studies that have shown women respond better than men to the selective serotonin reuptake inhibitors (SSRIs) e.g. fluoxetine [7,11].

In the prophylactic treatment of bipolar depression with lithium the incidence of hypothyroidism was higher in women but little research has been carried out in this area [10], this could be a reflection of the population as a whole where hypothyroidism is more prevalent in women.

3.2. Corticosteroids

In addition to the pharmacokinetic differences discussed in section 3.3.1.1, Lew *et al.* [19] found that premenopausal women were more sensitive to immunosuppressive action of methylprednisolone as evidenced by changes in circulating basophil and helper T cell counts. The women were all in the luteal phase of their cycle when hormone levels were relatively high and constant and none was taking oral contraceptives, which according to Gustavson *et al.* [20] can decrease clearance rates. It was postulated that either oestrogen or progesterone was responsible for the increased sensitivity or therefore the menstrual cycle will affect the pharmacodynamics of methylprednisolone, although because of the opposing pharmacokinetics (higher clearance) there is an overall similar net response in males and females.

3.3. NSAIDS

Walker *et al.* assessed gender variability in the response to NSAIDs and suggested that only men showed any analgesic response to ibuprofen when subjected to cutaneously applied stimulation as compared to premenopausal women. Baseline differences in pain threshold had been taken into consideration and plasma concentrations were similar in both genders[21].

3.4. Neuromuscular Blockers

Atracurium is a neuromuscular blocker used in anaesthesia. Parker *et al.* analysed its effects for gender related differences using electromyographic monitoring and measuring four different parameters [22]. The only statistically significant difference was that the rate constant for exit of the drug from the effect compartment (k_{eo}), was greater in women than in men. They speculated that this may be due to differences in muscle blood flow but there was no evidence to support this.

3.5. Antihypertensives

There is little medical literature on gender differences in the treatment of hypertension even though Kitler suggests that, on average hypertension is a more important risk factor for heart disease in women than in men [23]. Data from the Medical Research Council showed that stepped care hypertensive medication was not as effective in some women with moderate and severe diastolic hypertension [24] and that it could actually be harmful to white women [23]. However, Anastos *et al.* suggest that the evidence for all women is inconclusive and most of the findings on gender differences were incidental as the studies were not designed for this and did not include significant numbers of women [24].

4. INTERACTION BETWEEN GENDER EFFECTS AND AGE

Where gender-related differences in pharmacokinetics or pharmacodynamics have been observed, the most frequent causative factor offered as an explanation is the effect of the female hormones, particularly oestrogen. As oestrogen production declines substantially after the menopause, it could be anticipated that where gender differences are found between young men and young women, these differences should lessen in older subjects. Evidence consistent with this hypothesis is the disappearance of the gender-related differences in theophylline metabolism [25] and the antimigraine drug zolmitriptan [26], although the pathways responsible for the latter are not clear.

Unfortunately, this point does not appear to have been appreciated by some researchers, who after finding differences between young men and young women claim that this is a gender effect rather than a possible age/ gender interaction.

5. SPECIFIC ASPECTS OF FEMALE REPRODUCTIVE PHYSIOLOGY

Given that female hormones are often thought to be the causative factor in gender-related differences in drug handling and response, and that plasma levels of the hormones vary widely during the menstrual cycle, it is reasonable to anticipate that additional hormonal therapy (e.g. oral contraceptives or hormone replacement therapy), the timing of the menstrual cycle, pregnancy or menopause may affect drug kinetics or response.

5.1. Oral contraceptives (OCs)

Oral contraceptives can interfere with the metabolism or activity of numerous therapeutic agents.

5.1.1. Benzodiazepines

It has been shown in many studies that oral contraceptives can inhibit enzyme hydroxylation activity and reduce clearance of some benzodiazepines, e.g. diazepam and nitrazepam [27,28,29]. Ellinwood *et al.* [30] postulated that OCs decreased the rate of absorption of diazepam and during the week off hormones the plasma levels quickly rose and women became 'intoxicated' during the menses. This may lead to associated pharmacodynamic changes especially in motor and mental functions. However, some other

benzodiazepams, bromazepam and clotiazepam do not have their metabolism impaired by OCs, but are not commonly used.

5.1.2. Methylxanthines

Abernethy and Todd [31] reported a reduction in the clearance of caffeine by up to 40% when taken with OCs, similarly Roberts *et al.* [32] suggested lower clearance rates and a longer half-life with theophylline. Although no clinically relevant effects dynamic changes were reported, a change in clearance of this magnitude is likely to be important for theophylline given its narrow therapeutic index.

5.1.3. Analgesics

Miners *et al.* [33] suggest that salicylic acid clearance was increased by 40% in OC users due to an increase in both the glycine and glucuronic acid conjugation pathways in pill users. They postulated that this could also be an explanation of why OCs may enhance morphine clearance.

5.1.4. Corticosteroids

There have been several studies of the possible inhibition of prednisolone metabolism by OCs. OCs can reduce clearance and prolong half life, but interpretation is confounded by the increase of the corticosteroid binding protein, transcortin, by oestrogen [28].

5.1.5. Antidepressants

OCs are reported to reduce clearance of imiprimine, amitryptyline and nortriptyline.

5.2. Menstrual cycle

The possible effects of the phase of the menstrual cycle of drugs have been reviewed recently by Kashuba [34]. Consistent effects of the menstrual cycle of drug absorption and distribution are lacking. Clearance of theophylline, caffeine and paracetamol is reduced in the luteal phase but the difference is not thought to be clinically significant. No consistent effect of the phase of the menstrual cycle has been detected for CYP 2C, 2D6, 2E and 3A4 substrates.

In addition to potential pharmacokinetic changes, there may be interactions between the target disease and menstrual cycle which could affect drug response. For example, it is well known that migraine is often more frequent in a female patient around the time of menstruation, and it has been suggested that such attacks are particularly resistant to treatment. However, the clinical response to zolmitriptan was unaffected by whether the attack was peri-menstrual [35].

5.3. Pregnancy

Pregnancy has been reported to increase the clearance of the antiepileptic drugs phenytoin, phenobarbital and carbamazepine [36] to a clinically important degree, which requires dose increase, presumable due to hepatic enzyme induction. In contrast, pregnancy reduces caffeine clearance. For some drugs used in pregnancy, e.g. zidovudine [37], no significant effect was observed

6. CLINICAL SIGNIFICANCE OF THE VARIABILITY DUE TO GENDER

With the recent interest in gender as a source of variability in drug response, the potential effect of gender on most important pharmacokinetic processes has been examined. Although there are consistent trends for differences between the genders, particularly for some drug metabolism pathways, the overall extent of a kinetic difference is small, and usually less than the general between-subject variability.

However, the same extent of data is lacking when examining potential pharmacodynamic differences. It is important to examine whether the concentration-response relationship differs, as a difference in dose-response can be due to pharmacokinetic factors.

For some categories, particularly psychotropic drugs, there may be clinically important gender differences. With such drugs, individual clinical response can be hard to judge and so it is important in the development of such drugs that potential gender differences are positively sought in a systematic manner, not only for the therapeutic effect but also adverse effects. Although the authors are unaware of any drugs for which the dosing recommendations differ for men and women (except for gender-specific conditions), it is possible that closer attention to potential differences in the dose-concentration-effect relationships between the genders may reveal the need for such labelling in the future.

REFERENCES

1. Dept. of Health and Human Services, Food and Drug Administration. Guideline for the study and evaluation of gender differences in the clinical evaluation of drugs. Federal Register. 1993;58:139.
2. Aarons L, Hopkins K, Rowland M. Route of administration and sex differences in the pharmacokinetics of aspirin, administered as its lysine salt. Pharm Res 1989;6:660-666.
3. Knight V, Yu CP, Gilbert BE, Divine GW. Estimating the dose of ribavirin aerosol according to age and other variables. J Infect Dis 1988;158:443-448.
4. Bennett WD, Zeman KL, Kim C. Variability of fine particle deposition in healthy adults: effect of age and gender. Am J Resp Crit Care Med 1995;153:1641-1647.
5. Thomasson HR. Gender differences in alcohol metabolism. Physiological responses to ethanol. Recent Dev Alcohol 1995;12:163-179.
6. Greenblatt DJ, Friedman H, Burnstein ES, *et al.* Trazodone kinetics: effects of age, gender and obesity. Clin Pharmacol Ther 1987;42:193-200.
7. Harris RZ, Benet LZ, Schwartz JB. Gender effects in pharmacokinetics and pharmacodynamics. Drugs 1995;50:222-239.
8. Ortiz de Montellano PR, Kunze KL. Self catalysed inactivation of cytochrome P-450 by ethynyl substrates. J Biol Chem 1980;255:5578-85.
9. Gaudry SE, Sitar DS, Smyth DD, *et al.* Gender and age as factors in the inhibition of the renal clearance of amantadine by quinine and quinidine. Clin Pharmacol Ther 1993;54:23-7.
10. Yonkers KA, Kando JC, Cole JO, Blementhal S. Gender differences in pharmacokinetics and pharmacodynamics of psychotropic medication. Am J Psychiatry 1992;149:587-595.

11. Dawkins K, Potter WZ. Gender differences in pharmacokinetics and pharmacodynamics of psychotropics: focus on women. Psychopharmacol Bull 1991;27:417-426.
12. Chouinard G, Annable L. Pimozide in the treatment of newly admitted schizophrenic patients. Psychopharmacology (Berlin) 1982;76:13-19.
13. Chouinard G, Annable L, Steinberg S. A controlled clinical trial of fluspirilene, a long acting injectable neuroleptic, in schizophrenic patients with acute exacerbation. J Clin Psychopharmacol 1986;6:21-26.
14. Simpson G M, Yakalam KG, Levinson DP *et al.* Single dose pharmacokinetics of fluphenazine after fluphenazine decanoate administration. J Clin Psychopharm 1990;10:417-421.
15. Ereshefsky L. Saklad SR, Watanabe MD, *et al.* Thiothixene pharmacokinetic interactions: a study of hepatic enzyme inducers, clearance inhibitors and demographic variabilities. J Clin Psychopharm 1991;11:296-301.
16. Chouinard G, Annable L, Ross-Chouinard A, Nestoros JN. Factors related to tardive dyskinesias. Am J Psychiatry 1979;136:79-83.
17. Smith JM, Dunn DD. Sex differences in the prevalence of severe tardive dyskinesia. Am J Psychiatry 1979;136:1080-1082.
18. Raskin A. Age-sex differences in response to antidepressant drugs. J Nerv Ment Dis 1974;159:120-130.
19. Lew KH, Ludwig EA, Milad MA, Donovan K, Middleton Jr. E, Ferry JJ, Jusko WJ. Gender-based effects on methylprednisolone pharmacokinetics and pharmacodynamics Clin Pharmacol Ther 1993;54:402-14.
20. Gustavson LE and Benet LZ. Menopause: Pharmacodynamics and Pharmacokinetics. Exp Gerontol 1994;29:437-444.
21. Walker JS, Carmody JJ. Experimental pain in healthy human subjects: gender differences in nociception and in response to ibuprofen. Anesth Analg 1998;86:1257-1262.
22. Parker CJR, Hunter JM and Snowdon SL. Effect of age, gender and anaesthetic technique on the pharmacodynamics of atracurium. Br J Anaesthesia 1993;70:38-41.
23. Kitler ME. Differences in men and women in coronary heart disease, systemic hypertension and their treatment. Am J Cardiol 1992;70:1077-1080.
24. Anastos K, Charney P, Charon RA, Cohen E, Jones CY, Marte C, Swiderski DM, Wheat M and Williams S. Hypertension in women: What is really known? Ann Intern Med 1991;115:287-293.
25. Cuzzolin L, Schinella M, Tellini U, *et al.* The effect of sex and cardiac failure on the pharmacokinetics of a slow-release theophylline formulation in the elderly. Pharmacol Res 1990;22:137-8.
26. Peck RW, Seaber E, Dixon R *et al.* The pharmacodynamics and pharmacokinetics of the 5-HT $_{1B/1D}$ agonist zolmitriptan in healthy young and elderly men and women. Clin Pharmacol Ther 1998;63:342-53.
27. Back DJ and Orme ML. Pharmacokinetic drug interactions with oral contraceptives. Clin Pharmacokin 1990;18:472-484.
28. Shenfield GM, Griffin JM. Clinical pharmacokinetics of contraceptive steroids: An update Clin Pharmacokin 1991;20:15-37.
29. Shenfield GM. Oral contraceptives. Are drug interactions of clinical significance? Drug Saf. 1993;9:21-37.

30. Ellinwood EH, Easier, Linnoila M, Molter DW, Heattherly DG, Bjornsson TD. Effects of oral contraceptives and diazepam induced psychomotor impairment. Clin Pharmacol Ther 1983;35:360-366.
31. Abernethy DR, Todd EL. Impairment of caffeine clearance by chronic use of low-dose oestrogen containing oral contraceptives. Eur J Clin Pharmacol 1985;28:425-428.
32. Roberts RK, Grice J, McGuffie C, Heilbronn L. Oral contraceptives impair the elimination of theophylline. J Lab Clin Med 1983;101:821-825.
33. Miners JO, Grgurinovich N, Whitehead AG, Robson RA, Birkett DJ. Influence of gender and OC steroids on the metabolism of salicylic acid and acetylsalicylic acid. Brit J Clin Pharmacol 1986;22:135-142.
34. Kashuba AD, Nafziger AN. Physiological changes during the menstrual cycle and their effects on the pharmacokinetics and pharmacodynamics of drugs. Clin Pharmacokin 1998;34:203-218
35. Rolan PE, Martin GR. Zolmitriptan: a new acute treatment for migraine. Exp Opin Invest Drugs 1998;7:633-652.
36. Lander CM, Eadie MJ,. Plasma antiepileptic drug concentrations during pregnancy. Epilepsia 1991;32:257-66.
37. O'Sullivan MJ, Boyer PJ, Scott GB *et al.* The pharmacokinetics and safety of zidovudine in the third trimester of pregnancy for women infected with the human immunodeficiency virus and their infants: phase I acquired immunodeficiency syndrome clinical trials support group study. Am J Obstet Gynecol 1993;168:1510-6.

Discussion: Gender as a source of variability in human pharmacokinetics and pharmacodynamics

A.J.J. Wood:
From the data that you have presented, the general idea was that there were not many gender-related differences. What would be your recommendation? Should we stop looking for gender-related differences or should we just include women randomly in trials?

P. Rolan:
If you exclude women, you are reducing your trial population unnecessarily. Additionally, at the moment, the regulatory climate is requiring to include women in the clinical trials, even though pharmacokinetic differences are unlikely to be important. I mentioned that pharmacodynamic differences are likely to be important, and if you do not include enough women in your trials, you will not see them. In conclusion, I believe it is quite important that you do include women as early as possible. From a practical point of view, it is not necessary to have young volunteer women in your first studies. I am still concerned that, despite all the care that you can bring about, people still get pregnant in studies. We know that perhaps 90% of molecules that go into Phase I do not get any further, and I would not suggest we have women in every early study. But not to include women in later studies is really shooting yourself in the foot from both the regulatory point of view, and because there are drugs with a gender-related difference in drug response.

A.J.J. Wood:
If we just include them as part of the regular population, should we stratify by gender?

P. Rolan:
Definitely. Because if you do not stratify, you cannot do the appropriate analysis.

J. Urquhart:
There are a couple of quite notable gender differences. One of them is that if you look at actuarial data or age-specific death rates, there is roughly a twofold difference in age-specific mortality, and this is at every stage of life from childbirth to very advanced age. The biology of that has got to be multifactorial because the biology is different at all those ages. If you look in the early 1920s there is an even bigger difference between the sexes attributable to accidental death in males because they drive crazier than women do. The other notable difference is on alcohol toxicity. The threshold for cirrhosis, estimated in daily alcohol intake, is about 50% lower in women.

P. Rolan:
I will only allude to the fact that the kinetic-gender differences in alcohol have been extensively studied. But they do not explain adequately this well-known difference in toxicity.

T. Salmonson:
I agree with you that we do not see gender differences very often and that differences tend to go away when they are studied in elderly women. However, I would not agree with the

statement that differences do not exist. Possibly due to publication bias or to other reasons, there is a wish not to find these differences. We approved a stroke medicine which due to both pharmacokinetic and pharmacodynamic explanations was not effective in women. But there are also anti-migraine and other drugs that despite pharmacokinetic differences were recently approved. As Alasdair Breckenridge commented earlier, perhaps the regulators are not performing very well when it comes to these issues. From my subjective point of view the pharmaceutical companies do not want to see as important these gender differences, because they would restrict labelling. They are happy to change the dose for a twofold increase or decrease in clearance if it is a decreased kidney function, but not by gender differences. In migraine, for example, they have included women in Phase III studies and no difference in adverse effects has appeared. But obviously, these studies were not sized to pick up these types of differences. As long as you are not showing that this twofold difference in clearance lacks effect, you have to assume that there is an effect, just as you would do for a decreased kidney function.

P. Rolan:

There is an accepted culture to reduce the dose for decreased renal function but to avoid any gender label, However, pharmaceutical companies may be a bit more willing to accept the latter. When you get the dose wrong, what happens is that it incurs the company financial disadvantage. In this situation, the prescriber will halve the dose in those people and they will get as good a response. And the drug company only gets half the income from the female population. So the companies that try and use the wrong dose for a large slab of the population, it will actually be to their economic disadvantage.

T. Salmonson:

Time will tell if you are right. We have not been able to force them to have a different dosing. But I admit, when it comes to anti-migraine, it may be that we underdose men rather than overdose females.