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Clinically Significant Pharmacokinetic Interactions Between Dietary Caffeine and Medications

Juan A. Carrillo and *Julio Benitez*

Department of Pharmacology and Psychiatry, Medical School, University of Extremadura, Badajoz, Spain

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Abstract

Caffeine from dietary sources (mainly coffee, tea and soft drinks) is the most frequently and widely consumed CNS stimulant in the world today. Because of

its enormous popularity, the consumption of caffeine is generally thought to be safe and long term caffeine intake may be disregarded as a medical problem. However, it is clear that this compound has many of the features usually associated with a drug of abuse. Furthermore, physicians should be aware of the possible contribution of dietary caffeine to the presenting signs and symptoms of patients.

The toxic effects of caffeine are extensions of their pharmacological effects. The most serious caffeine-related CNS effects include seizures and delirium. Other symptoms affecting the cardiovascular system range from moderate increases in heart rate to more severe cardiac arrhythmia. Although tolerance develops to many of the pharmacological effects of caffeine, tolerance may be overwhelmed by the nonlinear accumulation of caffeine when its metabolism becomes saturated. This might occur with high levels of consumption or as the result of a pharmacokinetic interaction between caffeine and over-the-counter or prescription medications.

The polycyclic aromatic hydrocarbon–inducible cytochrome P450 (CYP) 1A2 participates in the metabolism of caffeine as well as of a number of clinically important drugs. A number of drugs, including certain selective serotonin reuptake inhibitors (particularly fluvoxamine), antiarrhythmics (mexiletine), antipsychotics (clozapine), psoralens, idrocilamide and phenylpropanolamine, bronchodilators (furafylline and theophylline) and quinolones (enoxacin), have been reported to be potent inhibitors of this isoenzyme. This has important clinical implications, since drugs that are metabolised by, or bind to, the same CYP enzyme have a high potential for pharmacokinetic interactions due to inhibition of drug metabolism. Thus, pharmacokinetic interactions at the CYP1A2 enzyme level may cause toxic effects during concomitant administration of caffeine and certain drugs used for cardiovascular, CNS (an excessive dietary intake of caffeine has also been observed in psychiatric patients), gastrointestinal, infectious, respiratory and skin disorders. Unless a lack of interaction has already been demonstrated for the potentially interacting drug, dietary caffeine intake should be considered when planning, or assessing response to, drug therapy.

Some of the reported interactions of caffeine, irrespective of clinical relevance, might inadvertently cause athletes to exceed the urinary caffeine concentration limit set by sports authorities at 12 mg/L. Finally, caffeine is a useful and reliable probe drug for the assessment of CYP1A2 activity, which is of considerable interest for metabolic studies in human populations.

Caffeine (1,3,7-trimethylxanthine) is probably humankind's most widely consumed drug. The intake of caffeine is so much a part of dietary habits that one seldom looks at its consumption as a health concern. Therefore, its use is generally considered to be safe. The popularity of caffeine is related to central nervous system (CNS) stimulant properties, which are manifested as elevated mood, somnolytic actions, decreased fatigue and increased capacity for work.

In contrast, when ingested on a long term basis, caffeine has been implicated in several clinical conditions such as cardiovascular disease, reproductive disorders, osteoporosis, carcinogenicity, psychiatric disturbances and drug abuse liability (several books and publications review this topic[1-6]). Despite widespread consumption however, there is little concern about the possibility of drug-food interactions based on the concomitant intake of dietary caffeine and medications.

This article reviews the importance of dietary caffeine in clinical practice. The emphasis is on the mechanisms, clinical significance as well as implications for doping control during sports events of

pharmacokinetic interactions between caffeine and medications. The information was obtained from a number of sources: (i) preliminary information was based on *in vitro* studies at the cytochrome P450 (CYP) 1A2 enzyme level. However, because of limitations of *in vitro* interactions to accurately predict *in vivo* drug interactions; (ii) clinical case reports; and (iii) controlled *in vivo* clinical pharmacokinetic studies were investigated as well. The interactions are grouped by pharmacological class of the interacting drug.

1. Dietary Sources of Caffeine

Controversy has long surrounded the issue of caffeine consumption. Proponents tout its beneficial stimulatory effects, whereas detractors cite a variety of associated health risks. Although government regulatory agencies place few restrictions on the use of dietary caffeine, the Australia New Zealand Food Authority (ANZFA) and the US Food and Drug Administration (FDA) are currently assessing the safety of caffeine in food. At present, in Australia, caffeine is not permitted in soft drinks except those that are cola-flavoured. Investigations will focus on the effects of low dose caffeine exposure on people's health (in particular, behavioural effects in children).

The major dietary sources of caffeine are coffee, tea and soft drinks. However, the caffeine content of coffee and tea beverages is dependent on the particular bean or leaf and on the method of preparation.[7,8] In an attempt to provide a consistent estimate of caffeine intake in the diet, table I gives information concerning the major dietary sources of caffeine and the amounts of caffeine that might be considered 'standard' for these products.

Coffee is undoubtedly the major dietary source of caffeine for both adults and children. Europeans consume the largest amount of caffeine, with consumption about 4.6 kg/person/year. Europe is followed by North and Central America (3.6 kg/person/year), Oceania and South America (2.3 kg/person/year), Africa (0.6 kg/person/year) and Asia (0.3 kg/person/year). Tea is the major source of caffeine in Asia. World average consumption is 1.2 kg/person/year. Nineteen countries consume at least 4 kg/person/year (14 of them in Europe), and the Nordic countries are the highest consumers in the world with a figure of more than 10 kg/person/year.[8]

Among children, cola drinks are also a significant source of caffeine, and hence an increasing health concern. Data from the US Soft Drink Association (1999) indicate that caffeine concentrations in cola drinks range from 30 to 60mg per 360ml can (table I).

Caffeine is also used for therapeutic purposes, and is included in a wide variety of fixed combination prescription drugs and over-the-counter (OTC) medications (table I). The diverse pharmacological actions of caffeine have found many therapeutic applications (for review see Serafin[10] and Sawynok[11]). Caffeine is used alone for the treatment of apnoea in preterm infants. The recommended therapeutic range is 8 to 20 mg/L, with a loading dose of 10 mg/kg and maintenance doses of 2.5 mg/kg/day. Caffeine is also used as a somnolytic, for postprandial hypotension, for prolongation of seizures in electroconvulsive therapy and for bodyweight loss in obese patients. Caffeine is also used in combination with several drugs (ergotamine, nonsteroidal anti-inflammatory drugs) as an adjunctive analgesic.

Safe and efficacious clinical use of caffeine requires assessment of the patterns and levels of dietary intake of caffeine by the patient. In some cases, this background intake may predispose the patient to adverse events following either cessation of intake or enzyme saturation (table II), whereas in others the clinical effect may be minimised because of pre-existing tolerance to caffeine. Because of the increasing number of caffeine-containing OTC products available and the number of patients reliant on self-medication with these drugs,[13] toxicity may be caused by concomitant consumption of a number of caffeine-containing medications (OTC and prescription) in addition to caffeine from dietary sources.

It has been estimated that about 80% of adults in North America are regular caffeine consumers,

Table I. Caffeine content of beverages and foods as well as a representative list of caffeine-containing drugs. Data from the US Department of Nutritional Services,[a] US Soft Drink Association[a] and Barone and Roberts.[9] The amount of caffeine is estimated on the basis of per tablet/capsule for over-the-counter (OTC) remedies and prescription drugs

	Source	Approximate content of caffeine per unit
Coffee	Decaffeinated	<5mg/150ml; 5oz cup
	Ground roasted (brewed)	70-130mg/150ml; 5oz cup
	Instant	50-70mg/150ml; 5oz cup
Tea	Iced	65-75mg/360ml; 12oz can
	Instant	25-35mg/150ml; 5oz cup
	Leaf or bag	30-50mg/150ml; 5oz cup
Chocolate	Chocolate milk	4mg/180ml; 6oz glass
	Cocoa/hot chocolate	4mg/150ml; 5oz cup
	Chocolate candy[b]	1.5-6.0mg/1oz (5-20mg/100g)
	Milk chocolate	6mg/1oz
	Sweet chocolate	20mg/1oz
Soft drinks (mg/360ml; 12oz can)	Aspen	36
	Canada Dry Cola	30
	Coca Cola, Diet Coke	45
	Dr Pepper	40
	Diet Right Cola	36
	Diet Rite	36
	Mr. Pibb	41
	Mr. Pibb, Diet	57
	Mountain Dew	54
	Pepsi Cola	38
	Pepsi Light, Diet	36
	Royal Crown Cola	36
	Shasta Cola	44
	Tab	45
OTC stimulants	Caffedrine	200/capsule
	Durvitan	300/capsule
	NoDoz	200/tablet
	Vivarin	200/tablet
OTC pain relievers	Anacin Analgesic	32/tablet
	Cope	32/tablet
	Dristan	30
	Excedrin	65/tablet
	Midol	64
	Vanquish	33
OTC diuretics (standard dose)	Aqua Ban	200
	Permathene Water Off	200
OTC cold remedies	Coryban-D	30
	Neo-Synephrine	15
	Triaminicin	30
Prescription drugs	Cafergot	100/tablet
	Darvon Compound	32/tablet
	Fiorinal	40/capsule

a Data were obtained from several internat websites.

with an estimated average intake, when corrected for bodyweight, of 2.5 mg/kg/day (200 to 250 mg/day). In children under the age of 18 years the mean caffeine intake is about 1 mg/kg/day. A 27kg

child drinking 3 cola drinks and eating 3 small chocolate bars in a day will consume approximately 7.2 mg/kg.

The average caffeine intake for adult Europeans has been estimated to be 3.5 mg/kg/day. Both adults and children in Denmark and the UK have reported higher levels of caffeine intake.[3,8,9]

2. Pharmacodynamics

2.1 Mechanism of Action

Adenosine produces a spectrum of effects in a range of physiological systems, and these are frequently opposite to those produced by caffeine. In fact, antagonism of the actions of adenosine at cell surface receptors is believed to underlie most of the pharmacological effects of caffeine.[14]

Caffeine is a nonselective antagonist at adenosine A_1 and A_{2A} receptors, with inhibition constant (K_i) values of 44 and 40 μmol/L, respectively.[14] These concentrations correspond well with plasma concentrations encountered following the consumption of average amounts of caffeine from dietary sources.[3] Other mechanisms include phosphodiesterase inhibition (K_i 480 μmol/L) and calcium mobilisation from intracellular storage sites in skeletal and cardiac muscle and neuronal tissue. However, the phosphodiesterase inhibition and calcium mobilisation mechanisms may not be involved in the *in vivo* effects of average doses of caffeine, since higher than therapeutic concentrations (100 to 1000 μmol/L) are required to produce them and therefore they may be more relevant to the toxic effects of the drug.[14]

2.2 Pharmacological Effects

Caffeine affects several organ systems throughout the body. The following sections summarise the salient points (for further documentation see Serafin[10]).

2.2.1 Central Nervous System

The basis of the widespread use of caffeine is related to its CNS stimulant properties. In humans, the stimulant actions of caffeine are manifested as:

- increased arousal and vigilance
- decreased fatigue
- increased capacity for work
- decreased motor reaction time for some tasks
- elevated mood.

The precise mechanisms underlying these stimulant actions remain poorly defined.[3,10]

Caffeine also stimulates the medullary respiratory centre. This action is of importance in pathophysiological states such as Cheyne-Stokes respiration and apnoea in preterm infants, and when respiration is depressed by drugs such as opioids. The mechanism of action involves an increased sensitivity of medullary centres to the stimulatory actions of CO_2, and respiratory minute volume is increased at any given value of alveolar partial pressure of CO_2.

2.2.2 Cardiovascular Effects

The effects of caffeine on the circulatory system have been extensively reviewed.[10] They are complex and sometimes antagonistic, but the resulting effects largely depend on the conditions prevailing at the time of their administration, the dose used, and the history of exposure to this xanthine in the individuals.[10] It seems that moderate inges-

Table II. Symptoms of caffeine intoxication in the different organ systems[4,12]

Organ system	Symptom
Central nervous system	Agitation
	Anxiety
	Delirium
	Headache
	Insomnia
	Irritability
	Muscle tremor
	Restlessness
	Seizures
	Sensory disturbances
Cardiovascular system	Cardiac arrythmia
	Circulatory failure
	Palpitations
	Tachycardia
Gastrointestinal system	Abdominal pain
	Diarrhoea
	Nausea
	Vomiting
Kidney	Increased diuresis

tion of caffeine does not increase the frequency or severity of cardiac arrhythmias in healthy individuals, patients with ischaemic heart disease, or those with pre-existing serious ventricular ectopy.[15] A single dose of caffeine to caffeine-naive individuals causes a slight decrease in heart rate, systemic release of epinephrine, norepinephrine, free fatty acids and renin, but an increase in blood pressure.[16] The caffeine metabolite paraxanthine (1,7-dimethylxanthine) also contributes to the sympathomimetic actions reported with caffeine.[17] These effects are minimal when a similar dose is given to drinkers of average amounts of caffeinated beverages.[18] In fact, there is controversy whether the increased circulating catecholamine levels or plasma renin activity are related to the cardiovascular effects in caffeine-naive individuals. However, the development of tolerance to many of the pharmacological effects of caffeine explains the disparity between the short term effects and the relative absence of deleterious effects observed in a number of studies with large populations.[16]

2.2.3 Adjunctive Analgesia/Antinociception

Caffeine seems to produce intrinsic antinociceptive actions in animal models and adjunctive analgesic (or in some cases intrinsic analgesic) properties in humans (for review see Sawynok and Yaksh[19]). Briefly, the analgesic activity of caffeine has been proposed to result from several mechanisms:[19]

- blockade of peripheral pronociceptive actions of adenosine
- activation of central noradrenergic pathways that constitute an endogenous pain-suppressing system
- CNS stimulation with a consequent modulation of the effective component of pain.

2.2.4 Renal Effects

Caffeine has a diuretic effect, and the pattern of enhanced excretion of water and electrolytes is similar to that produced by the thiazide drugs.[10] It is believed that this effect results from direct action on the renal tubule. Caffeine causes an increased rate of sodium and chloride excretion. Potentiation occurs with the coadministration of carbonic anhydrase inhibitors.[3]

2.2.5 Effects on Muscle

There are 2 effects on muscle attributable to caffeine. Although theophylline is more effective, caffeine also produces a relaxation of the bronchial smooth muscle, leading to an increase in vital capacity. Caffeine also stimulates skeletal muscle, thus increasing the capacity for work.[10]

2.2.6 Other Effects

In addition to the aforementioned pharmacological effects, caffeine causes other miscellaneous effects such as increased secretion of acid and pepsin in the gastrointestinal (GI) tract. Some researches question this increased acid secretion because noncaffeinated beverages made from roasted grain also cause increased acid production.[12]

2.3 Tolerance and Physical Dependence

The available data on caffeine dependence, tolerance, reinforcement and withdrawal point to caffeine having the principal features usually associated with a drug of abuse, but the mechanisms underlying this process are not completely elucidated.[1,3,6,20] When caffeine is consumed on a regular schedule throughout the day, most individuals develop complete tolerance to many of the effects of the agent within a few days. Therefore, the effect of caffeine in an individual depends on how much caffeine he or she usually consumes, the schedule of consumption and probably the individual's elimination half-life for caffeine.[3,21,22]

Caffeine physical-dependence and withdrawal symptoms after the end of drug use have been documented in numerous case reports and experimental studies.[23-25] Significant withdrawal symptoms can occur reliably even at low dosages (100 mg/day) and after as few as 3 consecutive days of caffeine exposure.[25] The most commonly reported withdrawal effects from caffeine include increases in headache, drowsiness and fatigue and decreases in feelings of contentment and sociability. Other commonly reported symptoms include anxiety, restlessness and insomnia. Symptoms reported less frequently are tremor, muscle stiffness, rhinorrhea and confusion. The severity of symptoms depends on the amount of caffeine regularly consumed.[23,25]

There is evidence that caffeine withdrawal symptoms enhance the reinforcing effects of caffeine and thus are integrally related to the maintenance of long term patterns of caffeine self-administration.[24,26]

3. Toxicity in Humans

The adverse effects of caffeine are, for the most part, extensions of their pharmacological effects.[4,12] Therefore, the sites of toxicity include the CNS, cardiovascular system, GI tract and kidneys. This is summarised in table II. Awareness of these symptoms may help clinicians to solve some of the unexpected problems in clinical practice arising from the consumption of caffeine in the diet. Indeed, the symptomatology might result from a pharmacokinetic interaction between caffeine and drug therapy. The most serious CNS effects can be delirium and seizures. Potential cardiac symptoms range from a moderate increase of heart rate to more severe cardiac arrythmia (atrial fibrillation, atrial flutter, premature atrial contractions, supraventricular tachycardia and multifocal atrial tachycardia, among others) and circulatory failure.

An oral dose of caffeine 1 mg/kg in humans (considered equivalent to a cup of coffee) produces peak plasma drug concentrations (C_{max}) of 1 to 2 mg/L (or 5 to 10 μmol/L). Such concentrations increase sleep latency and enhance alertness. Doses of 5 to 8 mg/kg produce a C_{max} of 8 to 10 mg/L (or 40 to 50 μmol/L), yielding mild anxiety, respiratory stimulation, cardiovascular effects, excessive urinary output and increased gastric secretion. However, untoward CNS effects, including psychotic symptoms, may be observed following excessive doses of 1g or more [15 mg/kg; C_{max} about 30 to 50 mg/L (or 150 to 250 μmol/L)]. In patients who are prone to anxiety or panic attacks, even modest doses of caffeine can provoke intense feelings of anxiety, fear or panic, as this population exhibits an enhanced response to caffeine.[27]

Although tolerance develops to many of the pharmacological effects, it may not fully compensate for some of the caffeine-related symptoms of toxicity. This could be explained by the fact that mechanisms of tolerance may be overwhelmed by the nonlinear accumulation of caffeine when its metabolism becomes saturated.[16] This may occur with high levels of consumption or whenever the rate of caffeine elimination is reduced.[28]

The lethal oral dose of caffeine for adults is estimated to be about 5 to 10g. However, death from excessive dietary caffeine ingestion is rare, since 50 to 100 cups per day would be required if an average of approximately 100mg was present in a cup of coffee (or 50 to 100mg in tea) and also because of the emetic effect of the drug.[4,10] However, several caffeine-related fatalities resulted from accidental or suicidal administration have been reported.[29-31]

4. Pharmacokinetics

4.1 Absorption and Distribution

After oral administration, caffeine is rapidly and completely absorbed from the GI tract, and C_{max} is reached at about 1 hour thereafter.[32] No significant first-pass effect occurs after oral caffeine in humans. Caffeine is sufficiently hydrophobic to pass through all biological membranes and is rapidly distributed in the body. The volume of distribution is about 0.7 L/kg.[33] There appears to be no accumulation of caffeine in any organs or tissues and it has also been detected in all body fluids. It enters saliva, semen, breast milk and bile. Indeed, the assessment of caffeine in saliva has been widely used as a valid and noninvasive alternative to serum in monitoring caffeine concentrations.[34-36]

4.2 Metabolism and Elimination

The metabolism of caffeine shows high complexity because of the participation of a large variety of enzymes and intermediate products (fig. 1). More than 25 metabolites have been identified in humans.[37] *In vivo*[32,38,39] and *in vitro*[40] studies have shown that caffeine is predominantly eliminated via N^3-demethylation to 1,7-dimethylxanthine (paraxanthine). When only demethylation pathways are considered, this reaction accounts for

approximately 84% of primary caffeine demethylation. Formation of 3,7-dimethylxanthine (N^1-demethylation) and 1,3-dimethylxanthine (N^7-demethylation) accounts for approximately 11 and 5%, respectively, of the 3 primary demethylations of caffeine.[38,40]

The hepatic N^3-demethylation of caffeine is specifically catalysed by CYP1A2.[40-44] In addition, CYP1A2 is also involved in the N^1- and N^7-demethylations. Thus, CYP1A2 accounts for more than 95% of the primary caffeine metabolism and also for the wide variability in the great majority of individuals.[40,45] A small proportion of the N^1- and N^7-demethylations cannot be explained by CYP1A2 activity; this can be quantitatively accounted for by the catalytic action of CYP2E1, the ethanol-inducible CYP.[40] Each of the 3 dimethylxanthines can be further demethylated to monomethylxanthines. Via an unknown intermediate, 1,7-dimethylxanthine is converted to 5-acetylamino-6-formylamino-3-methyluracil (AFMU) by the polymorphic *N*-acetyltransferase (NAT2).[46] In addition, 1,7-dimethylxanthine is hydroxylated to 1,7-dimethyluric acid and demethylated to 1-methylxanthine by CYP1A2. Thus, 1,7-dimethylxanthine is both a product and substrate of the enzyme. The subsequent breakdown of 1-methylxanthine includes hydroxylation to 1-methyluracil by xanthine oxidase (fig. 1).[45]

The major urinary metabolites of caffeine are 1-methyluric acid, 5-acetylamino-6-formylamino-3-methyluracil, 1-methylxanthine, 1,7-dimethyluric acid and 1,7-dimethylxanthine. Only a small percentage (1 to 2%) of the ingested dose in humans is excreted unchanged in urine.[39,47] In athletes participating in competitive sport, the presence of caffeine concentrations higher than 12 mg/L in urine is considered a deliberate attempt at doping and hence, regarded as a disqualifying factor by the International Olympic Committee (IOC). As well as the metabolic variability of caffeine, renal factors (i.e. urine flow rate) play an important role in modulating the fate of caffeine and some of its metabolites *in vivo*.[45] Therefore, urinary concentration of caffeine is extremely vulnerable to variations of the timing of urine sample collection. Elimination half-life of caffeine for most people ranges from 3 to 6 hours in adults but, is almost 2-fold longer in nondrinkers compared with those who are accustomed to drinking large amounts of coffee (7.5 and 4 hours, respectively).[3,32] This finding could be related to a higher incidence and severity of caffeine-related toxic effects in caffeine-naive or nontolerant individuals when compared with regular consumers.[3,16,18,21-23,25] Neonates eliminate caffeine very slowly with half-lives averaging 100 hours.[3,6,47]

5. The Human Polycyclic Aromatic Hydrocarbon–Inducible Cytochrome P450 (CYP1) Family

5.1 CYP1A1

The human polycyclic aromatic hydrocarbon (PAH)–inducible CYP1A subfamily consists of the structurally related isozymes CYP1A1 and 1A2. Although there is an apparent selectivity for some compounds, both enzymes exhibit overlapping

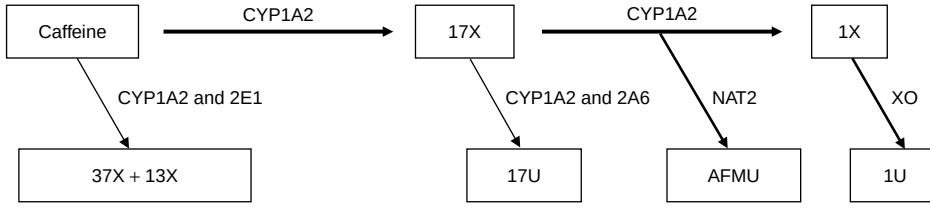

Fig. 1. Major pathways of caffeine (1,3,7-trimethylxanthine) biotransformation, with primary enzymes shown at each important step. The thickness of arrows shows the relative importance of each pathway. **1U** = 1-methyluric acid; **1X** = 1-methylxanthine; **13X** = 1,3-dimethylxanthine (theophylline); **17U** = 1,7-dimethyluric acid; **17X** = 1,7-dimethylxanthine (paraxanthine); **37X** = 3,7-dimethylxanthine (theobromine); **AFMU** = 5-acetylamino-6-formylamino-3-methyluracil; **CYP** = cytochrome P450; **NAT2** = polymorphic *N*-acetyltransferase type 2; **XO** = xanthine oxidase.

substrate specificities.[48,49] CYP1A1 is predominantly expressed in extrahepatic tissues, notably the lung, mammary gland, lymphocytes and placenta, where it metabolises and is markedly induced by PAHs, such as those in cigarette smoke.[50-53]

The regulatory mechanisms of CYP1A1 induction involve transcriptional events and have been thoroughly elucidated.[54]

Briefly, the expression of CYP1A1 is regulated at the level of transcription by a process which is initiated by the binding of an appropriate inducing agent to the cytosolic polycyclic aromatic hydrocarbon (Ah) or dioxin receptor and are translocated into the nucleus. The transcriptional process includes a sequence of events: ligand-dependent heterodimerisation between the Ah receptor and an Ah receptor nuclear translocator (the aryl hydrocarbon nuclear translocator protein), and interaction of the heterodimer with a xenobiotic-responsive enhancer. This interaction leads to increased transcription of the CYP1A genes, synthesis of the appropriate mRNA and *de novo* production of CYP-1A protein.

5.2 CYP1A2

In contrast to CYP1A1, CYP1A2 is one of the most abundant CYP isoenzymes in the liver, accounting for about 15% of the total CYP content.[53] Human CYP1A2, together with CYP1A1, metabolically activate a large number of procarcinogens to reactive intermediates that can interact with cellular nucleophiles and can ultimately trigger carcinogenesis.[55]

Additionally, the human CYP1A2 is responsible for the metabolism of several clinically important drugs (table III). CYP1A2 is among the isoenzymes with pronounced interindividual variation in activity[28,39,105,106] but, in contrast to reports by some authors,[107] its activity seems not to be polymorphically distributed in humans.[39,45,108] This variability is also reflected in the pharmacokinetics of drugs that are substrates for CYP1A2. It may also have important clinical implications, since drugs that are metabolised by, or bind to, the same enzyme have a high potential for pharmacokinetic

Table III. Drugs whose metabolism is partially or entirely dependent on human cytochrome P450 (CYP) 1A2. Michaelis-Menten constant (Km) values were obtained from human liver microsomes and several CYP1A2 expression systems such as B-lymphoblastoid cells, yeast and Hep G2 cells

Drug	Km (μmol/L)	C_{max} *in vivo* (μmol/L)	References
Antiandrogens			
Flutamide		0.2	56, 57
Antidepressants			
Amitriptyline	87[a]	1.0	58, 59
Clomipramine		1.0	60, 61
Fluvoxamine		1.0	62, 63
Mianserin	125[a]	0.5	64, 65
Imipramine	10[b]	1.0	66, 67
Antipsychotics			
Clozapine	60[c]	3.0	68-70
Haloperidol?		0.05	71, 72
Olanzapine	40[c]	0.3	73-75
Thioridazine?		2.0	76, 77
Antiserotonergic			
Ondansetron		0.2	78, 79
Cardiovascular drugs and anticoagulants			
Lidocaine		26.0	80, 81
Mexiletine	14[a]	10	82-84
Propafenone		2.5	85, 86
Propranolol	200[c]	3.5	87-89
Triamterene			90
Verapamil		0.5	91
Warfarin	1400[c]	10	92
Cholinesterase inhibitors			
Tacrine		0.15	93-95
Local anesthetic			
Ropivacaine	16[c]	7.5	96, 97
Nonsteroidal anti-inflammatory drugs (NSAIDs)			
Paracetamol (acetaminophen)	3500[d]	33	98
Phenacetin[e]	30[c]		41, 49
Quinolones			
Pefloxacin	750[c]	40	99, 100
Xanthines			
Caffeine[e]	500[c]	50	101, 102
Theophylline	200-1000[a]	100	9, 103, 104

a B-lymphoblastoid cells.

b Yeast.

c Human liver microsomes.

d Hep G2 cells.

e Phenacetin *O*-de-ethylation and caffeine N^3-demethylation are 2 well-established markers for the assessment of human CYP1A2 metabolic activity.

C_{max} = peak plasma concentration of the drug *in vivo*; **?** = not fully elucidated, indirect evidence from *in vivo* studies.

Table IV. Non-drug factors reported to affect cytochrome P450 (CYP) 1A2 metabolic activity in humans

Factor	Effect on CYP1A2 activity	References
Body mass index?		109
lean individuals	↑	
obese individuals	↓	
Coffee	↑	109
Cruciferous vegetables	↑	110, 111
Exercise	↔	111, 112
Alcohol (ethanol)	↓	112, 113
Grapefruit juice	↓	114
Grilled meat	↑	115, 116
Liver disease	↓	117
Gender?		28, 32, 109
males	↑	
females	↓	
Gender-specific		
menstrual cycle?	↓ (luteal phase)	118
pregnancy	↓	119
Smoking	↑	39, 109, 120, 121

? = not fully elucidated; ↑ = increase; ↓ = decrease; ↔ = no effect.

interactions. In the apparent absence of a functionally relevant genetic polymorphism, constitutional and environmental factors have been suggested to be responsible for the marked interindividual variability in human CYP1A2. Table IV lists the constitutional and environmental factors, excluding drugs, that are known to influence the metabolic activity of CYP1A2.

Currently, the regulation of CYP1A2 expression is not as well characterised as that of CYP1A1. Smoking has a dose-dependent inducing effect on CYP1A2.[28,120,121] Induction of CYP1A2 by PAHs is mainly transcriptional and involves the Ah receptor, but also other unknown factors.[122] CYP1A2 can also be induced by charcoal-broiled meat[115,123] and by a high intake of cruciferous vegetables, such as broccoli or Brussels sprouts.[110,111] Induction of CYP1A2 also seems to be related to high dietary coffee consumption, either caused by caffeine or other coffee constituents.[109,112,115] Induction may result in a reduction of pharmacological effects, caused by increased drug metabolism, or create an undesirable imbalance between toxification and detoxification.[122,124-126] Indeed, it is not clear whether activation of the Ah receptor pathway confers a risk by increased activation of procarcinogens or a benefit by a more rapid elimination of potentially dangerous chemicals.[55,122,124-126]

Conversely, grapefruit juice (and its components)[114] and alcohol,[112,113] as well as liver disease,[117] have an inhibitory effect on CYP1A2. Surprisingly, body mass index has been shown to be a source of variability, and hence caffeine clearance is higher in lean compared with obese individuals (on a ml/min/kg bodyweight basis).[109]

Several authors[28,109,127,128] have found gender-related differences in CYP1A2 activity in healthy volunteers, with females having lower values. Furthermore, we found that nonsmoking females are at the highest risk of caffeine toxicity.[28] In addition, other gender-specific factors such as menstrual cycle phase[118,129] and pregnancy[119] seem to affect the pharmacokinetics of CYP1A2 substrates (table IV). Further research into these areas will provide a better insight into the impact of gender differences on CYP1A2 activity and hence drug response.

Notwithstanding, in the absence of a defined genetic polymorphism in CYP1A2, individual CYP1A2 activities are presently measured by phenotypic analysis. The availability of a reliable probe drug providing a measure of CYP1A2 activity is of considerable interest. Caffeine has become popular as an *in vivo* metabolic probe drug for the human xenobiotic-metabolising enzymes; as well as CYP1A2, NAT2 and xanthine oxidase may be assessed with the use of this probe *in vivo*.[32,39,45]

5.3 CYP1B1

CYP1B1 is a novel member of the CYP1 family. This enzyme is also highly inducible by PAHs and has catalytic activities overlapping CYP1A1 and 1A2 with respect to the oxidation of drugs and model CYP substrates such as caffeine and theophylline, 2 prototypic substrates for CYP1A2.[130] Unless they are induced, CYP1A1, and especially CYP1B1, are unlikely to be quantitatively of great importance in drug metabolism, but the contribu-

tion of both enzymes to the increased clearance of known CYP1A2 substrates, such as caffeine, may be of importance for individuals exposed to PAH-like inducers.

Intriguingly, CYP1B1 has been found to be expressed at a high frequency in a wide range of human cancers of different histogenetic types, including cancers of the breast, colon, lung, oesophagus, skin, lymph node, brain and testis.[131]

6. Drugs That Interact with Caffeine

Caffeine is both a low-clearance and low-affinity drug for CYP1A2 [Michaelis-Menten constant (Km) 500 μmol/L]. This is very important because the relative enzyme affinity of substrates and inhibitors determines the extent of interaction (tables III and V). Pharmacokinetic interactions between caffeine and medications, as well as their clinical relevance, are displayed in tables VI and VII.

The role of the PAH-inducible CYP1A2, the main enzyme involved in the metabolism of caffeine, is increasingly acknowledged in the metabolism of drugs. Thus, clinically defined pharmacokinetic interactions between caffeine and medications tend to occur at the level of CYP1A2. A close examination of the literature reveals that in most cases *in vitro* interaction studies were carried out to assess the potential of pharmacokinetic interactions by comparing the relative affinities of the substrate (Km) and inhibitor (K_i) with their concentration ranges found in clinical studies. One of the most common approaches is the use of *in vitro* Km and K_i values together with *in vivo* values of the C_{max} of the inhibitor to forecast the possibility of metabolic interactions.[124,189]

6.1 Allopurinol

The administration of allopurinol to healthy individuals causes a specific, dose-dependent inhibition of the conversion of the caffeine metabolite 1-methylxanthine to 1-methyluracil, a metabolic pathway dependent on xanthine oxidase activity (fig. 1).[190,191] Because there is only a minor contribution from the xanthine oxidase-mediated pathway to the overall metabolism of caffeine, this interaction seems to be of no clinical relevance.

An *in vitro* study has shown an inhibitory effect of caffeine on xanthine oxidase activity.[192] In contrast, a longitudinal study carried out in 11 healthy male volunteers over several months with systematic variation of caffeine dose and lifestyle factors revealed no effect of dietary caffeine on the cytosolic enzyme.[193]

6.2 Antimycotic Drugs

The effects of single oral doses of ketoconazole 400mg and terbinafine 500mg on the hepatic microsomal system have been investigated in 8 healthy males.[139] The inhibitory effect of terbinafine on the metabolism of caffeine was more pronounced than that of ketoconazole: clearance was decreased by 21% and by 11%, respectively, and the corresponding half-life was increased from 5.8 hours in the controls to 7.6 and 6.7 hours, respectively. The serum concentrations of the anti-

Table V. Inhibition affinity of drugs for cytochrome P450 (CYP) 1A2, as assessed by inhibition of 2 well-established CYP1A2-mediated reactions, the N^3-demethylation of caffeine or the *O*-de-ethylation of phenacetin in human liver microsomes

Drug	K_i (μmol/L)	C_{max} *in vivo* (μmol/L)	References
Ciprofloxacin	180[a]	5.0	132, 133
Desmethylsertraline	9.5[b]	0.1	134
Enoxacin	140[a]	10	99, 132
Fluoxetine	4.4[b]	1	134, 135
Fluvoxamine	0.2[b]	1	135, 136
Furafylline	0.25-0.7[b]	10	43, 44, 134
Ketoconazole	32[b]	10	134
Mexiletine	6.9[b]	10	84, 91
Norfloxacin	100[a]	5.0	99, 133
Norfluoxetine	15.9[b]	1	134, 135
Paroxetine	5.5[b]	0.2	134, 135
Pefloxacin	1000[a]	40	99, 100
Pipemidic acid	210[a]		132
Propafenone	5.4[b]	2.5	86, 137
Sertraline	8.8[b]	0.1	134, 135

a N^3-Demethylation of caffeine.

b *O*-De-ethylation of phenacetin.

C_{max} = peak plasma concentration of the drug *in vivo* after clinically relevant doses; **K_i** = inhibition constant (the smaller the value, the greater the potency).

Table VI. Effect of drugs on the pharmacokinetics of dietary caffeine and the clinical significane (classified as general, occasional, unclear relevance or irrelevant)

Drugs	Gender (age) [disease][a]	Dosage regimen	Altered parameter of caffeine	Clinical significance[b]	References
Antimycotics					
Fluconazole	Young (23 ± 2y)	MD 200-400 mg/day	↓ CL (by 25%)	Unclear	138
	Elderly (69 ± 2y)	MD 200-400 mg/day			
Ketoconazole	8M (20-32y)	SD 400mg	↓ CL (by 11%)	Unclear	139
Terbinafine	8M (20-32y)	SD 500mg	↓ CL (by 21%)	Unclear	139
Cardiovascular drugs					
Diltiazem[c]	5M/3F (54-73y) COPD/asthma	MD 60 mg/day	↓ CL (by 22%)	Unclear	140
Mexiletine	Cardiac arrhythmias	NA	↓ CL (by 50%)	General	141
Verapamil[c]	6M/1F (27-38y)	MD 360 mg/day	↓ CL (by 20%)	Unclear	142
CNS drugs					
Clozapine	1 patient	MD 200 mg/day	ND	General	143-145
Fluvoxamine	8	MD 50-100 mg/day	↓ CL (by 80%)	Occasional	146, 147
Olanzapine	8 patients	MD 8 mg/day	↓ UR (by 30%)	Unclear	148
Methylxanthines					
Furafylline	5M/4F (23-28y)	SD 125mg, MD 30 mg/day	↑ C_{ss} (above 150-fold), ↑ $t_{½}$ (10-fold)	General	43
Theophylline	6M (24-50y)	SD 340mg	↑ C_{ss} (by 190%)	Occasional	149, 150
Miscellaneous					
Cimetidine	12	MD 1000 mg/day	↓ CL (by 31%)	Irrelevant	151, 152
Idrocilamide	4		↑ $t_{½}$ (9-fold)	General	153
Oral contraceptives	31	MD	↓ CL (by 40%)	Unclear	32, 154-156
Phenylpropanolamine	13M/3F (19-36y)	SD 75mg	↑ C_{max} (by 280%)	General	157, 158
Psoralens					
Methoxsalen	4M/1F (27-55y) psoriasis	SD 1.2 mg/kg	↓ CL (by 70%)	General	159, 160
5-Methoxypsoralen	6M/2F (20-76y) psoriasis	SD 1.2 mg/kg	↓ CL (by 31%)	General	161
Proton pump inhibitors					
Lansoprazole[c]	8	MD 30-60 mg/day	↑ CL (by 10%)	Irrelevant	162
Omeprazole	11M/7F (18-82y)	MD 40 mg/day	↑ CL (by 40%)[d]	Unclear	163-165
Pantoprazole[c]	8M (25-30y)	MD 30 mg/day	None	Irrelevant	166
Quinolones					
Ciprofloxacin	12M (24-39y)	MD 500 mg/day	↓ CL (by 33%)	Occasional	167-169
Enoxacin	12M (24-39y)	MD 800 mg/day	↓ CL_{ss} (by 80%)	General	99, 167
Fleroxacin	12M/12F	MD 400 mg/day	None	Irrelevant	168

mycotics were within the therapeutic range in each volunteer.[139]

Nix et al.[138] found that fluconazole inhibited the metabolism of caffeine (decreased clearance by 25%) in a concentration-dependent manner.

Despite the fact that antimycotic drugs are generally considered to be potent inhibitors of CYP3A enzymes, as shown by their effect on the metabolism of midazolam, a probe drug for CYP3A,[189,194] fluconazole, ketoconazole and terfinafine clearly also inhibit the metabolism of caffeine, a well-established CYP1A2 probe drug. Although no adverse symptomatology was reported, the clinical significance of these findings remains to be elucidated.

6.3 Cardiovascular Drugs

Kobayashi et al.[137] recently reviewed the effects of 11 antiarrhythmic drugs on phenacetin *O*-de-ethylation,[41] a marker reaction for CYP1A2, by human liver microsomes and cDNA-expressed CYP1A2. Among the antiarrhythmic drugs studied, 2 CYP1A2 substrates, propafenone[137] and mexiletine[82,83] (table III), potently inhibited the enzyme in a competitive manner (K_i 5.5 and 6.9 μmol/L, respectively; table V).[137] Recently, Labbé et al.[83] found that with concomitant intake of a single oral dose of mexiletine 200mg, caffeine concentrations increased by 23% in healthy individuals, but the change was not statistically significant ($p < 0.1$). Nevertheless, increased plasma concentrations of caffeine with the coadministration of mexiletine may still be of concern in patients with cardiac arrhythmia, and some adverse effects of mexiletine might be attributable to decreased caffeine elimination (by 50%), as reported by Joeres et al.[141] Likewise, mexiletine has been reported to elevate plasma concentrations of theophylline, with subsequent toxicity.[195,196]

Additionally, in the study of Labbé et al.,[83] the total clearance of mexiletine was not significantly altered by coadministration of caffeine to extensive metabolisers (EMs) and poor metabolisers (PMs) by CYP2D6, but a stereroselective decrease averaging 15% in the urinary recovery of *N*-

Grepafloxacin[c]	16	MD 600 mg/day	↓ CL (by 50%)	Unclear	170
Lomefloxacin	16	MD 400 mg/day	None	Irrelevant	171, 172
Norfloxacin	8M (20-37y)	MD 800 mg/day	↓ CL (by 35%)	Occasional	173, 174
Ofloxacin	12M (24-39y)	MD 400 mg/day	None	Irrelevant	167, 175, 176
Pefloxacin	6M/6F (22-29y)	MD 800 mg/day	↓ CL (by 47%)	Occasional	99
Pipemidic acid	8M (20-37y)	MD 800 mg/day	↓ CL (by 63%)	Unclear	173, 174
Rufloxacin	12	SD 400mg	None	Irrelevant	177
Temafloxacin	12M	MD 1200 mg/day	None	Irrelevant	178
Tosufloxacin[c]	7M	MD 450 mg/day	↓ CL (by 34%)	Unclear	179
Trovafloxacin[c]	12M	MD 200 mg/day	None	Irrelevant	180

a Individuals are healthy unless otherwise specified.

b The clinical relevance of pharmacokinetic interactions comes from controlled studies as well as isolated case reports.

c The interaction has been reported to occur with theophylline, therefore a comparable interaction with caffeine also seems likely to occur.

d This effect was reported in poor metabolisers of CYP2C19 after omeprazole 40 mg/day. A comparable induction (by 28%) was obtained in extensive metabolisers but after 120 mg/day.

C_{max} = peak plasma drug concentration; **CL** = plasma clearance; **CL_{ss}** = plasma clearance at steady state; **COPD** = chronic obstructive pulmonary disease; **C_{ss}** = steady-state concentration; **CYP** = cytochrome P450; **F** = females; **M** = males; **MD** = multiple dose; **NA** = not available; **ND** = not determined; **SD** = single dose; **$t_{½}$** = half-life; **UR** = urinary ratio of CYP1A2 [(AFMU + 1-methyluric acid + 1-methylxanthine + 1,7-dimethyluric acid + 1,7-dimethylxanthine)/caffeine].

Table VII. Drugs that may have pharmacokinetic interactions with dietary caffeine, and the clinical significance of the effect

Interacting drug	Gender (age) [disease state][a]	Drug regimen	Effect on interacting drug	Clinical relevance	References
Aspirin (acetylsalicylic acid)	12M	SD 650mg	↑ C_{max} (by 15%)	Augmented efficacy?	181, 182
Clozapine	6M/1F (25-41y) schizophrenia	MD 200 mg/day	↑ C_{ss} (by 50%)	Toxicity	183, 184
Lithium	11 Psychiatric patients	NA	↓ C_{ss} (by 24%), ↑ CL_R	Therapeutic failure	185, 186
Mexiletine[b]	14 (28 ± 4y)	SD 200mg	↓ UR (by 15%)	Irrelevant	83
Paracetamol (acetaminophen)	10M	SD 500mg	↑ AUC	Augmented efficacy?	187
Theophylline	8M (20-26y)	MD 300 mg/day	↓ CL (by 29%)	Toxicity	188
	6M (24-50y)	SD 340mg	↓ CL (by 23%)		150

a Individuals are healthy unless otherwise specified.

b A stereoselective decrease in the urinary recovery of *N*-hydroxymexiletine from the (*R*)-(–)-enantiomer was found in extensive metabolisers and poor metabolisers of debrisoquine.

AUC = area under the serum or plasma concentration-time curve; $\mathbf{C_{max}}$ = peak plasma concentration; $\mathbf{C_{ss}}$ = plasma concentration at steady-state; **CL** = total **body** clearance; $\mathbf{CL_R}$ = renal clearance; **F** = females; **M** = males; **MD** = multiple dose; **NA** = not available; **SD** = single dose; **UR** = urinary recovery.

hydroxymexiletine from the *R*-(–)-enantiomer was found in EMs and PMs of debrisoquine.

On the other hand, the calcium channel blocker verapamil produced a 35% inhibition of caffeine N^3-demethylation (CYP1A2) in liver microsomes.[197] Thus, a pharmacokinetic interaction between verapamil and caffeine, as shown with theophylline,[142,198] also seems likely. In addition, theophylline clearance decreased by 22% after diltiazem therapy in patients with bronchospastic airway disease.[140]

6.4 CNS Drugs

Excessive caffeine intake is especially prevalent in psychiatric patients, with 22% of psychiatric inpatients using more than 750 mg/day compared with 9% of the general population.[199-203] An elevated incidence of caffeine-related symptoms of anxiety, depression, fear or panic has been reported in these patients.[27,201] These patients may, therefore, require increased doses of medication to counteract the effects of caffeine resulting in a higher risk of pharmacokinetic interactions between caffeine and psychoactive drugs.[4,204]

6.4.1 Antidepressants

Citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline are widely prescribed medications that belong to the class of drugs called selective serotonin reuptake inhibitors (SSRIs). Currently, there is much debate regarding SSRIs and drug interactions, mainly through the potential of these compounds to inhibit CYP isozymes.[76,205-207] Paroxetine and fluoxetine (and its metabolite norfluoxetine) are particularly potent inhibitors of CYP2D6, whereas fluvoxamine has little effect on this enzyme.[208-212] In contrast, fluvoxamine is a potent inhibitor of PAH-inducible CYP1A2 activity (K_i 0.2 μmol/L) *in vitro* and *in vivo*,[136,210] leading to increased plasma concentrations of the CYP1A2 substrates clozapine[213,214] and caffeine.[146] However, fluoxetine and norfluoxetine, paroxetine, sertraline and desmethylsertraline also inhibit CYP-1A2 with K_i values ranging from 4.4 to 16 μmol/L (table V). The clearance of caffeine decreased by 80% and half-life increased by 500% during concomitant intake of fluvoxamine.[146]

Recently, Spigset[147] raised an interesting hypothesis, suggesting that many of the adverse drug reactions traditionally attributed to fluvoxamine are in fact caffeine-related symptoms of toxicity as a consequence of inhibition by fluvoxamine of the metabolism of caffeine from dietary sources. This effect could be more pronounced in those patients reported to be PM of the CYP2D6 metabolic activity.[76] Clinicians should be aware of this, as these 'symptoms' often lead to the discontinuation of

fluvoxamine therapy instead of an appropriate adjustment in the consumption of caffeine-containing beverages.

6.4.2 Antipsychotics

A chemical interaction between several phenothiazines and constituents of caffeinated beverages has been observed. The dilution of phenothiazine drug elixirs with coffee or tea caused the formation of precipitates that could have inactivated an oral dose of the antipsychotic, but the clinical significance of this finding remains unclear.[215,216]

Clozapine was the first marketed antipsychotic agent labelled as atypical. Although the metabolism of most of the classical antipsychotic drugs cosegregates with genetically determined CYP2D6 activity,[217] no such relationship was found for clozapine.[218] Conversely, we found that clozapine is metabolised by CYP1A2 to a major extent[68] (table III).

Several episodes of acute exacerbation of psychotic symptoms were reported in one patient with schizophrenia when started on clozapine therapy.[143] This patient drank coffee (5 to 10 cups per day) for many years without experiencing any adverse effect while being treated with classical antipsychotics. The patient was encouraged to avoid the intake of caffeine and no further acute psychotic episodes were noted. The authors of this report postulated a pharmacodynamic interaction at the receptor level, but the effect could have been due to a competitive pharmacokinetic interaction between clozapine and caffeine at the CYP1A2 enzyme level.[144]

Beale et al.[145] reported a case of supraventricular tachycardia in a patient receiving electroconvulsive therapy, clozapine and caffeine. Caffeine was discontinued, improving the tolerability of the electroconvulsive therapy.

In order to obtain further clinical evidence on the likelihood of a pharmacokinetic interaction between clozapine and dietary caffeine, we carried out a controlled study in patients with schizophrenia.[183] Plasma clozapine concentrations significantly decreased by an average of 47% after caffeine withdrawal from the diet. The largest percentage decrease (80%) was registered in the patient with the heaviest smoking behaviour (40 cigarettes/day) and caffeine consumption (greater than 1 g/day).

Odom-White and de Leon[184] reported a case of a nonsmoking woman on clozapine 550 mg/day for 5 months. The patient consumed large amounts of caffeine during this period, both dietary (1 g/day) and medication (0.2 g/day). During this concomitant intake of clozapine and caffeine, plasma clozapine concentrations above 1500 μg/L and an increasing worsening of clinical status were reported. She was advised to discontinue caffeine, and her plasma clozapine concentrations decreased to approximately 600 μg/L.

These findings are compatible with competitive inhibition of the metabolism of clozapine by caffeine. In fact, clozapine has a higher affinity than caffeine for the CYP1A2 enzyme (Km values 60 and 500 μmol/L, respectively; table III), but because of the higher concentrations of caffeine (typical C_{max} values 3 and 50 μmol/L, respectively), Michaelis-Menten kinetics predict that caffeine will occupy most of the CYP1A2 binding sites. This is sufficient to inhibit the metabolism of clozapine.

Some of the severe clozapine-induced adverse effects (confusion, delirium and generalised seizures) are dose dependent and, consequently, related to serum clozapine concentrations.[219,220] Supporting this hypothesis, McCarthy[221] described an episode of a grand mal seizure in a clozapine-treated patient with schizophrenia following smoking cessation, probably because of a lower activity of the smoking-inducible CYP1A2 and hence increased plasma concentrations of clozapine. Thus, drastic changes in the consumption of caffeine and/or smoking could influence the pharmacokinetics of clozapine, but these factors may not be appreciated as the causes of severe adverse affects during antipsychotic drug therapy in patients with schizophrenia.[28,183] The monitoring of clozapine and metabolite concentrations may be warranted in such situations.[69,183,220]

Olanzapine is also an atypical antipsychotic drug that shares many pharmacological properties

with clozapine. *In vitro*[73,222] and *in vivo*[223,224] investigations have demonstrated the involvement of the smoking-inducible CYP1A2 in the metabolism of this drug (table III). We have recently demonstrated that olanzapine may significantly impair the clearance of caffeine, mainly through CYP1A2 inhibition.[148] In 8 patients with schizophrenia a caffeine urinary assay was performed on 2 occasions, prior to (baseline) and after receiving monotherapy with a stable daily oral dosage of olanzapine 0.11 ± 0.02 mg/kg (mean ± SD) for 15 days. The ratio of metabolites (AFMU + 1-methyluric acid + 1-methylxanthine + 1,7-dimethyluric acid + 1,7-dimethylxanthine) to caffeine, all measured in urine, was calculated and used as an index of CYP-1A2 activity. This ratio decreased from 79 (baseline) to 50 (after olanzapine therapy) with a mean percentage decrease of 41% ($p < 0.02$). In contrast, in a study conducted in healthy volunteers, olanzapine did not affect the pharmacokinetics of the CYP1A2 substrate theophylline.[225]

However, the clinical significance of these findings remain unclear.

6.4.3 Lithium

Because the kidney exclusively removes lithium, its pharmacokinetic fate is highly influenced by any variable affecting individual renal blood flow regardless of metabolic capacity. An increase in lithium excretion rates because of caffeine intake was reported in a single dose study,[226] but the magnitude of this interaction was not specified. However, caffeine withdrawal has been documented to increase serum lithium concentrations by an average of 24% in a prospective nonblind study of 11 psychiatric patients.[185] Jefferson[186] has reported 2 cases of patients in whom lithium tremor worsened after the withdrawal of caffeine from the diet. A reduction in renal lithium clearance resulting in increased serum lithium concentrations seems to be the mechanism.

6.5 Histamine H_2 Receptor Antagonists

The effects of cimetidine on the metabolism of caffeine seem to be contradictory. In support of data obtained with theophylline,[227-229] a significant reduction in the systemic clearance of caffeine has been observed in individuals who received pretreatment with cimetidine.[151,152] Conversely, in a study carried out in children receiving cimetidine for gastritis, the performance of a caffeine breath test did not show a significant change in the 2-hour cumulative labelled CO_2 excretion following the administration of cimetidine.[230]

The association of caffeine and cimetidine is unlikely to produce clinically relevant adverse effects. However, famotidine induced a significant slowing of theophylline elimination with a cimetidine-like interaction profile.[231]

6.6 Idrocilamide

The myorelaxant idrocilamide greatly alters the pharmacokinetics of caffeine when given concomitantly. Although initially considered well tolerated, a series of neuropsychiatric adverse drug reactions linked to idrocilamide have been reported in the French literature. Idrocilamide inhibits the biotransformation of caffeine (mainly acting through CYP1A2 inhibition) in regular consumers of caffeine-containing foods and beverages, leading to a 9-fold increase in half-life as well as the occurrence of caffeine-related adverse effects that included insomnia, anxiety, hyperactivity, elevated mood, confusion and delirium.[153] Thus, partial or total avoidance of caffeine-containing products is recommended during treatment with idrocilamide.

6.7 Methylxanthines

6.7.1 Furafylline

Furafylline is a xanthine derivative that was introduced as a long-acting replacement for theophylline in the treatment of patients with asthma, but, unlike theophylline, it appeared to be essentially devoid of stimulant effects on the CNS.[43] However, several investigations in healthy volunteers following the administration of single (125mg) and multiple (30 mg/day after initial loading of 90mg) doses of furafylline showed an excessive accumulation of caffeine from normal dietary intake. In some volunteers, plasma caffeine concentrations and half-life increased more than 150- and

10-fold, respectively.[43] Not unexpectedly, the volunteers experienced a wide variety of caffeine-related adverse effects, including heartburn, mental confusion and headache. Furafylline is a very potent and selective mechanism-based inhibitor of CYP1A2, as assessed by *in vitro* inhibition of phenacetin *O*-de-ethylation (K_i 0.25 to 0.7 μmol/L) [table V].[44]

6.7.2 Theophylline

Theophylline (1,3-dimethylxanthine) is closely related chemically to caffeine, but its metabolism is much less complex. The PAH-inducible CYP1A2 catalyses 80 to 90% of the *N*-demethylations and about 50% of the 8-hydroxylation (the main metabolic pathway) to 1,3-dimethyluric acid *in vitro* (apparent Km ranges from 200 to 1000 μmol/L) [table III]. CYP2E1 is responsible for the remainder of the 8-hydroxylation, and the apparent Km of this reaction is about 15 000 μmol/L, suggesting that CYP2E1 may be the low-affinity high-capacity isoform involved in theophylline metabolism.[103,104,232]

One case report in a patient given theophylline for alleviating chronic obstructive pulmonary disease showed that caffeine from the diet may accumulate to toxic concentrations during therapy with theophylline.[149] Sato et al.[150] showed that the concomitant intake of dietary caffeine and theophylline led to a decreased elimination of both compounds in healthy men. The mean serum concentrations of caffeine increased by 158%. Accordingly, the apparent elimination half-life of theophylline was prolonged from 6.3 to 8.3 hours and the total body clearance was reduced by 23%.[150] These findings were corroborated by Jonkman et al.[188] in 2 individuals who did not consume caffeine regularly but experienced methylxanthine-related toxic symptoms (headache and nausea) during concomitant administration of caffeine and theophylline.

In order to avoid adverse reactions during bronchodilator therapy with theophylline, consumption of caffeine should be controlled.

6.8 Nonsteroidal Anti-Inflammatory Drugs

Caffeine decreases the clearance of paracetamol (acetaminophen) and it has been postulated that caffeine can significantly potentiate its therapeutic effects in humans by pharmacodynamic (co-analgesic) or pharmacokinetic mechanisms.[19,187] Caffeine also seems to increase the bioavailability of aspirin (acetylsalicylic acid) in humans without any other effects on salicylate disposition. Therefore, following administration of a single oral dose of caffeine 120mg (equivalent to 60mg of free base), it was found that the C_{max} and area under the concentration-time curve (AUC) values of salicylic acid were increased by 16% and 12%, respectively.[181,182]

However, these findings seem to be of little clinical significance.

6.9 Oral Contraceptives and Estrogen Replacement Therapy

Oral contraceptives (OCs) are among the most frequently prescribed drugs in the world. In clinical practice, they are a major gender-specific factor in drug metabolism.[233] Several investigations have shown that healthy women on long term OCs have a CYP1A2-mediated impairment of caffeine clearance (by 40%).[109,154-156] The mechanism seems to be mediated through CYP1A2 inhibition.[32,108,109,234] The presence of ethinylestradiol[235,236] or estradiol[237,238] in medications seems to account for the inhibition mechanism, but it is not clear whether it is related to competition or down-regulation of enzyme synthesis.[238]

With respect to the long term effects of OCs on oxidative metabolism, it appears that after reaching a peak between the 4th and 12th weeks, the changes decrease after 6 months.[109] Unfortunately, women receiving long term OCs have been greatly under-represented in drug trials, so the scope of these effects remains to be determined.

6.10 Phenylpropanolamine

Phenylpropanolamine is mainly used in mixtures given orally to produce nasal decongestion,

but in some countries it is still available as an OTC anorectic agent.[12] Considering the prevalence of caffeine consumption, it is likely that the 2 compounds frequently continue to be co-ingested. Moreover, the relative ineffectiveness of some OTC drugs may contribute to overdose[13] in an effort by users to achieve the advertised effects, and hence cause unexpected and potentially serious toxicity.

Phenylpropanolamine seems not to be harmful at moderate or recommended doses, but much of the concern with the OTC availability of this drug is related to its cardiovascular effects.[239,240] In addition, the adverse effects of caffeine also include cardiovascular stimulation.[3,12] Furthermore, reports of severe adverse drug reactions affecting the cardiovascular system and CNS, including several deaths, after this combination suggested a potential for a dangerous interaction between the compounds.[239,157]

In an investigation carried out in healthy individuals, a combination of caffeine 400mg plus phenylpropanolamine 75mg led to increased caffeine concentrations (by 280%). Adverse effects were reported more frequently after the phenylpropanolamine-caffeine combination than after either drug alone or placebo. These data indicated that phenylpropanolamine inhibits the metabolism of caffeine and explain the elevated incidence of adverse effects reported after their combined use.[158]

6.11 Proton Pump Inhibitors

Almost a decade ago, Diaz et al.[163] described an omeprazole-related induction of the CYP1A subfamily in human liver both *in vitro* and *in vivo*. Subsequently, many authors have shown the potential of these compounds to induce CYP1A2 metabolic activity.[164,241,242] Omeprazole is not a direct ligand for the Ah receptor.[241] However, recent evidence suggests that omeprazole is metabolised to a sulfenamide intermediate that interacts with the ligand-binding domain of the Ah receptor.[243] Since the polymorphically expressed CYP2C19 (*S*-mephenytoin hydroxylase) mediates the major metabolic transformations of omeprazole, lansoprazole and pantoprazole,[244] the inducibility of CYP1A2 by omeprazole seems to depend on CYP2C19 status. Therefore, PMs of CYP2C19 exhibited the highest increase (up to 40%) of CYP1A2 activity during treatment with omeprazole 40 mg/day,[164,165] whereas a high dosage (120 mg/day) has to be given in order to demonstrate a comparable induction (by 28%) in EMs.[165] With drugs acting as inducers of the Ah receptor, a main concern is related to the need of dosage adjustment for CYP1A2 substrates. There are only a few currently used drugs that are primarily metabolised by CYP1A2: these are theophylline, caffeine, tacrine, clozapine, olanzapine and flutamide.[109] However, a lack of CYP1A2 induction by omeprazole at recommended therapeutic dosages of 20 mg/day has been reported using 3 well-established *in vivo* markers of CYP1A2 activity, caffeine,[245] theophylline[246] and phenacetin.[247] Lansoprazole 60 mg/day had a minimal effect on the pharmacokinetics of theophylline (increased clearance by 10%) and hence, on CYP1A2.[244] However, lansoprazole at the lower recommended therapeutic dosage of 30 mg/day had no influence on the metabolism of caffeine in healthy volunteers.[245]

Recently, 2 studies concluded that none of the 3 proton pump inhibitors omeprazole (20 to 40 mg/day), lansoprazole (30 to 60 mg/day) and pantoprazole (40 to 80 mg/day), administered in a range of therapeutic dosages at steady state, is an inducer of CYP1A2, either in PMs or in EMs of CYP2C19, as measured by means of the rate of caffeine[248] and theophylline[249] metabolism. The debate is, however, contradictory and not yet unequivocally resolved. On the other hand, it remains to be elucidated whether activation of the Ah receptor pathway by omeprazole could be a risk of activation of procarcinogens during long term therapy.

6.12 Psoralens

Methoxsalen (8-methoxypsoralen), a naturally occurring linear furocoumarin, is used to treat more than 30 dermatoses including psoriasis, vitiligo, and cutaneous T cell lymphoma. This compound is a potent inhibitor of the metabolism of both caf-

feine[159] and theophylline.[250] The clearance of caffeine declined markedly by 70% after the use of methoxsalen in patients with psoriasis.[159]

Another psoralen, 5-methoxypsoralen, was proposed as an alternative to methoxsalen in the treatment of patients with psoriasis since it has similar efficacy but shows better tolerability.[251] However, 5-methoxypsoralen also leads to a CYP1A2-mediated inhibition of the metabolism of caffeine in patients with psoriasis.[161] Inhibition of CYP1A2 by methoxsalen and 5-methoxypsoralen is likely to be related to suicide inhibition, involving the inactivation of a proportion of CYP1A2 by reactive metabolites.[252-254]

Some of the adverse effects frequently observed in patients with psoriasis, such as nervousness, insomnia or excitation, may result from unusually high plasma concentrations of caffeine during concomitant methoxypsoralen administration (table II).[160] Interactions of psoralens with drugs metabolised by CYP1A2 seem less likely when they are used topically in conjunction with ultraviolet A light.[255] However, methoxsalen is a very potent inhibitor and, even minute doses absorbed through the skin might affect the pharmacokinetics of coadministered drugs. Therefore, in order to avoid a potential risk of adverse effects, advice on the need to decrease coffee consumption during psoralen treatment should be given.

6.13 Quinolones

Quinolone antibacterials exert a well-known competitive and dose-dependent inhibitory effect on CYP1A2 (table V).[99,132] A competitive-type inhibition suggests binding of the quinolone to the active site of the enzyme and implies that the quinolone may also be metabolised by the enzyme. Thus, a significant contribution of CYP1A2 (approximately 50%) to the $N^{4'}$-demethylation of pefloxacin to norfloxacin has recently been documented (table III).[99]

A number of studies on pharmacokinetic interactions between xanthines and quinolones have focused on the impaired elimination of theophylline.[170,179,256-259] Because of the contribution of CYP1A2 to the metabolism of caffeine, the likelihood of an interaction between quinolones and caffeine is similar to that reported for theophylline. A significant increase in the AUC and decrease of plasma clearance of caffeine has been documented during concomitant intake of caffeine and a number of quinolones, including enoxacin, ciprofloxacin, norfloxacin and pipemidic acid, in humans.[167,173,175]

Carbo et al.[173] postulated that although no adverse effects were reported in their study, this was probably because of the fact that all volunteers were males who smoked regularly and therefore had induced CYP1A2. A rather pronounced influence of ciprofloxacin on the metabolism of caffeine was seen in another study in healthy volunteers.[168] The relative inhibitory potency of quinolones on the metabolism of caffeine in humans was established by Barnett et al.[176] as enoxacin >>> pipemidic acid >> ciprofloxacin = norfloxacin. Tosufloxacin also has an inhibitory effect on theophylline elimination, with a 34% reduction of total clearance.[179]

Recently, a study of 12 healthy volunteers showed that pefloxacin and enoxacin caused a 2-fold (by 47%) and 6-fold (by 83%) decrease in caffeine clearance, respectively.[99] Furthermore, there was apparently a higher incidence of adverse events in the periods with coadministration of the quinolone, during which higher caffeine concentrations were found. The participants reported neurological (headache, drowsiness, depressive mood, tremor, sleeplessness and nervousness) and cardiovascular (palpitations, orthostatic dysregulation, tachycardia and arrhythmia) symptoms.[99]

Additionally, a decrease in theophylline clearance (by 29%) has been reported when pefloxacin 400mg was coadministered twice daily for 6 days to patients treated with twice daily theophylline 300 to 600mg for obstructive lung disease.[256] Likewise, during grepafloxacin treatment the total clearance of theophylline was reduced by approximately 50%.[170] In contrast, ofloxacin,[175,176,260] fleroxacin,[169] temafloxacin,[178] lomefloxacin,[171,259,261-263] rufloxacin[177]

and trovafloxacin[180] appear to have only minimal effects upon xanthine metabolism.

CNS and cardiovascular disturbances are commonly reported adverse events with fluoroquinolones. These symptoms resemble those of caffeine toxicity.[264] Consequently, in some cases the effects of the consumption of caffeine and concomitant intake of potentially inhibitory quinolones may be underestimated.[265,266]

7. Implications for Doping Control During Sports Events

The effects of caffeine on arousal, reaction time, fatigue and work capacity are such that caffeine intake by athletes during international sporting events is monitored by urine caffeine concentrations. The IOC currently classifies urinary concentration of caffeine above 12 mg/L as a doping offence. Since less than 2% of the administered dose is excreted unchanged in urine, we could speculate that this concentration can only be reached by an excessive intake of coffee (about 7 to 8 cups) or caffeine-containing drugs and tonics (table I). However, the caffeine content of beverages varies considerably from one country to another, so caffeine intake may be highly variable.[8] Furthermore, the metabolic variability and flow dependence of renal excretion rate of caffeine determine the existence of large differences in the rate at which caffeine is eliminated from the body in humans.[45,105,106] Therefore, some athletes could well exceed the current regulatory limit even with a modest coffee intake (about 3 to 6 cups) of average strength brewed coffee per day, particularly if a urine sample is collected around a time of peak plasma caffeine concentration.[267] In addition, some of the reported interactions between caffeine and medications, irrespective of whether they are clinically relevant or not, might also contribute to inadvertently flunk the urinary caffeine concentration limit. Given the severe consequences of a single urine caffeine concentration above the upper authorised official limit in doping controls, the aforementioned factors as well as gender, bodyweight, and sampling delay after exercise should also be considered before using caffeine as an ergogenic aid.[28,267,268]

8. Conclusions

There is no doubt that regardless of age, social, geographical or ethnic differences, caffeine is probably the most frequently and widely consumed drug in the world. However, it is also clear that caffeine has the principal features usually associated with a drug of abuse. In fact, long term administration results in the development of tolerance to many of its effects and a physical dependence that may lead to withdrawal symptoms.

Because of the popularity of caffeine, clinicians should be aware of the potential risks of a pharmacokinetic interaction between dietary caffeine and OTC and prescription medications. Unless a lack of interaction has already been demonstrated for a particular drug, consumption of caffeine-containing food and beverages should be restricted as appropriate. It is recommended that drugs interacting with caffeine should be appropriately labelled.

The role of the PAH-inducible CYP1A2 in drug metabolism is increasingly acknowledged, and this isoenzyme is the target site for the majority of clinically relevant interactions between dietary caffeine and medications so far investigated. However, a number of other factors, including gender, cigarette smoking and other dietary components of foods and beverages, affect the activity of this enzyme and should be specifically studied in clinical trials of new drugs. Because of its wide use and particular metabolic pattern, caffeine has become the model drug of choice for the quantitative measurement of CYP1A2 activity, and of several other metabolic processes, *in vivo*.

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References

1. Garattini S. Caffeine, coffee, and health. New York: Raven Press Ltd, 1993
2. Barone JJ, Grice HC. Seventh International Caffeine Workshop, Santorini, Greece 13-17 June 1993. Food Chem Toxicol 1994; 32 (1): 65-77
3. Benowitz NL. Clinical pharmacology of caffeine. Annu Rev Med 1990; 41: 277-88
4. Stavric B. Methylxanthines: toxicity to humans. 2. Caffeine. Food Chem Toxicol 1988; 26 (7): 645-62
5. Massey LK. Caffeine and the elderly. Drugs Aging 1998; 13 (1): 43-50
6. James JE. Caffeine and health. London: Academic Press Ltd, 1991
7. Lelo A, Miners JO, Robson R, et al. Assessment of caffeine exposure: caffeine content of beverages, caffeine intake, and plasma concentrations of methylxanthines. Clin Pharmacol Ther 1986; 39 (1): 54-9
8. D'Amicis A, Viani R. The consumption of coffee. In: Garattini S, editor. Caffeine, coffee, and health. New York: Raven Press Ltd, 1993: 1-16
9. Barone JJ, Roberts HR. Caffeine consumption. Food Chem Toxicol 1996; 34 (1): 119-29
10. Serafin WE. Drugs used in the treatment of asthma. In: Hardman JG, Limbird LE, Molinoff PB, et al., editors. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York: McGraw Hill, 1996: 659-82
11. Sawynok J. Pharmacological rationale for the clinical use of caffeine. Drugs 1995; 49 (1): 37-50
12. Ellinwood EH, Lee TH. Central nervous system stimulants and anorectic agents. In: Dukes MNG, editor. Meyler's side effects of drugs. Amsterdam: Elsevier Science B.V., 1996: 1-30
13. Honig PK, Gillespie BK. Clinical significance of pharmacokinetic drug interactions with over-the-counter (OTC) drugs. Clin Pharmacokinet 1998; 35 (3): 167-71
14. Daly JW. Mechanism of action of caffeine. In: Garattini S, editor. Caffeine, coffee, and health. New York: Raven Press Ltd, 1993: 97-150
15. Myers MG. Caffeine and cardiac arrhythmias. Ann Intern Med 1991; 114 (2): 147-50
16. Denaro CP, Brown CR, Jacob PD, et al. Effects of caffeine with repeated dosing. Eur J Clin Pharmacol 1991; 40 (3): 273-8
17. Benowitz NL, Jacob III P, Mayan H, et al. Sympathomimetic effects of paraxanthine and caffeine in humans. Clin Pharmacol Ther 1995; 58 (6): 684-91
18. Sharp DS, Benowitz NL. Pharmacoepidemiology of the effect of caffeine on blood pressure. Clin Pharmacol Ther 1990; 47 (1): 57-60
19. Sawynok J, Yaksh TL. Caffeine as an analgesic adjuvant: a review of pharmacology and mechanisms of action. Pharmacol Rev 1993; 45 (1): 43-85
20. Nehlig A. Are we dependent upon coffee and caffeine? A review on human and animal data. Neurosci Biobehav Rev 1999; 23 (4): 563-76
21. Robertson D, Wade D, Workman R, et al. Tolerance to the humoral and hemodynamic effects of caffeine in man. J Clin Invest 1981; 67 (4): 1111-7
22. Shi J, Benowitz NL, Denaro CP, et al. Pharmacokinetic-pharmacodynamic modeling of caffeine: tolerance to pressor effects. Clin Pharmacol Ther 1993; 53 (1): 6-14
23. Griffiths RR, Evans SM, Heishman SJ, et al. Low-dose caffeine physical dependence in humans. J Pharmacol Exp Ther 1990; 255 (3): 1123-32
24. Garrett BE, Griffiths RR. Physical dependence increases the relative reinforcing effects of caffeine versus placebo. Psychopharmacology 1998; 139 (3): 195-202
25. Evans SM, Griffiths RR. Caffeine withdrawal: a parametric analysis of caffeine dosing conditions. J Pharmacol Exp Ther 1999; 289 (1): 285-94
26. Hughes JR, Oliveto AH, Bickel WK, et al. Caffeine self-administration and withdrawal: incidence, individual differences and interrelationships. Drug Alcohol Depend 1993; 32 (3): 239-46
27. Charney DS, Heninger GR, Jatlow PI. Increased anxiogenic effects of caffeine in panic disorders. Arch Gen Psychiatry 1985; 42 (3): 233-43
28. Carrillo JA, Benitez J. CYP1A2 activity, gender and smoking, as variables influencing the toxicity of caffeine. Br J Clin Pharmacol 1996; 41 (6): 605-8
29. Garriott JC, Simmons LM, Poklis A, et al. Five cases of fatal overdose from caffeine-containing 'look-alike' drugs. J Anal Toxicol 1985; 9 (3): 141-3
30. Dubray C, Paire M, Vanlieferinghen P, et al. Caffeine poisoning in infants resulting from confusion between dosage forms. Aropos of 5 cases [in French]. Therapie 1984; 39 (5): 601-4
31. McGee MB. Caffeine poisoning in a 19-year-old female. J Forensic Sci 1980; 25 (1): 29-32
32. Carrillo JA, Christensen M, Ramos SI, et al. Evaluation of caffeine as an in vivo probe for CYP1A2 using measurements in plasma, saliva and urine. Ther Drug Monit. In press
33. Bonati M, Latini R, Tognoni G, et al. Interspecies comparison of in vivo caffeine pharmacokinetics in man, monkey, rabbit, rat, and mouse. Drug Metab Rev 1984; 15 (7): 1355-83
34. Zylber-Katz E, Granit L, Levy M. Relationship between caffeine concentrations in plasma and saliva. Clin Pharmacol Ther 1984; 36 (1): 133-7
35. Fuhr U, Rost KL. Simple and reliable CYP1A2 phenotyping by the paraxanthine/caffeine ratio in plasma and in saliva. Pharmacogenetics 1994; 4 (3): 109-16
36. Lee TC, Charles BG, Steer PA, et al. Saliva as a valid alternative to serum in monitoring intravenous caffeine treatment for apnea of prematurity. Ther Drug Monit 1996; 18 (3): 288-93
37. Somani SM, Gupta P. Caffeine: a new look at an age-old drug. Int J Clin Pharmacol Ther Toxicol 1988; 26 (11): 521-33
38. Lelo A, Miners JO, Robson RA, et al. Quantitative assessment of caffeine partial clearances in man. Br J Clin Pharmacol 1986; 22 (2): 183-6
39. Carrillo JA, Benitez J. Caffeine metabolism in a healthy Spanish population: N-acetylator phenotype and oxidation pathways. Clin Pharmacol Ther 1994; 55 (3): 293-304
40. Gu L, Gonzalez FJ, Kalow W, et al. Biotransformation of caffeine, paraxanthine, theobromine and theophylline by cDNA-expressed human CYP1A2 and CYP2E1. Pharmacogenetics 1992; 2 (2): 73-7
41. Butler MA, Iwasaki M, Guengerich FP, et al. Human cytochrome P-450PA (P-450IA2), the phenacetin O-deethylase, is primarily responsible for the hepatic 3-demethylation of caffeine and N-oxidation of carcinogenic arylamines. Proc Natl Acad Sci U S A 1989; 86 (20): 7696-700
42. Berthou F, Flinois JP, Ratanasavanh D, et al. Evidence for the involvement of several cytochromes P-450 in the first steps of caffeine metabolism by human liver microsomes. Drug Metab Dispos 1991; 19 (3): 561-7
43. Tarrus E, Cami J, Roberts DJ, et al. Accumulation of caffeine in healthy volunteers treated with furafylline. Br J Clin Pharmacol 1987; 23 (1): 9-18

44. Sesardic D, Boobis AR, Murray BP, et al. Furafylline is a potent and selective inhibitor of cytochrome P450IA2 in man. Br J Clin Pharmacol 1990; 29 (6): 651-63
45. Kalow W, Tang BK. The use of caffeine for enzyme assays: a critical appraisal. Clin Pharmacol Ther 1993; 53 (5): 503-14
46. Grant DM, Tang BK, Kalow W. A simple test for acetylator phenotype using caffeine. Br J Clin Pharmacol 1984; 17 (4): 459-64
47. Arnaud MJ. Metabolism of caffeine and other components of coffee. In: Garattini S, editor. Caffeine, coffee, and health. New York: Raven Press Ltd, 1993: 43-95
48. Eugster HP, Probst M, Wurgler FE, et al. Caffeine, estradiol, and progesterone interact with human CYP1A1 and CYP1A2; evidence from cDNA-directed expression in *Saccharomyces cerevisiae*. Drug Metab Dispos 1993; 21 (1): 43-9
49. Tassaneeyakul W, Birkett DJ, Veronese ME, et al. Specificity of substrate and inhibitor probes for human cytochromes P450 1A1 and 1A2. J Pharmacol Exp Ther 1993; 265 (1): 401-7
50. Guengerich FP. Roles of cytochrome P-450 enzymes in chemical carcinogenesis and cancer chemotherapy. Cancer Res 1988; 48 (11): 2946-54
51. Guengerich FP. Metabolic activation of carcinogens. Pharmacol Ther 1992; 54 (1): 17-61
52. Shimada T, Yun CH, Yamazaki H, et al. Characterization of human lung microsomal cytochrome P-450 1A1 and its role in the oxidation of chemical carcinogens. Mol Pharmacol 1992; 41 (5): 856-64
53. Shimada T, Yamazaki H, Mimura M, et al. Interindividual variations in human liver cytochrome P-450 enzymes involved in the oxidation of drugs, carcinogens and toxic chemicals: studies with liver microsomes of 30 Japanese and 30 Caucasians. J Pharmacol Exp Ther 1994; 270 (1): 414-23
54. Hankinson O. The aryl hydrocarbon receptor complex. Annu Rev Pharmacol Toxicol 1995; 35: 307-40
55. Guengerich FP, Shimada T, Iwasaki M, et al. Activation of carcinogens by human liver cytochromes P-450. Basic Life Sci 1990; 53: 381-96
56. Shet MS, McPhaul M, Fisher CW, et al. Metabolism of the antiandrogenic drug (Flutamide) by human CYP1A2. Drug Metab Dispos 1997; 25 (11): 1298-303
57. Doser K, Guserle R, Kramer R, et al. Bioequivalence evaluation of two flutamide preparations in healthy female subjects. Arzneimittelforschung 1997; 47 (2): 213-7
58. Venkatakrishnan K, Greenblatt DJ, von Moltke LL, et al. Five distinct human cytochromes mediate amitriptyline N-demethylation in vitro: dominance of CYP 2C19 and 3A4. J Clin Pharmacol 1998; 38 (2): 112-21
59. von Moltke LL, Greenblatt DJ, Shader RI. Clinical pharmacokinetics of antidepressants in the elderly: therapeutic implications. Clin Pharmacokinet 1993; 24 (2): 141-60
60. Nielsen KK, Flinois JP, Beaune P, et al. The biotransformation of clomipramine in vitro, identification of the cytochrome P450s responsible for the separate metabolic pathways. J Pharmacol Exp Ther 1996; 277 (3): 1659-64
61. Noguchi T, Shimoda K, Takahashi S. Clinical significance of plasma levels of clomipramine, its hydroxylated and desmethylated metabolites: prediction of clinical outcome in mood disorders using discriminant analysis of therapeutic drug monitoring data. J Affect Disord 1993; 29 (4): 267-79
62. Carrillo JA, Dahl ML, Svensson JO, et al. Disposition of fluvoxamine in humans is determined by the polymorphic CYP2D6 and also by the CYP1A2 activity. Clin Pharmacol Ther 1996; 60 (2): 183-90
63. Spigset O, Granberg K, Hagg S, et al. Relationship between fluvoxamine pharmacokinetics and CYP2D6/CYP2C19 phenotype polymorphisms. Eur J Clin Pharmacol 1997; 52 (2): 129-33
64. Koyama E, Chiba K, Tani M, et al. Identification of human cytochrome P450 isoforms involved in the stereoselective metabolism of mianserin enantiomers. J Pharmacol Exp Ther 1996; 278 (1): 21-30
65. Goodnick PJ. Pharmacokinetic optimisation of therapy with newer antidepressants. Clin Pharmacokinet 1994; 27 (4): 307-30
66. Lemoine A, Gautier JC, Azoulay D, et al. Major pathway of imipramine metabolism is catalyzed by cytochromes P-450 1A2 and P-450 3A4 in human liver. Mol Pharmacol 1993; 43 (5): 827-32
67. Brøsen K, Gram LF, Klysner R, et al. Steady-state levels of imipramine and its metabolites: significance of dose-dependent kinetics. Eur J Clin Pharmacol 1986; 30 (1): 43-9
68. Bertilsson L, Carrillo JA, Dahl ML, et al. Clozapine disposition covaries with CYP1A2 activity determined by a caffeine test. Br J Clin Pharmacol 1994; 38 (5): 471-3
69. Freeman DJ, Oyewumi LK. Will routine therapeutic drug monitoring have a place in clozapine therapy? Clin Pharmacokinet 1997; 32 (2): 93-100
70. Eiermann B, Engel G, Johansson I, et al. The involvement of CYP1A2 and CYP3A4 in the metabolism of clozapine. Br J Clin Pharmacol 1997; 44 (5): 439-46
71. Shimoda K, Someya T, Morita S, et al. Lower plasma levels of haloperidol in smoking than in nonsmoking schizophrenic patients. Ther Drug Monit 1999; 21 (3): 293-6
72. Ulrich S, Wurthmann C, Brosz M, et al. The relationship between serum concentration and therapeutic effect of haloperidol in patients with acute schizophrenia. Clin Pharmacokinet 1998; 34 (3): 227-63
73. Ring BJ, Catlow J, Lindsay TJ, et al. Identification of the human cytochromes P450 responsible for the in vitro formation of the major oxidative metabolites of the antipsychotic agent olanzapine. J Pharmacol Exp Ther 1996; 276 (2): 658-66
74. Perry PJ, Sanger T, Beasley C. Olanzapine plasma concentrations and clinical response in acutely schizophrenic patients. J Clin Psychopharmacol 1997; 17 (6): 472-7
75. Olesen OV, Linnet K. Olanzapine serum concentrations in psychiatric patients given standard doses: the influence of comedication. Ther Drug Monit 1999; 21 (1): 87-90
76. Carrillo JA, Ramos SI, Herraiz AG, et al. Pharmacokinetic interaction of fluvoxamine and thioridazine in schizophrenic patients. J Clin Psychopharmacol 1999; 19 (6): 494-9
77. Dahl SG. Plasma level monitoring of antipsychotic drugs: clinical utility. Clin Pharmacokinet 1986; 11 (1): 36-61
78. Dixon CM, Colthup PV, Serabjit-Singh CJ, et al. Multiple forms of cytochrome P450 are involved in the metabolism of ondansetron in humans. Drug Metab Dispos 1995; 23 (11): 1225-30
79. Roila F, Del Favero A. Ondansetron clinical pharmacokinetics. Clin Pharmacokinet 1995; 29 (2): 95-109
80. Imaoka S, Enomoto K, Oda Y, et al. Lidocaine metabolism by human cytochrome P-450s purified from hepatic microsomes: comparison of those with rat hepatic cytochrome P-450s. J Pharmacol Exp Ther 1990; 255 (3): 1385-91
81. Nattel S, Arenal A. Antiarrhythmic prophylaxis after acute myocardial infarction: is lidocaine still useful? Drugs 1993; 45 (1): 9-14
82. Nakajima M, Kobayashi K, Shimada N, et al. Involvement of CYP1A2 in mexiletine metabolism. Br J Clin Pharmacol 1998; 46 (1): 55-62

83. Labbé L, Abolfathi Z, Robitaille NM, et al. Stereoselective disposition of the antiarrhythmic agent mexiletine during the concomitant administration of caffeine. Ther Drug Monit 1999; 21 (2): 191-9
84. Labbé L, Turgeon J. Clinical pharmacokinetics of mexiletine. Clin Pharmacokinet 1999; 37 (5): 361-84
85. Botsch S, Gautier JC, Beaune P, et al. Identification and characterization of the cytochrome P450 enzymes involved in N-dealkylation of propafenone: molecular base for interaction potential and variable disposition of active metabolites. Mol Pharmacol 1993; 43 (1): 120-6
86. Bryson HM, Palmer KJ, Langtry HD, et al. Propafenone: a reappraisal of its pharmacology, pharmacokinetics and therapeutic use in cardiac arrhythmias. Drugs 1993; 45 (1): 85-130
87. Masubuchi Y, Hosokawa S, Horie T, et al. Cytochrome P450 isozymes involved in propranolol metabolism in human liver microsomes: the role of CYP2D6 as ring-hydroxylase and CYP1A2 as N-desisopropylase. Drug Metab Dispos 1994; 22 (6): 909-15
88. Marathe PH, Shen DD, Nelson WL. Metabolic kinetics of pseudoracemic propranolol in human liver microsomes: enantioselectivity and quinidine inhibition. Drug Metab Dispos 1994; 22 (2): 237-47
89. Yoshimoto K, Echizen H, Chiba K, et al. Identification of human CYP isoforms involved in the metabolism of propranolol enantiomers: N-desisopropylation is mediated mainly by CYP1A2. Br J Clin Pharmacol 1995; 39 (4): 421-31
90. Kober S, Spahn-Langguth H, Kurz A, et al. Triamterene hydroxylation in human liver microsomes is mediated by the cytochrome P450 isoform CYP1A2. Naunyn-Schmiedeberg's Arch Pharmacol 1996; 353 Suppl. 1: R157
91. Kroemer HK, Gautier JC, Beaune P, et al. Identification of P450 enzymes involved in metabolism of verapamil in humans. Naunyn Schmiedebergs' Arch Pharmacol 1993; 348 (3): 332-7
92. Zhang Z, Fasco MJ, Huang Z, et al. Human cytochromes P4501A1 and P4501A2: R-warfarin metabolism as a probe. Drug Metab Dispos 1995; 23 (12): 1339-46
93. Madden S, Woolf TF, Pool WF, et al. An investigation into the formation of stable, protein-reactive and cytotoxic metabolites from tacrine in vitro. Studies with human and rat liver microsomes. Biochem Pharmacol 1993; 46 (1): 13-20
94. Fontana RJ, deVries TM, Woolf TF, et al. Caffeine based measures of CYP1A2 activity correlate with oral clearance of tacrine in patients with Alzheimer's disease. Br J Clin Pharmacol 1998; 46 (3): 221-8
95. Madden S, Spaldin V, Park BK. Clinical pharmacokinetics of tacrine. Clin Pharmacokinet 1995; 28 (6): 449-57
96. Ekström G, Gunnarsson UB. Ropivacaine, a new amide-type local anesthetic agent, is metabolized by cytochromes P450 1A and 3A in human liver microsomes. Drug Metab Dispos 1996; 24 (9): 955-61
97. Emanuelsson BM, Persson J, Sandin S, et al. Intraindividual and interindividual variability in the disposition of the local anesthetic ropivacaine in healthy subjects. Ther Drug Monit 1997; 19 (2): 126-31
98. Patten CJ, Thomas PE, Guy RL, et al. Cytochrome P450 enzymes involved in acetaminophen activation by rat and human liver microsomes and their kinetics. Chem Res Toxicol 1993; 6 (4): 511-8
99. Kinzig-Schippers M, Fuhr U, Zaigler M, et al. Interaction of pefloxacin and enoxacin with the human cytochrome P450 enzyme CYP1A2. Clin Pharmacol Ther 1999; 65 (3): 262-74
100. Bressolle F, Goncalves F, Gouby A, et al. Pefloxacin clinical pharmacokinetics. Clin Pharmacokinet 1994; 27 (6): 418-46
101. Campbell ME, Grant DM, Inaba T, et al. Biotransformation of caffeine, paraxanthine, theophylline, and theobromine by polycyclic aromatic hydrocarbon-inducible cytochrome(s) P-450 in human liver microsomes. Drug Metab Dispos 1987; 15 (2): 237-49
102. Scott NR, Stambuk D, Chakraborty J, et al. The pharmacokinetics of caffeine and its dimethylxanthine metabolites in patients with chronic liver disease. Br J Clin Pharmacol 1989; 27 (2): 205-13
103. Rasmussen BB, Mäenpää J, Pelkonen O, et al. Selective serotonin reuptake inhibitors and theophylline metabolism in human liver microsomes: potent inhibition by fluvoxamine. Br J Clin Pharmacol 1995; 39 (2): 151-9
104. Ha HR, Chen J, Freiburghaus AU, et al. Metabolism of theophylline by cDNA-expressed human cytochromes P-450. Br J Clin Pharmacol 1995; 39 (3): 321-6
105. Grant DM, Tang BK, Kalow W. Variability in caffeine metabolism. Clin Pharmacol Ther 1983; 33 (5): 591-602
106. Kalow W. Variability of caffeine metabolism in humans. Arzneimittelforschung 1985; 35 (1A): 319-24
107. Kadlubar FF, Talaska G, Butler MA, et al. Determination of carcinogenic arylamine N-oxidation phenotype in humans by analysis of caffeine urinary metabolites. In: Mendelsohn ML, Albertini RJ, editors. Mutation and environment. Part B: Metabolism, testing methods, and chromosomes. New York: John Wiley, 1990: 107-14
108. Rasmussen BB, Brøsen K. Determination of urinary metabolites of caffeine for the assessment of cytochrome P4501A2, xanthine oxidase, and N-acetyltransferase activity in humans. Ther Drug Monit 1996; 18 (3): 254-62
109. Tantcheva-Poór I, Zaigler M, Rietbrock S, et al. Estimation of cytochrome P-450 CYP1A2 activity in 863 healthy Caucasians using a saliva-based caffeine test. Pharmacogenetics 1999; 9 (2): 131-44
110. Vistisen K, Loft S, Poulsen HE. Cytochrome P450 IA2 activity in man measured by caffeine metabolism: effect of smoking, broccoli and exercise. Adv Exp Med Biol 1991; 283: 407-11
111. Vistisen K, Poulsen HE, Loft S. Foreign compound metabolism capacity in man measured from metabolites of dietary caffeine. Carcinogenesis 1992; 13 (9): 1561-8
112. Le Marchand L, Franke AA, Custer L, et al. Lifestyle and nutritional correlates of cytochrome CYP1A2 activity: inverse associations with plasma lutein and alpha-tocopherol. Pharmacogenetics 1997; 7 (1): 11-9
113. Rizzo N, Hispard E, Dolbeault S, et al. Impact of long-term ethanol consumption on CYP1A2 activity. Clin Pharmacol Ther 1997; 62 (5): 505-9
114. Fuhr U, Klittich K, Staib AH. Inhibitory effect of grapefruit juice and its bitter principal, naringenin, on CYP1A2 dependent metabolism of caffeine in man. Br J Clin Pharmacol 1993; 35 (4): 431-6
115. Sinha R, Rothman N, Brown ED, et al. Pan-fried meat containing high levels of heterocyclic aromatic amines but low levels of polycyclic aromatic hydrocarbons induces cytochrome P4501A2 activity in humans. Cancer Res 1994; 54 (23): 6154-9
116. Sinha R, Caporaso N. Heterocyclic amines, cytochrome P4501A2, and N-acetyltransferase: issues involved in incorporating putative genetic susceptibility markers into epidemiological studies. Ann Epidemiol 1997; 7 (5): 350-6
117. Denaro CP, Wilson M, Jacob P, et al. The effect of liver disease on urine caffeine metabolite ratios. Clin Pharmacol Ther 1996; 59 (6): 624-35

118. Lane JD, Steege JF, Rupp SL, et al. Menstrual cycle effects on caffeine elimination in the human female. Eur J Clin Pharmacol 1992; 43 (5): 543-6
119. Aldridge A, Bailey J, Neims AH. The disposition of caffeine during and after pregnancy. Semin Perinatol 1981; 5 (4): 310-4
120. Brown CR, Jacob PD, Wilson M, et al. Changes in rate and pattern of caffeine metabolism after cigarette abstinence. Clin Pharmacol Ther 1988; 43 (5): 488-91
121. Kalow W, Tang BK. Caffeine as a metabolic probe: exploration of the enzyme-inducing effect of cigarette smoking. Clin Pharmacol Ther 1991; 49 (1): 44-8
122. Waxman DJ. P450 gene induction by structurally diverse xenochemicals: central role of nuclear receptors CAR, PXR, and PPAR. Arch Biochem Biophys 1999; 369 (1): 11-23
123. Sinha R, Rothman N. Role of well-done, grilled red meat, heterocyclic amines (HCAs) in the etiology of human cancer. Cancer Lett 1999; 143 (2): 189-94
124. Lin JH, Lu AY. Inhibition and induction of cytochrome P450 and the clinical implications. Clin Pharmacokinet 1998; 35 (5): 361-90
125. Smith G, Stubbins MJ, Harries LW, et al. Molecular genetics of the human cytochrome P450 monooxygenase superfamily. Xenobiotica 1998; 28 (12): 1129-65
126. Carrillo JA, Benitez J. Are antipsychotic drugs potentially chemopreventive agents for cancer? [letter]. Eur J Clin Pharmacol 1999; 55 (6): 487-8
127. Relling MV, Lin JS, Ayers GD, et al. Racial and gender differences in N-acetyltransferase, xanthine oxidase, and CYP1A2 activities. Clin Pharmacol Ther 1992; 52 (6): 643-58
128. Krul C, Hageman G. Analysis of urinary caffeine metabolites to assess biotransformation enzyme activities by reversed-phase high-performance liquid chromatography. J Chromatogr B Biomed Sci Appl 1998; 709 (1): 27-34
129. Bruguerolle B, Toumi M, Faraj F, et al. Influence of the menstrual cycle on theophylline pharmacokinetics in asthmatics. Eur J Clin Pharmacol 1990; 39 (1): 59-61
130. Shimada T, Gillam EM, Sutter TR, et al. Oxidation of xenobiotics by recombinant human cytochrome P450 1B1. Drug Metab Dispos 1997; 25 (5): 617-22
131. Murray GI, Taylor MC, McFadyen MC, et al. Tumor-specific expression of cytochrome P450 CYP1B1. Cancer Res 1997; 57 (14): 3026-31
132. Fuhr U, Wolff T, Harder S, et al. Quinolone inhibition of cytochrome P-450-dependent caffeine metabolism in human liver microsomes. Drug Metab Dispos 1990; 18 (6): 1005-10
133. Mandell G, Petri Jr WA. Antimicrobial agents: sulfonamides, trimethoprim-sulfamethoxazole, quinolones, and agents for urinary tract infections. In: Hardman JG, Limbird LE, Molinoff PB, et al., editors. Goodman and Gilman's the pharmacological basis of therapeutics. 9th ed. New York: MacGraw Hill, 1996: 1057-72
134. von Moltke LL, Greenblatt DJ, Duan SX, et al. Phenacetin O-deethylation by human liver microsomes in vitro: inhibition by chemical probes, SSRI antidepressants, nefazodone and venlafaxine. Psychopharmacology Berl 1996; 128 (4): 398-407
135. Preskorn SH. Clinically relevant pharmacology of selective serotonin reuptake inhibitors: an overview with emphasis on pharmacokinetics and effects on oxidative drug metabolism. Clin Pharmacokinet 1997; 32 Suppl. 1: 1-21
136. Brøsen K, Skjelbo E, Rasmussen BB, et al. Fluvoxamine is a potent inhibitor of cytochrome P4501A2. Biochem Pharmacol 1993; 45 (6): 1211-4
137. Kobayashi K, Nakajima M, Chiba K, et al. Inhibitory effects of antiarrhythmic drugs on phenacetin O-deethylation catalysed by human CYP1A2. Br J Clin Pharmacol 1998; 45 (4): 361-8
138. Nix DE, Zelenitsky SA, Symonds WT, et al. The effect of fluconazole on the pharmacokinetics of caffeine in young and elderly subjects. In: Reidenberg MM, editor. 93rd Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics; 1992; St. Louis. Clin Pharmacol Ther 1992: 183
139. Wahllander A, Paumgartner G. Effect of ketoconazole and terbinafine on the pharmacokinetics of caffeine in healthy volunteers. Eur J Clin Pharmacol 1989; 37 (3): 279-83
140. Soto J, Sacristan JA, Alsar MJ. Diltiazem treatment impairs theophylline elimination in patients with bronchospastic airway disease. Ther Drug Monit 1994; 16 (1): 49-52
141. Joeres R, Klinker H, Heusler H, et al. Influence of mexiletine on caffeine elimination. Pharmacol Ther 1987; 33 (1): 163-9
142. Nielsen-Kudsk JE, Buhl JS, Johannessen AC. Verapamil-induced inhibition of theophylline elimination in healthy humans. Pharmacol Toxicol 1990; 66 (2): 101-3
143. Vainer JL, Chouinard G. Interaction between caffeine and clozapine [letter]. J Clin Psychopharmacol 1994; 14 (4): 284-5
144. Carrillo JA, Jerling M, Bertilsson L. Comments to 'interaction between caffeine and clozapine' [letter]. J Clin Psychopharmacol 1995; 15 (5): 376-7
145. Beale MD, Pritchett JT, Kellner CH. Supraventricular tachycardia in a patient receiving ECT, clozapine, and caffeine. Convuls Ther 1994; 10 (3): 228-31
146. Jeppesen U, Loft S, Poulsen HE, et al. A fluvoxamine-caffeine interaction study. Pharmacogenetics 1996; 6 (3): 213-22
147. Spigset O. Are adverse drug reactions attributed to fluvoxamine caused by concomitant intake of caffeine? [letter]. Eur J Clin Pharmacol 1998; 54 (8): 665-6
148. Carrillo JA, Ramos SI, Herráiz AG, et al. CYP1A2 activity and smoking influence the risk/benefit ratio of olanzapine in schizophrenic patients. In: Balant LP, Benítez J, Dahl SG, et al., editors. Clinical pharmacology in psychiatry: finding the right dose of psychotropic drugs. Brussels: European Commision, COST B1, 1998: 291-5
149. Iversen SA, Murphy PG, Leakey TE, et al. Unsuspected caffeine toxicity complicating theophylline therapy. Hum Toxicol 1984; 3 (6): 509-12
150. Sato J, Nakata H, Owada E, et al. Influence of usual intake of dietary caffeine on single-dose kinetics of theophylline in healthy human subjects. Eur J Clin Pharmacol 1993; 44 (3): 295-8
151. Broughton LJ, Rogers HJ. Decreased systemic clearance of caffeine due to cimetidine. Br J Clin Pharmacol 1981; 12 (2): 155-9
152. May DC, Jarboe CH, VanBakel AB, et al. Effects of cimetidine on caffeine disposition in smokers and nonsmokers. Clin Pharmacol Ther 1982; 31 (5): 656-61
153. Brazier JL, Descotes J, Lery N, et al. Inhibition by idrocilamide of the disposition of caffeine. Eur J Clin Pharmacol 1980; 17 (1): 37-43
154. Patwardhan RV, Desmond PV, Johnson RF, et al. Impaired elimination of caffeine by oral contraceptive steroids. J Lab Clin Med 1980; 95 (4): 603-8
155. Callahan MM, Robertson RS, Branfman AR, et al. Comparison of caffeine metabolism in three nonsmoking populations after oral administration of radiolabeled caffeine. Drug Metab Dispos 1983; 11 (3): 211-7
156. Abernethy DR, Todd EL. Impairment of caffeine clearance by chronic use of low-dose oestrogen- containing oral contraceptives. Eur J Clin Pharmacol 1985; 28 (4): 425-8

157. Lake CR. Manic psychosis after coffee and phenylpropanolamine. Biol Psychiatry 1991; 30 (4): 401-4
158. Lake CR, Rosenberg DB, Gallant S, et al. Phenylpropanolamine increases plasma caffeine levels. Clin Pharmacol Ther 1990; 47 (6): 675-85
159. Mays DC, Camisa C, Cheney P, et al. Methoxsalen is a potent inhibitor of the metabolism of caffeine in humans. Clin Pharmacol Ther 1987; 42 (6): 621-6
160. McEvoy MT, Stern RS. Psoralens and related compounds in the treatment of psoriasis. Pharmacol Ther 1987; 34 (1): 75-97
161. Bendriss EK, Bechtel Y, Bendriss A, et al. Inhibition of caffeine metabolism by 5-methoxypsoralen in patients with psoriasis. Br J Clin Pharmacol 1996; 41 (5): 421-4
162. Landes BD, Petite JP, Flouvat B. Clinical pharmacokinetics of lansoprazole. Clin Pharmacokinet 1995; 28 (6): 458-70
163. Diaz D, Fabre I, Daujat M, et al. Omeprazole is an aryl hydrocarbon-like inducer of human hepatic cytochrome P450. Gastroenterology 1990; 99 (3): 737-47
164. Rost KL, Brosicke H, Brockmoller J, et al. Increase of cytochrome P450IA2 activity by omeprazole: evidence by the ^{13}C-[N-3-methyl]-caffeine breath test in poor and extensive metabolizers of S-mephenytoin. Clin Pharmacol Ther 1992; 52 (2): 170-80
165. Rost KL, Roots I. Accelerated caffeine metabolism after omeprazole treatment is indicated by urinary metabolite ratios: coincidence with plasma clearance and breath test. Clin Pharmacol Ther 1994; 55 (4): 402-11
166. Schulz HU, Hartmann M, Steinijans VW, et al. Lack of influence of pantoprazole on the disposition kinetics of theophylline in man. Int J Clin Pharmacol Ther Toxicol 1991; 29 (9): 369-75
167. Staib AH, Stille W, Dietlein G, et al. Interaction between quinolones and caffeine. Drugs 1987; 34 Suppl. 1: 170-4
168. Healy DP, Polk RE, Kanawati L, et al. Interaction between oral ciprofloxacin and caffeine in normal volunteers. Antimicrob Agents Chemother 1989; 33 (4): 474-8
169. Nicolau DP, Nightingale CH, Tessier PR, et al. The effect of fleroxacin and ciprofloxacin on the pharmacokinetics of multiple dose caffeine. Drugs 1995; 49 Suppl. 2: 357-9
170. Efthymiopoulos C, Bramer SL, Maroli A, et al. Theophylline and warfarin interaction studies with grepafloxacin. Clin Pharmacokinet 1997; 33 Suppl. 1: 39-46
171. Robson RA, Begg EJ, Atkinson HC, et al. Comparative effects of ciprofloxacin and lomefloxacin on the oxidative metabolism of theophylline. Br J Clin Pharmacol 1990; 29 (4): 491-3
172. Robson RA. The effects of quinolones on xanthine pharmacokinetics. Am J Med 1992; 92 (4A): 22S-5S
173. Carbo M, Segura J, De la Torre R, et al. Effect of quinolones on caffeine disposition. Clin Pharmacol Ther 1989; 45 (3): 234-40
174. Harder S, Staib AH, Beer C, et al. 4-Quinolones inhibit biotransformation of caffeine. Eur J Clin Pharmacol 1988; 35 (6): 651-6
175. Stille W, Harder S, Mieke S, et al. Decrease of caffeine elimination in man during co-administration of 4-quinolones. J Antimicrob Chemother 1987; 20 (5): 729-34
176. Barnett G, Segura J, de la Torre R, et al. Pharmacokinetic determination of relative potency of quinolone inhibition of caffeine disposition. Eur J Clin Pharmacol 1990; 39 (1): 63-9
177. Cesana M, Broccali G, Imbimbo BP, et al. Effect of single doses of rufloxacin on the disposition of theophylline and caffeine after single administration. Int J Clin Pharmacol Ther Toxicol 1991; 29 (4): 133-8
178. Mahr G, Sorgel F, Granneman GR, et al. Effects of temafloxacin and ciprofloxacin on the pharmacokinetics of caffeine. Clin Pharmacokinet 1992; 22 Suppl. 1: 90-7
179. Takagi K, Hasegawa T, Ogura Y, et al. Comparative studies on interaction between theophylline and quinolones. J Asthma 1988; 25 (2): 63-71
180. Vincent J, Teng R, Dogolo LC, et al. Effect of trovafloxacin, a new fluoroquinolone antibiotic, on the steady-state pharmacokinetics of theophylline in healthy volunteers. J Antimicrob Chemother 1997; 39 Suppl. B: 81-6
181. Yoovathaworn KC, Sriwatanakul K, Thithapandha A. Influence of caffeine on aspirin pharmacokinetics. Eur J Drug Metab Pharmacokinet 1986; 11 (1): 71-6
182. Thithapandha A. Effect of caffeine on the bioavailability and pharmacokinetics of aspirin. J Med Assoc Thai 1989; 72 (10): 562-6
183. Carrillo JA, Herraiz AG, Ramos SI, et al. Effects of caffeine withdrawal from the diet on the metabolism of clozapine in schizophrenic patients. J Clin Psychopharmacol 1998; 18 (4): 311-6
184. Odom-White A, de Leon J. Clozapine levels and caffeine [letter]. J Clin Psychiatry 1996; 57 (4): 175-6
185. Mester R, Toren P, Mizrachi I, et al. Caffeine withdrawal increases lithium blood levels. Biol Psychiatry 1995; 37 (5): 348-50
186. Jefferson JW. Lithium tremor and caffeine intake: two cases of drinking less and shaking more. J Clin Psychiatry 1988; 49 (2): 72-3
187. Iqbal N, Ahmad B, Janbaz KH, et al. The effect of caffeine on the pharmacokinetics of acetaminophen in man. Biopharm Drug Dispos 1995; 16 (6): 481-7
188. Jonkman JH, Sollie FA, Sauter R, et al. The influence of caffeine on the steady-state pharmacokinetics of theophylline. Clin Pharmacol Ther 1991; 49 (3): 248-55
189. Pelkonen O, Mäenpää J, Taavitsainen P, et al. Inhibition and induction of human cytochrome P450 (CYP) enzymes. Xenobiotica 1998; 28 (12): 1203-53
190. Grant DM, Tang BK, Campbell ME, et al. Effect of allopurinol on caffeine disposition in man. Br J Clin Pharmacol 1986; 21 (4): 454-8
191. Fuchs P, Haefeli WE, Ledermann HR, et al. Xanthine oxidase inhibition by allopurinol affects the reliability of urinary caffeine metabolic ratios as markers for N-acetyltransferase 2 and CYP1A2 activities. Eur J Clin Pharmacol 1999; 54 (11): 869-76
192. Sumbaev VV, Rozanov A. Effect of caffeine on xanthine oxidase activity. Ukr Biokhim Zh 1997; 69 (5-6): 196-200
193. Kalow W, Tang BK. Use of caffeine metabolite ratios to explore CYP1A2 and xanthine oxidase activities. Clin Pharmacol Ther 1991; 50: 508-19
194. Carrillo JA, Ramos SI, Agundez JA, et al. Analysis of midazolam and metabolites in plasma by high-performance liquid chromatography: probe of CYP3A. Ther Drug Monit 1998; 20 (3): 319-24
195. Loi CM, Wei XX, Vestal RE. Inhibition of theophylline metabolism by mexiletine in young male and female nonsmokers. Clin Pharmacol Ther 1991; 49 (5): 571-80
196. Kendall JD, Chrymko MM, Cooper BE. Theophylline-mexiletine interaction: a case report. Pharmacotherapy 1992; 12 (5): 416-8
197. Fuhr U, Woodcock BG, Siewert M. Verapamil and drug metabolism by the cytochrome P450 isoform CYP1A2 [letter]. Eur J Clin Pharmacol 1992; 42 (4): 463-4

198. Stringer KA, Mallet J, Clarke M, et al. The effect of three different oral doses of verapamil on the disposition of theophylline. Eur J Clin Pharmacol 1992; 43 (1): 35-8
199. De Freitas B, Schwartz G. Effects of caffeine in chronic psychiatric patients. Am J Psychiatry 1979; 136 (10): 1337-8
200. Furlong FW. Possible psychiatric significance of excessive coffee consumption. Can Psychiatr Assoc J 1975; 20 (8): 577-83
201. Greden JF, Fontaine P, Lubetsky M, et al. Anxiety and depression associated with caffeinism among psychiatric inpatients. Am J Psychiatry 1978; 135 (8): 963-6
202. Schreiber GB, Maffeo CE, Robins M, et al. Measurement of coffee and caffeine intake: implications for epidemiologic research. Prev Med 1988; 17 (3): 280-94
203. Hughes JR, McHugh P, Holtzman S. Caffeine and schizophrenia. Psychiatr Serv 1998; 49 (11): 1415-7
204. Hyde AP. Response to 'effects of caffeine on behavior of schizophrenic inpatients' [comment]. Schizophr Bull 1990; 16 (3): 371-2
205. Baumann P. Pharmacokinetic-pharmacodynamic relationship of the selective serotonin reuptake inhibitors. Clin Pharmacokinet 1996; 31 (6): 444-69
206. Sproule BA, Naranjo CA, Bremner KE, et al. Selective serotonin reuptake inhibitors and CNS drug interactions. Clin Pharmacokinet 1997; 33 (6): 454-71
207. Wagner W, Vause EW. Fluvoxamine: a review of global drug-drug interaction data. Clin Pharmacokinet 1995; 29 Suppl. 1: 26-31; discussion 31-2
208. Crewe HK, Lennard MS, Tucker GT, et al. The effect of selective serotonin re-uptake inhibitors on cytochrome P4502D6 (CYP2D6) activity in human liver microsomes. Br J Clin Pharmacol 1992; 34 (3): 262-5
209. Skjelbo E, Brøsen K. Inhibitors of imipramine metabolism by human liver microsomes. Br J Clin Pharmacol 1992; 34 (3): 256-61
210. Jeppesen U, Gram LF, Vistisen K, et al. Dose-dependent inhibition of CYP1A2, CYP2C19 and CYP2D6 by citalopram, fluoxetine, fluvoxamine and paroxetine. Eur J Clin Pharmacol 1996; 51 (1): 73-8
211. Xu ZH, Xie HG, Zhou HH. In vivo inhibition of CYP2C19 but not CYP2D6 by fluvoxamine. Br J Clin Pharmacol 1996; 42: 518-21
212. Brøsen K. Differences in interactions of SSRIs. Int Clin Psychopharmacol 1998; 13 Suppl. 5: S45-7
213. Jerling M, Lindstrom L, Bondesson U, et al. Fluvoxamine inhibition and carbamazepine induction of the metabolism of clozapine: evidence from a therapeutic drug monitoring service. Ther Drug Monit 1994; 16 (4): 368-74
214. Hiemke C, Weigmann H, Härtter S, et al. Elevated levels of clozapine in serum after addition of fluvoxamine [letter]. J Clin Psychopharmacol 1994; 14 (4): 279-81
215. Curry ML, Curry SH, Marroum PJ. Interaction of phenothiazine and related drugs and caffeinated beverages [letter]. DICP 1991; 25 (4): 437-8
216. Hirsch SR. Precipitation of antipsychotic drugs in interaction with coffee or tea [letter]. Lancet 1979; 2 (8152): 1130-1
217. Dahl ML, Bertilsson L. Genetically variable metabolism of antidepressants and neuroleptic drugs in man. Pharmacogenetics 1993; 3 (2): 61-70
218. Dahl ML, Lerena A, Bondesson U, et al. Disposition of clozapine in man: lack of association with debrisoquine and S-mephenytoin hydroxylation polymorphisms. Br J Clin Pharmacol 1994; 37: 71-4
219. Simpson GM, Cooper TA. Clozapine plasma levels and convulsions. Am J Psychiatry 1978; 135 (1): 99-100
220. Olesen OV. Therapeutic drug monitoring of clozapine treatment: therapeutic threshold value for serum clozapine concentrations. Clin Pharmacokinet 1998; 34 (6): 497-502
221. McCarthy RH. Seizures following smoking cessation in a clozapine responder. Pharmacopsychiatry 1994; 27 (5): 210-1
222. Ring BJ, Binkley SN, Vandenbranden M, et al. In vitro interaction of the antipsychotic agent olanzapine with human cytochromes P450 CYP2C9, CYP2C19, CYP2D6 and CYP3A. Br J Clin Pharmacol 1996; 41 (3): 181-6
223. Fulton B, Goa KL. Olanzapine. A review of its pharmacological properties and therapeutic efficacy in the management of schizophrenia and related psychoses. Drugs 1997; 53 (2): 281-98
224. Kassahun K, Mattiuz E, Nyhart Jr E, et al. Disposition and biotransformation of the antipsychotic agent olanzapine in humans. Drug Metab Dispos 1997; 25 (1): 81-93
225. Macias WL, Bergstrom RF, Cerimele BJ, et al. Lack of effect of olanzapine on the pharmacokinetics of a single aminophylline dose in healthy men. Pharmacotherapy 1998; 18 (6): 1237-48
226. Thomsen K, Schou M. Renal lithium excretion in man. Am J Physiol 1968; 215 (4): 823-7
227. Bauman JH, Kimelblatt BJ, Caraccio TR, et al. Cimetidine-theophylline interaction: report of four patients. Ann Allergy 1982; 48 (2): 100-2
228. Roberts RK, Grice J, McGuffie C. Cimetidine-theophylline interaction in patients with chronic obstructive airways disease. Med J Aust 1984; 140 (5): 279-80
229. Grygiel JJ, Miners JO, Drew R, et al. Differential effects of cimetidine on theophylline metabolic pathways. Eur J Clin Pharmacol 1984; 26 (3): 335-40
230. Parker AC, Pritchard P, Preston T, et al. Lack of inhibitory effect of cimetidine on caffeine metabolism in children using the caffeine breath test. Br J Clin Pharmacol 1997; 43 (5): 467-70
231. Dal Negro R, Pomari C, Turco P. Famotidine and theophylline pharmacokinetics: an unexpected cimetidine-like interaction in patients with chronic obstructive pulmonary disease. Clin Pharmacokinet 1993; 24 (3): 255-8
232. Robson RA, Miners JO, Matthews AP, et al. Characterisation of theophylline metabolism by human liver microsomes: inhibition and immunochemical studies. Biochem Pharmacol 1988; 37 (9): 1651-9
233. Harris RZ, Benet LZ, Schwartz JB. Gender effects in pharmacokinetics and pharmacodynamics. Drugs 1995; 50 (2): 222-39
234. Catteau A, Bechtel YC, Poisson N, et al. A population and family study of CYP1A2 using caffeine urinary metabolites. Eur J Clin Pharmacol 1995; 47 (5): 423-30
235. Roberts RK, Grice J, McGuffie C, et al. Oral contraceptive steroids impair the elimination of theophylline. J Lab Clin Med 1983; 101 (6): 821-5
236. Balogh A, Klinger G, Henschel L, et al. Influence of ethinylestradiol-containing combination oral contraceptives with gestodene or levonorgestrel on caffeine elimination. Eur J Clin Pharmacol 1995; 48 (2): 161-6
237. Laine K, Palovaara S, Tapanainen P, et al. Plasma tacrine concentrations are significantly increased by concomitant hormone replacement therapy. Clin Pharmacol Ther 1999; 66 (6): 602-8
238. Pollock BG, Wylie M, Stack JA, et al. Inhibition of caffeine metabolism by estrogen replacement therapy in postmenopausal women. J Clin Pharmacol 1999; 39 (9): 936-40
239. Lee KY, Beilin LJ, Vandongen R. Severe hypertension after ingestion of an appetite suppressant (phenylpropanolamine) with indomethacin. Lancet 1979; 1 (8126): 1110-1

240. O'Connell MB, Gross CR. The effect of multiple doses of phenylpropanolamine on the blood pressure of patients whose hypertension was controlled with beta blockers. Pharmacotherapy 1991; 11 (5): 376-81
241. Curi-Pedrosa R, Daujat M, Pichard L, et al. Omeprazole and lansoprazole are mixed inducers of CYP1A and CYP3A in human hepatocytes in primary culture. J Pharmacol Exp Ther 1994; 269 (1): 384-92
242. Nousbaum JB, Berthou F, Carlhant D, et al. Four-week treatment with omeprazole increases the metabolism of caffeine. Am J Gastroenterol 1994; 89 (3): 371-5
243. Dzeletovic N, McGuire J, Daujat M, et al. Regulation of dioxin receptor function by omeprazole. J Biol Chem 1997; 272 (19): 12705-13
244. Andersson T. Pharmacokinetics, metabolism and interactions of acid pump inhibitors: focus on omeprazole, lansoprazole and pantoprazole. Clin Pharmacokinet 1996; 31 (1): 9-28
245. Rizzo N, Padoin C, Palombo S, et al. Omeprazole and lansoprazole are not inducers of cytochrome P4501A2 under conventional therapeutic conditions. Eur J Clin Pharmacol 1996; 49 (6): 491-5
246. Taburet AM, Geneve J, Bocquentin M, et al. Theophylline steady state pharmacokinetics is not altered by omeprazole. Eur J Clin Pharmacol 1992; 42 (3): 343-5
247. Xiaodong S, Gatti G, Bartoli A, et al. Omeprazole does not enhance the metabolism of phenacetin, a marker of CYP1A2 activity, in healthy volunteers. Ther Drug Monit 1994; 16 (3): 248-50
248. Andersson T, Holmberg J, Rohss K, et al. Pharmacokinetics and effect on caffeine metabolism of the proton pump inhibitors, omeprazole, lansoprazole, and pantoprazole. Br J Clin Pharmacol 1998; 45 (4): 369-75
249. Dilger K, Zheng Z, Klotz U. Lack of drug interaction between omeprazole, lansoprazole, pantoprazole and theophylline. Br J Clin Pharmacol 1999; 48 (3): 438-44
250. Apseloff G, Shepard DR, Chambers MA, et al. Inhibition and induction of theophylline metabolism by 8-methoxypsoralen: *in vivo* study in rats and humans. Drug Metab Dispos 1990; 18 (3): 298-303
251. Honigsmann H, Jaschke E, Gschnait F, et al. 5-Methoxypsoralen (Bergapten) in photochemotherapy of psoriasis. Br J Dermatol 1979; 101 (4): 369-78
252. Tinel M, Belghiti J, Descatoire V, et al. Inactivation of human liver cytochrome P-450 by the drug methoxsalen and other psoralen derivatives. Biochem Pharmacol 1987; 36 (6): 951-5
253. Labbe G, Descatoire V, Letteron P, et al. The drug methoxsalen, a suicide substrate for cytochrome P-450, decreases the metabolic activation, and prevents the hepatotoxicity, of carbon tetrachloride in mice. Biochem Pharmacol 1987; 36 (6): 907-14
254. Fouin-Fortunet H, Tinel M, Descatoire V, et al. Inactivation of cytochrome P-450 by the drug methoxsalen. J Pharmacol Exp Ther 1986; 236 (1): 237-47
255. Tantcheva-Poór I, Scharffetter-Kochanek K, Fuhr U. Pronounced effect of oral but not of bath PUVA (methoxsalen plus UVA) on CYP1A2 activity in dermatological patients. In: Dahlqvist R, Offerhaus L, McDevitt D, et al., editors. First Joint Meeting of the German Clinical Pharmacologists; 1999 Jun 10-12; Berlin. Berlin: Springer, 1999: A23
256. Wijnands WJ, Vree TB, van Herwaarden CL. The influence of quinolone derivatives on theophylline clearance. Br J Clin Pharmacol 1986; 22 (6): 677-83
257. Davey PG. Overview of drug interactions with the quinolones. J Antimicrob Chemother 1988; 22 Suppl. C: 97-107
258. Staib AH, Harder S, Fuhr U, et al. Interaction of quinolones with the theophylline metabolism in man: investigations with lomefloxacin and pipemidic acid. Int J Clin Pharmacol Ther Toxicol 1989; 27 (6): 289-3
259. LeBel M, Vallee F, St-Laurent M. Influence of lomefloxacin on the pharmacokinetics of theophylline. Antimicrob Agents Chemother 1990; 34 (6): 1254-6
260. Lamp KC, Bailey EM, Rybak MJ. Ofloxacin clinical pharmacokinetics. Clin Pharmacokinet 1992; 22 (1): 32-46
261. Marchbanks CR. Drug-drug interactions with fluoroquinolones. Pharmacotherapy 1993; 13 (2 Pt 2): 23S-8S
262. Healy DP, Schoenle JR, Stotka J, et al. Lack of interaction between lomefloxacin and caffeine in normal volunteers. Antimicrob Agents Chemother 1991; 35 (4): 660-4
263. Nix DE, Norman A, Schentag JJ. Effect of lomefloxacin on theophylline pharmacokinetics. Antimicrob Agents Chemother 1989; 33 (7): 1006-8
264. Lipsky BA, Baker CA. Fluoroquinolone toxicity profiles: a review focusing on newer agents. Clin Infect Dis 1999; 28 (2): 352-64
265. Simpson KJ, Brodie MJ. Convulsions related to enoxacin [letter]. Lancet 1985; 2 (8447): 161
266. Christ W. Central nervous system toxicity of quinolones: human and animal findings. J Antimicrob Chemother 1990; 26 Suppl. B: 219-25
267. Birkett DJ, Miners JO. Caffeine renal clearance and urine caffeine concentrations during steady state dosing: implications for monitoring caffeine intake during sports events. Br J Clin Pharmacol 1991; 31 (4): 405-8
268. Duthel JM, Vallon JJ, Martin G, et al. Caffeine and sport: role of physical exercise upon elimination. Med Sci Sports Exerc 1991; 23 (8): 980-5

Correspondence and offprints: Dr *Juan Antonio Carrillo*, Departamento de Farmacología y Psiquiatría, Facultad de Medicina, Universidad de Extremadura, Avda. de Elvas s/n, E-06071 Badajoz, Spain.
E-mail: carrillo@unex.es