DRUG SAFETY CONCEPTS

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Treatment of Concomitant Illneses in Patients Receiving Anticonvulsants

Drug Interactions of Clinical Significance

Pierre Loiseau

Department of Neurology, University Hospital, Bordeaux, France

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Abstract

As epilepsy often is a chronic condition requiring prolonged therapy with anticonvulsants, patients being treated for epilepsy can be at risk when they are prescribed other drugs for concomitant diseases. Pharmacokinetic interactions

can occur at each step of drug disposition (absorption, distribution, metabolism and elimination). Although such interactions may occur frequently with some drugs, only some will be clinically relevant. Alterations in the hepatic biotransformation of metabolised drugs due to hepatic isoenzyme induction or inhibition is of particular concern.

The consequences of pharmacokinetic interactions are either accumulation of the drug leading to toxicity, or lowering of plasma concentrations resulting in reduced efficacy. Clinically relevant interactions depend on the structure, dosage and duration of administration of interacting agents, and on the individual's genetic make-up.

In the past, drug interactions have been analysed empirically. At present, at least for interactions between drugs that are biotransformed in the liver, the risk should be predicted by considering the individual cytochrome P450 isoforms involved in the metabolism of coadministered drugs.

Although drug-drug interactions can be predicted, their extent cannot be due to large interindividual variability. Even if nearly all drug combinations could be used with close clinical surveillance and blood concentration determinations, drugs that are not metabolised and are not highly protein bound, as are several of the new anticonvulsants, such as gabapentin, lamotrigine and vigabatrin, have a clear advantage in terms of a lower interaction potential.

1. Extent of the Clinical Problem

Drug-drug interactions are the direct consequence of the interaction between 2 or more drugs administered simultaneously.[1] Pharmacokinetic interactions alter drug disposition while pharmacodynamic interactions produce synergistic or antagonistic pharmacological effects, unrelated to pharmacokinetic changes.

Many pharmacokinetic interactions between established anticonvulsants and drugs from other therapeutic classes have been reported, but only some of them are of clinical significance. The clinical significance of an interaction depends not only on the clinical effects produced, but also on whether or not it leads to a need to adjust the drug dosages.[2]

2. Mechanisms of Interactions

Pharmacokinetic drug-drug interactions can result from either changes in absorption, displacement from plasma protein binding sites or induction or inhibition of hepatic enzymatic metabolism.[3]

2.1 Absorption

Coadministration of antineoplastic drugs[4] and, more commonly, of antacids[5] and activated charcoal,[6] impairs the absorption of anticonvulsants such as phenytoin, phenobarbital (phenobarbitone) and carbamazepine, and hence decreases their bioavailability. It seems wise to recommend that, whenever possible, anticonvulsants be administered at least 2 to 3 hours before ingestion of antacids and activated charcoal.[7]

2.2 Distribution and Protein Binding

Drug interactions that result in the displacement of an anticonvulsant from plasma proteins are potentially of clinical relevance. However, this applies only to anticonvulsants that are highly protein bound.[2] Competition for saturable and nonspecific binding sites among drugs at steady state usually results in a decline in the total plasma concentration, whereas the free concentration may remain unchanged. Thus, a higher free fraction of the drug in the plasma may be obtained during laboratory investigation. In this case, a lower total blood concentration may be misinterpreted and lead to an inappropriate change in drug dose.[8] Exceptions to

this course of events occur if the primary drug concentrations are high and if the free drug concentration saturates the elimination mechanism, as may occur with phenytoin.[2]

2.3 Elimination

Drugs are eliminated from the body through excretion of unchanged drug or through biotransformation to 1 or more metabolites. Almost all of the conventional anticonvulsants are metabolised extensively by cytochrome P450 (CYP) isoenzymes located predominantly in the microsomes of the liver cells. Inhibition of drug metabolism can occur when a coadministered drug competes for binding sites on the relevant isoenzyme required for metabolism.[9]

Interactions in which the biotransformation of a drug is inhibited lead to accumulation of this drug. Several anticonvulsants have the ability to induce the synthesis of metabolic oxidative and, to a lesser extent, conjugating enzymes. However, because different anticonvulsants stimulate different specific isoenzymes, their interactions with other drugs can be different.

3. Consequences of Interactions

Drug interactions in general have been overemphasised with respect to both frequency and clinical importance. Modest changes demonstrable by measurement of drug concentrations are far more frequent than clinically significant interactions.[2] Only a small percentage of patients will experience significant clinical repercussions.[10] The consequences of pharmacokinetic interactions are either overaccumulation of drug leading to toxicity, or accelerated metabolism leading to loss of efficacy. Inhibition of drug metabolism leads to the highest potential danger.

3.1 Toxicity

In the case of metabolic inhibition, the amount of enzyme inhibited is dependent upon the concentration of the inhibiting agent and the duration of the exposure.[11] The drug whose metabolism is inhibited has a decreased clearance and its blood concentration increases when the inhibiting agent drug is added. Clinical signs of toxicity appear when serum concentrations reach specific higher levels,[12] most often within a few days. Here, dosage adjustment of the inhibited drug must be made immediately. However accumulation may also be progressive, as occurs with phenytoin.[9] As inhibition is generally competitive, toxic signs and symptoms disappear after discontinuation of the offending agent; the drug regimen will again need modification when the inhibiting agent is discontinued.[12] The time for reversal of the inhibition interactions is drug- and dose-dependent; it would correspond to 5 half-lives of the remaining drug.[9]

3.2 Reduced Efficacy

Induction of drug oxidative metabolism results in lower plasma concentrations of the affected agent. This decrease is usually progressive. Enzyme induction requires some time, as new proteins must be synthesised, and these effects can be observed only after some delay,[13] i.e. about 2 to 3 weeks.[9] The clinical result is a reduced effect of the drug. However, this may not be immediately clear.[12] In the case of anticonvulsants, breakthrough seizures will manifest themselves, but only if the drug dosage offers no security margin. In the case of other drugs, e.g. anticoagulants or glucocorticoids, whose metabolism may be enhanced by concomitant administration of other inducing agents, a reduced efficacy may have no immediate consequence. However, larger drug doses will be required to achieve the proper therapeutic effect. When the inducing agent is withdrawn the doses of the other drug(s) must be progressively readjusted.

4. Factors Affecting Interactions

4.1 The Drug

Adverse effects are more likely to arise with drugs that have a narrow therapeutic margin. Risk of interaction is much higher in drugs that are metabolised than in drugs excreted without biotrans-

formation. Interaction also depends on the doses of the interacting agents and the duration of their association. An important interaction is likely to occur only if both drugs bind to the same hepatic enzyme.[10]

4.2 The Individual

Interpatient variability in disease response to a drug is well known. Genetic polymorphisms are the cause of some extremely large differences among patients with epilepsy in the ability to metabolise anticonvulsants through oxidative processes.[14] The potential for drug interactions is extremely high in elderly patients. The metabolic disposition of some drugs is impaired with increased age.[15] In addition, concomitant diseases, as occurs often in the elderly, necessitate multiple therapies, and this greatly enhances the likelihood of adverse drug reactions.[16]

5. Discovery of Interaction

5.1 Classical Approach

Interactions have been investigated empirically by examining whether the pharmacokinetics of the new added drug were altered by the drug(s) patients were already taking, or whether the serum concentrations of previously prescribed drugs changed following the addition of a new agent.[17]

Close monitoring of clinical events should be carried out as soon as 2 or more drugs are associated. Blood concentration determinations are appropriate at the time when therapy with another drug is initiated or discontinued. The timing of blood concentration determination is critical. It depends on the half-life of the drug and the dose of the concomitant inducing/inhibiting drug. Both factors determine the time required for the remaining drug to reach its new steady-state plasma concentrations. When a patient exhibits signs or symptoms suggestive of possible drug toxicity, blood should be drawn at the time of the peak drug concentration or when symptoms are present.

In contrast, determination of the trough blood concentration is of particular interest in a patient who experiences breakthrough seizures. When deinduction occurs, measurement of the peak and trough concentrations is especially useful.[18]

5.2 Rational Approach

In recent years, improved understanding of the functional specificity of primary drug metabolising enzymes has provided a rational framework for classifying interactions.[17] Advances in the molecular biology of the CYP isozyme system have made it possible to qualitatively and quantitatively predict the interactions between drugs that are biotransformed entirely or partially in the liver. As a result, for any new drug the spectrum of inhibition-based interactions can be predicted even before the drug reaches the clinical phases of development.[19]

The CYP enzyme system consists of a superfamily of haemoproteins. It is now known that there are a number of individual CYP isozymes (or isoforms), each of which is a specific gene product with characteristic substrate specificity, and it is possible to correlate individual isozymes with specific metabolic pathways of drugs.

Consideration of the enzymes involved in the metabolism of a drug should signal the potential for an interaction with another. A comprehensive table of enzymes involved in the metabolism of anticonvulsants has been developed. It has been suggested that more than 75% of the drugs are metabolised by a limited number of isoforms: CYP1A2, CYP2C9/10, CYP2D6 and CYP3A4.[19]

Chemically and pharmacologically unrelated drugs exhibit similar spectra of drug interactions if they are metabolised by the same isozyme. Induction or inhibition is isoform-specific and substrate-independent.[19] Some drugs are more prone to interactions because they have 1 major metabolic pathway catalysed primarily by a single enzyme. If an added drug inhibits 1 isoform at therapeutic concentrations, it will interact with any substrate of this isoform. It is important to note that a drug may inhibit an isoform whether or not it is a substrate of this isoform.[20]

6. Management of Interactions

6.1 Prescription of Non-Anticonvulsants in Patients Treated for Epilepsy

With appropriate adjustment of dosages and monitoring of plasma drug concentrations, nearly all drug combinations could be used, if clinically indicated.[2] However, it is better to avoid potentially dangerous interactions when other agents with lesser potentials for drug interactions exist in the same therapeutic class.

6.1.1 Contraceptive Pills

As a result of case reports and clinical studies, the potential for a number of anticonvulsants to decrease the efficacy of oral contraceptives has been widely recognised.[21] Clinically relevant complications, attributed to concomitant anticonvulsant treatment, are irregular bleeding during the contraceptive cycle and unwanted pregnancies. It is of interest to note that the combination pill was first approved in 1960 and that the first report of pill failure did not appear until 1972.[22]

In the first years, the dosage of estrogen and progesterone was relatively high but, because of adverse effects, the estrogen fraction was decreased in 1972. Plasma concentrations of ethinylestradiol and levonorgestrel are decreased considerably by enzyme-inducing anticonvulsants.[21] Contraceptive failure seems to depend largely on the concentration of the estrogen fraction.[23] Thus, it was suggested that women receiving anticonvulsants as long term therapy and who required oral contraceptive corticosteroid therapy, be given a preparation containing ≥ ethinylestradiol 50μg. Induction of CYP3A-mediated metabolism of oral contraceptive corticosteroids is produced by phenobarbital, phenytoin, carbamazepine, oxcarbazepine, felbamate and topiramate, but not by valproic acid (sodium valproate), lamotrigine, gabapentin and tiagabine (see section 7).

6.1.2 Anticoagulants

Anticonvulsants which induce hepatic isoenzymes may reduce anticoagulant effectiveness, thereby increasing the risk of thrombus formation. During such anticonvulsant administration, unacceptable fluctuations in prothrombin control may occur, owing to the shortened half-life of the anticoagulant. However, when these anticonvulsants are stopped and the anticoagulant is continued, the enzyme-stimulating effect ceases, and the anticoagulant is metabolised less rapidly, which may result in haemorrhage from hypoprothrombinaemia.[24]

6.1.3 Calcium Antagonists

Combination of calcium antagonists (substrates of CYP3A4) and anticonvulsants may be necessary in some patients. Verapamil and diltiazem predispose to neurotoxicity when in combination with anticonvulsants metabolised by the CYP3A4 system. Nifedipine has little effect on hepatic CYP450 oxidative metabolism and should be preferred.[25,26]

6.1.4 Macrolide Antibacterials

Some macrolide antibacterials (substrates of CYP3A4) are potent enzyme-inhibitors and may lead to carbamazepine toxicity when added to regimens containing this latter drug, whereas other antibacterials cause less significant interactions with anticonvulsants and others still are of likely little or no concern.[27]

6.2 Prescription of Anticonvulsants in Patients Receiving Long Term Non-Anticonvulsant Therapy

From a pharmacokinetic perspective, many of the newer anticonvulsant drugs possess advantageous features. All of the new drugs exhibit linear pharmacokinetics. The availability of compounds which are eliminated primarily in unchanged form may be particularly advantageous in the management of patients taking concomitant medication known to interfere with hepatic drug metabolism.[28,29]

Table I. Medications that increase carbamazepine plasma concentrations and resulting consequences

Agents	Consequences	References
Analgesics		
Dextropropoxyphene	45-77% increase in 7 patients, clinical toxicity in 5	34
	Possible but infrequent clinical toxicity	2, 35
Cimetidine	Frequent but spontaneously reversible interaction, in a few days	36
Antibacterials		
Troleandomycin	Very frequent and marked clinical toxicity	37
Erythromycin	Frequent clinical toxicity	37-39
Other macrolides	Infrequent toxic signs (less potent inhibitors of CYP3A4)	40-46
Isoniazid	Patent toxic signs in almost all patients	47, 48
Cardiovascular drugs		
Diltiazem	Neurotoxicity in almost all patients	49, 50
Verapamil	Neurotoxicity in almost all patients	50, 51
Psychotropic drugs		
Viloxazine	Signs of intoxication in 4 our of 7 patients	52
Fluoxetine	Contradictory data	53-55
Fluvoxamine	Contradictory data	55, 56
Danazol	50 to 100% increase in carbamazepine plasma concentrations	57

7. Drug-Drug Interactions

7.1 Benzodiazepines

Accumulation of benzodiazepines caused by other drugs, and vice versa, has been observed, usually without clinical signs of toxicity. Clinically significant interactions involving clobazam,[30] diazepam,[31] lorazepam,[32] and nitrazepam[33] are rare.

7.2 Carbamazepine

Carbamazepine has a narrow therapeutic index. Carbamazepine is moderately protein bound (75%) and interactions due to protein-displacement are unlikely. It is almost completely cleared by hepatic metabolism, the major pathway being epoxidation to carbamazepine 10,11-epoxide which is almost entirely converted by the enzyme epoxide hydrolase to a *trans-diol* derivative which is excreted in urine.

Drugs known to cause episodes of carbamazepine intoxication by inhibition of its metabolism are listed in table I. CYP3A4 has been identified as the primary hepatic isoform catalysing oxidation to the epoxide, with CYP2C8 as a minor contributor.[58] Inhibition of CYP3A4 explains the interactions with macrolide antibacterials, nafimidone, cimetidine and danazol. However, some interactions remain unexplained at present, because it is not known whether these drugs or their metabolites inhibit CYP3A4, e.g. antipsychotics and doxycycline.[58]

Furthermore, drugs containing an acid amide group might have an inhibitory effect on epoxide hydrolase; hence, possible accumulation of active epoxide and signs of intoxication without significant changes in serum carbamazepine concentration may occur.[59] In 4 out of 6 patients, valnoctamide coadministration resulted in clinical toxicity.[60]

Carbamazepine is also a potent enzyme inducer (table II). It is thought to induce several CYP isoforms because it alters the biotransformation of other drugs that do not appear to be CYP3A4 substrates. In the future, a better knowledge of the isoforms inducible by carbamazepine will allow anticipation of interactions that result from CYP isoenzyme induction.[58]

7.3 Felbamate

Felbamate bioavailability was not modified by coadministration of antacid.[74] Felbamate is extensively metabolised by the liver It has been shown that felbamate is a competitive inhibitor of CYP2C19 and substrates of CYPC19 may also be

Table II. Carbamazepine (CBZ) induction of metabolism of other drugs

Agents	Consequences	References
Antiasthma agents		
Theophylline	Theophylline dose should be increased by 40-50%	61
Anticoagulants		
Warfarin	Warfarin dose must be ↑ or ↓ when adding or discontinuing CBZ	62
Antimicrobial and antihelmintic agents		
Doxycycline	Doxycycline half-life significantly shorter with potential ↓ efficacy	63
Praziquantel	Praziquantel concentration reduced by 75% with ↓ efficacy	64
Psychotropic drugs		
Midazolam	↓ midazolam pharmacodynamic effects observed	65
Imipramine	Imipramine doses may need to be ↑	66
Nortriptyline	Nortriptyline doses may need to be ↑	67
Haloperidol	Haloperidol concentrations ↓ >50% with possible clinical worsening	68, 69
Clozapine	Clozapine concentrations 1.5-2 times lower	70
Oral contraceptives		
Ethinylestradiol	Possible breakthrough bleeding and/or unwanted pregnancy	71
Antifungals		
Itraconazole	Itraconazole ↓ efficacy in systemic mycoses	72
Immunosuppressants		
Cyclosporin	Cyclosporin ↓ efficacy	73

↑ = increased; ↓ = decreased.

affected by it.[75,76] These aspects of felbamate therapy do not appear to have been investigated *in vivo*.

7.4 Gabapentin

Gabapentin does not bind to plasma proteins and is not metabolised in humans. Thus, drug-drug interactions are unlikely. Gabapentin neither induces nor inhibits hepatic mixed function oxidase enzymes, and hepatic enzyme inducing and inhibiting drugs have had no effect on gabapentin pharmacokinetics.[77] Norethisterone (norethindrone) and ethinylestradiol steady-state pharmacokinetics did not change significantly when gabapentin 400mg every 8 hours on days 16 to 22 of the menstrual cycle was added to the oral contraceptive regimen in the course of 3 consecutive menstrual cycles in healthy women.[78]

7.5 Lamotrigine

Lamotrigine is approximately 55% protein bound, is eliminated primarily through hepatic glucuronidation and is then renally excreted.[79] It does not affect microsomal enzyme activity as indicated by urinary 6β-hydroxycortisol excretion.[80] Because of its lack of influence on hepatic metabolism, lamotrigine does not alter the serum concentration of other agents.[79] However, its glucuronidation is susceptible to both hepatic microsomal enzyme inducing and inhibiting agents.[81] Although a slight increase in clearance was noted on coadministration with paracetamol (acetaminophen), this effect is unlikely to be clinically relevant.[82]

Healthy female volunteers, already established on a combined oral contraceptive pill, took lamotrigine 150mg for 14 days. Plasma ethinylestradiol and levonorgestrel concentrations were not significantly reduced, ovulation remained suppressed and there were no reports of breakthrough bleeding.[83]

7.6 Oxcarbazepine

Whereas carbamazepine is mainly eliminated through oxidative metabolism, the major metabo-

lic pathway for oxcarbazepine is reduction to a monohydroxy derivative. Elimination of oxcarbazepine and the active metabolite is mainly catalysed by noninducible cytosolic reductases.[84] Studies have been performed that show that there is no significant change in the metabolism and elimination of oxcarbazepine and its metabolite caused by drugs such as dextropropoxyphene,[85] erythromycin,[86] cimetidine,[87] verapamil,[88] and viloxazine.[89] Oxcarbazepine did not affect the anticoagulant effect of warfarin.[90]

Oxcarbazepine produced a smaller reduction in felodipine bioavailability than carbamazepine.[91] However, it has been suggested that oxcarbazepine may be a selective inducer of CYP3A isozymes[13] and this has important clinical consequences for women of childbearing potential. Oxcarbazepine has been found to decrease the bioavailability of ethinylestradiol by 48% and levonorgestrel by 32%.[92] When receiving oxcarbazepine with an oral contraceptive, 4 of 6 women developed breakthrough bleeding.[93] Thus, induction of oral contraceptives seems at present the only clinically significant interaction of this anticonvulsant, but a definite picture will emerge only after more extended clinical use.[94]

7.7 Phenobarbital (Phenobarbitone) and Primidone

The main pharmacokinetic interactions of primidone are due to its biotransformation to phenobarbital. The clinical significance of phenobarbital, and hence primidone, interactions with other drugs varies. Although almost any drug combination with them is compatible, only in a few combinations are the pharmacokinetic changes large enough to predictably necessitate dosage adjustments in most patients.[95]

Only 50% of phenobarbital is bound to plasma proteins. Therefore, it is unlikely that it would displace other drugs or be displaced by other drugs to any significant extent.[95] Phenobarbital is extensively metabolised in the liver via oxidative pathways. Alteration of its kinetics by other drugs has been documented. Phenobarbital clearance was markedly reduced by chloramphenicol,[96] dicoumarol,[97] and moderately reduced by dextropropoxyphene.[35] However, due to the high therapeutic index of the agent, these changes are unlikely to be of clinical significance. Phenobarbital plasma concentrations were lowered by phenylbutazone,[98] thioridazine,[99] chlorpromazine and prochlorperazine,[100] folic acid,[101] and pyridoxine.[102]

Even when the effect is small it may be clinically significant in difficult-to-control patients. More frequent and more important are situations in which phenobarbital causes changes in the pharmacokinetics of other drugs because it is a potent inducer of isoenzymes of the subfamilies CYP2B and CYP2C. Effects of induction by phenobarbital on other drugs are listed in table III. These effects in individual patients are largely unpredictable, depending on a genetically determined inducing capacity.[95]

7.8 Phenytoin

Phenytoin possesses a relatively narrow therapeutic index. Its absorption is vulnerable to and may be altered by the presence of drugs in the intestinal tract. Phenytoin is 90% protein bound and other drugs may compete for its binding sites. Its metabolism is saturable, and when the metabolising enzyme system approaches saturation, small changes in enzyme activity produce a disproportionately large increase in plasma concentrations. Interactions resulting in phenytoin intoxication via inhibition of its metabolism are listed in table IV. Major interactions are associated with inhibition of CYP2C9, whereas minor interactions are linked to inhibition of CYP2C19.[19]

On the other hand, coadministration of oxacillin,[154] rifampicin (rifampin),[155] antineoplastic agents,[156-158] antacids,[159] diazoxide,[160] folic acid,[101] and pyridoxine[102] result in lower phenytoin plasma concentrations, and hence a possible lack of anticonvulsant efficacy.

Phenytoin is a potent inducer of CYP isoenzymes of the subfamilies CYP2B or CYP2C. Effects of phenytoin hepatic isoenzyme induction on other drugs are listed in table V.

Table III. Phenobarbital (phenobarbitone) induction of the metabolism of other drugs

Agents	Consequences	References
Analgesics		
Antipyrine	Antipyrine ↓ efficacy	98
Aminophenazone (amidopyrine)	Aminophenazone ↓ efficacy	103
Paracetamol (acetaminophen)	↑ production of a toxic paracetamol metabolite	11
Pethidine (meperidine)	↑ pethidine toxicity	104
Antiasthma agents		
Theophylline	17 to 33% ↑ theophylline clearance with ↑ dosage requirement	61
Prednisone	Attacks of asthma in prednisone-dependent patients	105
Anti-infectious and antifungal agents		
Chloramphenicol	↑ chloramphenicol dosage requirement	106
Doxycycline	↑ doxycycline dosage requirement	107
Griseofulvin	↑ griseofulvin dosage requirement	98
Antiulcer agents		
Cimetidine	↑ cimetidine clearance with ↓ efficacy	108
Cardiovascular drugs		
Dicoumarol	In all patients, ↑ dicoumarol dosage required (average 33%)	97, 109
Warfarin	Warfarin dosage adjustments guided by prothrombin time determination	24, 97, 98
Digitoxin	↑ digitoxin dosage requirement	98
Verapamil	Possible ↑ verapamil dosage requirement	110
Immunosuppressants		
Cyclosporin	Markedly ↓ cyclosporin clinical efficacy	111
Psychotropic drugs		
Nortriptyline	Unclear how often nortriptyline dosage adjustment necessary	112
Desipramine	Unclear how often desipramine dosage adjustment necessary	113
Haloperidol	With or without ↓ haloperidol efficacy	114
Corticosteroids		
Dexamethasone	↓ response to dexamethasone	98, 115
Prednisone	Significantly ↓ prednisone efficacy	116
Oral contraceptives		
Ethinylestradiol	Breakthrough bleeding in ≥ 50%, contraceptive failure	71, 117, 118

↑ = increased; ↓ = decreased.

7.9 Tiagabine

The protein binding of tiagabine is very high, approximately 96%,[172] suggesting the possibility of drug interactions. However, thus far no such interactions have been observed *in vivo*.[172]

Tiagabine is extensively metabolised by CYP3A4. Thus, its metabolism was expected to be inhibited by CYP3A inhibitors such as erythromycin or ketoconazole. *In vitro* findings supported this prediction.[173] However, coadministration of erythromycin did not significantly modify tiagabine pharmacokinetic parameters.[174] Tiagabine does not appear to have inhibitory or inducing effects on the hepatic microsomal enzymes.[175]

Tiagabine 2mg 4 times daily had no effect on the degree of ovulation suppression produced by oral contraceptives and no influence on plasma concentrations of pill hormones in 10 healthy female volunteers over 2 pill-taking cycles.[176] Two participants reported breakthrough bleeding, but had non-ovulatory levels of follicle-stimulating hormone (FSH), luteinising hormone (LH) and progesterone, and no significant reduction in pill hormone concentrations throughout.

Table IV. Agents that increase phenytoin concentrations and resulting consequences

Agents	Consequences due to increase in phenytoin plasma concentrations	References
Analgesics		
Phenylbutazone	Possible toxicity, need for dosage adjustment	2, 119, 120
Dextropropoxyphene	Possible but infrequent toxicity depending on previous phenytoin concentration	2, 35
Antimicrobial and antifungal agents		
Sulfonamides	Toxicity in a few patients requiring close clinical and plasma concentration monitoring	121, 122
Chloramphenicol	Modest to marked elevation of concentrations	2, 96
Isoniazid	Toxicity in slow acetylators (10-15% of patients)	122-124
Fluconazole	Possible toxicity	125
Miconazole	Cases of toxicity	126, 127
Antineoplastic agents		
Tamoxifen	Toxicity	128
Antiulcer agents		
Cimetidine	Depends on duration of coadministration and previous phenytoin concentration	129-133
Cardiovascular drugs		
Dicoumarol	Rare toxicity	134
Phenprocoumon	Significantly increased half-life of phenytoin	135
Diltiazem	Toxicity in 3 out of 14 patients	50
Amiodarone	Possible toxicity	136
Digitoxin	Reported toxicity	137
Ticlopidine	Possible toxicity	138
Psychotropic drugs		
Diazepam	Low incidence of clinical problems	139, 140
Viloxazine	Frequent toxicity with interpatient variability (increase 7-94%)	141
Methylphenidate	Rare cases of toxicity	142
Chlorpromazine	Rare intoxications	143
Thioridazine	Intoxication in some patients	144
Imipramine	Mild intoxication	145
Trazodone	One reported case of intoxication	146
Miscellaneous drugs		
Phenyramidol	High doses may cause intoxication	147
Chlorpheniramine	Toxicity reported	148
Calcium carbimide	Possible toxicity	149
Azapropazone	May result in toxicity	150
Disulfiram	Toxicity in the majority of patients	149, 151-153

The risk of clinically relevant interactions between tiagabine and theophylline, warfarin, digoxin, cimetidine and triazolam has been reported as negligible.[177]

7.10 Topiramate

Topiramate is only slightly bound to plasma proteins. It is eliminated primarily as unchanged drug by the kidneys. However, it was shown to be a weak inducer of CYP. Topiramate co-medication resulted in a small but significant increase in digoxin clearance[178] and ethinylestradiol serum concentrations significantly decreased with marked interindividual variation.[29,179] Thus, the efficacy of the contraceptive pill is likely to be reduced.

7.11 Valproic Acid (Sodium Valproate)

Valproic acid has a large therapeutic index. About 90% of valproic acid in plasma is bound to albumin. It is eliminated almost exclusively by hepatic metabolism and metabolised extensively by a

Table V. Phenytoin induction of the metabolism of other drugs

Agents	Consequences	References
Analgesics		
Pethidine (meperidine)	Higher pethidine doses needed	122
Methadone	Possible methadone withdrawal signs	122
Antiasthma agents		
Theophylline	May necessitate higher or more frequent theophylline doses	61
Antimicrobial and anthelmintic agents		
Doxycycline	Higher doxycycline doses needed	107
Praziquantel	Praziquantel plasma concentration reduced by 75% with decreased efficacy	64
Cardiovascular drugs		
Dicoumarol	Higher dicoumarol doses needed	161
Warfarin	Variable effect	162
Quinidine	Larger quinidine doses required to maintain effective plasma concentrations	163
Digitoxin	Modest effect[a]	137
Disopyramide	Inconstant effect[a]	164
Felodipine	Markedly reduced felodipine bioavailability	165
Nisoldipine	Markedly reduced nisoldipine bioavailability	166
Furosemide	Decreased furosemide efficacy	167
Immunosuppressants		
Cyclosporin	Decreased cyclosporin efficacy	168
Psychotropic drugs		
Midazolam	Decreased midazolam efficacy	65
Corticosteroids		
Dexamethasone	Clearly decreased dexamethasone efficacy	169, 170
Prednisolone	Clearly decreased prednisolone efficacy	171
Methylprednisone	Clearly decreased methylprednisolone efficacy	169
Oral contraceptives	Breakthrough bleeding in 2/3 of patients, pregnancies reported	22, 23

a Some cases have been reported, without serious or frequent clinical consequences.

variety of conjugative and oxidative processes. It inhibits CYP3A4.[180]

Valproic acid absorption can be reduced by other drugs such as antacids,[181] and doxorubicin and cisplatin,[4] with the attendant risk of reduced anticonvulsant efficacy.

Few drug-drug interactions causing valproic acid accumulation have been reported. Naproxen[182] and salicylates[183] have been found to displace valproic acid from its binding sites. Furthermore, aspirin (acetylsalicylic acid) has been found to alter valproic acid metabolism by competing with valproic acid for mitochondrial oxidation. This leads to an increase in mitochondrial metabolism with production of 4-En-valproic acid, a toxic metabolite.[183]

Clinical valproic acid toxicity (tremor, ataxia) was shown to be induced by aspirin 12 to 20 mg/kg.[184] A patient in whom isoniazid resulted in clinical valproic acid toxicity has been reported.[185] Cimetidine coadministration results in a small reduction of valproic acid clearance, with undefined clinical significance.[186] Haloperidol and chlorpromazine[187] produce moderate elevations in plasma valproic acid concentrations. Valproic acid does not interact with oral contraceptives: it does not modify the plasma concentration of ethinylestradiol and levonorgestrel.[188]

7.12 Vigabatrin

Findings support the hypothesis that vigabatrin is devoid of drug interactions. Vigabatrin is not protein bound, is not appreciably metabolised in the liver and does not influence hepatic metabolism.[189,190] No major change was noted in the plasma concentrations of ethinylestradiol and levonorgestrel when administered with vigabatrin.[190]

8. Conclusions

Since anticonvulsant drugs are given for prolonged periods and often in combination, the issue of interactions is an important consideration. It must be remembered that the possibility of drug interactions exists anytime a drug is added or discontinued in the course of long term treatment.

Solid knowledge of basic pharmacological principles, as well as familiarity with the pharmacokinetics of the individual drugs and their main metabolites, is required in the management of comedicated patients.

A major issue is that because of the marked interindividual variability in these events they can be anticipated, but their extent cannot readily be predicted. However, with appropriate adjustment of dosages and monitoring of plasma drug concentrations, nearly all drug combinations involving anticonvulsants can be used, if clinically indicated.

Established anticonvulsants, such as phenytoin, carbamazepine and phenobarbital, have a high interaction potential, and many case reports and reviews describe drug-drug interactions that are actually found in daily practice. Compared to these anticonvulsants, valproic acid is superior.

Treatment of concomitant illnesses in patients with epilepsy will be easier with the new anticonvulsant drugs. Gabapentin and vigabatrin are not predisposed to drug-drug interactions. Clinically relevant interactions are unlikely to occur with lamotrigine. Oxcarbamazepine and tiagabine have clear advantages over carbamazepine and phenytoin (both first-line drugs for the treatment of partial epilepsies), in terms of lower interaction potential.

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Correspondence and reprints: Professor *Pierre Loiseau*, 4 allee de Carabin, 33460 Arsac, France.