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Adverse drug interactions in epilepsy

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Abstract

Adverse antiepileptic drug interactions may occur at pharmacokinetic and pharmacodynamic level. The most important adverse interactions in epilepsy therapy are pharmacokinetic and result from induction or inhibition of drug metabolizing enzymes. Pharmacodynamic interactions, on the other hand, take place directly at the sites of action, without any change in the concentration of the affected drug at receptor sites. In most situations. Adverse interactions can be prevented by avoiding unnecessary polytherapy, and by selecting comedications which are less likely to interact.

Most patients with epilepsy require treatment with antiepileptic drugs (AEDs) for many years, often for a lifetime. Therefore, there is a high probability that these patients will receive other medications for the management of intercurrent or concomitant conditions. Additionally, some patients may require combination therapy with more than one AED. Whenever multiple drug therapy is used, drug interactions may occur, which can have adverse clinical consequences. This article will highlight the main mechanisms involved and clinically relevant examples. For a more comprehensive discussion on this topic, a number of recent reviews are available.[1-7]

MECHANISMS OF AED INTERACTIONS

Adverse AED interactions may occur at pharmacodynamic and pharmacokinetic level. Pharmacodynamic interactions take place directly at the sites of action, without any change in the concentration of the affected drug at receptor sites. Examples of such interactions involve the reciprocal potentiation of central nervous system adverse effects which occurs when certain AEDs are used in polytherapy. As expected, adverse pharmacodynamic interactions tend to be more common when combining AEDs which act on a common target. For example, the tolerability of lamotrigine and carbamazepine, both of which have a blocking action on sodium channels, may be reduced when these agents are used in combination.[8]

Pharmacokinetic interactions involve a change in the absorption, distribution or elimination of the affected drug, and therefore they may modify adversely clinical response by altering the concentration of the affected drug (or its active metabolites) at the receptor sites. Among such interactions, those involving an alteration in gastrointestinal absorption are not common, but they may be occasionally important: one example is the marked impairment of phenytoin absorption caused by certain enteral tube feedings.[9] Distribution interactions occurs when a drug displaces another drug from plasma protein binding sites. Plasma protein binding interactions are generally clinically unimportant[10], because the amount of drug displaced from plasma proteins is typically very small compared with the amount of drug which is already present in extravascular spaces. Moreover, any change in the free (unbound) concentration of the affected drug is usually offset by a compensatory increase in drug elimination. The ultimate consequence of a plasma protein binding interaction is a reduction in the total plasma concentration of the displaced drug (as a result of its redistribution and elimination) without any significant change in its unbound, pharmacologically active concentration. Although clinical response is usually unaffected, clinicians should be aware that in the presence of such interactions the therapeutic and toxic effects of the displaced drug will be observed at total concentrations lower than usual.[10]

By far the most important adverse interactions are those which result from induction or inhibition of drug metabolizing enzymes.[4] Enzyme induction is the phenomenon by which a drug stimulates the synthesis, in the liver and in other organs, of enzymes involved in drug metabolism, resulting in accelerated metabolic clearance of medications which are substrates of those enzymes. Enzyme induction takes place gradually (typically, over a period of several days or even weeks), and it is reversible following discontinuation of the causative agent. Usually enzyme induction

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results in reduced efficacy of the affected drug, but potentiation of activity or toxicity may occur when induction leads to increased production of active or toxic metabolites. In contrast to enzyme induction, enzyme inhibition can be defined as the phenomenon by which a drug inhibits the activity of one or more drug metabolizing enzymes and thereby decreases the clearance of compounds metabolized by these enzymes. Unlike enzyme induction, enzyme inhibition usually becomes manifest rapidly after addition of the causative agent, though it its magnitude may increase over time depending on the half-life of both the causative and the affected drug. Enzyme inhibition is also reversible following discontinuation of the offending agent. Because of their importance in AED therapy, these interactions will be discussed separately in more detail.

INTERACTIONS CAUSED BY ENZYME INDUCTION

Carbamazepine, phenytoin, phenobarbital and primidone (henceforth referred to collectively as enzyme inducing AEDs) stimulate the activity of a variety of cytochrome P450 (CYP) enzymes, including CYP1A2, CYP2C9, CYP2C19 and CYP3A4, as well as glucuronyl transferases and epoxide hydrolase.[4,11] This allows to predict drug interactions simply based on knowledge of the isozymes responsible for the metabolism of specific medications: for example, knowledge that steroid oral contraceptives, statins, many anti-retroviral agents, many anticancer agents, many antipsychotics and many calcium antagonists are substrates of CYP3A4 allows to predict that the efficacy of conventional doses of these

Table 1. Examples of medications whose metabolism is stimulated by enzyme inducing AEDs. The list should not be regarded as exhaustive. For further information, please refer to recent reviews.[1-7]

Albendazole	Meperidine
Alprazolam	Methadone
Alprenolol	Metronidazole
Amiodarone	Methylprednisolone
Amitriptyline	Metyrapone
Atorvastatin	Midazolam
Carbamazepine	Nifedipine
Chlorpromazine	Nimodipine
Clobazam	Nisoldipine
Clomipramine	Olanzapine
Clonazepam	Paroxetine
Clozapine	Praziquantel
Cortisol	Prednisone
Cyclosporyn A	Propranolol
Desipramine	Quetiapine
Dexamethasone	Quinidine
Diazepam	Risperidone
Dicoumarol	Simvastatin
Disopyramide	Sirolimus
Doxycicline	Steroid oral contraceptives
Efavirenz	Tacrolimus
Ethosuximide	Teniposide
Felbamate	Theophylline
Felodipine	Thyroxine
Haloperidol	Tiagabine
Hydrocortisone	Topiramate
Imipramine	Valproic acid
Indinavir	Verapamil[1]
Itraconazole	Warfarin[2]
Lamotrigine	Ziprasidone

[1] Interaction only relevant after oral administration of verapamil

[2] Phenytoin may cause an initial decrease in anticoagulant effect, followed by an increase in plasma warfarin concentration and possibly increased anticoagulant effect.

medications is reduced or even lost in patients taking concomitant enzyme inducing AEDs.[12] Likewise, induction of glucuronyl transferases explains the marked increase in lamotrigine clearance observed in patients comedicated with enzyme inducers (Table 1).

Although in some cases adequate clinical responses can be restored by increasing the dosage of the affected medication, caution needs to be exerted when the enzyme inducing AED is withdrawn or substituted with a non-enzyme inducing AED. In fact, removal of the enzyme inducing agent will cause the metabolism of the affected drug to slow, and toxic symptoms may develop if the dosage of the latter is not reduced appropriately. In patients receiving oral anticoagulants and enzyme inducing AEDs, fatal hemorrhage has occurred when the AED was removed without monitoring the anticoagulant response and adjusting the anticoagulant's dosage accordingly.[4]

Most new generation AEDs are devoid of enzyme inducing activity.[13] However, oxcarbazepine, lamotrigine (in a study which used a 300 mg/day lamotrigine dosage) , felbamate and, at dosages ≥ 200 mg/day, topiramate, stimulate the metabolism of oral contraceptive steroids, possibly by tissue-selective stimulation of CYP3A4 and/or glucuronyltransferases.[4] Additionally, oxcarbazepine may have a moderate inducing effect on the metabolism of lamotrigine and felodipine.

INTERACTIONS CAUSED BY ENZYME INHIBITION

AEDs causing inhibition of drug metabolism include valproic acid (which reduces the metabolic clearance of phenobarbital, lamotrigine, carbamazepine-10,11-epoxide) and oxcarbazepine (which may inhibit the metabolism of phenytoin and, to a lesser extent, phenobarbital).[4] Felbamate also inhibits the metabolism of several AEDs. Other interactions are those whereby the metabolism of an AED is inhibited by drugs used for other indications, one example being the clinically important inhibition of carbamazepine metabolism by erythromycin or verapamil (Table 2). Again, these interactions can be predicted by knowledge of what drugs are substrates of the inhibited enzyme(s).[12]

The most common consequence of interactions mediated by enzyme inhibition is an increase in the plasma concentrations of the affected drug,

Table 2. Medications which may increase the plasma concentration of AEDs, presumably by inhibiting their metabolism of AEDs. The list should not be regarded as exhaustive. For further information, please refer to recent reviews.[1-7]

Affected AED	Interfering drugs
Carbamazepine	Cimetidine, danazol, clarithromycin, dextropropoxyphene diltiazem, erythromycin, felbamate, fluconazole, fluoxetine, fluvoxamine, isoniazid, ketoconazole, metronidazole, ritonavir, ticlopidine, troleandomycin, verapamil
Ethosuximide	Isoniazid
Lamotrigine	Sertraline, valproic acid
Phenobarbital	Chloramphenicol, dextropropoxyphene, felbamate, phenytoin, sulthiame, valproic acid
Phenytoin	Allopurinol, amiodarone, azapropazone, chloramphenicol, chlorpheniramine, cimetidine, dextropropoxyphene, diltiazem, disulfiram, efavirenz, felbamate, fluconazole, fluorouracil, fluoxetine, fluvoxamine, isoniazid, miconazole, omeprazole, oxcarbazepine, sertraline, sulfaphenazole, sulthiame, tacrolimus, ticlopidine, tolbutamide, trazodone, valproic acid[1]
Valproic acid	Cimetidine, felbamate, isoniazid, sertraline

[1] The inhibition of phenytoin metabolism by valproic acid is inconsistent and limited to an increase in unbound plasma phenytoin concentration. Total plasma phenytoin concentration usually decreases due to displacement from plasma protein binding sites.

potentially resulting in toxicity if dosage is not adjusted accordingly. These interactions can have a major influence on dose requirements, as illustrated by the need for markedly lower starting and maintenance dosages, and slower titration rates, of lamotrigine in patients comedicated with valproate.[4]

CONCLUSIONS

Adverse AED interactions are frequently observed, and most can be predicted by knowledge of the underlying mechanism. In many situations, these interactions can be prevented by avoiding unnecessary polytherapy, and by selecting comedications which are less likely to interact. Clinical response and, whenever possible, plasma drug concentrations should be monitored carefully whenever a potentially interacting drug is added or removed from a patient's regimen. Appropriate dosage adjustments, when needed, are crucial in preventing serious toxicity or therapeutic failure.

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