Johannessen Landmark, Cecilie; Patsalos, Philip N.
Interactions between antiepileptic drugs and herbal medicines
Universidad de Santiago de Chile
Santiago, Chile

Available in: http://www.redalyc.org/articulo.oa?id=85670209
Interactions between antiepileptic drugs and herbal medicines

[Interacciones entre fármacos antiepilépticos y medicinas herbales]

Cecile JOHANNESSEN LANDMARK¹ and Philip N. PATSALOS²*

¹Department of Pharmacy, Faculty of Health Sciences, Oslo University College, Oslo, Norway.
²Pharmacology and Therapeutics Unit, Department of Clinical and Experimental Epilepsy, Institute of Neurology, Queen Square, London and Chalfont Centre for Epilepsy, Chalfont St Peter, Chesham Lane, Buckinghamshire, SL9 ORJ, UK.

*Contact: E-mail: p.patsalos@ion.ucl.ac.uk

Submitted January 15, 2008; Accepted February 4, 2008

Abstract

As a therapeutic class, antiepileptic drugs (AEDs) have a high propensity to interact and many interactions with concomitant medications have been described. Increasingly, herbal remedies are often used by patients with epilepsy and the risk that these may interact with their AED medication is now being realised. The purpose of this review is to highlight the interactions that have been reported between AEDs and herbal medicines. Overall, the published data are sparse and comprise of both pharmacodynamic (preclinical only) and pharmacokinetic (preclinical and clinical) interactions. Pharmacodynamic interactions between diazepam and the Chinese herb Saiboku-to and with Ginkgo biloba, and between phenytoin, valproate and gabapentin and Centella asiatica have been described. Pre-clinical studies suggest that the Japanese herbs Sho-seiryu-to and Sho-saiko-to, the herbal infusion preparation from Cassia auriculata, the traditional Chinese herbal medicine Paeoniae Radix and the herb Mentat can affect the pharmacokinetics of carbamazepine by various mechanisms. Pharmacokinetic interactions have also been reported with phenytoin (Paenoniae Radix, Ayurvedic syrup shankhapushpi), phenobarbital (Ginkgo biloba) and diazepam (the Chinese herbs Angelica dahurica and Salvia miltiorrhiza Bge). Clinical studies have reported a reduction in serum carbamazepine concentrations when co-administered with the traditional Chinese herb Free and Easy Wanderer Plus and also a reduction in serum midazolam concentrations by Echinacea and by St John’s Wort. The mechanism of these interactions is considered to be induction of hepatic metabolism. In contrast, piperine elevates serum phenytoin concentrations, possibly by enhancing the gastrointestinal absorption of phenytoin. More research and information are required in order to clarify the propensity of AEDs and herbal medicine to interact and therefore potentially compromise the therapeutics of AEDs.

Keywords: Antiepileptic drugs, interactions, herbal medicines, Carbamazepine, Phenytoin, Valproate.

Resumen

Los fármacos antiepilépticos (FAE), como una clase terapéutica, tienen una alta propensión a interactuar y se han descrito muchas interacciones concomitantes con medicamentos. El uso de las medicinas herbales es cada vez más frecuente en pacientes con epilipsia y en la actualidad se investiga el riesgo de que estas puedan interactuar con estos FAE. En general, los datos publicados son escasos y comprometen tanto interacciones farmacodinámicas (solamente preclínicas) como farmacocinéticas (preclínicas y clínicas). Se han descrito las interacciones farmacodinámicas entre diazepam y la hierba china Saiboku-to y con Ginkgo biloba y entre fenitoína, valproato y gabapentina y Centella asiatica. Los estudios preclínicos sugieren que las hierbas japonesas Sho-seiryu-to y Sho-saiko-to, la infusión de Cassia auriculata, la hierba medicinal tradicional china Paeoniae Radix y la hierba Mentat pueden afectar la farmacocinética de carbamazepina por varios mecanismos. Las interacciones farmacocinéticas han sido también publicadas con fenitoína (Paenoniae Radix, sirope ayurvédico shankhapushpi), fenobarbital (Ginkgo biloba) y diazepam (las hierbas chinas Angelica dahurica y Salvia miltiorrhiza Bge). La reducción de las concentraciones de carbamazepina en suero cuando es co-administrada con la hierba tradicional china Free y Easy Wanderer Plus ha sido publicada en estudios clínicos. También se ha estudiado la reducción en suero de las concentraciones de midazolam por Echinacea y la hierba de San Juan. Se considera que el mecanismo de estas interacciones es a través de la inducción del metabolismo hepático. Por el contrario, piperina eleva las concentraciones de fenitoína en suero, posiblemente por el aumento de la absorción gastrointestinal de la fenitoína. Se requiere más información e investigación para esclarecer las interacciones entre los FAE y las medicinas herbales.

Palabras clave: Fármacos antiepilépticos, interacciones, medicinas herbales, Carbamazepina, Fenitoína, Valproato.
INTRODUCTION

Antiepileptic drug (AED) interactions with drugs used in the management of non-epilepsy co-morbidities are numerous and common (Patsalos and Perucca, 2003b). Furthermore, over the counter medications including herbal medicines (plant-based remedies) are increasingly being used by patients with epilepsy and the risks that these may interact with their AED medication is now being realised. Also, there are various traditions for the use of herbal medicines in different parts of the world and consequently in many countries the potential for clinically relevant interactions is much greater. A recent cohort study of 400 patients with epilepsy reported that 34% had used or were using complementary and alternative medicines for general health purposes and stated that they believed that these medicines had little or no effect on their epilepsy, and the majority of patients (63%) had not informed their doctor (Easterford et al., 2005).

Because patients may often be unaware of the interaction potential between AEDs and herbal medicines and because many patients do not consider such medicines as drugs, most patients do not inform their doctor that they are taking these additional potentially interacting medications. It should be emphasized that most herbal preparations are not included in the regulatory framework, and a complication is that the quality and quantity of the active ingredients in herbal medicines is often variable and often with unknown additional ingredients and thus potential interactions may be variable and difficult to predict (Samuels et al., 2008; Skalli et al., 2007). The clinical consequence of interactions may be lack of efficacy, toxic reactions, unexpected effects, unforeseen side effects, and non-compliance, and it is therefore of major importance for patient outcome. Vulnerable patient groups should be extra cautious regarding their increased risk of interactions and toxic effects, and include the elderly, cancer patients and pregnant women (Skalli et al., 2007). Both pregnant women and the elderly undergo changes in physiological and pharmacokinetic para-meters, and cancer patients and elderly patients are often prescribed polytherapy. Also these groups may often choose herbal medicines in addition or as a substitute for marketed drugs.

Interactions can be divided into two types, pharmacodynamic and pharmacokinetic. Pharmacodynamic interactions relate to interactions at the site of action of a drug and may be additive, synergistic or antagonistic in nature. AEDs mainly target proteins involved in neuronal excitation, via modulation of voltage-gated sodium or calcium channels or ligand-gated receptors for GABA (γ-aminobutyric acid) and glutamate, or by affecting intracellular pathways, and most AEDs have several mechanisms of actions (Johannessen Landmark, 2007). Consequently, there are many sites at which a pharmacodynamic interaction could be elicited. In contrast pharmacokinetic interactions relate to the processes of absorption, distribution, metabolism and excretion and by far the most important site of interaction is that of metabolism involving cytochrome P450 (CYP) and uridine glucuronyl transferases (UGTs) in the liver (Patsalos and Perucca, 2003a).

Overall, interactions between AEDs and herbal medicines are poorly described in the literature although the widely used herbal medicines Ginkgo biloba and St. John’s Wort have recently been reviewed with regards to their interactions with commonly used drugs (Hu et al., 2005). The purpose of this review is to highlight the interactions between AEDs and commonly used herbal drugs, including drugs from traditional Chinese and Japanese (Kampo) medicine, and also Indian Ayurvedic herbal preparations. The review first describes the putative pharmacodynamic interactions followed by the pharmacokinetic interactions and these in turn are divided into preclinical and clinical observations.

Search strategy and selection criteria

The present review is based on recently published articles and searches in PubMed November-January 2008. Relevant peer-reviewed articles in recognized international journals in English (1987-2007) were included in the review. Primary sources were preferred, but review articles of specific importance were also included. Relevant published case reports were included and also abstracts when a complete published article was not available. Both preclinical and clinical findings were included. Furthermore, searches of the various AEDs in combination with interactions and herbal medicine were used. The AEDs included were carbamazepine, diazepam, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, midazolam, phenobarbital (pentobarbital), phenytin, pregabalin, rufinamide, tiagabine, topiramate, valproate, and zonisamide.
I. PHARMACODYNAMIC INTERACTIONS

Preclinical studies

**Diazepam**

The mechanism of action of diazepam in that it acts by binding to the GABA$_A$ receptor, a receptor that is well characterized. Consequently, diazepam is a drug of choice to study pharmacodynamic interactions with herbal drugs that have yet to be characterized with regards to their cellular mechanisms of action. Diazepam (1.0 mg/kg s.c.) administered in combination with the Chinese herb Saiboku-to (2 g/kg/day; traditionally used for cold, inflammation and anxiety disorders) resulted in a potentiated anxiolytic-like effect in the rat, which could not be attributed to alteration in diazepam blood concentrations or metabolism of diazepam (Yuzurikara et al., 2002). In another study in rats with the same compounds, it was suggested that Saiboku-to (2 g/kg/day) potentiated the pharmacological effect of diazepam via an action on the GABA$_A$ receptor (Ikarashi et al., 2002). This was ascertained by measurement of diazepam-mediated acetylcholine release in striatum and hippocampus using intracerebral microdialysis, as this release is dependent on GABAergic activity (Ikarashi et al., 2002). As to exactly what component of Saiboku-to is responsible for this effect is unknown since the Saiboku-to preparation contains 10 different herbs (Ikarashi et al., 2002).

Diazepam (1.0 mg/kg s.c.) in combination with an extract from *Ginkgo biloba* (EGb 761, in single doses of 1-16 mg/kg i.p. and in repeated doses from 24-96 mg/kg/day p.o.) increased a social contact test in a rat model to a greater extent than with diazepam alone in a dose-dependent manner, and this effect was explained by a possible interaction at the GABAA receptor (Chermat et al., 1997). This herb has traditionally been used to improve blood flow, protect against oxidative cell damage and to enhance memory and concentration, although the documentation is conflicting (NIH, 2005). *Ginkgo biloba* has also been proposed to have pro-convulsive properties, as it contains a neurotoxin (a vitamin B6 derivative, Ginkgotoxin, 4-O-methopridoxine) that inhibits GABA synthesis via competitive antagonism of pyridoxil phosphate, a coenzyme of the enzyme responsible for the conversion of glutamate to GABA, glutamate decarboxylase (Samuels et al., 2007).

**Phenytoin, valproate and gabapentin**

An isobolographic study with phenytoin (13 mg/kg), valproate (104 mg/kg) and gabapentin (310 mg/kg) in combination with *Centella asiatica* (0.2-0.3 ml of the prepared herbal extract/25 g body weight; traditionally used to improve circulation and with putative antibacterial effects) in mice demonstrated additive anticonvulsant activity and a significant decrease in the effective dose of the AEDs needed for seizure protection, by 62% for phenytoin, 72% for valproate and 75% for gabapentin (Vattanajun et al., 2005). The pentylentetrazole test was used to determine the effective dose, and the rotarod test was used to determine neurotoxicity, but blood or brain concentrations of phenytoin, valproate and gabapentin were not measured (Vattanajun et al., 2005). The exact mechanism of the pharmacodynamic anticonvulsant potentiation was unknown, a possible pharmacokinetic contribution at the level of absorption was excluded since the herb was administered orally and the AEDs intraperitoneally. Nevertheless, the findings suggest that *Centella asiatica* may be used with potential favourable outcome as an adjunctive medication for patients with epilepsy (Vattanajun et al., 2005).

Clinical studies

Pharmacodynamic interactions between AEDs and herbal medicines have not been reported in patients, and they may be difficult to document and evaluate.

II. PHARMACOKINETIC INTERACTIONS

Preclinical studies

**Carbamazepine**

Two commonly used Japanese herbs (*Sho-seiryu-to* and *Sho-saiko-to*) (traditionally used for the management of inflammation and cold symptoms) affect the pharmacokinetics of carbamazepine, as studied in rats (Ohnishi et al., 1999; 2002). Simultaneous administration of carbamazepine (50 mg/kg) and *Sho-seiryu-to* (TJ-19, 1 g/kg) lengthened the time to reach the peak plasma concentration ($T_{max}$), but did not influence the maximal plasma concentration ($C_{max}$), the area under the plasma concentration-time curve (AUC) or elimination half-life ($t_{1/2}$). Carbamazepine $T_{max}$ values and the elimination rate constant were increased after 1-week daily pretreatment with *Sho-seiryu-to*, by 83% and 88%, respectively; while the $t_{1/2}$ and the mean residence

Antiepileptic drugs and herbal medicine interactions

Johannessen Landmark & Patsalos


Antiepileptic drugs and herbal medicine interactions

Johannessen Landmark & Patsalos


time (MRT) decreased by 52% and 34%, respectively (Ohnishi et al., 1999). These results indicate that in rats oral administration of Sho-seiryu-to delays the oral absorption of carbamazepine, while 1-week pretreatment with Sho-seiryu-to induces the metabolism of carbamazepine (Ohnishi et al., 1999).

When the herb Sho-saiko-to (TJ-9, 1 g/kg) was administered orally in combination with carbamazepine (50 mg/kg) a 50% reduction in carbamazepine C_{max} and a tendency for T_{max} to increase was observed and this was accompanied by a 40% reduction in gastric emptying (Ohnishi et al., 2002). Using hepatic microsomes it was observed that Sho-saiko-to was associated with a concentration-dependent inhibition of epoxide hydrolase, with a K_{i} of 540 µg/ml (Ohnishi et al., 2002). However, following 1-week pre-treatment with Sho-saiko-to, there were no differences in these pharmacokinetic parameters (Ohnishi et al., 2002).

The Japanese herb Saiko-ka-ryukotsu-borei-to (1 g/kg; traditionally used to treat a variety of neurological symptoms) in combination with carbamazepine (50 mg/kg) in rats was not associated with any pharmacokinetic interactions as measured by the same parameters as described above (Ohnishi et al., 2001).

Concomitant use of carbamazepine (100 mg/kg/day) and the herbal infusion preparation from Cassia auriculata (an extract corresponding to 20 g fresh plant material/kg p.o.) (traditionally used for the treatment of diabetes, inflammation and infections and considered to have antioxidant properties) in rats resulted in a 63 ± 10% increase in carbamazepine blood concentrations after four weeks (Thabrew et al., 2004). No concurrent increase in toxicity was observed, as measured by general behaviour, liver function, haematological parameters and kidney function. Although the dose of the herb used in this study was approximately 10 times higher than that typically ingested by humans, the authors concluded that this infusion preparation has the potential to inhibit the metabolism of carbamazepine, probably via an action on CYP3A4, and therefore patients should avoid the infusion (Thabrew et al., 2004).

The traditional Chinese herbal medicine Paenoniae Radix (300 mg/kg p.o. of the herbal extract; traditionally used to relieve pain and inflammation) in combination with carbamazepine (100 mg/kg) decreased carbamazepine T_{max} by 55% in rats, but no statistically significant changes were found in carbamazepine plasma concentrations, t_{1/2}, C_{max}, AUC, MRT, oral clearance (Cl/F) or oral volume of distribution (V_{d}/F) (Chen et al., 2002). The authors explained these findings by increased absorption, but an interaction involving metabolism was also suggested despite the reported data (which were highly variable in a small number of animals; n =6). A small decrease (8%) in carbamazepine protein binding was also observed but the potential clinical significance of this is uncertain (Chen et al., 2002).

Carbamazepine (50 mg/kg) and phenytoin (50 mg/kg) in combination with the herb Mentat (500 mg/kg p.o.; traditionally used for its psychotropic effects) in rabbits was associated with a 35% and 55% increase in AUC for carbamazepine and phenytoin, respectively, and the changes were explained on the basis of an increase in absorption or a decrease in carbamazepine and phenytoin metabolism (Tripathi et al., 2000).

Phenytoin

The administration of phenytoin (100 mg/kg) in combination with Paenoniae Radix (300 mg/kg of the herb extract) increased phenytoin T_{max} 3-fold in a rat model and this was attributed to a delay in phenytoin absorption (Chen et al., 2001). There were no significant changes in other pharmacokinetic parameters, except for a 44% reduction in V_{d}/F.

A study of Ayurvedic syrup shankhapushpi (0.5 ml, containing six different herbs; traditionally used to treat seizures) in combination with phenytoin, which was administered using a multiple dosing regimen (40 mg/kg/day for five days) reported a 50% reduction in phenytoin plasma concentrations and a concurrent lowering of seizure threshold by >50% (Dandekar et al., 1992). It was suggested by the authors that both a pharmacodynamic and a pharmacokinetic interaction is occurring.

Diazepam

The Chinese herb Angelica dahurica (1 g/kg p.o.; traditionally used to treat pain, headache, inflammation and fever) increased the first pass metabolism of diazepam (10 mg/kg) in rats, as measured by a four-fold increase in C_{max} (Ishihara et al., 2000). The herb inhibited the activity of CYP2C, CYP3A and CYP2D1 but since diazepam was associated with a high clearance, underwent hepatic blood flow rate-limited metabolism and a change of intrinsic clearance; hepatic clearance was therefore unaffected (Ishihara et al., 2000). It has also been suggested that the herb may modulate GABA_A.
receptors and thus result in a pharmacodynamic interaction with diazepam as well (Hu et al., 2005).

In a study of diazepam (15 mg/kg) and the Chinese herb *Salvia miltiorrhiza* Bge (100 mg/kg/day p.o.; traditionally used to treat cardiovascular diseases) administered in combination to rats, diazepam clearance was increased two-fold and $C_{\text{max}}$ and AUC were decreased by 27% and 55%, respectively. These findings were accompanied by an increase in microsomal protein content and non-specific CYP enzyme levels (Jinping et al., 2003).

*Sho-saiko-to* (used for the treatment of inflammation), a traditional Chinese and Japanese herbal medicine, and *Saiko-keisi-to* (used to treat a variety of neurological symptoms) a traditional Japanese herbal medicine, shortened the pentobarbital-induced sleeping time in mice by 35% for both herbs, following their administration (0.55 and 0.5 g/kg, respectively) for four weeks and the administration of 60 mg/kg pentobarbital 48 hours after the final dose of the herbal preparation (Nose et al., 2003). The administration of *Sho-saiko-to* (0.55 g/kg) for two weeks reduced the pentobarbital-induced sleeping time in rats slightly (14%) following administration of 30 mg/kg pentobarbital 48 hours after the final dose of the herbal preparation (Nose et al., 2003). Administration of *Sho-saiko-to* for two weeks also up-regulated mRNA expression of CYP2B, CYP3A1, CYP2E1 and CYP4A1 from two to eight-fold in rats, and the administration of *Saiko-keishi-to* (0.5 g/kg) for two weeks also up-regulated the mRNA expression of CYP2B, CYP3A1 and CYP4A1 two to four-fold in rats, and the administration of *Sho-saiko-to* (0.5 g/kg) for two weeks also up-regulated the mRNA expression of CYP2B, CYP3A1 and CYP4A1 from two to eight-fold in rats. These data suggest that the two herbs may have the potential to influence the pharmacokinetics of AEDs in man.

**Phenobarbital**

An extract from *Ginkgo biloba* (an enhancer of memory and concentration) has been demonstrated to induce the activity of CYP2B (Umegaki et al., 2002) and since phenobarbital is a substrate for CYP2B in rats, the potential interaction between the two was investigated. *Ginkgo biloba* (0.1, 0.5 and 1.0% *G. biloba* extract) reduced the hypnotic potency of phenobarbital (50 mg/kg) in rats, as measured by the duration of sleep (from loss to recovery of righting reflex; Kubota et al., 2004). A 40% decrease in phenobarbital $C_{\text{max}}$ and 20% reduction in phenobarbital AUC$_{0-24}$ were observed and these changes were possibly due to an enhancement of CYP2B expression, since liver weight was increased by 35% with the highest dose of concentration of *Ginkgo biloba* (Kubota et al 2004).

**Clinical studies**

**Carbamazepine**

St. John’s Wort (*Hypericum perforatum*), is a commonly used herbal drug, and in one study, more than 5% of patients with epilepsy used the herbal drug for mood disturbance (mild to moderate depression) and fatigue (Patsalos et al., 2002). St. John’s Wort has the potential to increase the metabolism of AEDs, since it induces CYP3A4, CYP2C9 and CYP2C19 and possibly by affecting drug transporter activity in the gastrointestinal tract (Roby et al., 2000; Wang et al., 2004; Zhou et al., 2004). St. John’s Wort (300 mg tablet with 0.3% hypericin) did not, however, alter the plasma concentration of carbamazepine at steady state in an open cross over study of eight volunteers (5 men and 3 women aged 24-43 years old; Burstein et al., 2000). The subjects received carbamazepine daily titrated from 200 mg to 400 mg for 20 days, and then the combination of drug and herb for 14 days. No differences were seen in carbamazepine peak or trough concentrations, AUC or oral clearance values (Burstein et al., 2000). These data suggested that CYP3A4 was not further induced by St. John’s Wort over and above that consequent to carbamazepine autoinduction, but careful monitoring of carbamazepine was recommended, as carbamazepine clearance was increased by 24% in one patient (Burstein et al., 2000).

In another study, the opposite interaction effect was studied, namely the induction effect of carbamazepine (200 mg/day, days 1-12 and 400 mg/day, days 13-18) upon the metabolism of hypericin and pseudohypericin (300 mg extract of *Hypericum* with 92 µg hypericin and 262 µg pseudohypericin) from St. John’s Wort. The study entailed 33 healthy male volunteers (18-50 years old; Johne et al., 2004) and although it demonstrated a 30% reduction in pseudohypericin AUC, which was attributed to induction of CYP3A4 by carbamazepine, the interaction was not regarded as clinical significant with regards to the use of St. John’s Wort (Johne et al., 2004). Because of...
the extensive use of St. John’s Wort, its interaction with carbamazepine and other AEDs requires further study.

In a randomized controlled study of 188 patients (86 men and 102 women aged 18-65 years old) with bipolar disorder, the use of the traditional Chinese herb Free and Easy Wanderer Plus (FEWP, 36 g/day; used in mood disorders) and carbamazepine (mean dose 460 mg/day) in combination demonstrated lower discontinuation rate and fewer side effects compared to placebo plus carbamazepine (Zhang et al., 2007). It was concluded that FEWP improves tolerability of carbamazepine in long-term use and may be attributed to the observed 75% decrease in mean serum carbamazepine concentrations (5.6 ± 5.8 µg/ml versus 2.4 ± 2.9 µg/ml) consequent to possibly multiple mechanisms including enzyme induction of CYP3A4, a delay in oral absorption, and a reduction in protein binding, caused by FEWP (Zhang et al., 2007). However, based on these data an increase in oral clearance of 56% could be calculated and enzyme induction is the most reasonable explanation, since a limitation in absorption is rarely a problem with carbamazepine (0.88 ml/kg/min, assuming an average weight of 70 kg). Because the FEWP formulation used contained 11 different herbs, it was not possible to ascertain which constituent(s) was/were responsible for the pharmacological effect and the interaction (Zhang et al., 2007). It seems reasonable to assume that this same interaction could occur in patients with epilepsy.

**Midazolam**

In an open-label study of 12 healthy volunteers (six women and six men aged 31 years old on average), the interaction between midazolam (0.05 mg/kg i.v., a known CYP3A substrate, and the herb *Echinacea* (400 mg *Echinacea purpurea* root) was investigated (Gorski et al., 2004). This herb is traditionally used for the management of colds and inflammation. A pharmacokinetic interaction was demonstrated, as the systemic clearance of midazolam was increased by 34% and AUC reduced by 23%. It was suspected that the herb induced CYP3A by acting as a ligand for the pregnane X receptor, which also may affect other enzymes and transporters in the intestine and liver (Gorski et al., 2004). It was, however, pointed out by Gurley et al. (2004) that the oral clearance may not be altered, and that the herb affects CYP3A4 activity in opposite ways, by induction in the liver and inhibition in the intestine, and that there may be a multiplicity of biologically active phytochemicals in *Echinacea*.

The metabolism of midazolam was also affected by St. John’s Wort in a study of 21 young healthy volunteers (10 men 19-31 years old and 11 non-pregnant women aged 20-55 years old; Dresser et al., 2003). The study was a two-way open-label cross over study, and midazolam was administered 4 mg orally and 1 mg [145N]midazolam i.v., and 300 mg of extract from St. John’s Wort (with 0.3% hypericin) was administered three times a day from day three to 14 of the study (Dresser et al., 2003). Blood samples were taken after 1-24 hours following administration of midazolam, and the results demonstrated a 2.7-fold increase in oral clearance, a 50% reduction in Cmax and a 44% reduction in t1/2 of midazolam, possibly caused by induction of CYP3A4 activity in the intestine and in the liver (Dresser et al., 2003).

**Valproate**

In a randomized, open-label, two-way crossover study of 6 healthy volunteers (3 men and 3 women, aged 30-40 years old), the traditional Chinese medicine *Paenoiae Radix* (traditionally used as a spasmolytic and pain-relieving agent; 1.2 g powder of herb extract) in combination with valproate (200 mg) was studied (Chen et al., 2000). Serial plasma samples were obtained after seven days, in addition to clinical biochemistry analyses and adverse event monitoring, and no differences were observed in t1/2, Cmax, Tmax, AUC, MRT, CL/F, Vd/F, protein binding or overall safety (Chen et al., 2000).

**Phenytoin**

In a series of 20 patients (males and females aged 20-45 years) with uncontrolled epilepsy prescribed phenytoin (either 150mg bd – 10 patients or 200 mg bd – 10 patients), the effect of a single dose of piperine (20 mg; the active component of *Piper longum, Piper nigrum,* and *Zingiber officinalis*) on the pharmacokinetics of phenytoin was investigated (Pattanaik et al., 2006). It was observed that at steady-state piperine significantly increased mean phenytoin serum concentrations and this was associated in significant increases in phenytoin AUC (9% versus 17%), and Cmax (10% versus 22%) values for the 300 mg and 400 mg phenytoin groups respectively. The mechanism of interaction is considered to be enhancement of phenytoin absorption by piperine (Pattanaik et al., 2006; Bano et al., 1987).
Potential AED interactions

_Ginkgo biloba_ induces CYP2C19, as demonstrated in a pharmacogenetic study with 18 volunteers (male Chinese aged 20-24, 54-71 kg and previously genotyped for CYP2C19), (Yin et al., 2004). Of the subjects, there were six homozygous extensive metabolizers, five heterozygous extensive metabolizers, and seven poor metabolizers (Yin et al., 2004). Omeprazole was used as a substrate and an index of CYP2C9 activity. The results demonstrated that _Ginkgo biloba_ (70 mg _Ginkgo biloba_ leaf extract) decreased the AUC of omeprazole by 41%, 27%, and 40% in the homozygote and heterozygote extensive metabolizers, and the poor metabolizers, respectively (Yin et al., 2004). The plasma concentrations of omeprazole and its sulfone metabolite were reduced by approximately 30% compared to controls. Based on these data, it is possible that _Ginkgo biloba_ would reduce serum concentrations of AEDs that are substrates for CYP2C19, such as phenytoin, phenobarbital and diazepam (Patsalos and Perucca, 2003b).

Anthranioid-containing plants with laxative properties, including senna (_Cassia senna_) and cascara (_Rhamnus purshiana_) and soluble fibres (including _Guar gum_ and _Psyllium_) increase the intestinal transit time and may decrease the absorption of most intestinally absorbed drugs (Fugh-Berman, 2000), and potential interactions between these products and AEDs (Figure 1 and Table 1) need more close consideration (Patsalos and Perucca, 2003a).

CONCLUSION

The use of herbal medicines by patients with epilepsy is increasing and most patients consider herbal medicines as safe because they are of natural origin. However, these medicines, which may vary in quality and ingredient content, have the potential to interact with AEDs and therefore affect seizure control or induction AED-related adverse effects. To date the literature describing these interactions is limited and most relate to pre-clinical studies. Clearly more research is required.

---

Figure 1. Schematic illustration showing the possible pharmacodynamic or pharmacokinetic sites of interactions between antiepileptic drugs and herbal drugs.

Abbreviations: CYPs = cytochrome P450 isoenzymes, UGTs = uridine glucuronyl transferases
Table 1. Interactions between antiepileptic drugs (AED) and herbal drugs.

<table>
<thead>
<tr>
<th>AED</th>
<th>Herbal drug</th>
<th>Interaction</th>
<th>Type of study</th>
<th>Mechanism</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Cassia auriculata</td>
<td>PK</td>
<td>Preclinical</td>
<td>CYP3A4 inhibition?</td>
<td>↑ C&lt;sub&gt;p&lt;/sub&gt;</td>
</tr>
<tr>
<td></td>
<td>FEWP</td>
<td>PK</td>
<td>Clinical, RCT</td>
<td>CYP3A4 induction</td>
<td>↓ C&lt;sub&gt;p&lt;/sub&gt;, ↑ CL</td>
</tr>
<tr>
<td></td>
<td>Mentat</td>
<td>PK</td>
<td>Preclinical</td>
<td>CYP inhibition?</td>
<td>↑ AUC</td>
</tr>
<tr>
<td></td>
<td>Paenoiae Radix</td>
<td>PK</td>
<td>Preclinical</td>
<td>Increased absorption?</td>
<td>↓ T&lt;sub&gt;max&lt;/sub&gt;</td>
</tr>
<tr>
<td></td>
<td>Saiko-ka-ryukotsu-to</td>
<td>PK</td>
<td>Preclinical</td>
<td>No interaction</td>
<td>No changes</td>
</tr>
<tr>
<td></td>
<td>Sho-saiko-to</td>
<td>PK</td>
<td>Preclinical</td>
<td>Decreased absorption</td>
<td>↓ C&lt;sub&gt;p&lt;/sub&gt;</td>
</tr>
<tr>
<td></td>
<td>Sho-seiryu-to</td>
<td>PK</td>
<td>Preclinical</td>
<td>Decreased absorption</td>
<td>↑ T&lt;sub&gt;max&lt;/sub&gt;</td>
</tr>
<tr>
<td></td>
<td>St. John’s Wort</td>
<td>PK</td>
<td>Clinical, healthy</td>
<td>No CYP3A4 induction</td>
<td>↑CL in 1 subject</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CYP3A4 induction by</td>
<td>↓ AUC of hypericin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>carbamazepine</td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>Angelica dahurica</td>
<td>PK</td>
<td>Preclinical</td>
<td>CYP2C/D,3A inhibition</td>
<td>↑ C&lt;sub&gt;max&lt;/sub&gt;, ↓ CL&lt;sub&gt;tot&lt;/sub&gt; (but not CL&lt;sub&gt;int&lt;/sub&gt;)</td>
</tr>
<tr>
<td></td>
<td>Ginkgo biloba</td>
<td>PD</td>
<td>Preclinical</td>
<td>Potentiation of GABA</td>
<td>↑ increased social contact</td>
</tr>
<tr>
<td></td>
<td>Saiboku-to</td>
<td>PD</td>
<td>Preclinical</td>
<td>Potentiation of GABA</td>
<td>A “diazepam sparing”</td>
</tr>
<tr>
<td></td>
<td>Salvia miltiorrhiza Bge</td>
<td>PK</td>
<td>Preclinical</td>
<td>CYP induction</td>
<td>↑ CL, ↓ AUC, ↓ C&lt;sub&gt;max&lt;/sub&gt;</td>
</tr>
<tr>
<td>AED</td>
<td>Herbal drug</td>
<td>Interaction</td>
<td>Type of study</td>
<td>Mechanism</td>
<td>Consequence</td>
</tr>
<tr>
<td>-----------</td>
<td>-------------------</td>
<td>-------------</td>
<td>------------------------</td>
<td>----------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Centella asiatica</td>
<td>PD?</td>
<td>Preclinical</td>
<td>Synergistic effect?</td>
<td>Reduced effective AED dose</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Echinacea purpurea</td>
<td>PK</td>
<td>Clinical, healthy</td>
<td>CYP3A induction</td>
<td>↑ CL, ↓ AUC</td>
</tr>
<tr>
<td></td>
<td>St. John’s Wort</td>
<td>PK</td>
<td>Clinical, healthy</td>
<td>CYP3A4 induction</td>
<td>↑ CL, ↓ C&lt;sub&gt;max&lt;/sub&gt; t&lt;sub&gt;1/2&lt;/sub&gt;</td>
</tr>
<tr>
<td>Phenobarbital (Pentobarbital)</td>
<td>Ginkgo biloba</td>
<td>PK</td>
<td>Preclinical</td>
<td>CYP2B induction</td>
<td>↓ C&lt;sub&gt;max&lt;/sub&gt; and AUC</td>
</tr>
<tr>
<td></td>
<td>Sho-saiko-to</td>
<td>PK</td>
<td>Preclinical</td>
<td>CYP2B,3A1,2E1,4A1 induction</td>
<td>↓ induced sleeping time</td>
</tr>
<tr>
<td></td>
<td>Saiko-keisi-to</td>
<td>PK</td>
<td>Preclinical</td>
<td>CYP2B,3A1,2E1,4A1 induction</td>
<td>↓ induced sleeping time</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Centella asiatica</td>
<td>PD?</td>
<td>Preclinical</td>
<td>CYP inhibition?</td>
<td>↑ AUC</td>
</tr>
<tr>
<td></td>
<td>Mentat</td>
<td>PK</td>
<td>Preclinical</td>
<td>Decreased absorption?</td>
<td>↑ T&lt;sub&gt;max&lt;/sub&gt;</td>
</tr>
<tr>
<td></td>
<td>Paenoeiae Radix</td>
<td>PK</td>
<td>Preclinical</td>
<td>Increased absorption?</td>
<td>↑ AUC, ↑ C&lt;sub&gt;max&lt;/sub&gt;</td>
</tr>
<tr>
<td></td>
<td>Piperine</td>
<td>PK</td>
<td>Clinical, healthy</td>
<td>CYP induction?</td>
<td>↓ C&lt;sub&gt;p&lt;/sub&gt;, ↑ seizure protection</td>
</tr>
<tr>
<td></td>
<td>Shankhapushi</td>
<td>PK + PD</td>
<td>Preclinical</td>
<td>Synergistic effect?</td>
<td></td>
</tr>
<tr>
<td>Valproate</td>
<td>Centella asiatica</td>
<td>PD?</td>
<td>Preclinical</td>
<td>Synergistic effect?</td>
<td>Reduced effective AED dose</td>
</tr>
<tr>
<td></td>
<td>Paenoeiae Radix</td>
<td>No PK</td>
<td>Clinical, healthy</td>
<td>Increased absorption?</td>
<td>No change (C&lt;sub&gt;p&lt;/sub&gt;-PK parameters)</td>
</tr>
</tbody>
</table>

Abbreviations: FEWP = Free and Easy Wanderer Plus, RCT = randomized controlled trial, PK = pharmacokinetic; PD = pharmacodynamic; CL = clearance, CL<sub>int</sub> = intrinsic clearance, CL<sub>tot</sub> = total clearance, C<sub>p</sub> = plasma concentration, Css = plasma concentration at steady state, t<sub>1/2</sub> = elimination half-life, Tmax = time to reach maximum plasma concentration, Cmax = maximum plasma concentration
REFERENCES


