POSSIBLE INTERACTION OF HERBAL TEA AND CARBAMAZEPINE

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SUMMARY

A study was conducted using Wistar rats to determine the effect of concurrent administration of a herbal tea prepared from dried flowers of *Cassia auriculata* and carbamazepine on (a) blood levels of the prescription drug and (b) changes in toxicity (as assessed by changes in hematological parameters, liver and kidney function, and histology of major body organs) that may occur due to drug interaction. Results demonstrate that in rats receiving the herbal tea and carbamazepine, the blood levels of the prescription drug were significantly enhanced by 47.1% ($p < 0.04$) when compared with the levels in animals receiving only carbamazepine, with no apparent changes in toxicity. Concurrent ingestion of the herbal tea prepared from *Cassia auriculata* flowers with carbamazepine may therefore influence the bioavailability of the prescribed drug and hence its therapeutic potential.

KEY WORDS

carbamazepine, *Cassia auriculata*, herbal tea, drug interaction

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INTRODUCTION

During the past few years there has been a worldwide increase in the use of herbal products, including herbal teas /1/. These can be obtained as over the counter purchases or prescribed by Ayurvedic or other traditional medical practitioners. On the assumption that herbal products are harmless, they are often consumed concurrently with conventional medications prescribed for specific disease conditions. Herbal formulations alone may not produce any adverse effects. However, on concurrent administration with prescribed drugs, the possibility of at least some interaction influencing the efficacy as well as the toxicity of either medication exists; the conventional drugs are usually affected most because they are generally more pharmacologically active /2,3/. This view is supported by the global increase in the number of reports of suspected interactions between herbal products and prescribed drugs, although there is only limited experimental evidence to demonstrate such interactions /1,4,5/.

With respect to antiepileptic drugs, available clinical evidence suggests that their pharmacokinetics could be significantly influenced by some herbs, such as *Piper longum, Piper nigrum, Populus alba* and *Salvia officinalis* /6-8/. In Sri Lanka, a herbal tea prepared from the dried flowers of *Cassia auriculata* is consumed by a large proportion of the population, because it is considered to be beneficial for individuals suffering from diabetes mellitus and diseases of the urinary tract /9/. Even individuals on antiepileptic drug treatment are known to consume this herbal tea. *Cassia auriculata* flowers are also used in the preparation of some herbal teas (e.g. Five Herb Tea) sold in the UK and other Western countries. Concomitant use of *Cassia auriculata* tea may lead to interactions that could influence the therapeutic actions of antiepileptic drugs, such as carbamazepine, and /or a change in toxicity. To test this hypothesis, a preliminary investigation was carried out to determine the impact of concurrent administration of *Cassia auriculata* tea and carbamazepine on (a) blood levels of the drug and (b) drug-induced toxicity, as assessed by changes in general behavior, liver and kidney functions, and histopathological alterations of major body organs.

MATERIALS AND METHODS

Animals

Male Wistar rats (200-250 g body weight) were used in all experiments. The animals were housed under standard animal house conditions of temperature and humidity, and maintained on a rat chow diet prepared by the Medical Research Institute, Sri Lanka, according to a formula recommended by the WHO /10/. Animals had free access to water.

Plant collection and identification

Flowers of *Cassia auriculata* were collected from Matara, Sri Lanka, dried in a low temperature oven (60°C), ground to a powder, and stored at -20°C. The fresh plant material was identified by the botanist at the Bandaranayake Memorial Ayurvedic Research Institute, Nawinna, Sri Lanka.

Preparation and administration of the herbal tea and carbamazepine

Herbal tea: When required, an amount of *Cassia auriculata* powder corresponding to 200 g wet weight of plant material was steeped in 200 ml boiling water for 30 min. After filtration through gauze, a volume of the extract providing 20 g/kg body weight was orally administered by gavage to each rat in the test groups.

Carbamazepine: From a suspension containing 500 mg drug/25 ml distilled water, a volume providing the equivalent of 100 mg/kg was administered orally by gavage to each rat per day.

The dosage of each drug (herbal tea and carbamazepine) administered to the rats corresponded to ten times the normal therapeutic dosage administered to humans, as rodents have been shown to be ten times less sensitive than humans to the effects of drugs /11/.

Experimental protocol

Rats (n = 20) were randomly divided into two groups (Groups A and B) of ten animals each. Initially both groups were given the test drug (carbamazepine), the dose of which was calculated on a body weight basis. After a 1-week period of treatment with this drug only, to allow serum levels to stabilize, Group A was fed concurrently

carbamazepine and the herbal preparation for a 1-week period. During this period, animals in Group B continued to receive only the test drug at the same dosage. At the end of this period, the herbal preparation was discontinued and both groups continued to receive carbamazepine only for a further week. At the end of this period, Group B was administered the herbal preparation together with carbamazepine for 1 week while animals in group A continued to receive only the test drug. This protocol is shown in Table 1.

This protocol was based on the assumption that a significant difference in the drug levels in the two groups at the ends of week 2 and week 4 would validate the hypothesis that the herbal tea has an effect on the metabolism of the drug, while the lack of a significant difference would negate this hypothesis.

Preparation of serum for HPLC

Each of the specimens for analysis was prepared according to the following procedure: to a serum sample (0.5 ml) containing the internal standard, 5-ethyl-5-*p*-tolybarbituric acid (50 μg/ml; 200 μl) and ethyl acetate (3.0 ml) was added and mixed well for 5 min with the assistance of a vortex mixer. The mixture was then centrifuged at 2,500 rpm for 10 min in a bench centrifuge. The resulting upper ethyl acetate layer was carefully transferred to a glass test tube and evaporated to dryness at 40°C for approximately 1 h on a Bucher vortex evaporator coupled to a Savant Universal Vacuum System (UVS 400 A). The residue was redissolved in acetonitrile (100 μl). After filtration through a 0.45 μm, 13 mm Millipore filter, 20 μl of the solution was injected into the analytical column (Symmetry® C8, 5 μm, 100 A) of a high pressure liquid chromatography (HPLC) system (Water's Gesellschaft mbh, Austria) connected to a photodiode array detector (Model 996).

HPLC analysis

The HPLC conditions for detection of carbamazepine in serum samples were as follows: mobile phase, 100 mM potassium phosphate, pH 6.9/acetonitrile/methanol/H_2O (17/25/5/53 v/v/v/v); flow rate, 1.0 ml/min; detection, 214 nm /12/. The recovery of carbamazepine from serum samples was in the range 90-95%.

Toxicity study

At the end of the pharmacokinetic study for HPLC analysis of blood, rats in Groups A and B were administered the carbamazepine and the herbal extract for a further 4- and 3-week period, respectively (a total of 4 weeks of drug plus herb administration). At the end of these periods, toxicity was assessed by comparing the following parameters with those in a separate control group of rats (n = 10) administered only carmamazepine:

Hematological parameters: Hemoglobin, blood cell counts, and packed cell volume (PCV) were determined by methods described by Ghai /13/.

Liver function: Serum levels of bilirubin, alanine and aspartate aminotransferases (ALT and AST) and alkaline phosphatase (ALP) were assessed by methods described in commercially available Randox (UK) assay kits purchased from Tanyo Medicals Ltd., Sri Lanka.

Kidney function: Blood creatinine level was estimated according to Merck /14/.

Major body organs - heart, kidney, liver, lungs and intestine - were preserved in 10% buffered formalin. Paraffin sections were stained with hematoxylin and eosin prior to examination under a light microscope (Olympus) for histopathological changes.

Statistical analysis

Student's t-test was used for determination of means and standard deviations within each group. For comparison of data between groups, Student's t-test and one way analysis of variance (ANOVA) were used. A difference of $p < 0.05$ was considered to be statistically significant.

RESULTS

Blood levels of carbamazepine

Results presented in Table 1 summarize the areas under the concentration-time curve (AUCs) of carbamazepine in animals of Groups A and B. A comparison of the AUCs at the end of each week between the two groups as well as within each of the individual

TABLE 1

Changes in the areas under the concentration-time curve (AUC) for carbamazepine on concurrent administration of the drug with *Cassia auriculata* tea

Group A	Week 1 (C only)	Week 2 (C + H)	Week 3 (C only)	Week 4 (C only)
AUC for C at end of week	1,193,345 ± 146,717	1,806,864 ± 144,091[a, b]	1,334,863 ± 143,213	1,081,233 ± 191,208
Group B	**Week 1 (C only)**	**Week 2 (C only)**	**Week 3 (C only)**	**Week 4 (C + H)**
AUC for C at end of week	1,240,945 ± 136,330	1,316,456 ± 135,184	1,107,576 ± 267,770	1,770,749 ± 142,125[c,d]

C = carbamazepine; H = *Cassia auriculata* tea.
Results are presented as means ± SEM.
In group A, a, b – significantly different from animals in the same group at the end of week 1 and the corresponding animals in group B, respectively ($p = 0.025$ and 0.044, respectively).
In group B, c, d = significantly different from animals in the same group at the end of week 1 and from corresponding animals in group A, respectively ($p = 0.002$ and 0.028, respectively).

groups (A and B) demonstrates that concurrent administration of *Cassia auriculata* tea and carbamazepine resulted in a significantly enhanced blood level of carbamazepine when compared to that in animals receiving only carbamazepine.

A comparison of the AUCs between Groups A and B shows that significant differences could be observed only at the end of weeks 2 and 4. In Group A, at the end of week 2 (carbamazepine + herbal tea), the AUCs were significantly higher ($p = 0.044$) than those of the corresponding animals in Group B (carbamazepine only). Similarly, at the end of week 4 (carbamazepine + herbal tea), animals in Group B exhibited significantly ($p = 0.028$) higher AUCs than the corresponding animals in Group A (carbamazepine only). Thus, the AUCs of each group receiving the herbal preparation plus carbamazepine were

significantly higher than those of the corresponding animals of the second group receiving only carbamazepine during that time period.

On comparing the AUCs of carbamazepine for Group A animals at the end of week 1 (carbamazepine only) and week 2 (carbamazepine + herbal tea), it was observed that the AUCs were significantly ($p = 0.025$) higher at the end of week 2. Similarly, in Group B animals, when the AUCs at the end of the week 1 (carbamazepine only) were compared with those at the end of week 4 (carbamazepine + herbal tea), the AUCs at the end of the fourth week were found to be significantly ($p = 0.002$) higher than those at the end of week 1 (Table 1).

Alterations in toxicity

No significant differences were observed in general behavior, liver function (assessed by serum levels of ALT, AST and ALP), kidney function (assessed by estimation of serum creatinine concentration), or histology of the major body organs (heart, liver, kidney and lungs) in animals treated for 4 weeks with only carbamazepine and those receiving carbamazepine plus the herbal tea. Results of the effects on liver and kidney function are shown in Table 2, and the effects on hematological parameters in Table 3. The herbal tea alone, at the

TABLE 2

Effects of carbamazepine and carbamapezine plus *Cassia* tea on serum levels of alanine and aspartate aminotransferases (ALT and AST), alkaline phosphatase (ALP) and creatinine in rats

	Controls	Carbamazepine treated	Carbamazepine + *Cassia* treated
ALT (IU/l)	23.6 ± 4.4	25.2 ± 1.3	24.9 ± 3.2
AST (IU/l)	74.9 ± 19.1	78.0 ± 21.8	75.2 ± 16.4
ALP (IU/l)	84.0 ± 9.4	80.4 ± 12.2	86.2 ± 15.2
Creatinine (mg/dl)	2.91 ± 0.9	2.82 ± 1.2	2.87 ± 1.3

Results are presented as means ± SEM.
Values of enzyme activities in the test groups are not significantly different from those in the control group ($p > 0.05$).

TABLE 3

Effects of carbamazepine only and carbamazepine plus *Cassia* tea on hematological parameters of rats

	Controls	Carbamazepine treated	Carbamazepine + *Cassia* treated
PCV (%)	52.8 ± 1.6	52.2 ± 1.4	53.3 ± 1.4
Hb (g/dl)	15.9 ± 1.3	15.5 ± 1.2	16.3 ±2.0
RBC ($\times 10^6/mm^3$)	8.5 ±1.2	8.6 ± 1.2	8.4 ± 1.0
WBC ($\times 10^6/mm^3$)	16.8 ± 1.0	14.8 ± 2.0	15.6 ± 3.9
Neutrophils ($\times 10^3/mm^3$)	20.7 ± 3.8	19.5 ± 4.8	20.8 ± 1.0
Eosinophils ($\times 10^3/mm^3$)	2.0 ± 1.0	2.0 ± 1.3	2.0 ± 1.1
Basophils ($\times 10^3/mm^3$)	Nil	Nil	Nil
Monocytes ($\times 10^3/mm^3$)	2.7 ± 0.8	2.5 ± 0.8	2.8 ± 1.6
Lymphocytes ($\times 10^3/mm^3$)	76.8 ± 2.3	77.2 ±4.1	76.5 ± 2.1

Results are presented as means ± SEM. No significant differences were found.

concentration used in the present study, did not produce any significant changes in serum levels of ALT, AST, ALP or creatinine, or histology of the major body organs, when given to rats orally for the experimental period.

DISCUSSION

Results of the present investigation suggest that concurrent ingestion of the herbal tea prepared from *Cassia auriculata* and the

drug carbamazepine could have an influence on the bioavailability of the prescribed drug. Herbal products have been demonstrated to alter blood levels of conventional drugs by mechanisms such as interference with intestinal absorption, serum protein binding, or metabolism via cytochrome P450-mediated drug metabolizing enzymes /1/. Bioavailability of some herbal drugs have also been shown to be influenced by other herbal products, via similar mechanisms /15/.

Antiepileptic drugs, such as carbamazepine and phenytoin, are metabolized by the hepatic P4503A family of microsomal enzymes /16/. In the case of carbamazepine, grapefruit juice has been shown to increase its bioavailability by inhibiting the cytochrome P4503A4 enzyme of the gut wall and liver /17/. Whether the increased blood levels of carbamazepine resulting from concurrent administration of the drug with *Cassia auriculata* tea is due to a direct effect of the herbal components on the activity of the cytochrome P4503A family of drug metabolizing enzymes is not clear. However, it has been reported recently that some herbal teas, such as those prepared from dandelion, peppermint or chamomile, can, like black and green tea, modulate activities of Phase I and Phase II drug metabolizing enzymes in rat liver /18/.

Increased blood levels of drugs, related to a decreased activity of the P4503A family of enzymes, could result in signs and symptoms of toxicity that are not normally apparent /16/. In humans, blood levels of carbamazepine in excess of the normal therapeutic range have been reported to produce a variety of neurological (ataxia, slurred speech, nystagmus, dystonia and various degrees of central nervous system depression), cardiovascular (hypotension, bradycardia, and conduction disorders), gastrointestinal, and hepatic and respiratory effects (respiratory depression, apnoea and pulmonary edema) /19-22/. Conversely, induction of the above enzymes may cause enhanced catabolism, giving rise to sub-therapeutic levels and loss of therapeutic control /16/. In the present study, no overt toxicity was observed with respect to the general behavior of the animals on concurrent administration of the herbal preparation and carbamazepine. Furthermore, no significant changes in liver function, kidney function, or histology of the major body organs (heart, liver, kidney, lungs) were apparent in the above group of animals when compared with animals treated only with carbamazepine. An alteration in the bioavailability of curcumin, with no change in toxicity, has also been

observed in a previous study concerned with assessing the effect of concurrent administration of piperine and curcumin to rats and humans /15/. Although no serious toxicity was observed in rats exposed concurrently to the herbal tea and carbamazepine, in view of the effects of the herb on blood levels of the conventional drug, it may be advisable to avoid the use of herbal teas containing *Cassia auriculata* flowers (e.g. Five Herb Tea) by individuals on antiepileptic drug treatment.

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