Print ISSN 2319-2003 | Online ISSN 2279-0780

IJBCP International Journal of Basic & Clinical Pharmacology

doi: 10.5455/2319-2003.ijbcp20150401

Research Article

Interaction of two memory enhancing herbal drugs Memory Plus and Mentat with diazepam and phenytoin sodium in mice

Neera R. Gupta[1]*, Varsha J. Patel[2], Kartik N. Shah[2]

[1]Medical Education, Novo Nordisk India Pvt Ltd, Bengaluru, Karnataka, India, [2]Department of Pharmacology, Smt NHL Municipal Medical College, Ahmedabad, Gujarat, India

Received: 02 January 2015
Accepted: 17 February 2015

***Correspondence to:**
Dr. Neera R. Gupta,
Email: drneera.gupta@gmail.com

ABSTRACT

Background: The non-medical self-administration of memory enhancing drugs is a common practice. Present study was designed to evaluate interactions of two such herbal drugs Memory Plus (MP) and Mentat, with other central nervous system (CNS) active drugs.
Methods: Two activities - pentobarbitone sleeping time (PST) and maximal electroshock seizures (MES) were performed using adult albino mice weighing 25-30 g to observe the interactions of the herbal drugs with diazepam and phenytoin sodium, respectively. For each activity, animals were divided into seven groups of six mice each. Group I was a control group receiving 0.2 ml of 1% Tween 80 i.p/0.2 ml saline p.o, Group II, III and IV acute treatment groups; received single dose of herbal (2 mg/kg i.p MP or 200 mg/kg p.o Mentat) CNS-active drugs alone in subeffective doses group II - diazepam 5 mg/kg i.p, Group III PS 15 mg/kg i.p and Group IV - MP/Mentat+diazepam or PS, respectively. Groups V, VI, and VII were subchronic treatment groups, received drugs once daily for 8 days same as acute treatment groups. Sleeping time was measured as the interval between the loss and recovery of righting reflex and anticonvulsant activity by giving supra maximal shock via ear electrodes using a techno electro convulsiometer.
Results: Both MP and Mentat showed potentiation of effect of diazepam and PS in subchronic treatment groups by significantly prolonging PST ($p<0.05$) and by showing significant percentage protection in MES method ($p<0.05$) compared to control group.
Conclusion: Subchronic administration of MP and Mentat shows significant interaction with diazepam and PS. Further human studies are warranted to confirm these findings.

Keywords: Herb-drug interaction, Memory enhancer/Nootropic, Pentobarbitone sleeping time, Maximal electroshocks seizures, Diazepam, Phenytoin sodium

INTRODUCTION

Traditional medicines derived from medicinal plants are used by about 60% of the world's population.[1] More than 70% of India's 1.1 billion populations still use these non-allopathic systems of medicine.[2] Nootropic is the term for supplements/extracted and purified components of medicinal plants, also known as smart drugs that improve brain function. Memory Plus (MP) containing bacosides from *Bacopa* monniera "Brahmi," which has been used in the Ayurvedic system of medicine for centuries, traditionally, as a brain tonic to enhance memory development, learning, and concentration, and to provide relief to patients with anxiety or epileptic disorders.[3] Besides the improvement in cognitive functions, MP has shown tranquilizing effects in rats and dogs, central nervous system (CNS) depressant effect in dogs, antinociceptive and anticonvulsant effects in animal experiments.[4-6] The proposed mechanisms of action are that bacosides improved memory and facilitated learning by increasing protein kinase activity and new protein synthesis especially in the brain hippocampus.[7] Biochemical studies have shown that bacosides leading to increase in serotonin content.[8] and prevents rate of depletion of blood acetylcholine levels.[9]

Mentat (BR-16A) a polyherbal psychotropic preparation is claimed to enhance cognition and to ameliorate various forms of brain deficits. Of its several ingredients the important ones include *Bacopa monniera* for cognitive impairment, *Embellica officinalis* as adaptogenic and rejuvenator *Acorus calamus* as sedative, analgesic and anticonvulsant, *Withania somnifera* as sedative and rejuvenator, *Mucuna puriens* as nervine tonic, *Nardostachys jatamansi* in insomnia, hysteria and epilepsy and *Valeriana wallichi* for mental disorders

and epilepsy.[10] In experimental studies, Mentat has shown anticonvulsant against PTZ induced seizures,[11,12] anti-nociceptive,[13] antidepressant and anxiolytic properties.[14] The proposed mechanism of action for Mentat is that it improves mental functions by modulation of cholinergic and GABAergic neurotransmission,[12] it also helps to reduce the level of tribulin, an endogenous monoamine oxidase (MAO) inhibitor that is elevated in various levels of anxiety.[10]

The evidence on herb-drug interactions with these herbal preparations from experimental or clinical studies is very limited. Most often these herbal drugs are consumed as self-medication, often likely to be taken as supplement for a prolonged period of time and along with other medications. This study was conducted in mice to evaluate potential of these herbal medicines to modify the action of CNS-active drugs.

METHODS

Adult albino mice weighing 25-30 g were used for all the experiments. The animals were housed under standard conditions with natural light-dark cycle and fed standard feed. For each activity, animals were divided into seven groups of six mice in each.

The test drugs used were; MP (2 mg/kg, i.p), dispersed in 1% Tween 80 and Mentat (200 mg/kg, p.o) in aqueous suspension. The CNS-active drugs (prototype of the relevant class) were used in sub-effective doses, i.e., a dose which is substantially lower than the dose which usually produces significant activity. Diazepam was used in dose of 5 mg/kg i.p and phenytoin sodium (PS) 15 mg/kg i.p. For Acute Treatment Groups, single dose of the drug was given and in subchronic treatment groups animals received once-daily injection for 8 days.

Study design

CNS depressant activity by pentobarbitone sleeping time (PST)

Prolongation or shortening of PST method (as described by Kopera and Armitage 1954 and Shethi and Sheth 1967) was used to see the interaction with diazepam. Pentobarbitone sodium was injected to each animal 30 mins after the test compound or Tween 80 or saline. In subchronic treatment groups, experiments were conducted on 8th day of dosing 30 mins after dosing. Sleeping time was measured as the interval between the loss and recovery of righting reflex. The reflex was considered in effect if the animal placed on its side recovers from this position within 1 mins. It was considered lost when the recovery required longer period. The time has been expressed in minutes.

Anticonvulsant activity by maximal electroshock seizure (MES) method

MES method was used to see the interaction with PS. Thirty minutes after the drug treatment, each mouse was given supramaximal shock of 50 mA for 0.2 sec via ear electrodes using an Electro Convulsiometer (Techno Lab, Lucknow). Abolition of tonic hindlimb extensor component of seizures was considered as protection against maximal electroshock seizures as described by Toman et al. 1946.

Statistical analysis

The values were expressed as mean±standard error of the mean. Results for CNS depressant activity were statistically analyzed using one-way analysis of variance (ANOVA), and Post ANOVA Tukey's multiple range test was used to define the significant difference ($p<0.05$). The results of anticonvulsant activity were analyzed using Chi-square test with Yates's correction.

Treatment groups	Groups	PST				MES method			
		Memory Plus groups		Mentat groups		Memory Plus groups		Mentat groups	
		Drug (i.p)	Dose (mg/kg)	Drug	Dose (mg/kg)	Drug (i.p)	Dose (mg/kg)	Drug	Dose (mg/kg)
Control	I	1% Tween 80	0.2 ml	Saline p.o	0.2 ml	1% Tween 80	0.2 ml	Saline p.o	0.2 ml
Acute treatment groups (single dose)	II	MP	2	Mentat p.o	200	MP	2	Mentat p.o	200
	III	Diazepam	5	Diazepam i.p	5	PS	15	PS i.p	15
	IV	MP+ Diazepam	2+5	Mentat p.o+ Diazepam i.p	200+5	MP+PS	2+15	Mentat p.o+ PS i.p	200+15
Subchronic treatment groups (Once daily for 8 days)	V	MP	2	Mentat p.o	200	MP	2	Mentat p.o	200
	VI	Diazepam	5	Diazepam i.p	5	PS	15	PS i.p	15
	VII	MP+ Diazepam	2+5	Mentat p.o+ Diazepam i.p	200+5	MP+PS	2+15	Mentat p.o+ PS i.p	200+15

PST: Pentobarbitone sleeping time, MES: Maximal electroshock seizure, MP: Memory Plus, PS: Phenytoin sodium

RESULTS

CNS depressant activity with MP and Mentat

Acute treatment groups:

1. Acute treatment with MP or Mentat alone did not modify PST acute treatment with sub-effective dose of diazepam did not show any significant effect on PST. Single dose treatment with a combination of MP+diazepam or Mentat plus+diazepam did not show significant prolongation of PST.

Subchronic treatment groups:

1. Subchronic treatment with MP or mentat showed prolongation of PST, which was not statistically significant. Subchronic treatment with sub-effective dose of diazepam alone did not show any effect on PST subchronic treatment with a combination of MP+diazepam or Mentat+diazepam, showed significant prolongation of PST ($p<0.05$).

Anticonvulsant activity with MP and Mentat

Acute treatment groups:

1. Single dose of MP or Mentat did not show a significant increase in % protection compared to the control group acute treatment with phenytoin alone in subeffective dose did not show significant protection. Acute treatment with a combination of MP and PS or Mentat and PS did not show a significant increase in % protection compared to the control group.

Subchronic treatment groups:

1. Subchronic treatment with MP or Mentat showed non-significant increase in % protection subchronic treatment with phenytoin alone in sum effective dose did not show significant protection. Subchronic treatment with a combination of MP and PS or Mentat and PS showed a significant increase in % protection (100%) compared to the control group ($p<0.05$).

DISCUSSION

Some herb-drug interactions that have been reported between herbal medicines and prescribed drugs include severe spontaneous bleeding with Ginkgo biloba when taken along with warfarin or aspirin and similar interaction with Ginseng. Among other interactions; of Ginseng with MAO inhibitors and of Kava with benzodiazepines[15] are of importance. Psychiatric patients use an array of herbal medicines and more likely to face adverse concerns of herb–drug interactions. A study by Kenneth has reported that herbal medicines do pose a potential for herb–drug interactions.[16]

Table 1: Effect of MP and Mentat with diazepam on PST.

MP groups (N=6 in each group)			Mentat groups (N=6 in each group)		
Treatment groups	**Dose (mg/kg i.p)**	**PST in minutes (mean±SEM)**	**Treatment groups**	**Dose (mg/kg)**	**PST in minutes (mean±SEM)**
Control					
1% Tween 80	0.2 ml	79.3±9.0	Saline p.o	0.2 ml	31±2.6
Acute treatment groups (single dose)					
MP	2	99±10	Mentat p.o	200	45±7.8
Diazepam	5	122±31	Diazepam i.p	5	122±31
MP+diazepam	2+5	135±21	Mentat p.o+ diazepam i.p	200+5	129±23
Subchronic treatment groups (once daily for 8 days)					
MP	2	145.3±21	Mentat p.o	200	128±28
Diazepam	5	128±9.4	Diazepam i.p	5	128±9.4
MP+diazepam	2+5	219±36[#]	Mentat p.o+ diazepam i.p	200+5	234±13[#]
F 3.85			F 3.2		
df 6,35			df 6,35		
Difference of mean: 99 Post ANOVA Tukey's test			Difference of mean: 132 Post ANOVA Tukey's test		
[#]$p<0.05$ versus control			[#]$p<0.05$ versus control		

PST: Pentobarbitone sleeping time, MP: Memory Plus, SEM: Standard error deviation

Table 2: Anticonvulsant activity of MP and Mentat with phenytoin.

MP groups (N=6 in each group)			Mentat groups (N=6 in each group)		
Treatment groups	**Dose (mg/kg i.p)**	**% protection**	**Treatment groups**	**Dose (mg/kg)**	**% protection**
Control					
1% Tween 80	0.2 ml	0	Saline p.o	0.2 ml	0
Acute treatment groups (single dose)					
MP	2	16.6	Mentat p.o	200	50
PS	15	50	PS i.p	15	50
MP+PS	2+15	66.6	Mentat p.o+PS i.p	200+15	66.6
Subchronic treatment groups (once daily for 8 days)					
MP	2	50	Mentat p.o	200	50
PS	15	50	PS i.p	15	50
MP+PS	2+15	100#	Mentat p.o+PS i.p	200+15	100#
χ^2 with Yates correction used for statistical analysis			χ^2 with Yates correction used for statistical analysis		
#p<0.05 versus control			#p<0.05 versus control		

MP: Memory Plus, PS: Phenytoin sodium

The present study demonstrates that in a single dose Mentat and MP did not have a significant effect on CNS depressant or anticonvulsant action of diazepam or phenytoin, respectively. Subchronic administration of diazepam alone has not shown prolongation of PST, while subchronic administration of MP or Mentat with sum effective doses of diazepam resulted in statistically significant prolongation of PST, suggesting the possibility of potentiating effect of diazepam on subchronic treatment. The results are supported by some studies. Extract of Brahmi (*Bacopa monneira*) has been found to enhance pentobarbitone induced sleeping time.[17] A rat model of clinical anxiety has demonstrated that *Bacopa* extract of 25% bacoside A, exerted anxiolytic activity comparable to lorazepam.[18] Mentat has also shown effects on ethanol withdrawal induced anxiety in mice model[11] and in another study significant anxiolytic activity compared to non-benzodiazepine agent buspirone.[14]

Results from anticonvulsant activity in our study show that in acute treatment groups, single dose administration of MP with PS and a single dose of Mentat with PS did not significantly increase protection against MES seizures. Subchronic administration of MP or Mentat alone showed no significant protection, compared to control group while subchronic administration of MP or Mentat with sum effective dose of PS resulted in statistically significant increase in percentage protection (100%) against MES seizures, suggesting the possibility of potentiating effect of PS on subchronic administration.

Overall, interactions of herbal medicines with antiepileptic drugs are poorly described in the literature some widely used herbal medicines Ginkgo biloba and St. John's Wort have been reviewed with regards to their interactions.[19] Our finding is in agreement with study by Vohra and Pal who reported potential corrective effect of *Bacopa* in cognitive deficit associated with phenytoin therapy.[6] Research in animals shows anticonvulsant activity of *Bacopa* at high doses over extended period of time. Ganguly and Malhotra demonstrated protective effects of *Bacopa* against seizures in mice.[18] and anticonvulsant activity by intraperitoneal injections of high doses of *Bacopa* extract given for 15 days. When administered acutely at lower doses anticonvulsant activity is not observed.[20] as in our study. In a study by Dadkar Mentat has shown to significantly increase the seizure threshold for metrazole-induced seizures as compared to placebo.[21] In another study, Mentat 100 mg/kg p.o has shown protective effects against PTZ induced seizures, comparable to diazepam.[12] Study by Tripathi et al. on pharmacokinetic interactions of Mentat with carbamazepine and phenytoin on rabbits has reported that co-administration of Mentat could improve the effectiveness of anti-epileptic drugs due to the increased bioavailability of the latter.[22]

These findings that both MP and Mentat containing bacosides and *B. monneira* as important active ingredients have potential to enhance the actions of drugs acting on CNS like diazepam and PS. The result of this interaction could be beneficial when used concurrently with sedative-hypnotics or anticonvulsants if there is no enhancement of adverse reactions. On the other hand, this interaction is likely to increase the severity and/or frequency of adverse reactions. Further clinical studies are necessary to explore the interaction in humans including patients who may self-medicate with these herbal remedies.

CONCLUSION

Our study on mice demonstrates that MP and Mentat, both with *Bacopa* monneira as an important ingredient potentiate

the activity of centrally active drugs such as diazepam and phenytoin.

ACKNOWLEDGMENTS

Authors are thankful to the staff of the department of pharmacology of Smt. NHL Municipal Medical College for their support in carrying out the experiments.

Funding: No funding sources
Conflict of interests: None declared
Ethical approval: This study was approved by the Institutional Animal Ethics Committee No 395/CPCSEA

REFERENCES

1. Modak M, Dixit P, Londhe J, Ghaskadbi S, Devasagayam TP. Indian herbs and herbal drugs used for the treatment of diabetes. J Clin Biochem Nutr. 2007;40(3):163-73.
2. Vaidya AD, Devasagayam TP. Current status of herbal drugs in India: an overview. J Clin Biochem Nutr. 2007;41(1):1-11.
3. Chopra RN. Indigenous Drugs of India. 2nd Edition. Calcutta, India: U.N. Dhur and Sons; 1958: 341.
4. Malhotra CL, Das PK, Dhalla NS. Investigations on the mechanism of potentiation of barbiturate hypnosis by hersaponin, acorus oil, reserpine and chlorpromazine. Arch Int Pharmacodyn Ther. 1962;138:537-47.
5. Gupta SS. A few observations on the psychotropic and anticonvulsant effects of same ayurvedic remedies. Indian J Physiol Pharmacol. 1962;6:25-7.
6. Vohra D, Pal SN. Effect of locomotor activity on passive avoidance test for evaluation of cognitive function. Indian J Pharmacol. 2000;32:242-5.
7. Dahanukar SA, Kulkarni RA, Rege NN. Pharmacology of medicinal plants and natural products. Indian J Pharmacol. 2000;32:581-618.
8. Dey PK, Datta C. Effect of psychotropic phytochemicals on cerebral amino acid level in mice. Indian J Exp Biol. 1966;4(4):216-9.
9. Tripathi YB, Chaurasia S, Tripathi E, Upadhyay A, Dubey GP. *Bacopa monniera* Linn. as an antioxidant: mechanism of action. Indian J Exp Biol. 1996;34(6):523-6.
10. The Himalaya Company, Mentat A Product Monograph, 2001.
11. Kulkarni SK, Verma A. Mentat, herbal preparation improves learning and memory performance in mice. Indian Drugs. 1993;3(30):97.
12. Kulkarni SK, George B. Pentylenetetrazol-induced kindling in animals: protective effect of BR-16A. Indian J Exp Biol. 1995;33(6):424-7.
13. Kulkarni SK, Verma A. Prevention of development of tolerance and dependence to opiate in mice by BR-16A (Mentat), a herbal psychotropic preparation. Indian J Exp Biol. 1992;30(10):885-8.
14. Bhattacharya SK. Nootropic effect of BR-16A (Mentat) a psychotropic herbal formulation in cognitive deficits induced by prenatal under nutrition, postnatal environmental impoverishment and hypoxia in rats. Indian J Exp Biol. 1994;32:31-6.
15. Izzo AA, Ernst E. Interactions between herbal medicines and prescribed drugs: a systematic review. Drugs. 2001;61(15):2163-75.
16. Kenneth BJ. Herbal medicines pose potential drug interaction hazard. Psychiatr Times. 1998;XV(8).
17. Sakina MR. Dandiya PC. A psycho-neuropharmacological profile of *Centella asiatica* extract. Fitoterapia. 1990;61:291.
18. Ganguly DK, Malhotra CL. Some behavioural effects of an active fraction from *Herpestis monniera*, Linn. (Brahmi). Indian J Med Res. 1967;55:473-82.
19. Hu Z, Yang X, Ho PC, Chan SY, Heng PW, Chan E, et al. Herb-drug interactions: a literature review. Drugs. 2005;65(9):1239-82.
20. Martis G, Rao A. Neuropharmacological activity of *Herpestis monniera*. Fitoterapia. 1992;63:399-404.
21. Dadkar VN. Effect of mentat, a herbal preparation, on metrazole-induced seizures and restraint stress ulcers – Preliminary findings in a controlled study. Probe. 1991; 3(XXX):268-70.
22. Tripathi M, Sundaram R, Rafiq M, Venkataranganna MV, Gopumadhavan S, Mitra SK. Pharmacokinetic interactions of Mentat with carbamazepine and phenytoin. Eur J Drug Metab Pharmacokinet. 2000;25(3-4):223-6.

doi: 10.5455/2319-2003.ijbcp20150401
Cite this article as: Gupta NR, Patel VJ, Shah KN. Interaction of two memory enhancing herbal drugs Memory Plus and Mentat with diazepam and phenytoin sodium in mice. Int J Basic Clin Pharmacol 2015;4:203-7.