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Efficacy of tablet huperzine-A on memory, cognition, and behavior in Alzheimer's disease

XU Si-Sun, GAO Zhi-Xu[1], WENG Zheng[2]; DU Zun-Ming[3], XU Wei-An[4], YANG Jian-Shen[5], ZHANG Ming-Lian[6], TONG Zhen-Hua, FANG Yong-Sheng[1], CHAI Xin-Sheng[2], LI Shu-Lan[3]
(*Zhejiang Supervision and Detection Station of Drug Abuse, Zhejiang Medical University, Hangzhou 310009*; [1]*Shanghai Mental Health Center, Shanghai 200030*; [2]*Shandong Mental Health Center, Ji-nan 250014*; [3]*Hangzhou Central Hospital of Railway, Hangzhou 310009*; [4]*Shanghai 3rd Mental Hospital, Shanghai 201905*; [5]*Suzhou Puji Hospital, Suzhou 215008*; [6]*Suzhou Guangji Hospital, Suzhou 215008, China*)

AIM: To evaluate the efficacy and safety of tablet huperzine-A (Hup) in patients with Alzheimer's disease. **METHODS**: Using multicenter, prospective, double-blind, parallel, placebo controlled and randomized method, 50 patients were administrated orally 0.2 mg (4 tablets) Hup and 53 patients were given *po* 4 tablets of placebo *bid* for 8 wk. All patients were evaluated with Wechsler memory scale, Hasegawa dementia scale, mini-mental state examination scale, activity of daily living scale, treatment emergency symptom scale, and measured with BP, HR, ECG, EEG, ALT, AKP, BUN, Cr, Hb, WBC, and urine routine. **RESULTS**: About 58 % (29/50) of patients treated with Hup showed improvements in their memory ($P<0.01$), cognitive ($P<0.01$), and behavioral ($P<0.01$ functions. The efficacy of Hup was better than placebo (36 %, 19/53) ($P<0.05$). No severe side effect was found. **CONCLUSION**: Hup is a promising drug for symptomatic treatment of Alzheimer's disease.

KEY WORDS huperzine-A; cholinesterase inhibitors; Alzheimer's disease; multicenter studies; double-blind method; randomized controlled trials; Wechsler scales; memory; cognition disorders; activity of daily living

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The loss of cholinergic neurons of the brain observed in Alzheimer's disease is considered an important pathogenetic element of dementia[2]. These finding provoked a series of pharmaceutical studies to look for a drug which might supplement the cholinergic function for its symptomatic treatment. Huperzine-A (Hup), a new Lycopodium alkaloid (Fig 1) first isolated from Chinese herb *Huperzia serrata* (Thunb) Trev by Chinese[3], is a potent, centrally active, and reversible cholinesterase inhibitor (ChEI)[4] with better therapeutic index than those of physostigmine and THA[5]. It was reported to ameliorate learning and memory retention in rodents and improve memory in aged[6,7].

The present study was to confirm the clinical efficacy and safety of Hup in treatment of Alzheimer's disease.

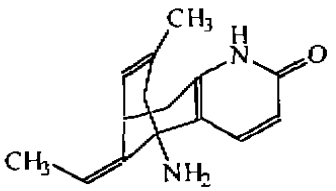

Fig 1. **Molecular representation of Huperzine-A.**

MATERIALS AND METHODS

Patients Patients ($n=103$) who met AD criteria

of DSM-IIIR[1] were selected for this study. Their entrance criteria were age over 50 a; memory quotient (MQ) < 90; Hasegawa dementia scale (HDS) < 15 (illiteracy), < 20 (primary), < 24 (middle); minimental state examination scale (MMS) score 13—23; activity of daily living scale (ADL) > 16; Hachinski ischemic scale (HIS) score < 4. Depression, severe physical or psychotic disorders, and non-AD dementia were ruled out. Their procurators agreed with the patients to participate in this study.

Methods Patients were abstained from any CNS stimulants, steroids, and nootropics for 1 wk. They were randomly divided into 2 groups given 4 tablets (0.2 mg of Hup or 70 mg of placebo) orally twice a day for 8 wk. The tablets, same in shape, color, weight, taste and the packaging, were provided by Hong-Qi pharmaceutical Factory of Shanghai Medical University. The clinicians and the patients were double-blind.

Assessment BP and HR were measured weekly. ECG and TESS were repeated half a month. ALT, AKP, BUN, Cr, Hb, WBC, and urine routine were repeated monthly. EEG, WMS, HDS MMS and ADL were repeated at the end of trial.

Data analysis The statistical analysis of the results were performed by POMS software. Pair t test was used for MQ, MMS, HDS, and ADL before and after trial. We analysed 4 additional items ('clear headed', 'memory improving', 'language improving' and 'unchanged') with X^2 method.

Duration of trial From 1993-09-01 to 1994-04-30

RESULTS

The blind was declassified on 1994-05-06 in Shanghai: 50 patients were in Hup group and 53 patients were in placebo group. The pretreatment data between the 2 groups showed no significant difference (Tab 1).

The intraclass correlation (ICC) ICC on MMS, HDS, and ADL from 4 districts (Zhejiang, Shanghai, and Shandong, Suzhou) were 0.98, 0.87, and 0.96, respectively ($P > 0.05$).

Psychological assessment There were significant differences on MMS, HDS, and ADL between 'before' and 'after' the 8-wk

Tab 1. Background data between the 2 groups of AD. All data showed no statistical significance between Hup and Pla group.

	Pla ($n=53$)	Hup ($n=50$)
Sex: ♂	29	28
♀	24	22
Age:	67±11	66±11
rage	55—89	53—90
Occupation:		
worker	30	21
peasant	3	2
administrator	13	16
technician	5	6
home-maker	2	5
Culture:		
college	5	6
senior high	9	9
junior high	9	10
elementary	26	18
illiteracy	4	7
Marriage:		
single, divorced	15	17
unmarried	0	1
married	38	32
Course: (year)	3.0±1.8	3.1±1.6
<2	8	8
2—	34	24
4—	8	16
6—	1	0
≥8	2	2
Severity:		
mild	27	33
moderate	23	17
severe	3	0
MQ baseline	48±21	56±21
MMS baseline	14±5	16±5
HDS baseline	16±6	16±6
ADL baseline	31±9	33±10
TESS baseline	1±4	1±3
Identified cerebral atrophy by CT or MR.	25 (47 %)	22 (44 %)

Hup treatment ($P<0.01$), but not in the placebo group except the MQ score ($P<0.01$); resulting in a significant difference on MQ, MMS, and HDS between 2 groups ($P<0.01$) (Tab 2). Rank sum test of WMS and MMS between 2 groups showed a significant improvement in 'number of recitation' item of WMS and 'time orientation' item of MMS.

Tab 2. comparison of MQ, MMS, HDS and ADL between 2 groups of AD.
[a]$P>0.05$, [b]$P<0.05$, [c]$P<0.01$ *vs* before treatment; [d]$P>0.05$, [e]$P<0.05$, [f]$P<0.01$ *vs* placebo.

	Pla ($n=53$)	Hup ($n=50$)
MQ baseline	48±21	56±21[d]
8-wk trial	52±26	64±26[e]
t (paired)	2.69[c]	5.15[c]
MMS baseline	14±5	16±5[d]
8-wk trial	15±6	19±6[f]
t (paired)	0.76[a]	5.62[c]
HDS baseline	16±5	16±6[d]
8-wk trial	15±7	20±6[f]
t (paired)	0.30[a]	7.04[c]
ADL baseline	31±9	33±10[d]
8-wk trial	31.9±0.7	29±9[d]
t (paired)	1.64[a]	4.51[c]

Subjective evaluation According to the reports of patients' intimate relatives, the 3 positive results ('clear headed', 'memory improving', and 'language improving') of Hup group were increased, whereas the negative result (complaint of 'unchanged') of the placebo group was increased. A significant difference was found between two groups ($P<0.01$) (Tab 3).

Tab 3. Complaints of the patient's legal representatives between 2 groups of AD. [c]$P<0.01$.

Complain	Pla ($n=53$)	Hup ($n=50$)	χ^2
Clear headed	13 (17.37)	26 (21.63)	
Memory improving	8 (10.69)	16 (13.31)	
Language improving	2 (4.45)	8 (5.55)	12.29[c]
Unchanged	34 (24.49)	21 (30.51)	
Total	57	71	

Neither the TESS score nor the laboratory changes showed any significant difference between 2 groups with paired or group t test (Tab 4,5).

Tab 4. Comparison of all measured data between 2 groups of AD. [a]$P>0.05$.

Item	Pla ($n=53$)		Hup ($n=50$)	
	baseline	8-week trial	baseline	8-week trial
BP/kPa				
systolic	17.4±2.1	17.5±2.4[a]	17.6±2.9	17.1±2.5[a]
diastolic	11.0±1.1	11.0±1.2[a]	11.0±1.6	10.9±1.3[a]
HR/min	74±9	74±8[a]	72±9	47±9[a]
Hb/g L^{-1}	128±18	129±15[a]	128±18	129±13[a]
WBC/1×10^9 L^{-1}	6.1±1.2	6.1±1.4[a]	6.0±1.4	6.2±1.5[a]
BUN/mmol L^{-1}	5.1±0.8	5.1±0.9[a]	5.1±1.0	5.1±1.1[a]
Cr/μmol L^{-1}	103±21	102±21[a]	94±19	94±19[a]
AKP/U L^{-1}	19.6±2.8	20±3[a]	19±4	19±4[a]
ALT/U L^{-1}	29±6	28±6[a]	29±7	29±6[a]

Tab 5. Comparison of cholinergic side effects between 2 groups of AD. *$P>0.05$.

Cholinergic side effects	Pla ($n=53$)	Hup ($n=50$)
Exciting	3 (5.7 %)	3 (6 %)*
Hyperactivity	3 (5.7 %)	5 (10 %)*
Nasal obstruction	4 (7.5 %)	4 (8 %)*
Nausea or vomiting	1 (1.9 %)	4 (8 %)*
Diarrhea	2 (3.8 %)	5 (10 %)*
Insomnia	4 (7.5 %)	5 (10 %)*
Anorexia	3 (5.7 %)	5 (10 %)*
Dizziness	6 (11.3 %)	4 (8 %)*

DISCUSSION

In order to avoid many interfering factors of treatment study in dementia[8], such as influences of intercurrent disease, age-related changes in pharmacokinetics, poor compliance with drug regimes, cognitive impairment, and loss of insight etc, we designed this strict study, in addition, there was a high ICC in evaluators, and comparable background data between 2 groups, we considered that the results of this study are reliable.

The results of this study exhibited that about 58 % (29/50) of patients treated with Hup showed clinical improvements in their memory ($P<0.01$), cognitive ($P<0.01$) and behavioral ($P<0.01$) functions. The efficacy of Hup was better than placebo (36 %, 19/53) ($P<0.05$). According to the MMS evaluation, an average improvement of 2.98 points was noted for patients treated with Hup, and with 54 % of these patients improving by 3.0 points or more. But the placebo group increased an average of 0.43 points, only with 30.2 % of them improving by 3.0 points or more ($P<0.05$).

As to the findings of significant improvement in 'number of recitation' item of WMS and 'time orientation' item of MMS, it was similarity to the discovery of some authors[9,10].

Throughout 8-wk study, no patient ALT value exceeded the upper limit of normal or renal toxicity in both groups, only a slight increase in some mild peripheral cholinergic side effects such as nausea or vomiting and diarrhea were occurred in Hup group. But there was no statistical significance in comparison with placebo group. This clinical finding is similar to the results of several experimental studies[4,6,7,11-13], ie Hup produced less peripheral side effects at optimal doses, it indicates that Hup is a safe drug and suitable for treating patients with Alzheimer's disease.

Both Hup and tetrahyd oaminoacrine (THA, tacrine)approved by FDA in 1993 belong to cholinergic agents, but the latter has a potential liver toxicity[13,14], and only a mean improvement of 2.0 points on MMS over 30 wk was noted for patients receiving THA 160 mg d^{-1}, with 43 % of these patients improving by 3.0 points or more[14], therefor THA is not an ideal drug in the treatment of patients with Alzheimer's disease. Whereas, according to the results of present study, both the efficacy and the safety of Hup are significantly better than THA, we consider that Hup is a promising candidate drug for symptomatic treatment in patients with Alzeimer's disease.

Although the results of this study are encouraging, there is no extensive, long-term and high-dose observation, especially there is no direct clinical comparison with THA. At the same time, we think the present study is not sufficient, so we hope that further studies will be undertaken to develop methods for identifying the efficacy and safety of Hup.

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石杉碱甲片对阿耳茨海默病记忆、认知和行为的疗效

徐嗣荪，高之旭[1]，翁 正[2]，杜尊铭[3]，徐维安[4]，杨健身[5]，张明廉[6]，童振华，方雍生[1]，柴新生[2]，李淑兰[3]（浙江医科大学浙江省药物滥用监测站，杭州310009；[1]上海市精神卫生中心，上海200030；[2]山东省精神卫生中心，济南250014；[3]杭州铁路中心医院，杭州310009；[4]上海市第三精神病院，上海201905；[5]苏州普济医院，苏州215008；[6]苏州广济医院，苏州215008，中国）

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目的：评估石杉碱甲片治疗阿耳茨海默病的疗效及其安全性。**方法**：采用多中心、前瞻性、双盲、平行、空白对照和随机方法，给50例阿尔采末病一日两次口服石杉碱甲片4片（每片含50微克），并给53例阿耳茨海默病一日两次口服安慰剂片4片，共8 wk。所有病人都用韦氏智力量表、简易精神状态量表、长谷川痴呆量表、日常生活能力量表、副反应量表和其他实验室检查。**结果**：发现58 %(29/50)的石杉碱甲片服用者改善了所有的记忆、认知和行为能力，而安慰剂组仅为35.8 %（19/53），两组疗效有显著差异（$\chi^2=5.07$，$P<0.05$），而两组均无严重不良反应发生。**结论**：石杉碱甲片显著增高记忆、认知和行为功能，是治疗阿耳茨海默病的一个有前景的药物。

关键词 石杉碱甲；胆碱脂酶抑制剂；阿耳茨海默病；多中心研究；双盲法；随机对照试验；韦氏量表；记忆；认知障碍；日常生活活动