Chapter

Clinical Evaluation of Adenosine Triphosphate Disodium Hydrate (ATP-2Na) for Asthenopia

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Abstract

To investigate the effect and the safety of Adenosine triphosphate disodium hydrate (ATP-2Na) for asthenopia. 40 subjects [35 females and 5 males, 25~87 years old (average: 62.5 years old)] with asthenopia ingested 200~300 mg/day ATP-2Na for 3 months. Before and after 1 and 3 months ingestion, subjects completed a questionnaire to determine their asthenopia symptom and fatigue symptom by visual analog scale (VAS). The scores were compared between before and after ingestion. 31 subjects completed a questionnaire for 1 month. The scores of asthenopia symptom before ingestion, 1 and 3 months were 4.05 ± 3.22, 2.67 ± 2.19 and 2.41 ± 2.16, respectively. The scores of fatigue symptom were 4.76 ± 3.05, 3.08 ± 2.93 and 3.10 ± 3.19, respectively. Both scores were significantly decreased ($p < 0.005$) at 1 month compared before ingestion. Three subjects had side effects (diarrhea for two, nausea for one), and all subjects improved by oral discontinuation. These results suggest that ATP-2Na is relatively early effective in improving asthenopia and accompanying fatigue symptoms.

Keywords: adenosine triphosphate disodium hydrate(ATP-2Na), asthenopia symptom, fatigue symptom, visual analog scale (VAS), 3 months

1. Introduction

Recent years, patients with asthenopia increased, because many people are engaged in visual display terminal (VDT) work and are using a portable terminal for example smartphone. The causes of asthenopia are dry eye [1, 2], lack of correction for hyperopia or presbyopia, overcorrection for myopia by contact lens or glasses for example. Eye treatment for these causes does not improve asthenopia in some cases. On the other hand, patients with asthenopia sometimes complain of systemic symptoms such as headache, stiff shoulder, nausea and fatigue. Symptoms by VDT work are serious problems in Japan, so Ministry of Health, Labor and Welfare established guideline for Occupational Health Environmental Management in 2002 [3]. In this guideline, at first, improvement of environment for VDT is necessary, and in serious cases patients should see clinical ophthalmologists. In questionnaire results in 2003 in Japan, many ophthalmologists prescribe glasses for near work or tear drop or Vitamin B12 eye drop to reduce asthenopia from VDT work [4].

Adenosine triphosphate disodium hydrate (ATP-2Na) is internal medicine which approved for asthenopia from the results of multicenter clinical researches or double blind clinical researches in 1970~1990 in Japan [5–7]. In this study, we researched the effect and the safety of ATP-2Na for present asthenopia.

2. Subjects and methods

2.1 Subjects

Subjects were patients with asthenopia in Kyoto Prefectural University of Medicine facilities in 2012~2014. We selected patients who had asthenopia symptoms, regardless of causes such as dry eye or inappropriate glasses. Subjects were 40 patients (35 females and 5 males), and 25~87 years old (average age: 62.5 years old).

2.2 Methods

Two or three times per day, subjects ingested Adetphos Kowa Granule 10% which is clinical medicine containing 100 mg of ATP-2Na. Before and after 1 and 3

		Date / /
Eye symptoms	Feeling of oppression of the eyes	0 Non — 10 Worst
	Pain in the back of the eyes	0 Non — 10 Worst
	Tough to open eyes	0 Non — 10 Worst
	Blurred vision	0 Non — 10 Worst
	Sense of heat of eyes	0 Non — 10 Worst
Systemic symptoms	Headache	0 Non — 10 Worst
	Stiff shoulder	0 Non — 10 Worst
	Fatigue	0 Non — 10 Worst
Mental symptoms	Depressed feeling	0 Non — 10 Worst
	No concentration feeling	0 Non — 10 Worst
Remarks column		

Table 1.
Visual analog scale (VAS).

months ingestion, subjects completed a questionnaire to determine their asthenopia symptom and fatigue symptom by visual analog scale (VAS) [8] (**Table 1**). In VAS scale, 0 is the best evaluated result and 10 is the worst evaluated result. Questionnaire items were 10 items; 5 items about eye symptoms (feeling of oppression of the eyes, pain in the back of the eyes, tough to open eyes, blurred vision, sense of heat of eyes), 3 items about systemic symptoms (headache, stiff shoulder, fatigue), and 2 items about mental symptoms (depressed feeling, no concentration feeling). The scores were compared between before and after ingestion.

In addition, the scores were compared about the background factors before administration. Researched background factors were gender, age, internal dose per body weight, whether or not other eye diseases, whether or not of using eye drop for asthenopia, and scores before ingestion. Within this study, subjects continued all drugs prescribed before the administration.

2.3 Statistical analysis

Paired t test was used to compare the change of scores between before and after ingestion. In analysis of background factors, student's t test was used the changes through 3 months. In both analysis, $p < 0.05$ was considered statistically significant.

3. Results

3.1 Subject characteristics

In 40 initial subjects, 33 subjects visited hospital at 1 month, and these subjects were targeted for evaluation of safety. In 33 subjects, one subject discontinued the ingestion because of diarrhea within 1 month, one refused to describe the questionnaire. 31 subjects completed a questionnaire for 1 month and were targeted for effect evaluation. Age distribution of 31 subjects (26 females, 5 males) was 25–87 years old, average age was 64.4 years old. Background factors are presented in **Table 2**. Average score of eye symptom in group with diabetes was larger than that in group without diabetes ($p < 0.01$). Average score of systemic symptom in group 65y younger was larger than that in group 65y older ($p < 0.05$). 26 subjects completed a questionnaire for 3 months.

3.2 Effect evaluations

3.2.1 Scores in each symptom

The scores about eye symptom before ingestion, 1 month, 3 months were 4.05 ± 3.22, 2.67 ± 2.19, and 2.41 ± 2.16, respectively. The scores were significantly decreased at 1 and 3 months (both $p < 0.005$, **Figure 1**). Among the symptoms about eye, the scores of "blurred vision" were no different between before and after (**Figure 2**). The scores about systemic symptom (average scores; before ingestion: 4.76 ± 3.05, 1 month: 3.08 ± 2.93, and 3 months: 3.13 ± 3.18) significantly decreased ($p < 0.005$). Similarly, the scores about mental symptom (average scores; before ingestion: 4.41 ± 3.46, 1 month: 2.97 ± 2.63, and 3 months: 3.10 ± 3.19) significantly decreased ($p < 0.005$).

		Score of first time		P
Sex		Female(n=26)	Male(n=5)	
	Eye symptoms	4.33±2.45	2.44±1.29	p=0.11
	Systemic symptoms	4.93±2.97	3.87±3.69	p=0.49
	Mental symptoms	4.51±3.53	3.90±3.35	p=0.72
Age		Under 65 years old(n=12)	Over 65 years old(n=19)	
	Eye symptoms	4.31±1.89	3.84±2.70	p=0.61
	Systemic symptoms	6.36±2.60	3.75±2.94	p<0.05
	Mental symptoms	4.99±3.41	4.04±3.53	p=0.47
Involvement				
Cataract		Yes(n=12)	No(n=19)	
	Eye symptoms	4.58±2.79	3.67±2.11	p=0.31
	Systemic symptoms	4.73±3.00	4.78±3.17	p=0.96
	Mental symptoms	5.40±3.45	3.78±3.40	p=0.21
Glaucoma		Yes(n=11)	No(n=20)	
	Eye symptoms	4.90±2.81	3.54±2.05	p=0.13
	Systemic symptoms	5.72±3.24	4.23±2.89	p=0.20
	Mental symptoms	5.05±3.72	4.05±3.35	p=0.45
Hypertension		Yes(n=11)	No(n=20)	
	Eye symptoms	3.62±2.74	4.24±2.22	p=0.50
	Systemic symptoms	4.27±3.25	5.03±2.99	p=0.52
	Mental symptoms	3.86±3.52	4.71±3.47	p=0.52
Diabetes		Yes(n=3)	No(n=28)	
	Eye symptoms	7.30±2.22	3.67±2.16	p<0.01
	Systemic symptoms	5.41±3.84	4.69±3.04	p=0.71
	Mental symptoms	4.88±3.87	4.36±3.48	p=0.81
Dose		200mg (n=23)	300mg(n=8)	
	Eye symptoms	4.31±2.57	3.20±1.65	p=0.27
	Systemic symptoms	5.09±3.09	3.82±2.93	p=0.32
	Mental symptoms	4.94±3.44	2.88±3.21	p=0.15
Other eye strain treatments		Yes(n=13)※1	No(n=18)	
	Eye symptoms	4.55±2.65	3.64±2.19	p=0.30
	Systemic symptoms	4.83±3.16	4.71±3.07	p=0.92
	Mental symptoms	4.27±3.70	4.51±3.38	p=0.85

VAS: Visual Analog Scale

※1 Concomitant medications: Oral administration of Methylcobalamin (6 person), Instillation of cyanocobalamin (4 person), Oral administration of Methylcobalamin + Instillation of cyanocobalamin (1 person), Over-the-counter drugs (2 person)

Table 2.
Comparison of baseline VAS scores between each groups classified by baseline characteristics (n = 31).

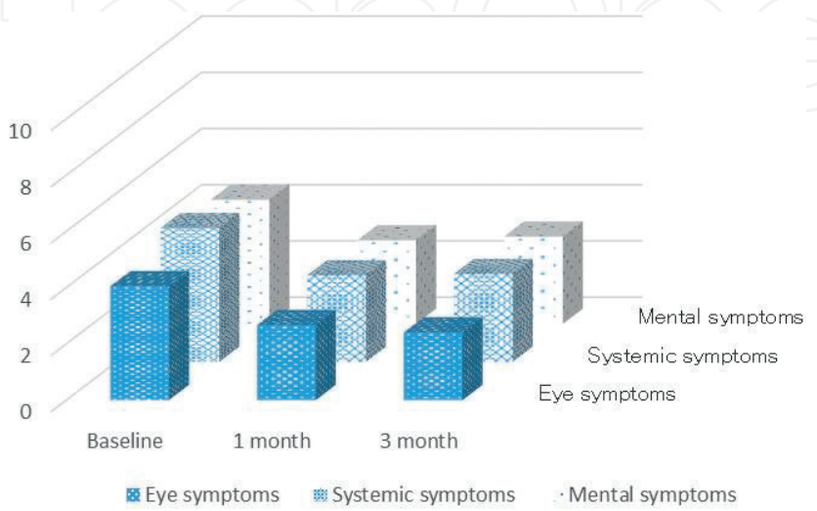

Figure 1.
Transition of scores of each symptom. Mean score of each symptom (5 eye symptoms, 3 systemic symptoms, 2 mental symptoms) before and 1, 3 months after ingestion. The scores were significantly decreased at 1 and 3 months (both p < 0.005) compared before ingestion. This result means that ingestion of ATP-2Na relatively early improved systemic symptoms and mental symptoms as well as eye symptoms.

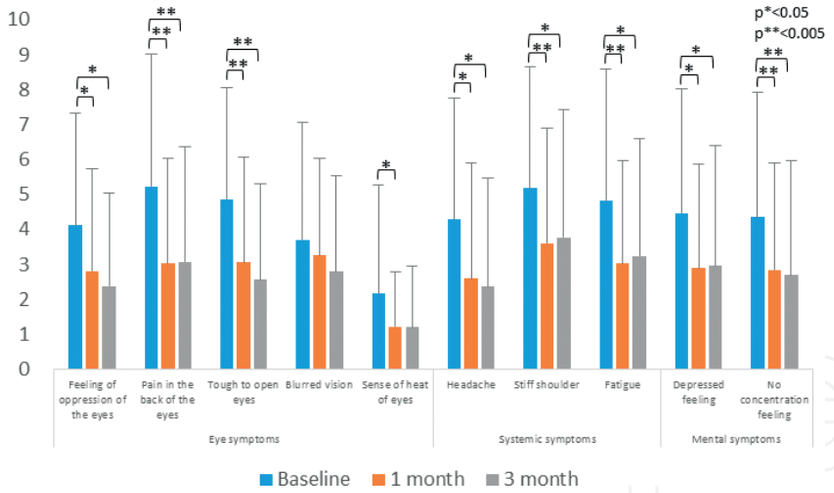

Figure 2.
Transition of scores of each detail symptom. Score of each detail symptoms at before, 1 month and 3 months after ingestion. Among the symptoms about eye, the scores of "blurred vision" were no different between before and after. This result means that the cause of "blurred vision" may be not only due to abnormality in accommodation but also due to cataract et al.

			The amount of change		P
Sex			Female(n=21)	Male(n=5)	
	Eye symptoms	1 month	-1.47±1.76	-0.73±1.45	p=0.39
		3 months	-1.61±1.73	-1.09±1.54	p=0.55
Age			Under 65 years old(n=10)	Over 65 years old(n=16)	
	Eye symptoms	1 month	-1.31±2.15	-1.37±1.43	p=0.93
		3 months	-1.73±1.73	-1.37±1.69	p=0.60
Complications					
Glaucoma			Yes(n=10)	No(n=16)	
	Eye symptoms	1 month	-1.58±1.18	-1.22±1.96	p=0.59
		3 months	-1.83±1.89	-1.30±1.56	p=0.45
Cataract			Yes(n=11)	No(n=15)	
	Eye symptoms	1 month	-1.70±1.57	-1.13±1.80	p=0.37
		3 months	-1.43±1.31	-1.56±1.95	p=0.86
Hypertension			Yes(n=11)	No(n=20)	
	Eye symptoms	1 month	-1.35±1.55	-1.35±1.84	p=1.00
		3 months	-1.25±1.16	-1.62±1.89	p=0.61
Diabetes			Yes(n=3)	No(n=28)	
	Eye symptoms	1 month	-1.56±0.19	-1.33±1.80	p=0.83
		3 months	-1.88±1.36	-1.46±1.74	p=0.69
Dose / Weight (Median 4.08)			Over Median (n=14)	Under Median (n=12)	
	Eye symptoms	1 month	-1.21±1.28	-1.50±2.12	p=0.65
		3 months	-1.69±1.64	-1.29±1.77	p=0.55
Other eye strain treatments			Yes(n=12)	No(n=14)	
	Eye symptoms	1 month	-1.67±0.98	-1.11±2.09	p=0.38
		3 months	-1.87±1.79	-1.20±1.83	p=0.32
Scores before administration	Eye symptoms (Median 4.19)		Severe (Over Median) (n=13)	Mild (Under median) (n=13)	
		1 month	-1.85±2.12	-0.81±0.93	P=0.09
		3 months	-2.25±1.81	-0.77±1.20	p<0.05
	Systemic symptoms (Median 4.78)		Severe (Over median) (n=13)	Mild (Under median) (n=13)	
		1 month	-2.84±1.85	-0.35±1.60	p<0.05
		3 months	-2.59±2.30	-0.35±1.60	p<0.05
	Mental symptoms (Median 3.84)		Severe (Over median) (n=13)	Mild (Under median) (n=13)	
		1 month	-2.97±2.64	-0.01±1.71	p<0.05
		3 months	-2.59±2.95	-0.47±1.48	p<0.05

Table 3.
Comparison of change of scores between each groups classified by background factor.

3.2.2 Comparison about the background factors

There was no difference among groups regarding the background factors about gender, age, whether or not other eye diseases, and whether or not of using eye drop for asthenopia (**Table 3**). The larger of initial scores improve larger effect in any symptoms.

3.3 Safety evaluations

Among 33 all subjects, 3 subjects had side effect. 1 subject feel nausea and 2 had diarrhea. There was no relation between subjects with side effect and internal dose per body weight or other background factors. And all subjects improved by oral discontinuation.

4. Discussions

In this study, regardless the causes, asthenopia symptoms improved with ingestion of ATP-2Na. And the systemic symptoms (headache, stiff shoulder, fatigue) caused by asthenopia improved, as well as the mental symptoms (depressed feeling or no concentration feeling).

Asthenopia symptoms from extremely strong eye fatigue cannot improve with rest. In report by Suzumura, the cause of asthenopia was categorized into three factors (external environmental factors, ophthalmologic factors, and internal /mental factors), and asthenopia symptoms got worse by collapse of balance between these three factors [9]. In this study, subjects were enrolled by symptoms. We did not research a cause of asthenopia symptoms. Ninety-two percent of subjects had systemic symptoms or mental symptoms. It is possible that the balance of several factors collapsed in enrolled subjects in this study. The more severe the symptoms before ingestion, the stronger the improvement effect was confirmed. Severe symptoms that caused a vicious circle related by various systemic/mental symptoms, possibly improved better than weak symptoms. ATP-2Na increases the blood flow in vertebrae and common carotid artery. For the reason, it is suggested that increased blood flow in ciliary body muscle stabilized accommodation, and increased blood flow in vertebrae improved symptoms such as stiff shoulder. In our study, asthenopia symptoms of subjects who were administered nerve stimulants such as Vitamin B12 improved. Then it is clear that ATP-2Na exerts the effect depending on the mechanism different from Vitamin preparations.

Several studies reported that improvement of accommodation by ATP-2Na was confirmed by examination such as near point meter or accommodo-polyrecorder [5–7]. In these studies, enrolled patients were 20~50 years old whose accommodation was not lost. But from our study ATP-2Na is effective for asthenopia in patients over 65 years old as same as in patients under 65 years old. However, ATP-2Na was not effective for blurred vision symptom. It is suggested that blurred vision symptom related several factors for example accommodative dysfunction or cataract. It is difficult to detect the abnormality in accommodation by traditional examination because of presbyopia. Kajita et al. reported that change of pupil diameter could detect ciliary muscle abnormality as objective findings of asthenopia [10]. It is thought that asthenopia of senior patients is possibly related to imbalance in ciliary muscle [11]. Asthenopia in younger subjects is possibly related to accommodative convulsion, on the other hands, asthenopia in older subjects is possibly related to accommodative semi-dysfunction [12]. Blood flow increase by ATP-2Na was effective for asthenopia symptoms from each mechanism.

Among 33 all subjects, 3 subjects had side effect (nausea for 1 and diarrhea for 2). All subjects improved from side effect by discontinuation of ingestion. In

this study, enrolled subjects were senior patients whose gastrointestinal function were slightly impaired, and side effect occurred because of pharmacological action of ATP-2Na that increases the gastrointestinal blood flow and that increases the gastrointestinal functions. Side effect occurrence rate was not difference among background factors in this study. However, it is considered better for safety that senior patient whose BMI is low level and whose gastrointestinal function is slightly impaired, ingests 200mg/day of ATP-2Na instead of 300mg/day. It is described in the package insert and need to explain to the patient.

Some limitations of this report need to be considered. First, this study sets no control group, because the effect of ATP-2Na revealed by double blind control study in previous studies. Second this study is based on subjective findings only. It is necessary to evaluate the objective findings from examinations as an index of asthenopia.

Even in present day where causes of asthenopia have diversified, ATP-2Na improved asthenopia symptoms relatively early in adult cases involving senior patients, moreover, ATP-2Na improved systemic/mental symptoms derived from asthenopia. Naturally, in the cases related presbyopia or VDT work, it is important to prescribe near glasses considering ages, working distance and refractive error. Moreover, this study evaluates ATP-2Na is one of effective treatment for asthenopia with systemic/mental symptoms.

Conflict of interest

No conflict of interest.

Notes

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