Efficacy of Neurotropin in chronic fatigue syndrome

-The U.S. National Institutes of Health have performed double-blind, cross-over, placebo-controlled studies of Neurotropin in patients with fibromyalgia (protocol number: 06-NR-0229)-

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Text

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Abstract

The efficacy of Neurotropin (NT) for chronic fatigue syndrome (CFS) is presented. Eleven CFS patients received NT as 4-8 tablets per day (average: 6.6 tablets). Subjective fatigue at the initial visit was considered 100, and subjective fatigue after treatment was an index of therapeutic efficacy. Patients whose subjective fatigue decreased to 30% or less with NT alone, or NT and other medicine(s), and whose subjective fatigue did not recur after discontinuation of treatment were 2 and 1, respectively. Patients whose subjective fatigue decreased to 30% or less with NT alone, or NT and other medicine(s), and whose medication was continued were 2 and 1, respectively. Patients whose subjective fatigue decreased to 90% or less but did not decrease to 30% or less with NT alone, or NT and other medicine(s) were 1 and 1, respectively. One patient discontinued treatment because of adverse effects (epigastric distress) of NT. Two patients discontinued treatment because of adverse effects (drug-induced liver injury) during administration of NT and other medicine(s).

In Japan, NT is widely used for chronic pain, such as low back pain, neck-shoulder-arm syndrome, osteoarthritis, subacute myelo-optico-neuropathy, postherpetic neuralgia, and complex regional pain syndrome. Analgesic effects of NT are thought to be the activation of a descending pain inhibitory system; however, it cannot account for the improvement of fatigue. Viral infection theory is a popular hypothesis in the etiology of CFS. NT may activate antivirus action.

Keywords Neurotropin, chronic fatigue syndrome, fibromyalgia, pharmacotherapy・chronic widespread pain

Introduction

Chronic fatigue syndrome (CFS) is a disorder that causes general fatigue and widespread pain. A double-blind randomized placebo-controlled crossover study showed that methylphenidate was effective for CFS, [1] but long-term medication is difficult because of its adverse effects.

Neurotropin (NT) was developed in Japan and is administered for chronic pain. The efficacy of NT for CFS is presented.

Material and Methods

Eleven CFS patients who received NT for at least 6 weeks in Hiroshima Prefectural Rehabilitation Center between April 2004 and March 2007 or Hatsukaichi Memorial Hospital between April 2007 and November 2008 were examined. Subjects who met the diagnostic criteria of the Centers for Disease Control and Prevention [2] were diagnosed with CFS. Patients with traumatic cerebrospinal fluid leak usually satisfied the criteria. However, treatment for traumatic cerebrospinal fluid leak [3] is completely different from CFS treatment, [4] therefore, patients with traumatic cerebrospinal fluid leak were excluded from this study. NT was administered first in all patients. Four or 8 NT tablets per day were administered. If NT provided partial fatigue relief, it was continued and a second medicine was added. Patients who did not respond to NT or who could not tolerate the adverse effects of NT in other hospitals were excluded from the study.

Subjective fatigue at the initial visit was considered 100, and subjective fatigue after treatment was considered as an index of therapeutic efficacy (Table 1). Cure: Subjective fatigue decreased to 30% or less with NT alone and subjective fatigue did not recur after discontinuation of treatment. Excellent (a): Subjective fatigue decreased to 30% or less with NT and other medicine(s) and did not recur after discontinuation of treatment. Excellent (b): Subjective fatigue decreased to 30% or less with NT alone, however, NT could not be discontinued. Effective (a): Subjective fatigue decreased to 30% or less with NT and other medicine(s); however, the medicines could not be discontinued. Effective (b): Subjective fatigue decreased to 90% or less but did not decrease to 30% or less with NT alone. Effective (c): Subjective fatigue decreased to 90% or less but did not decrease to 30% or less with NT and other medicine(s). No effect: Subjective fatigue did not decrease to 90% or less. Adverse effects (N): Treatment was discontinued because of

adverse effects of NT alone. Adverse effects (combined): Treatment was discontinued because of adverse effects of NT and other medicine(s).

Table 1. Definition of treatment results

	Neurotropin alone	Combination
Discontinuation	Cure: 2	Excellent (a): 1
30% or less fatigue	Excellent (b): 2	Effective (a): 1
90% or less fatigue	Effective (b): 1	Effective (c) 1
91% or more fatigue	No effect: 0	No effect : 0
Adverse effects	Adverse effects (N): 1	Adverse effects (Combined): 2

Subjective fatigue at the initial visit was considered 100, and
subjective fatigue after treatment was an index of therapeutic efficacy.

Results

The subjects consisted of 11 patients with CFS (9 females and 2 males) (Table 2). Age at the initial visit ranged from 12 to 62 years of age (average: 35.1 years). Duration of the disorder ranged from 12 to 552 months (average: 109 months). Duration of treatment ranged from 1.5 to 21 months (average: 9.7 months). The maximum dose in 4 patients was 4 tablets per day and that in 7 patients was 8 tablets per day; the mean maximum dose was 6.6 tablets per day.

Cure was achieved in 2 patients, excellent (a) in 1 patient, excellent (b) in 2 patients, effective (a) in 1 patient, effective (b) in 1 patients, and effective (c) in 1 patient (Table 1, 2). One patient (No. 9) was in the effective (a) group, but treatment was discontinued because of drug-induced liver injury during medication with NT and amitriptyline. One patient (No. 6) showed no effect, and treatment was discontinued because of drug-induced liver injury during multimedication, including supplements and medication from an other hospital. One patient (No. 8) showed no effect and treatment was discontinued because of adverse effects (epigastric distress) caused by NT alone. It is not clear whether NT caused adverse effects in these 2 patients.

Table 2 Treatment results of Neurotropin in chronic fatigue syndrome

Patient	sex	age	Disease Duration	Treatment period	Results	Maximum dose
1	M	28	48	3	Cure	4
2	F	31	84	14	Excellent (b)	8
3	F	52	15	8	Cure	8
4	F	29	21	21	Effective (c)	8
5	F	31	12	16	Effective (b)	8
6	M	29	48	4	No effect/Adverse Effect (combined)	8
7	F	62	168	11	Excellent (a)	8
8	F	29	72	10	No effect/Adverse Effect (N)	4
9	F	32	156	11	Effective (a)/Adverse effect (combined)	4
10	F	12	23	7	Effective (a)	4
11	F	51	552	1.5	Excellent (b)	8
average		35.1	109	9.7		6.6

Disease duration: months, Treatment period: months, Maximum dose: tablets

Discussion

NT is a non-protein extract from the inflamed skin of rabbits inoculated with vaccinia virus. [5] NT is not a single substance but a compound, and its components, especially analgesic components, are not clear. The analgesic effects of NT are thought to be the activation of a descending pain inhibitory system in the brain. [6] [7] The analgesic effects of antidepressants are similar, but the activation is thought to be in the dorsal horn of the spinal cord. Unlike non-steroidal anti-inflammatory drugs (NSAIDs), NT does not suppress prostaglandin synthesis; therefore, NT does not cause digestive ulcers. [8]

Instead, NT has a preventive effect against some experimental stress ulcers in rats. [9] NT was reported to prevent gastric mucosal lesion induced by NSAIDs in rats. [10] In Japan, NT is widely used for chronic pain, such as low back pain, neck-shoulder-arm syndrome, osteoarthritis, subacute myelo-optico-neuropathy (SMON), postherpetic neuralgia, fibromyalgia (FM), and complex regional pain syndrome (CRPS). A double-blind test showed that NT tablets were significantly more effective than a placebo for low back pain, [11] postherpetic neuralgia, [12] and neck-shoulder-arm syndrome. [13] A multicenter double-blind cross-over study [14] and multicenter double-blind study [15] showed that NT injection was statistically more effective than a placebo for SMON. The U.S. National Institutes of Health have performed double-blind, cross-over, placebo-controlled studies of NT in patients with FM (protocol number: 06-NR-0229). It is notable that NT is reported to be significantly safer than NSAIDs or to have a tendency to be safer than NSAIDs although there was no significant difference. [16-17] Double-blind studies have shown that the incidence of adverse effects of NT and the dropout rate due to adverse effects of NT were similar to with a placebo. [11-13, 17-18] Some studies have shown that the incidence of adverse effects and dropout rate due to adverse effects of NT were even lower than with a placebo, although they had no statistical significance. [12, 17-18] The main adverse effects of NT were a heat sensation in the body and pruritus, which are thought to be due to allergy, epigastric distress, diarrhea, or eczema. Because they are subjectively clear adverse effects, patients usually discontinue the medication based on their own judgment. In the event of a past history of sensitivity to NT, NT must not be administered. Medication need not be discontinued with NT, but patients can drink alcohol during administration. Because NT rarely causes drowsiness and muscle flaccidity, in all likelihood, it does not increase the frequency of falling, fractures, and traffic accidents over a long duration. Because NT fairly infrequently causes drowsiness or dizziness, it also fairly infrequently aggravates the symptoms of CFS. Because NT rarely causes thirst, it rarely aggravates the symptoms of burning mouth syndrome. Some patients who received 8 tablets of NT per day did not visit the office for personal reasons resulting in abrupt withdrawal of NT; however, they did not suffer any symptoms. However, if 8 tablets of NT per day are ineffective and administration is discontinued, it is preferable for medication to be discontinued after taking 4 tablets per day for several days. If 4 tablets of NT per day are discontinued, gradual tapering of the dose is not

needed and abrupt withdrawal does not cause any symptoms. Because NT does not cause withdrawal symptoms, it does not cause drug dependence. Although there are no concrete data, in my experience, NT does not disturb cognitive function. NT is widely used in Japan and is now also used in China. A weak point of NT is that it is not effective for acute pain.

Although analysis is impossible, the anti-fatigue effects of NT in CFS are stronger than the analgesic effects of NT in FM or CRPS in my experience. NT was administered to patients with CFS for the following reasons. 1: NT rarely causes adverse effects. 2: A medicine that is effective for CFS in a double-blind test is methylphenidate; however, it causes many adverse effects, therefore, long-term medication is difficult. 3: I frequently administered NT for chronic pain such as CRPS, lumbago, stiff neck, FM, and chronic widespread pain (CWP). In the course of treatment of such disorders, NT improved fatigue. 4: FM is a similar disorder to CFS. In my experience, medicine that is effective for FM is often effective for CFS. Two open studies [19] [20] and 1 case report [21] have shown the efficacy of NT for FM.

In my experience, NT is more efficacious than amitriptyline and NT has fewer adverse effects than amitriptyline in FM. [22] Therefore, NT is administered for FM as a first-line drug. [21] Because FM is thought to be the extreme end of a continuum of CWP rather than a distinct medical entity, [23] [24] the same therapy as for FM is administered for patients with CWP. Therefore, NT is administered for CWP as a first-line drug, as well as CFS. [25] As mentioned above, the analgesic effects of NT are thought to be the activation of a descending pain inhibitory system; however, this cannot account for the improvement of fatigue. Viral infection theory is a popular hypothesis in the etiology of CFS. From the viewpoint of a production method, NT may have antivirus action; however, it has no direct antivirus action. NT may indirectly activate antivirus action in a living body.

This study is an open study describing a few cases. A method for evaluating fatigue is not clear and a double blind study with sufficient patients is needed.

Conclusion

NT is effective for CFS, but a double blind study with sufficient patients is needed.

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奥付

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