An Open-label Study of Amitriptyline in Central Poststroke Paresthesia

Cheung-Ter Ong, Sheng-Feng Sung, Chi-Shun Wu, and Chien-Ning Lo

Abstract- Central poststroke paresthesia is characterized by a persistent abnormal sensation in the body after a cerebrovascular accident. Between 1998 and 2001, 89 stroke patients admitted to the Chia-Yi Christian Hospital were diagnosed as having central poststroke paresthesia. Fifty-two of them, 25 males and 27 females with a mean age of 58 years, participated in the two-phase study. During phase one, patients were observed without any specific treatment for the paresthesia. Forty-four patients then entered phase two and received amitriptyline therapy. Fourteen patients (31.8%) reported alleviation of the paresthesia. Our data indicated that amitriptyline might be useful in the management of central poststroke paresthesia.

Key Words: Amitriptyline, Paresthesia, Stroke

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INTRODUCTION

Paresthesia is an abnormal sensation in the absence of specific stimulation and may be caused by a variety of abnormalities in the sensory pathways, either central or peripheral. In the central nervous system, the most common etiologies include ischemia, compressive phenomena, infection, inflammation, and degenerative conditions[1]. Central poststroke paresthesia is a persistent unpleasant sensation in parts of the body following a stroke. Its occurrence was 18.2% according to our previous observation[2]. Although pharmacological management of paresthesia is an important clinical problem, many studies about the treatment of paresthesia have been focused on peripherally induced paresthesia. Tricyclic antidepressants have been successfully used in the treatment of postherpetic neuralgia[3,4] and diabetic neuropathy[5], and central poststroke pain was also reduced by tricyclic antidepressants[6,7]. Among the tricyclics, amitriptyline was the most commonly used drug in these studies and notably the cost of treatment was low[8]. We therefore tried to answer the question whether paresthesia following a cerebrovascular accident can be reduced by amitriptyline, and found that a significant proportion (31.8%) of such patients could benefit from amitriptyline therapy.

METHODS

Patients

All patients were recruited from the stroke unit at the Chia-Yi Christian Hospital. The diagnosis of stroke

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was based on clinical history, neurological examination, and neuroimaging studies. Central poststroke paresthesia was considered if the patient had abnormal sensations in parts of the body following the stroke.

The patients who exhibited peripheral neuropathy confirmed by nerve conduction studies were excluded from the study. Patients were also excluded if they had contraindications to the use of amitriptyline such as significant cardiac arrhythmia, glaucoma, urinary retention, and moderate to severe hypotension.

Evaluation

Patients were seen at outpatient clinic every two weeks after discharge from the stroke unit. The severity of paresthesia was defined as mild if the patients did not complain of paresthesia but recognized its existence after inquiry. It was defined as moderate if the patients complained of paresthesia which could still be tolerated, and severe if the patients experienced intolerable paresthesia and actively sought medications. Muscle strength as well as mood were evaluated, and the adverse effects of amitriptyline were documented.

Protocol

The study was divided into two consecutive phases, each lasting for 6 months. In phase one, the patients were put on only essential medications for stroke prevention such as antiplatelet agents or anticoagulants if indicated. In phase two, the patients continued their medications for stroke prevention and also received amitriptyline (starting from 10 mg/day). If no adverse effects occurred, the dose of amitriptyline was increased every two weeks by 10 or 15 mg until a maintenance dose of 75 mg/day is reached. The dose was adjusted every four weeks if there were mild adverse effects. Amitriptyline was withdrawn if the adverse effects were severe and intolerable.

We used chi-square test for comparison of proportions and McNemar's test for comparison of non-independent sample proportions. Statistical significance was set at $p<0.05$.

RESULTS

Among 684 patients with acute stroke admitted to the hospital from 1998 to 2001, 89 patients (13.0%) were diagnosed as having central poststroke paresthesia. In addition to sensory abnormalities, 82 of them had motor deficits. There were 52 patients, 25 males and 27 females with a mean age of 58 years (range 42-84), eligible for the study. Eight patients quitted the study because of recurrence of stroke (n=2), depression (n=3), and concurrent acupuncture treatment (n=3). We had totally 44 (84.6%) patients completing phase one study.

At the beginning of phase one study, the severity of paresthesia was severe in 1 patient, moderate in 24, and mild in 19. Because two patients (4.5%) reported partial relief in the sensory symptoms, the severity of paresthesia became moderate in 24 and mild in 20 at the end of phase one study. Improvement in the muscle strength was also observed in 13 patients.

Thirteen patients (29.5%) failed to finish phase two study. Eight of them stopped the medication due to severe adverse effects, including dry mouth (3/44, 6.8%), urinary retention (2/44, 4.5%), tinnitus (1/44, 2.3%), chest tightness (1/44, 2.3%), and fatigue (1/44, 2.3%). Three other patients discontinued the trial because of heart disease (1/44) and loss of follow-up (2/44). In the remaining 31 patients, four were free of parethesia by the end of phase two study. Another ten patients reported improvement in sensory symptoms (Fig.). Overall, 31.8% (14/44) of the patients responded to amitriptyline treatment. In comparison with the out-

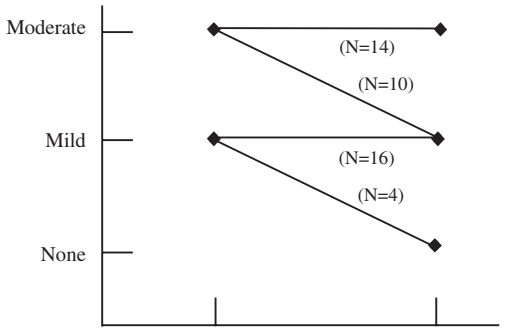

Figure. Improvement in severity of paresthesia after treatment with amitriptyline. (N= number of patients)

come of phase one, amitriptyline reduced the severity of central poststroke paresthesia (McNemar's test, $p<0.005$).

In the 31 patients completing the whole study, twenty had ischemic stroke and eleven had hemorrhagic stroke. Of them, ten and four patients reported improvement in paresthesia, respectively. There was no significant difference between different types of stroke (chi-square test, $p>0.1$).

DISCUSSION

Miscellaneous treatments have been applied to relieve central pain and dysesthesia. Tricyclic antidepressants, with both noradrenergic and anticholinergic properties, are usually the first-line therapeutic agents[9]. Amitriptyline appears to be the most effective[10,11]. However, adverse effects of amitriptyline limit its use in the treatment of central poststroke paresthesia especially because stroke is more prevalent in the elderly. Amitriptyline could produce adverse events in more than 30% of elderly patients[12]. This is probably partly ascribable to the longer half-life of amitriptyline in the elderly[13]. The anticholinergic effect of amitriptyline may account for its most common adverse effects such as dry mouth and urinary retention[14,15].

A maximal dose of 150 mg/day has been used in the study of postherpetic neuralgia. The effect is dose-dependent, and more relief of pain is associated with higher amitriptyline dose and higher serum tricyclic level[4]. However, a daily dose of 75 mg was suggested for central pain and dysesthesia[9]. In view of more adverse events in the elderly, we chose 75 mg as the maximal daily dose.

The sensory symptoms seldom decreased spontaneously in the majority of the patients with central poststroke paresthesia. In a study about the sensory sequelae of medullary infarction, only 4 of 55 patients (7.3%) reported that the symptomatic severity had decreased after a mean follow-up period of 21 months[16]. As observed in our phase one study, only 4.5% of patients reported reduction in sensory symptoms. But in phase two study, amitriptyline seemed to show a therapeutic effect on central poststroke paresthesia.

Since our study had an open-label uncontrolled design, the efficacy of amitriptyline for relieving central poststroke paresthesia could not be established unequivacally. Although a randomized clinical trial may be warranted to further assess the effect of amitriptyline, amitriptyline might be a promising agent in the pharmacological treatment of central poststroke paresthesia and other related sensory symptoms.

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