5-HT₃ Antagonist for the Treatment of Central Pain: Comparison with the Results of Pharmacological Tests

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Abstract

We reported previously that pharmacological classification of central post-stroke pain by the morphine, thiamylal and ketamine tests could be useful for predicting the effects of chronic motor cortex stimulation therapy. It has also been suggested that excitatory amino acids may be involved in the development of central post-stroke pain.

However, the fact that only about the half of the cases of central post-stroke pain were sensitive to the thiamylal or ketamine test reflects the complex pharmacological background of central post-stroke pain. 5-HT₃ antagonist, which has recently become available for clinical use, was employed for the treatment of central pain (thalamic pain, 10 cases; Wallenberg syndrome, 2 cases; post spinal cord injury pain, 2 cases), and the results of the morphine, thiamylal and ketamine tests were compared.

5-HT₃ antagonist showed excellent pain reduction in 2 cases of thalamic pain and 1 case of post spinal cord injury pain. These 3 cases were all resistant to thiamylal and ketamine, circumstances under which it is usually difficult to achieve an analgesic effect with chronic motor cortex stimulation therapy. Thus, 5-HT₃ antagonist therapy may provide a useful method for the treatment of central pain in thiamylal- and ketamine-resistant patients.

Key words: 5-HT₃ antagonist, central pain, thiamylal, ketamine, morphine

INTRODUCTION

In attempt to clarify the neurochemical background of central pain, we have evaluated the ketamine, thiamylal and morphine tests⁴³⁻⁴⁵. Ketamine is a non-competitive antagonist at the NMDA receptor site⁴⁰, and thiamylal is an ultrashort-acting barbiturate which is reported to be more effective in blocking the effects of excitatory amino acids (EAAs) in synaptic trans-
mission than is secobarbital or pentobarbital\(^3\). Barbirurate has also been found to exert effects on neural function including membrane stabilization, inhibition of the responses of neurons to EAAs, and inhibition of EAA release\(^{25,31,33}\). Morphine is generally non-effective for deafferentation pain, but can be effective for nociceptive pain\(^{30,44}\). Recent investigations have indicated that the 5–HT\(_3\) receptor is a site of action for the therapeutic use of antidepressants\(^{10}\), and is helpful in explaining the analgesic effect of antidepressants in central pain\(^9\).

In the present study, we investigated the analgesic effect of 5–HT\(_3\) antagonist in central pain patients. Further, the analgesic effects were compared with the results of the thiamylal, ketamine and morphine tests for the purpose of elucidating the characteristics of the 5–HT\(_3\) antagonist in the treatment of central pain.

**MATERIALS AND METHODS**

**Study population**

A total of 14 central pain patients, comprising 10 cases of thalamic pain, 2 cases of Wallenberg syndrome and 2 cases of post spinal cord injury pain, formed the subjects of study. They included 10 males and 4 females, aged 35 to 70 years (mean, 58.6 years). The interval between the onset of the original disease and the occurrence of pain was 1 to 6 months, and all patients had suffered from intractable pain for 6 to 18 months (mean, 8.8 months). All patients displayed intractable body pain associated with dysesthesia and allodynia. They complained of spontaneous pain of great intensity which they described as burning, tearing, or deep boring pain. Analgesia to the pinprick test of varying degrees and a dysesthetic response to light tactile stimuli were observed in all patients at the painful areas. All patients were subjected to the morphine, thiamylal and ketamine tests. 5–HT\(_3\) antagonist was also injected intravenously, and the resultant analgesic effects were compared with the results of these pharmacological tests. Each test was carried out on a separate day: the morphine test was performed on the first day, the thiamylal test on the second day, the ketamine test on the third day, and the 5–HT\(_3\) antagonist injection on the fourth day.

**Pharmacological examinations and pain assessment**

For the pharmacological evaluations, saline was first injected 2 times at an interval of 5 min in order to check the placebo effect in each test. Subsequently, for the morphine test, 3 mg of morphine hydrochloride (i.v.) was given every 5 min until 18 mg had been administered, and an injection of naloxone was then added. For the thiamylal test, 50 mg of thiamylal sodium (i.v.) was given every 5 min until 250 mg had been administered. For the ketamine test, 5 mg of ketamine hydrochloride (i.v.) was given every 5 min until 25 mg had been administered. The pain level on a visual analog scale was recorded at each 5 min, and the pain reduction rate was plotted on a pharmacological evaluation sheet (Fig. 1). In each test, a reduction of over 40% in the pain level, as compared to that before drug administration, was judged to represent a sensitive case.

For the intravenous injection of 5–HT\(_3\) antagonist; 3 mg of granisetron in 100 ml of saline was continuously injected over a period of 30 min, and the changes in pain level of each patient were evaluated. Each patient was asked to describe the pain levels on a visual analog scale. The effects of 5–HT\(_3\) antagonist injection were classified into four categories: excellent, reduction of the pain level by 75% to 100%; good, reduction of the pain level by 50% to 75%; fair, reduction of the pain level by 25% to 50%; and poor, reduction of pain level by less than 25%. The pain level was evaluated immediately after completion of the injection and at 24 hours after the injection. In cases where there was any pain reduction immediately or at 24 hours after the injection of 5–HT\(_3\) antagonist, the pain level was evaluated continuously once a day for 1 week.

**RESULTS**

Immediately after the injection of 5–HT\(_3\) antagonist, 7 of the 14 cases reported various levels of pain reduction. Among these subjects, 3 cases (thalamic pain, 2 cases; post spinal cord injury, 1 case) showed long-lasting (over 24
hours) excellent pain reduction, and 4 cases (thalamic pain, 2 cases; Wallenberg syndrome, 2 cases) showed transient (less than 24 hours) good or fair pain reduction. The other 7 cases (thalamic pain, 6 cases; post spinal cord injury, 1 case) revealed no pain reduction at all. In the excellent pain reduction cases, analgesic effects continued for about 1 week after a single intra-

venous injection of 5-HT₃ antagonist (3 mg of granisetron).

Comparison with the results of the pharmacological tests demonstrated that the 3 cases of excellent pain reduction with 5-HT₃ antagonist were all resistant to the morphine, thiamylal and ketamine tests. The 4 cases of good or fair pain reduction with 5-HT₃ antagonist were all morphine-resistant, thiamylal- and ketamine-sensitive. The other 7 cases of poor pain reduction with 5-HT₃ antagonist displayed variable results for the pharmacological tests (Table 1).

**DISCUSSION**

It has been reported that deafferentation of the sensory pathways can cause hyperactivity of neurons within the sensory pathways above the level of deafferentation²⁻⁷⁻¹⁸⁻¹⁹⁻²¹⁻²³⁻³². Recent evidence has suggested that EAAs may play an important role in such hyperactivities, especially after sensory deafferentation²⁻⁴⁻²⁴⁻²⁷⁻²⁸. Among the EAA subreceptors, NMDA receptor has been found to be mainly involved, since application of competitive or non-competitive NMDA blocker has the effect of reducing the hyperactivities, both in the spinal cord and in the cortex²⁻¹¹⁻³⁶⁻⁴².

Ketamine is a non-competitive antagonist at the NMDA receptor site, and it has been sug-
gusted that analgesic effects are also mediated at this site, especially in intractable pain following sensory input deafferentation\(^7\).\(^{27}\). Barbiturates have been utilized as anesthetics and sedatives for many years. Barbiturate has also been found to be effective for patients with deafferentation pain\(^{20,44}\). The mechanisms of action of barbiturates are known to include membrane stabilization\(^{53}\), inhibition of excitatory neurotransmitter release\(^{5,6,28}\), suppression of calcium channels\(^{41}\), lowering of post-synaptic kainate- and quisqualate-receptor mediated responses to EAA\(^{58}\), and enhancement of GABA neurotransmission\(^{28,33,35}\). Morphine is usually employed for nociceptive pain, and is generally non-effective for deafferentation pain\(^{13,44}\). There are many cases where it is difficult to identify the precise cause of intractable pain, whether due to deafferentation or of nociceptive origin. In addition, some patients demonstrate deafferentation pain and nociceptive pain together, and psychogenic factors are usually also evident in such intractable pain patients. From this standpoint, we clinically applied pharmacological tests using ketamine, thiamylal and morphine to evaluate patients who had been neurologically and radiologically classified as having central deafferentation pain.

We have shown that pharmacological classification of central post-stroke pain\(^{20}\) by the morphine, thiamylal and ketamine tests can be useful for predicting the effects of chronic motor cortex stimulation therapy\(^{40}\). However, the fact that only 23 of 39 cases (59.0%) of thalamic and suprathalamic pain were sensitive to the thiamylal or ketamine test reflects the complex pharmacological background of central post-stroke pain\(^{45}\). It has been reported that 5-HT\(_3\) receptor antagonist reduces the immediate early gene (c-fos) expression following noxious stimulation\(^{41}\), modulates the release of EAA\(_S\) in synaptic transmission and suppresses hyperalgesia\(^{1,9,15,37}\). Further antidepressants are known to produce analgesia in central pain patients, and the 5-HT\(_3\) receptor is a site of action for the therapeutic use of antidepressants\(^{49}\), while 5-HT\(_3\) receptors have been shown to mediate various forms of pain such as the pain perception in peripheral, migraine, angina and irritable bowel syndrome\(^{12,14}\).

The present results indicated that the 3 cases of excellent pain relief produced by injection of 5-HT\(_3\) receptor antagonist were all resistant to the morphine, thiamylal and ketamine tests. Motor cortex stimulation is effective in cases with morphine-resistance and thiamylal - and ketamine-sensitivity\(^{43-45}\). However, motor cortex stimulation therapy is not effective in other cases\(^{48}\). Thus, intravenous injection of the 5-HT\(_3\) receptor antagonist could possibly serve to supplement the effects of motor cortex stimulation therapy in central pain\(^{46,39,40}\). Moreover, 5-HT\(_3\) receptor antagonist therapy should be examined in cases of thiamylal - and ketamine-resistance which are not considered to be good candidates for chronic motor cortex therapy. Long-term follow-up studies with repeated injection of 5-HT\(_3\) receptor antagonist for the treatment of central pain are currently being planned.

REFERENCES


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