Effect of Spinal Intrathecal Administration of Baclofen on Central Pain of Supraspinal Origin

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Abstract

Besides antispastic effect, baclofen, an agonist of gamma aminobutylic acid (GABA), has antinociceptive effect and it suppresses touch evoked allodynic responses in experimental animals. We investigated the effects of a bolus injection of baclofen into the lumbar spinal subarachnoid space in six patients with intractable poststroke central pain. Five of them reported substantial pain relief which persisted for 12–24 hours. In three patients, the pain relief started from the leg and then progressed to the arm. In the other two, pain relief appeared both in the upper and lower limbs at the same time. One patient showed relief of facial pain as well. Although the mechanism of the pain relief with spinal intrathecal baclofen is difficult to explain, the present results support the hypothesis that the spinal GABA and/or glycine neurons are involved in development of central pain in human. This pilot study indicates feasibility of further controlled study of intrathecal baclofen for relief of central pain of supraspinal origin.

Key words: central pain, stroke, baclofen, pain relief, GABA

INTRODUCTION

Poststroke central pain is one of the most difficult to manage in pain syndromes. Medical treatment is generally unsatisfactory and stereotactic surgery to the thalamus or the midbrain may be indicated. In a patient who was given spinal intrathecal baclofen for poststroke spasticity, we incidentally found that dysesthetic pain of the extremities was substantially relieved and the effect persisted for about 24 hours following the bolus administration. Besides antispastic
effect, baclofen, an agonist of gamma aminobutyric acid (GABA) shows antinociceptive effect in experimental animals, which is not reversed by naloxone. Furthermore its intrathecal administration reduces touch evoked agitation response in an animal model of allodynia. Recently a favorable clinical effect of intrathecal baclofen on central pain caused by spinal lesions is reported.

These backgrounds lead the authors to investigate the effect of intrathecal administration baclofen in patients with central pain of supraspinal origin. We report its promising results and discuss possible mechanisms of relief of central pain with spinal intrathecal administration of baclofen.

**MATERIALS AND METHODS**

Six patients with chronic poststroke central pain were investigated. Table 1 presents the patients' demography. All patients had been extensively treated with oral anticonvulsants and antidepressants without satisfactory pain relief. Case 1 had undergone both deep brain stimulation and motor cortex stimulation and Case 2 had deep brain stimulation, but the effect was modest and transient in both patients. Diagnosis of central pain was made by clinical examination and confirmed by insensitivity to intravenous morphine. Radiological findings with computed tomographic scan and magnetic resonance image were consistent with the neurological manifestations in all of them. No patient had been taking oral baclofen before the investigation. The patients were admitted to the neurosurgical ward for this investigation.

Under the approval of the Ethics Committee of Tokyo Women’s Medical College, a bolus of intrathecal baclofen was administered once a day through a lumbar puncture at the L3-4 level. The baclofen solution for intrathecal use was supplied by Chiba Geigy Corporation (Basel, Switzerland). The original solution (0.5 mg/ml) was diluted ten times with normal saline for intrathecal injection. The patients were asked to report their subjective pain hourly using a 10-grade score, i.e., 0: no pain, 10: pain of pretreatment level. The injection was repeated 3-5 times over a week. Normal saline was used only once to exclude placebo effect. The placebo was given between baclofen injections. Experimental nature of this investigation and its possible risk were well explained to the patients and the family and informed consent to the use of baclofen for central pain was obtained.

**CASE REPORTS**

**Case 1**: A 60-year-old man had been suffering severe constant dysesthetic pain in his left upper and lower limbs for five years. The cause was a small bleeding in the right posterior thalamus. He had undergone deep brain stimulation and motor cortex stimulation which showed little effect. Allodynia to light touch and anesthesia to pinprick were noted in the left side of his body. A bolus of intrathecal baclofen (50 μg) was given and he was then allowed to walk around as usual. After one hour he reported marked reduction (2/10) of the leg pain and after four hours the the arm pain was relieved (3/10). The allodynia was also relieved but anesthesia to pinprick was not affected. The pain relief lasted for about 24 hours. We repeated the same procedure twice and obtained the consistent response. Placebo showed no pain relief. He

<table>
<thead>
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<th>Case</th>
<th>Lesion</th>
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<th>Allodynia</th>
<th>Hypoesthesia</th>
<th>Pain relief</th>
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<td>1</td>
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<td>5</td>
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<td>+</td>
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<tr>
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<td>15</td>
<td>-</td>
<td>-</td>
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<td>5</td>
<td>putamen</td>
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<tr>
<td>6</td>
<td>thalamus</td>
<td>12</td>
<td>+</td>
<td>+</td>
<td>3/10</td>
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reported mild transient headache after the injection. After the trial period we gave oral baclofen (60 mg/day), which showed no effect.

**Case 2**: A 57-year-old woman had been suffering intractable pain following a small bleeding in the left pons for 20 years. Deep brain stimulation had been ineffective. Her pain was noted in the right arm and leg. It was constant pain of dysesthetic and burning nature. Anesthesia to pinprick was noted in the painful area but allodynia was not observed. A bolus of 50 μg of intrathecal baclofen resulted in good pain reduction (5/10). The pain relief started from the leg and then progressed to the upper arm in three hours. There was no objective change in sensation. The effect continued for about 12 hours. We administered baclofen five times and increased the dose of baclofen gradually up to 150 μg, which resulted in pain relief of longer duration. However, her gait became unsteady with this dose. Both placebo and oral baclofen were ineffective.

**Case 3**: A 57-year-old woman had been suffering severe burning pain on her right extremities developed two months after a small infarction in the left thalamus. She expressed her pain as constant, burning and unbearable. There was marked allodynia to light touch and cold stimuli. Pin-pricking showed hyperesthesia. At first we administered 50 μg of baclofen intrathecally, with no pain relief. The dose was gradually increased to 150 μg but she reported no pain relief. Transient urinary retention was observed. Oral baclofen was also ineffective.

**Case 4**: A 62-year-old man had been suffering central pain due to cerebral hemorrhage in the left corona radiate. His pain was in the distal parts of both right upper and lower extremities. There was no allodynia. Hypoesthesia to pinprick was noted in the right half of his body. A bolus of 50 μg of intrathecal baclofen resulted in marked pain reduction in an hour (1–2/10), which developed in upper and lower limbs almost at the same time. The effect continued longer in the arm than in the leg (Fig. 1). This response was confirmed three times with repeat intrathecal injections of the same dose. There was no sensory change with the injection.

**Case 5**: A 47-year-old woman had had disabling central pain for the past two years. The pain was in the right half of her body including in the face. This pain started two months follow-
ing a hypertensive hemorrhage in the left putamen. Although there was no allodynia, hyperesthesia to pinprick stimuli was noted in the right half of the body. About one hour after intrathecal administration of baclofen (50 μg), pain relief developed in the face first, and then in the arm and leg. She reported that the pain score became 4/10. We gave the injection five times and the pain relief was consistent. The pain relief was always associated with suppression of hyperesthesia. Placebo did not relieve the pain. Oral baclofen was also ineffective.

**Case 6**: A 71-year-old man had been suffering severe dysesthetic pain in the right leg for 12 years. His pain started two years after an episode of hypertensive hemorrhage in the left thalamus. Both allodynia and hyperesthesia was noted mainly in the distal part of the right leg. We repeated the baclofen injection six times for over ten days. The best pain score he reported pain relief to be 2/10 and the effect persisted for about 24 hours. There was no side effect.

**DISCUSSION**

Contrary to general belief that intervention to the spinal cord does not control central pain of supraspinal origin, spinal intrathecal baclofen showed substantial pain relief in the present study. Obviously the pain relief is not due to placebo effect, because the response to baclofen was always consistent in each individual and the placebo was ineffective. Although the patients was not informed of the possible time course of pain relief, it was highly reproducible. The pain score after the injection varied among the patients, but all the patients except one (case 3) reported that no other treatments had been so effective as intrathecal baclofen.

In clinical studies, intrathecal baclofen relieves muscle spasm pain, which is generally believed secondary to relief of spasticity. However, there are a few clinical reports concerning pain relief with intrathecal baclofen. Magora et al. successfully alleviated chronic low back pain with intrathecal baclofen. Because of complex nature of chronic low back pain, it is difficult to conclude whether the effect is primary or secondary. Herman et al. reported that central pain caused by spinal lesions is successfully controlled with lumbar intrathecal baclofen and obviously this is not the secondary effect. In their report, a patient even with a C3 lesion experienced relief of leg pain.

The mechanism of relief of pain of supraspinal origin by spinal intrathecal baclofen is difficult to explain. Because the pain relief started from the leg in the initial two patients, we initially considered that the effect was segmental on the spinal cord. This does not, however, account for the pain relief observed in case 4 and 5. Patients with central pain often protect themselves by covering their hands and feet with gloves and socks. Joint movements often evoke pain, while lying flat in bed reduces pain. These clinical observations indicate that low threshold mechanical stimuli and impulses of deep sensation play a role on activation of central pain. Intrathecal baclofen may modulate such impulses at the spinal cord level.

In experimental animals, spinal intrathecal baclofen suppresses noxious pain and this effect is not reversed with naloxone, which indicates that baclofen analgesia is not mediated through the endogenous opiate system. Proudfoot and Levy showed that the neural structures rostral to the medulla and caudal to the midbrain are necessary for the analgesic effect of baclofen. Baclofen acts on GABA receptor sites which are present in high concentration in the spinal dorsal horn. These findings suggest that there might be an ascending opiate-independent pain control system which is triggered by GABA at the spinal cord level. It has been reported that GABA is released by electrical
spinal cord stimulation\textsuperscript{\textcircled{19}}, which technique has been clinically used for pain relief. This further supports the importance of GABA in pain mechanism.

Distinction should be made clearly, however, between noxious pain and central pain. An animal model of central pain is difficult to produce, and the study is mainly focused on anomalous pain state such as allodynia\textsuperscript{19}, which is often observed in patients with central pain. In animal model of allodynia induced by prostaglandin \(F_2\alpha\), intrathecal baclofen suppresses touch evoked agitation response\textsuperscript{12}. However it is also reported that a selective antagonist to GABA\(_B\) receptor, phaclofen, does not affect the touch evoked response\textsuperscript{19}. The latter finding suggests that not GABA but other system is involved in relief of allodynia. Because baclofen acts not only on the GABA\(_B\) receptor but it also activates glycine containing inhibitory neurons which are also present in the spinal dorsal horn\textsuperscript{11}, the effect of spinal intrathecal baclofen on allodynia might be mediated by these glycine neurons. If this is true, allodynia might be relieved by administration of glycine, which is readily permeable to the blood brain barrier.

The findings in the present clinical investigation support the hypothesis of Yaksh and Yamamoto\textsuperscript{19} that loss of dorsal horn GABA- and glycine-containing interneurons in human leads to an allodynic or hyperesthetic state, although it should be studied if such loss of the interneurons in the spinal dorsal horn does occur in central pain syndrome of supraspinal origin. Because peripheral mechanism may become involved in pain originally induced centrally\textsuperscript{6,10}, it is not illogical to consider that such changes occur in the spinal cord of patients with post-stroke central pain.

This pilot study indicates that a controlled clinical trial of continuous beclofen infusion is feasible for patients with central pain of supraspinal origin. This will further broaden the insights into the mechanism of central pain.

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