Baclofen in the Treatment of Trigeminal Neuralgia: Double-Blind Study and Long-Term Follow-up

Gerhard H. Fromm, MD,* Christopher F. Terrence, MD,† and Amrik S. Chattha, MD*

A double-blind crossover study of the effects of baclofen was conducted on 10 patients with typical trigeminal neuralgia. Baclofen significantly decreased the number of painful paroxysms in 7 of the 10 patients. An open trial in another 50 patients with trigeminal neuralgia refractory to or unable to tolerate carbamazepine showed that 37 (74%) were relieved of their attacks by baclofen, either alone (12 patients) or in combination with previously ineffective doses of carbamazepine or phenytoin (25). On long-term follow-up of one to five years (mean, 3.0 years), 18 of the 60 patients (30%) continued pain free while receiving baclofen; 10 (17%) went into remission after 3 to 6 months; 13 (22%) became refractory to baclofen after 1 to 18 months; and 2 (3%) elected operation despite a good response to baclofen. The results indicate that baclofen is a useful drug in the treatment of trigeminal neuralgia.

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Carbamazepine has become the drug of choice in the treatment of trigeminal neuralgia (tic douloureux) [5, 17, 18, 25, 29]. It can have undesirable side effects, however, and sometimes is ineffective. There is thus a need for more effective and safe drugs for the treatment of this condition.

Our previous work has demonstrated that the response of mechanoreceptive neurons in the spinal trigeminal nucleus oralis of cats to stimulation of the maxillary nerve is a good predictor of the effectiveness of drugs in the treatment of trigeminal neuralgia [8–11, 13]. Carbamazepine and phenytoin depress the response of these neurons to electrical stimulation. In addition, they facilitate the segmental inhibition elicited by delivering a conditioning stimulus to the maxillary nerve 100 ms prior to the test stimulus. Carbamazepine has a more marked effect than phenytoin, consistent with the observation that carbamazepine is more effective than phenytoin in the treatment of trigeminal neuralgia [5, 17, 18, 25, 29]. Phenobarbital lacks this effect on neurons in the spinal trigeminal nucleus and fails to relieve trigeminal neuralgia.

Baclofen resembles carbamazepine and phenytoin in facilitating the segmental inhibition and depressing the response to maxillary nerve stimulation of mechanoreceptive neurons in the spinal trigeminal nucleus oralis [9, 13]. A pilot clinical trial showed that baclofen also relieves the paroxysms of tic douloureux [12, 13]. We therefore conducted a double-blind crossover trial in 10 patients with typical trigeminal neuralgia, as well as a further long-term open trial in 50 patients with trigeminal neuralgia refractory to or unable to tolerate carbamazepine. We also examined the effect of baclofen in 10 patients with atypical facial neuralgia, a syndrome that does not respond to carbamazepine or phenytoin [16].

Subjects and Methods

Ten patients with typical trigeminal neuralgia were enrolled in a single-crossover, double-blind study after giving informed consent. The diagnosis of trigeminal neuralgia was made according to the usual criteria [5, 17, 25]. The patients had recurring, brief paroxysms of sharp, stabbing, burning, or electric-shock-like pain in the distribution of one or more branches of the trigeminal nerve. The attacks were precipitated by talking, chewing, swallowing, or touching the affected side of the face. Five patients had attacks in the second division of the trigeminal nerve and 4 in the third division, and in 1 patient the attacks involved both the second and third divisions. Six patients were receiving no other medications for treatment of their trigeminal neuralgia during this study. Three patients who had become partially refractory to carbamazepine continued to receive their previous dosage of that drug. One patient who could not tolerate carbamazepine, and who had become partially refractory to

From the *Department of Neurology, University of Pittsburgh School of Medicine, and the †Neurology Service, Veterans Administration Medical Center, Pittsburgh, PA 15261.

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Address reprint requests to Dr Fromm, Department of Neurology, School of Medicine, University of Pittsburgh, Pittsburgh, PA 15261.

phenytoin, was continued on his previous regimen of phenytoin. The patients' ages, duration of illness, and concomitant medications are listed in Table 1.

At the initial visit we recorded the average daily frequency of attacks of trigeminal neuralgia in the previous week. A baseline period of observation was not used in view of the excruciating nature of the pain in trigeminal neuralgia and the consequent need to try to relieve the attacks as soon as possible. The patients were then given identical-appearing tablets containing either placebo or 10 mg of baclofen for one week (phase A). The initial dosage of baclofen was 10 mg three times a day and was increased by 10 mg per day every other day. At the end of phase A the patients were given the other tablet (placebo or baclofen) for one week (phase B). A washout phase was not inserted in view of the short half-life of baclofen [6] and the desire to avoid having the patients free of medication any longer than necessary. At the end of phase B the code was broken. Patients for whom baclofen had been effective continued to take it. The number of paroxysms of tic douloureux was recorded each day by the patient. The average number of paroxysms per day was calculated and evaluated statistically by Student t test.

Forty-two of the 50 patients with typical trigeminal neuralgia in the open study had become partially or completely refractory to the maximum tolerated dose of carbamazepine, with some patients receiving as much as 1,800 mg a day (mean, 900 mg a day; SD, 384 mg). The other 8 patients were unable to tolerate carbamazepine because of leukopenia (4 patients), rash (2), gastrointestinal upset (1), and excessive drowsiness and dizziness (1). Twenty-one of the 50 patients had undergone one or more surgical procedures for trigeminal neuralgia. There were 27 women and 23 men. The ages ranged from 19 to 84 years (mean, 62.4 years; SD, 12.6 years). They had been suffering from trigeminal neuralgia for 6 months to 21 years (mean, 7.9 years; SD, 5.9 years).

After informed consent had been obtained, these patients were also placed on a regimen of baclofen, 10 mg three times a day. The dosage was increased by 10 mg a day every other day to 60 to 80 mg a day in three or four divided doses by the end of the second week of treatment. The number of paroxysms of tic douloureux was recorded each day by the patients, and the changes in the number of attacks per day were analyzed statistically by Student t test and the chi-square test. Concomitant medication for trigeminal neuralgia (carbamazepine or phenytoin) was kept constant during the first two weeks of treatment with baclofen. If the frequency of attacks decreased after the addition of baclofen, we gradually eliminated the carbamazepine or phenytoin to ascertain if baclofen alone would control the trigeminal neuralgia. Those patients who responded to baclofen, either alone or in combination with previously ineffective doses of carbamazepine or phenytoin, were given the opportunity to continue to receive the drug.

Baclofen was also given to 10 patients with atypical facial neuralgia. The diagnosis of atypical facial neuralgia was made in accordance with the criteria enumerated by Selby [25]. These patients all gave a history of constant and intolerable pain, usually involving the whole side of the face, aggravated by emotional factors and lacking any definite trigger areas. All were women; 5 had undergone previous surgical procedures for their facial pain. Their ages ranged from 25 to 86 years (mean, 58.0 years; SD, 18.0 years). They had been suffering from atypical facial neuralgia for 1 to 30 years (mean, 10.6 years; SD, 10.3 years).

After obtaining informed consent, we placed these patients also on a regimen of baclofen, 10 mg three times a day, and gradually increased the dosage to 60 to 80 mg a day in three or four divided doses.

Blood cell counts, twelve-factor automated blood chemistry analysis, and urinalysis were performed periodically on all patients.

Results

Baclofen significantly reduced the frequency of the paroxysms of trigeminal neuralgia in 7 of the 10 patients in the double-blind study (Table 1). Patient 8 experienced a marked decrease in the frequency of her attacks while receiving baclofen, but the same lower frequency of attacks continued during the placebo phase and persisted after the end of the trial. It appears, therefore, that she had experienced a partial remission unrelated to the administration of baclofen. Two patients showed no significant change between the baseline, placebo, and baclofen phases. The average daily frequency of painful paroxysms for all 10 patients was significantly lower during the baclofen phase than during the placebo phase ($t = 2.75$; $p < 0.05$) or the control period ($t = 2.26$; $p < 0.05$). There was no difference between the average frequency of attacks during the placebo phase and that during the control period ($t = 1.06$; $p > 0.30$), in agreement with previous studies that showed a lack of placebo response in trigeminal neuralgia [16, 24].

The administration of 40 to 80 mg a day of baclofen also decreased the frequency and severity of the attacks of tic douloureux in 37 of the 50 patients (74%) in the open trial ($t = 3.53$; $p < 0.01$). By the end of the second week, 28 of these patients were free of pain. Another 9 patients had a greater than 50% reduction in the number of attacks, as well as a decrease in the duration and intensity of the paroxysms that remained (Table 2).

In the open study, twice as many patients responded to the combination of baclofen with previously ineffective doses of carbamazepine or phenytoin than to the administration of baclofen alone ($\chi^2 = 10.32$; $p < 0.01$).

We did not find any other determinants of baclofen response or failure. Baclofen was effective in 21 of 23 patients (91%) who had not undergone previous surgical treatment, and in 16 of 19 (84%) who had had previous operation ($\chi^2 = 1.47$; $p > 0.1$). Seven of 8 patients (88%) who were unable to tolerate carbamazepine were benefitted by baclofen, and 30 of 36 patients (83%) who had become refractory to carbamazepine responded to baclofen. The average duration of illness was 7.9 years (SD, 6.1) in the patients who responded to baclofen, and 8.8 years (SD, 6.0) in

Table 1. Effect of Baclofen and Placebo on Average Number of Paroxysms of Trigeminal Neuralgia per Day

Patient No.	Age (yr)	Duration of Illness	Concurrent Medications	Paroxysms/Day		
				Baseline	Phase A	Phase B
1	74	7 yr	PHT	4.0	4.3(P)	1.6(B)
2	67	2 yr	CBZ	6.0	4.0(P)	2.4(B)
3	78	7 yr	. . .	3.0	2.0(P)	3.0(B)
4	66	11 yr	CBZ	6.0	6.0(P)	6.0(B)
5	76	4 yr	CBZ	5.0	3.2(P)	0.5(B)
6	69	15 yr	. . .	15.0	15.0(P)	0(B)
7	66	3 yr	. . .	11.0	10.2(P)	2.7(B)
8	73	2 yr	. . .	50.0	4.0(B)	4.0(P)
9	62	1 mo	. . .	5.0	0.5(B)	5.0(P)
10	59	1 yr	. . .	6.0	1.5(B)	8.7(P)

PHT = phenytoin; P = placebo; B = baclofen; CBZ = carbamazepine.

the patients who did not improve. The average age of patients was 62.8 years (SD, 12.4) in those who responded to baclofen and 57.2 years (SD, 13.1) in those who did not.

Six of the 50 patients in the open study were unable to tolerate baclofen because of drowsiness or nausea and vomiting (see Table 2). This problem occurred more commonly with a combination of baclofen and carbamazepine than with the administration of baclofen alone. One patient in the double-blind study also developed drowsiness and had to stop taking baclofen plus carbamazepine two weeks after the end of the double-blind study. No major side effects or abnormal laboratory findings were observed in any patient.

Thirteen patients (2 from the double-blind study and 11 from the open trial) became refractory to baclofen after 1 to 18 months of treatment and had a decompression of the trigeminal nerve or injection of glycerol into the trigeminal cistern. Another 2 patients elected to have a decompression of the trigeminal nerve even though they had a good response to baclofen.

Eighteen patients have continued pain free or almost pain free while receiving baclofen for one to five years (mean, 3.0 years). Disease in 6 of these patients was controlled with a regimen of baclofen alone, whereas 8 patients required baclofen plus carbamazepine and 4 required baclofen plus phenytoin. Attempts to reduce the dosage of baclofen have resulted in recurrences of painful paroxysms, and resuming the previous dosage of baclofen has controlled the attacks. Ten patients remained pain free when the baclofen was gradually eliminated after 3 to 6 months of treatment. Five of these 10 patients have had a subsequent bout of trigeminal neuralgia, which again responded to baclofen.

Table 2. Effect of Baclofen in Open Trial

Medication	No. of Patients			
	Pain Free	>50% Pain Reduction	No Change	Drug Intolerance
Baclofen	9	3	6	1
Baclofen + carbamazepine	13	4	1	5
Baclofen + phenytoin	6	2	0	0
Total	28	9	7	6

Only 1 of the 10 patients with atypical facial neuralgia showed any response to baclofen, and even this woman improved only partially. One patient was unable to tolerate baclofen because of nausea and sleepiness. No major side effects or abnormal laboratory findings were observed in any of these patients.

Discussion

Baclofen (β-[*p*-chlorophenyl] gamma-aminobutyric acid; Lioresal) is an analog of the inhibitory neurotransmitter gamma aminobutyric acid (GABA). It does not appear to resemble GABA in its mechanism of action, however [1, 2, 4, 14, 19, 20]. Instead, baclofen has been shown to antagonize excitatory transmission, possibly by depressing the release of an excitatory neurotransmitter [3, 7, 15, 21], such as glutamate or aspartate [22, 23]. We have found that baclofen also depresses excitatory transmission in the spinal trigeminal nucleus [9, 13]. This effect appears to be caused by the *l*-isomer of baclofen [28]. The fact that baclofen resembles carbamazepine and phenytoin in its effect on the spinal trigeminal nucleus suggested that baclofen would be effective in the treatment of trigeminal neuralgia.

As predicted by our experimental data, baclofen does prevent or decrease the painful paroxysms of trigeminal neuralgia. Baclofen significantly decreased the number of attacks of trigeminal neuralgia in 7 of 10

patients in the double-blind study, confirming the results in our pilot clinical trial [12, 13]. A further open trial in patients with refractory trigeminal neuralgia showed that 37 of 50 patients (74%) were relieved of their attacks of tic douloureux by baclofen. Thirteen patients became refractory to baclofen after 1 to 18 months of treatment, and 2 elected to have surgical treatment despite a good response. Twenty-eight patients have continued pain free or almost pain free for up to five years.

Baclofen appears to have a synergistic action with carbamazepine and phenytoin. In the open trial, the addition of baclofen to previously ineffective regimens of carbamazepine or phenytoin controlled the paroxysms of tic douloureux in twice as many patients as the administration of baclofen alone. The average maintenance dose of baclofen was 50 to 60 mg a day for patients receiving baclofen alone, and 30 to 40 mg a day for those who were also taking carbamazepine or phenytoin. In the latter patients, the average dosage of carbamazepine was 600 mg a day, and the average dosage of phenytoin was 300 mg a day.

We noted no evidence of organ toxicity in any of our patients, but 7 patients (6 patients in the open trial and 1 in the double-blind trial) were unable to tolerate baclofen because of drowsiness or nausea and vomiting. These complications were more common when baclofen and carbamazepine were administered together than when baclofen was given alone (see Table 2). The manufacturer recommends that baclofen administration be started at a dosage of 5 mg three times a day, but we have found that many patients can tolerate a starting dosage of 10 mg three times a day. In view of the excruciating nature of trigeminal neuralgia, we usually start with 10 mg three times a day and increase the total daily dose by 10 mg every other day to attain pain relief as soon as possible. In elderly patients or those who are taking other drugs that can depress the central nervous system, however, it is necessary to give a lower initial dose and increase the dosage more gradually.

Baclofen should not be suddenly discontinued after long-term administration [27]. Hallucinations, seizures, or both can occur following abrupt dosage reduction or discontinuation after more than 2 months of therapy. These complications can be treated by reinstituting the previous dosage and then gradually reducing it by 5 to 10 mg per day at weekly intervals.

The lack of serious side effects with baclofen administration makes the drug desirable for the treatment of trigeminal neuralgia. Because we have treated mainly patients who had already become refractory to carbamazepine, we do not know how baclofen compares with carbamazepine in newly affected patients. Our laboratory findings suggest that baclofen would be much more effective than phenytoin and almost as effective as carbamazepine [9]. In agreement with these findings, the double-blind study showed baclofen to be effective in 7 of 10 patients, whereas carbamazepine is initially effective in almost all patients with typical trigeminal neuralgia [16, 24]. Long-term treatment with carbamazepine continues to be effective in 56% of patients with trigeminal neuralgia followed for up to sixteen years [26]. In our studies, long-term treatment with baclofen continued to be effective in 28 of 60 patients, with 20 of them requiring a combination of baclofen and previously ineffective doses of carbamazepine or phenytoin. The clinical data therefore suggest that baclofen is not as effective as carbamazepine in the treatment of tic douloureux. The synergistic effect with carbamazepine and phenytoin, however, as well as the fact that it appears to be a safer drug than carbamazepine, makes baclofen valuable.

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