

## Tegretol\* in the treatment of trigeminal neuralgia in thirty patients

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THE earliest known description of a painful affliction of the face which might be considered as trigeminal neuralgia, according to Stookey and Ransohoff,<sup>1</sup> is found in the writings of Aretaeus in the first century A.D., and the first full description by a physician of tic douloureux together with an account of his treatment is that by Locke. In 1776, Fothergill<sup>2</sup> reported 14 cases of facial pain that was typical trigeminal neuralgia.

The medical treatment of this disease has been disappointing since the entity was first described. In recent years, anticonvulsants have been advocated as therapy for trigeminal neuralgia.<sup>3-7</sup> Blom<sup>5</sup> contended that diphenylhydantoin, in addition to its anticonvulsant properties, affects synaptic transmission at levels caudal to the mesencephalon, and on this basis he has used the drug in the treatment of tic douloureux. The beneficial effects have generally been confirmed,<sup>8-13</sup> however results with this drug are variable. Administered in low doses, diphenylhydantoin often is ineffective, while the high dosages sometimes necessary to control symptoms are poorly tolerated.

Blom<sup>3</sup> and others<sup>6-8, 14-23</sup> have reported their experience with Tegretol in the treatment of trigeminal neuralgia. The results have been most promising in that the drug produced a consistent decrease in painful paroxysms and was tolerated well by most patients. Our report is an evaluation of our experience using Tegretol in the treatment of trigeminal neuralgia in 30 patients.

### Materials and methods

Tegretol was administered to a total of 36 patients, of whom 30 had trigeminal neuralgia. The other six patients had atypical facial pain and are excluded from this study. The diagnosis of trigeminal neuralgia was made on the basis of the following four criteria: (1) paroxysmal pain with intervals of relief, (2) pain confined to the area of the trigeminal nerve, (3) no objective evidence of motor or sensory deficit along the distribution of the trigeminal nerve, and (4) the presence of trigger areas. The presence

\* Carbamazepine, G-32883, supplied for this study through the courtesy of T. P. S. Watts, M.D., Geigy Pharmaceuticals, Ardsley, New York 10502.

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of trigger areas is not absolutely necessary, but it is a valuable adjunct in confirming the diagnosis.<sup>1</sup>

All 30 patients with trigeminal neuralgia were seen and examined by one or by both of us. Their progress was followed by means of personal interview or by questionnaire at monthly intervals. Our evaluation of Tegretol, in the manner of an uncontrolled study, began in January 1965. It was concluded in January 1968, in order to have a six-month follow-up period for those patients who had been treated within the last year.

The patients' ages ranged from 27 to 86 years, with most of the patients beyond the fifth decade of life. There were 20 women and 10 men, a sex ratio of 2:1. The incidence of right-sided involvement was slightly more than the left-sided, and in one patient there was bilateral third-division involvement. The second and third divisions of the trigeminal nerve were most often affected, in about equal frequencies. Sixteen patients reported unilateral pain in more than one division. The duration of illness ranged from two months to 30 years, the average time being about eight years. Of the 30 patients, 21 had been treated previously with diphenylhydantoin in dosages ranging between 100 mg and 200 mg t.i.d. Four patients had good relief of pain, although temporary; two patients obtained some relief; and 15 patients had no relief of pain.

Ten patients had previously undergone surgical neurolysis of the sensory root of the trigeminal nerve, with poor results. Two patients had undergone neurolysis twice within one year, and in one patient neurolysis was done twice within six months.

None of the patients included in our study had associated illness, such as multiple sclerosis or a cerebellar-pontine angle tumor either initially or later.

Tegretol was administered to all 30 patients in dosages ranging from 200 mg t.i.d. to 200 mg q.i.d. Eight patients were totally asymptomatic on 200 mg b.i.d., and in one patient, 100 mg t.i.d. would completely control the pain. The duration of treatment ranged from six months to three years. The following six initial laboratory determinations were made for each patient before administration of Tegretol: complete blood count and differential count, platelet count, urinalysis, serum glutamic oxaloacetic transaminase content, serum alkaline phosphatase content, sulfobromophthalein retention. Determinations of the values were repeated at monthly intervals after administration of the drug.

## Results

All 30 patients were pain-free within 24 hr after receiving Tegretol. Two patients had recurrence of pain, one within the first week and the other after 48 days of treatment. Twenty-eight patients had complete remission of pain with no recurrences. All of the patients were once again able to eat solid food, drink hot and cold liquids, and brush their teeth.

Twenty-eight patients received the drug for times ranging from six

months to three years with no major adverse effects. The two patients receiving the drug for less than six months were those who had recurrence of pain. Administration of the drug to the first patient was stopped after one week, and to the other after 48 days. Both of those patients had complete relief of pain after undergoing neurolysis. The course of Tegretol had to be stopped after one week in a third patient because of the development of an erythematous rash. The drug was withheld for 10 days and then administered, with no recurrence of the rash. Other adverse effects included lethargy, headache, nausea, and light-headedness.

Of the 28 patients who obtained complete relief of pain, from the drug, nine discontinued treatment in the belief that they had been cured. All nine experienced pain again within 24 hr, but the pain disappeared when they again took Tegretol.

As stated previously, the progress of each patient was followed at monthly intervals. Only one patient had abnormal results of laboratory tests. This patient showed an increase in the sulfobromophthalein retention from 1 percent to 10 percent in one month. The course of Tegretol was discontinued for two weeks, after which time the sulfobromophthalein retention was 2.1 percent. The course of Tegretol was restarted and all succeeding sulfobromophthalein retention values have been normal; a laboratory error possibly could account for the discrepancy.

### Comment

Tegretol is an iminostilbene. It is related to the imipramine group of drugs but not to the hydantoins. Its main pharmacologic property is a potent anticonvulsant action, especially with respect to strychnine-produced seizure activity, suggesting that the site of action is at the spinal cord level.<sup>23</sup> The drug has been found to inhibit polysynaptic reflexes such as the linguo-mandibular reflex of cats; the monosynaptic reflexes such as the patellar reflex are only slightly affected.<sup>24</sup> The manufacturer of Tegretol states that the medication inhibits neuromuscular transmission and that it has a significant but not pronounced sedative effect and only a slight analgesic effect.

Although serious blood dyscrasias such as aplastic anemia<sup>25, 26</sup> have been reported after its use, we have not seen any serious adverse effects. Minor effects such as mild headache, nausea, light-headedness, lethargy, and a skin rash occurred in seven patients. These untoward effects were transitory and the patients did not have to discontinue use of the drug, except for one patient in whom it produced a skin rash. The medication was withheld from that patient for 10 days, during which time the rash regressed and the course of therapy was restarted with no further difficulty.

### Mechanism of action of Tegretol

The pathogenesis of trigeminal neuralgia is not known. Many theories of etiology have been proposed, but there has been little or no agreement.

There seems to be a major division among the various authors into those who propose a peripheral cause<sup>27-29</sup> as opposed to those suggesting disturbance in the brain stem.<sup>7, 12, 30</sup>

Similarly, the mechanism of action of Tegretol and of diphenylhydantoin in the control of tic douloureux is not known. There has been significant evidence, though, to suggest that the effect of both drugs is central, seeming to support the concept of a central pathogenesis of the disorder.

As stated previously, the pronounced anticonvulsant effect of the drug, especially with regard to strychnine-produced seizure activity suggests that its locus of action is in the spinal cord. Hernández-Peón<sup>10</sup> implanted multipolar electrodes into the spinal trigeminal sensory nucleus and in the centrum medianum of the thalami of cats that were awake. Sensory transmission of facial pain impulses was studied immediately before and after the administration of Tegretol at doses of 10 mg per kilogram of body weight. He concluded that the drug produced a partial but significant depression of the trigeminal-evoked potentials recorded from the bulbar level. The reduction observed in the spinal V sensory nucleus never went beyond 50 percent of the initial amplitude; however, the diminution of the thalamic potentials recorded from the centrum medianum frequently reached from 80 to 90 percent of those in the prepharmacologic control period. Therefore, the partial blocking of trigeminal pain impulses at their entrance to the central nervous system could be the cause of a diminution of pain in cases of trigeminal neuralgia. The complete disappearance of that pain, as observed clinically, can better be explained by the action of the drug on thalamic neurons affected in sensory integration and associated with pain perception.

Fromm and Killian<sup>8</sup> recorded extracellularly, with glass microelectrodes placed in the rostral part of the spinal trigeminal nucleus of cats, the activity of single neurons. Diphenylhydantoin, given in threshold doses of 3 mg per kilogram of body weight, was found to cause a transient increase in latency and a decrease in repetitive firing in response to orthodromic stimulation, while the response to antidromic stimulation remained unchanged. The increase in latency was quite variable. By contrast, a threshold dose of Tegretol (4 mg per kilogram of body weight) had a much more prolonged and less variable effect with response to increase in latency and decrease in repetitive firing in response to orthodromic stimulation. Tegretol also had no effect on response to antidromic stimulation.

Results both of Hernández-Peón<sup>10</sup> and of Fromm and Killian<sup>8</sup> substantiate the view that Tegretol inhibits polysynaptic transmission. Tegretol has been shown to inhibit polysynaptic transmission in both the spinal trigeminal nucleus and in the centrum medianum of the thalamus. Although the drug produces a more pronounced inhibition on polysynaptic transmission in the centrum medianum, it cannot be stated with certainty that this area is its main locus of action.

## Summary

Tegretol was given in dosages of from 100 to 800 mg to 30 patients who had trigeminal neuralgia. All of the patients were completely free of pain within 24 hr. In two patients the pain recurred and was finally relieved after neurolysis. Nine patients who discontinued use of the drug, in the belief that they were cured, promptly had return of pain within 24 hr. Their pain was once again completely relieved after the course of the drug was restarted. No major complications were noted. Good results were obtained in 28 patients.

Both peripheral and central causes of trigeminal neuralgia have been postulated by other authors. The probable mechanism and locus of action of Tegretol are the inhibition of polysynaptic transmission in the spinal trigeminal nucleus and thalamus. On the basis of our experience with the drug we believe that it has a sound and important place in the medical treatment of trigeminal neuralgia.

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