STILBAMIDINE ISETHIONATE THERAPY OF
TIC DOULOUREUX*

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Classical tic douloureux is a disease of unknown origin characterized, among other attributes, by periods of spontaneous remission. Any proposed medical therapy must therefore be scrutinized with specific attention to this factor. Previous attempts at medical relief, such as that assigned to the intake of massive doses of ferrous carbonate\(^9,10\) or to the injection of \(B_12^{1,11}\) have failed to alter substantially the natural course of this disease. The inhalation of trichloroethylene offers at best the momentary relief obtained by a short-acting analgesic.\(^19\)

The severe pain of tic douloureux is relieved permanently only by complete section of the sensory root of the trigeminal nerve. The time-tested procedures of sensory root section by the temporal route of Spiller-Frazier\(^25\) or the cerebellar approach of Dandy\(^7\) carry virtually no mortality in experienced hands and scant morbidity. Following sensory root section there remain, however, permanent analgesia and anesthesia over the sensory domain of the fifth nerve, including the cornea. The procedure is scarcely applicable to cases of bilateral or alternating tic douloureux and can be applied to the younger age group of patients only with extreme reluctance. More peripherally placed nerve sections or alcohol injections are effective measures only for the temporary relief of the pain of tic douloureux.

More recently, decompression of the ganglion and sensory root of the fifth nerve has been proposed by Taarnhøj\(^27\) as a means of relieving tic pain and at the same time avoiding the subjective distress of sensory loss over the face and the potential danger of the loss of corneal sensitivity. The operation of ganglionectomy is a variation on this theme.\(^21,26\) Whether based upon sound premises or not, the procedure is not unlike the partial section once advocated by Frazier\(^12\) and by Dandy\(^8\) and the recurrence rate of these newer procedures has also been high.\(^17,28\)

In 1942, Napier and Sen Gupta\(^18\) described a late chronic neuropathy confined largely to the distribution of the fifth nerve which occurred as an unexpected sequel to the administration of 4:4'-diamidino-diphenyl-ethyline to patients with kala-azar. The observation was extended by Sen Gupta\(^22\) and others\(^2,5,6,20\) in patients treated for kala-azar, trypanosomiasis and blastomycosis.

The majority of such patients treated with therapeutic doses of stil-
barnadine developed, after a time period of 2 to 5 months after the termination of therapy, the rather rapid onset of varying degrees of hypesthesia and hypalgesia over the face and over the upper cervical sensory dermatomes as well. To the diminution of pain and touch responses in these areas was added, in a smaller percentage of cases, intense formication and burning paresthesias noticed about the central area of the face, involving particularly the nose and eyes. Such paresthesias tended to subside but slowly. When administered properly, stilbamidine is not otherwise toxic. Solutions of the drug become markedly toxic and progressively lose their therapeutic potency upon exposure to ultraviolet radiation.\textsuperscript{3,13,14,15} When such unstable solutions are used, irreversible hepatic and renal injury may occur.\textsuperscript{4,16}

At the suggestion of Dr. Frank Ford of Baltimore, Maryland, Smith and Miller\textsuperscript{23} treated a single elderly patient with stilbamidine in April, 1952, with a total dosage of 2.25 gm. given intravenously in 15 divided doses. Relief of pain was apparent on July 18 and this relief of pain has been maintained. The same authors subsequently reported the treatment of 16 patients with stilbamidine isethionate with excellent results in 15 and good results in 1, using a dosage schedule of 0.15 gm. per day for 14 days for a total dosage of 2.1 gm.\textsuperscript{24}

The present series of 41 patients were selected from a total roster of 71 patients treated in the Duke Hospital over the years 1953 and 1954 for the pain of classical tic douloureux.

The first patient was treated on April 27, 1953 and the last on August 29, 1954. The period of post-therapy observation has ranged therefore from 2 years to 9 months. Stilbamidine isethionate 0.15 gm. was freshly dissolved in 150 cc. of 5 per cent glucose and distilled water and given intravenously over a period of 1 hour. Transient shock-like reactions associated with a more rapid administration of this drug have been reported, but were not observed in this group. The course of therapy consisted of 10 daily injections for a total dosage of 1.5 gm. of the drug. In 2 patients a localized thrombophlebitis developed at the point of injection. There were no late complications. Pre-therapy observations consisted of the usual ones directed toward evaluation of a demonstrable organic cause for the tic pain and included the neurological examination, roentgenograms of the internal acoustic meatus, audiometer tests, vestibular tests and the determination of spinal fluid total protein. Electroencephalograms were done in all patients and psychological tests in a group of 8 patients. Liver and kidney function tests were carried out before and after drug therapy.

Fifteen of the patients were males and 26 females; their ages ranged from 32 to 86 years. Multiple sclerosis was present in 1 patient, marked by a progressive paraparesis, and arteriosclerotic vascular disease of the brain with hypertension was present in 13 patients. In 4 patients, the disease had manifested itself bilaterally. Six patients had had previous alcohol injections, 2 patients had had decompression of the sensory root of the fifth nerve and 2 patients had had incomplete sections of the sensory root.
RESULTS

Because of the continued high incidence of pain, 2 patients who had received stilbamidine therapy were treated by sensory root section 60 and 72 days following termination of therapy. A third patient, not in this roster, had received 2.10 gm. of the drug at another clinic. Posterior root section was also carried out in this patient because of intractable pain 30 days after termination of drug therapy. All 3 patients subsequently manifested the characteristic evidence of chemical neuropathy in the unaffected side of the face. Two patients had recurrences of pain following free intervals of 4 months and 10 months. The first of these was the patient with multiple sclerosis and he responded favorably to a second series of treatments. Because of severe pain, the second patient was treated by sensory root section. Both had failed to show any evidence of the characteristic neuropathy during these time periods. In this respect, it is of interest that in 6 patients it was deemed necessary to give an additional 1.5 gm. of the drug because of an apparent failure to respond to the initial series. One patient died in an accident after a pain-free interval of 4 months.

Including those patients who received two series of treatments, and excluding the one with recurrence who had reacted favorably to a second series, 36 patients have remained free of pain to this writing, the longest period of relief being 2 years and the shortest 9 months. The notorious tendency for the pain of tic douloureux to waver in intensity makes any real analysis of the early effect of this drug untenable. Some patients did have slow remissions of pain in the latter portion of their injection series. Most of them had acute episodes thereafter. Lasting relief of pain occurred in a time period ranging between 40 and 150 days and was usually followed rapidly by the onset of the characteristic neuropathy.

The neuropathy that follows stilbamidine isethionate therapy is well known. In these patients, it appeared as two general complaints, the one that of numbness or a leathery feeling that was well accepted as the price of relief of pain; the other appeared as a disagreeable gamut of paresthesias, noted by patients in terms of itching, burning, tingling and watering of the eyes. As far as such manifestations could be assessed, the second group of complaints was described by 16 patients, noted in passing as annoying by 18 patients, and considered as a severe handicap of therapy by 7 patients. Only 2 patients volunteered that these abnormal sensations were improving.

The typical and perhaps atypical sensations are described best in patients' words.

C-79697: "The left side of my face is a lot stiffer or feels a lot thicker than the right side. All my face and lips are partly numb. When I sit down for a while, I catch myself rubbing my temples off on both sides because it just feels like I could scratch the skin off."

D-38338: "I am suffering just about all I can stand. I almost went crazy last night and my eyes are going out if I can't get some relief some way."
They itch so bad that I can't keep my hands off and the more I rub the more they itch."

92043: "I have suffered no real pain since my treatments ended; however, my face feels very very funny. It feels as if you are about to have a tooth drawn and the dentist deadens the nerves. It feels as if something is crawling under my skin."

D-94060: "I am in a tingling condition. My eyelids are thick, cold feeling and itch. I have to rub them so hard to relieve the itching. My tongue feels thick and dead. I am numb down below my shoulders and in my chest. I can't stand firelight. My head is tender and can't comb my hair. My ears are dead. Feels like cold cloths are on my back. Feels as though cold water is running from my nose."

4297: "When I left the hospital, I still had slight attacks. They got less frequent as I stayed out in the sun, and my face got more of a numb feeling. After about six weeks the pain quit recurring, although, when I am out in the bright sun, six to eight hours now, the left side of my face has a numb feeling."

D-84111: "The touching pain left me the latter part of May, 1954. The fourth of July, I had a sudden numbness in my face, felt swollen and numb and very cold. Now I have a tingling all over my face. My eyes give me a lot of trouble itching, also my nose and mouth."

In general, numbness and paresthesias appeared first on the side of the origin of the tic pain, although this was not invariably true. Although the roster was biased, complaints appeared more common among females and were more accentuated by them in letters and during examination periods. Only 2 patients volunteered the information that the formication was receding and if such remissions were occurring in other patients, they appeared more related to an acceptance of a disagreeable issue. In general, the formication and paresthesias were reminiscent of those appearing more rarely in patients after sensory root sections. Scattered references to spontaneous resolution of the abnormal sensory changes are made by writers upon this subject. Collard and Hargreaves noted after a 2-year period of observation, "there was no difficulty in detecting old stilbamidine cases in the wards by their miserable expressions with blinking and tearful eyes."

In this series, fortunately, as already noted, but 7 patients suffered severe forms of formication and paresthesias. Three patients volunteered distress from muscle twitching about the eyes.

The neurological changes that appear in these patients follow a definite pattern but vary considerably in the intensity of sensory loss. They appear unaffected in degree by dosages between 1.5 and 3.0 gm. of the drug. Corneal sensitivity has remained acute in all but one patient and in this instance, there was but a slight decrease in the corneal reflex, well within the range of examining error. In all patients, previously demonstrated trigger zones have been abolished. In all patients with relief of pain, some form of diminution to light touch sensation (cotton wisp) could be found, usually more evident over the side of the face originally affected by the tic pain. The change in
appreciation of light touch varied from minimal involvement of the first and second branches of the fifth nerve on one side to bilateral anesthesia in 2 cases. Hyposthesia also could be discerned over the upper cervical dermatomes. Subjective loss of touch was noted by a few patients over the shoulders and trunk but no objective changes could be found. Diminution of the modality of superficial pain appreciation (pin prick) was present in a lesser number of patients with relief of pain, was never complete and tended to correlate at this lower level to the degree of change in light touch perception. No striking alteration in the modalities of heat and cold appreciation could be demonstrated in these patients.

Napier postulated originally that dissociation of sensory loss, which he thought present in his patients, placed the area of drug influence upon these afferent systems in the pons. In these patients, no clear-cut dissociation of sensory loss appeared obvious. Other observers have recorded all degrees of change in light touch and superficial pain perception. In 3 patients, who had received 1.5 gm. or more of stilbamidine, complete sensory root section was performed before the onset of the chemical neuropathy. After its appearance, formication and paresthesias occurred only in the normal side of the face and the denervated or opposite side of the face remained free of these sometimes bitter complaints. These clinical observations suggest a distal area of drug influence.

SUMMARY

Intravenous stilbamidine isethionate has controlled the pain of tic douloureux in 36 of 41 patients in this preliminary series of observations for a time period ranging between 2 years and 9 months. The relief of pain is associated with sensory changes over the trigeminal and upper cervical dermatomes that suggest a true chemical neuropathy. In a small percentage of cases, unpredictable formication and paresthesias occur over the face which tend to decrease the potential value of this therapeutic agent. The deferred action of the drug in patients with severe and unrelenting tic pain is a severe trial to both patient and physician and may necessitate provisional methods of control before the onset of the chemical neuropathy. Although this drug in its intravenous form may not be the definitive medical therapy for tic douloureux, it represents a very valuable adjunct to the care of this often complex pain syndrome. These observations would encourage a continuing study of the influence of stilbamidine in both its intravenous and oral forms upon the course of this disease.

REFERENCES


