CARBAMAZEPINE IN THE TREATMENT OF TRIGEMINAL NEURALGIA

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Carbamazepine (Tegretol^{R}) is by far the most effective drug for the treatment of trigeminal neuralgia. It is an iminostilbene derivative, chemically related to imipramine hydrochloride. Although it is primarily an anticonvulsant, Blom (1963) has shown that it also inhibits the polysynaptic nociceptive linguo-mandibular reflex in decerebrate cats.

Many clinical trials conducted in various parts of the world during the last ten years testify that carbamazepine controls the pain of trigeminal neuralgia in about 70% of cases. In our series of 70 patients, the attacks were completely abolished in 41%, controlled to the patients' satisfaction in 29%, and partially relieved in a further 4% of cases. Analysis of an additional 198 cases reported in the literature prior to 1965 supported our findings (Burke, Grant and Selby, 1965) and more recent publications (Bonduelle and Lormeau, 1966; Krayenbuhl, 1969; Heyck, 1970) provide further confirmation.

Carbamazepine usually relieves pain within 12 to 48 hours and cessation of treatment produces an equally rapid recurrence. The age of the patient, the duration of his trigeminal neuralgia, or the particular division of the trigeminal nerve involved have no influence on therapeutic success.

Long-term follow-up studies have shown, however, that this drug may lose its effect even in large and potentially toxic doses after two years of successful treatment in from 10 to 30% of patients (Heyck, 1970). The reasons why some patients do not respond to carbamazepine at all, and others become refractory to it after months or years, are unknown. The cause need not lie in the pathological mechanisms producing the pain, but may be found in the pharmacodynamics of the drug, such as an accelerated induction of enzymes which metabolise it. Recurrence of tic after previous treatment by alcohol injection or peripheral neurectomy does not appear to influence the emergence of this drug resistance.

Side effects include temporary drowsiness in about 40% of patients, giddiness, and ataxia in 10 to 15%, and skin rashes in less than 10% of cases. A few patients complain of gastro-intestinal upsets, but only two of our 70 patients abandoned the drug because of side effects (Burke and Selby, 1965). Leucopaenia and aplastic anaemia were reported in isolated cases, but can be prevented by appropriate clinical and haematological supervision.

Minor side effects can be minimised by gradual increases in dosage, beginning with 100 mg. twice daily. The average effective dose ranges from 600 to 800 mg. per day and only a few people will tolerate a daily dose of 1,200 mg. If carbamazepine in the maximum tolerated dose does not control pain within 72 hours, therapeutic failure must be conceded. A few patients respond better to a combination of carbamazepine and diphenylhydantoin than to either drug alone.

Carbamazepine is ineffective in post-herpetic dysaesthesiae and in atypical facial neuralgias (Selby, unpublished observations; Krayenbuhl, and the proportion of successful results is lower in symptomatic than in idiopathic trigeminal neuralgia.

This specific effect of carbamazepine on the pain of trigeminal and glosso-pharyngeal neuralgia must be in some way related to the pathogenesis of these diseases.

Trigeminal neuralgia is not a specific disease, but a symptom which can be produced by various pathological processes. A variety of small, benign, slow-growing tumours, as well as vascular malformations and even tiny "aberrant" arteries which compress, distort or encircle the trigeminal root can cause tic douloureux, which is in every respect – including long remissions – indistinguishable from the "idiopathic" form of the syndrome.

As the evidence derived from the often incomplete observations at operation or autopsy failed to reveal structural lesions in most cases, various anomalies of the bone and dura in the region of the petrous apex and Meckel's cave were considered responsible for compressing or stretching the ganglion and root.

The only intrinsic pathological process capable of causing paroxysms of trigeminal neuralgia identical to those of the "idiopathic" form is multiple sclerosis where the plagues of demyelination were always shown to involve fibres of the trigeminal root at their zone of entry into the pons (Olafson, Rushton and Sayre, 1966).

There is still some argument, particularly among electron microscopists, about the validity of ultrastructural changes seen in the trigeminal ganglia and roots from patients with tic douloureux. It may be accepted, however, that partial demyelination and loss of some axons are implicated in the pathogenetic mechanisms. Remyelination could then be considered as an event contributing to the natural remissions characteristic of trigeminal neuralgia. Dynamic forces, such as movements of the head and neck, changes in cerebro-spinal fluid pressure and arterial pulsation, may later cause sufficient minor trauma to the trigeminal root, already compromised by extrinsic compression and intrinsic degenerative changes, to precipitate a new series of pain paroxysms.

The peripheral structural lesions we have so far considered do not provide a sufficient explanation for many of the highly specific features of the pain of trigeminal neuralgia, including:

1. the brief, paroxysmal nature of this pain;
2. triggering of many attacks by minute tactile or proprioceptive stimuli;
3. occurrence of trigger spots located predominantly in the central (most anterior) parts of the face;
4. radiation of pain along linear tracks, usually confined to one or two divisions, but hardly ever diffusing over an entire dermatome;
5. absence of demonstrable neurological deficit.

The paroxysmal character of trigeminal and glosso-pharyngeal tic is unlike any other painful affliction of man, and the only common denominator for these neuralgias is the anatomical convergence of their exteroceptive afferents in the caudal part of the spinal tract and nucleus of the trigeminus.

Kugelberg and Lindblom (1959) have shown that a spatial and temporal summation of tactile impulses is usually necessary to trigger a proxysm of pain. During the refractory period which follows the attack, only stimulation of high intensity will elicit pain, which is then of shorter duration and less severity. The anticonvulsant drugs lidocine caine and hydnatoin raise the threshold for effective stimuli and shorten the duration of the attack by diminishing its tendency to self maintenance.

Physiological studies in animals have shown that stimulation of peripheral branches of the trigeminal nerve evokes both an immediate and a delayed response; the latter arises from cells in the caudal part of the spindal trigeminal nucleus and is conducted centrifugally (antidromically) into peripheral components of the trigeminal nerve. This trigeminal dorsal root reflex can be activated at the same threshold as touch fibres (King et al., 1956; et. al., Crue 1968). These observation indicate that at least part of the patho-physiological mechanism responsible for the paroxysmal pain of tic douloureux is centrally situated, probably in the spinal trigeminal nucleus.

The concept of a trigeminal dorsal root reflex, evoked by tactile stimuli and capable of generating a repetitive, self-exciting after-discharge provides a tentative explanation for the tactile triggers and for the brief, paroxysmal nature of the pain of trigeminal neuralgia. The anatomical substrate for the cutaneous trigger zones in the central part of the face may be the concentric onion-skin pattern of sensory representation in the spinal trigeminal nucleus, where the fibres from central regions of the face are projected to the most rostral part of the nucleus caudalis.

From the clinical and physiological data reviewed above, a working hypothesis of the pathophysiology of tic douloureux can be constructed. Mild mechanical trauma to the trigeminal root, or a plaque of demyelination in multiple sclerosis, results in a partial and differential loss of some large myelinated axons. This reduces the normal inhibitory influence of these fibres on the earliest relays in the nucleus caudalis, which is functionally homologous to the substantia gelatinosa of the spinal cord and may therefore be concerned in the gate control theory of pain proposed by Melzack and Wall (1965). The "gate" has been opened, and the secondary and internuncial neurone pools in the rostral parts of the spinal trigeminal nucleus are now in a deranged, excitatory state. This augments the self-exciting, repetitive discharge of the trigeminal dorsal root reflex, so that a barrage (summation) of afferent impulses is consciously appreciated as a pain paroxysm. The long latent period between the trigger stimulus and the onset of pain, and the subsequent refractory period are consistent with such a hypothesis. It does not explain, however, why a bout of pain terminates, or why during such a temporary remission stimula-

tion of the trigger zone fails to evoke another paroxysm. This is analogous to the enigma of the cession of an epileptic seizure while the irritative epileptogenic focus persists. The balance between excitation and inhibition is obviously very unstable; either exhaustion of the excitatory synaptic transmitter or accumulation of an inhibitory transmitter would provide an explanation. Remyelination and regeneration of a sufficient number of damaged fibres restores the normal inhibitory state and allows for a prolonged remission. A "subliminal" degree of disinhibition of the central neurone pool in the spinal nucleus, however, persists. Further mechanical trauma to the root can thus evoke the next attack more readily, and relapses become progressively more frequent, prolonged and severe.

The precise mechanism of action of carbamazepine in relieving the pain of trigeminal and glossopharyngeal neuralgia is not fully understood, but it is thought to suppress polysynaptic transmission. Physiological experiments in cats after electrical stimulation of the infra-orbital nerve and recording from the ipsilateral spinal trigeminal nucleus and from the centrum medianum of the contralateral thalamus have shown that the drug depresses discharges in the spinal nucleus and abolishes them almost completely in the thalamus (Hernandex-Peon, 1965).

The conscious appreciation of pain and its precise localisation must involve the connections between the trigeminal nuclei and the thalamus and somato-sensory cortex. The role of the various pre- and post-synaptic inhibitory and facilitatory feedback mechanisms on the complex physiology of pain is still obscure.

On present evidence, it would seem that more effective and lasting control of pain in trigeminal neuralgia has to await the discovery of more pharmacological agents which can either suppress synaptic excitation or enhance inhibition in the spinal trigeminal nucleus.

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