Treatment of post-herpetic neuralgia and acute herpetic pain with amitriptyline and perphenazine

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Summary

A fixed-ratio combination of amitriptyline and perphenazine was successful in treating 8 of 9 patients suffering from post-herpetic neuralgia. Side-effects were minimal. Summaries of 4 case histories are presented. In addition, 3 patients suffering from severe acute herpetic pain were successfully treated with the same drug combination.

Post-herpetic neuralgia (PHN) occurs in 10-15% of patients who have had herpes zoster. This complication can be severely incapacitating, depriving patients of sleep, food intake and normal daily activities; it may even drive them to suicide. The commonly used analgesics are notoriously unsuccessful in treating PHN. Drugs which have had some success are the so-called 'non-analgesic analgesics', which include the phenothiazines and tricyclic antidepressants. We used amitriptyline 2 mg and perphenazine 25 mg in a fixed-ratio combination (Triavil; MSD) (available in South Africa as Etrafon-D; Scherag) to treat 9 patients suffering from PHN.

Patients and results

Nine patients with PHN received a combination of perphenazine and amitriptyline for the treatment of pain. The criteria for diagnosis included: (i) pain of long duration (>4-8 weeks) following an attack of herpes zoster; (ii) a peculiar 'burning', 'shooting' and 'stabbing' quality to the pain; and (iii) pain occurring in the distribution of the herpetic lesion.

The patients were referred to the Clinical Pharmacology Unit, Strong Memorial Hospital, Rochester, New York, USA, by staff physicians, at the hospital. These patients had not obtained sufficient pain relief from conventional medical treatment, including aspirin, paracetamol, codeine and oxycodone.

Patients were begun on a standard dose of the combination, 2 tablets at night and 1 in the morning. Dosage and schedule were titrated according to the degree of analgesia and the occurrence of side-effects. All the patients were ambulant and were seen periodically during the treatment period.

In Table 1 the patient characteristics, response to treatment and side-effects are summarized. Relief of pain is the measure of achievement of the treatment goal. The overall result of treatment was classified as excellent, good, fair and poor, according to the patient's subjective assessment.

The mean age of the patients was 67 years (range 40 - 70 years); the male/female ratio was 3:2. Two patients had underlying diseases which predisposed them to herpes zoster. Eight of the patients either obtained complete pain relief or had mild residual pain which did not cause distress. One patient did not respond at all, and the treatment was discontinued after 2 weeks. The onset of pain relief occurred within 2 - 7 days in the patients who responded. Only mild adverse effects were noted in 6 of the 9 patients; these included dry mouth, dizziness and sedation. Six patients took the drug for 6 or more months. When it was withdrawn gradually, partial relapse occurred in only 1 patient.

In 2 patients who were forced to discontinue treatment after 1 and 6 months respectively because of concurrent illness relapse occurred, complete in one case and partial in the other.

Case histories of 4 of the patients, on whom complete long-term follow-up is available, are summarized below.

Case 1. A 64-year-old woman was in fairly good health but had a healed vesicular skin lesion along the T6-7 nerve-root distribution, typical of herpes zoster. She felt as if her nerves were being pulled and described her pain as 'like an electric shock'. She had been suffering from severe pain, especially at night, for about 2 months. She had received some relief from codeine and paracetamol in the usual therapeutic dosage. The perphenazine-amitriptyline combination was given in a standard dose. Significant relief was obtained within 2 days, and she was able to sleep well. Six months later the drug was withdrawn slowly. No relapse occurred. The patient complained only of a dry mouth and slight dizziness early in the treatment period.

Case 2. A 63-year-old psychiatrist, otherwise in good health, had been suffering from PHN in the right arm and palm for 9 months. Symptoms were incapacitating; she lost sleep, had crying spells, and was unable to work. She had tried many analgesics and minor tranquilizers — codeine, phenacetin, aspirin, oxycodone hydrochloride and diazepam — without obtaining relief. She was given the perphenazine-amitriptyline combination in a standard dose; significant relief occurred within 4 days, and after 2 weeks she was able to return to work. Breakthrough pain in the afternoon responded well to an additional noon dose. After 3 months the dose was reduced to 1 tablet a day, but her pain recurred. More gradual reduction over a 2-month period was successful without relapse occurring.

Case 3. A 76-year-old carpenter, in good general health, had had PHN of the scalp for 2½ years, which interfered with sleep and work. He obtained complete relief within 1 week of initiation of treatment with standard doses of the perphenazine-amitriptyline combination, on which he remained for over a year. He was unwilling to attempt reduction of the dosage and was last seen 14 months after starting the medication. The only side-effect has been a dry mouth.

Case 4. A 74-year-old woman generally in good health had PHN of T7-8 nerve-root distribution of 2 years' duration. Within 2 days of initiation of treatment with the perphenazine-
amitriptyline combination she had obtained a significant degree of relief. Maintenance treatment was continued for 6 months, during which time she complained of dizziness and dry mouth. Medication was then stopped because of an intercurrent illness and she had a partial relapse, with recurrence of a moderately severe burning sensation in the affected nerve-root distribution.

We have also used this drug combination successfully in 3 patients with acute herpetic pain, a 63-year-old woman with inflammatory breast cancer, a 15-year-old boy with a successfully treated malignant ependymoma and a 46-year-old man on immunosuppressant therapy after a renal transplant. In all 3 cases the pain was of a sharp, shooting quality, was severe enough to disturb sleep and did not respond to peripherally acting or centrally acting analgesics. On the perphenazine-amitriptyline combination pain lessened after the first dose and became tolerable within 2 days in all cases.

Discussion

The use of tricyclic antidepressants for treating PHN was first described by Woodforde et al.1 Dallessio2 used combinations of phenothiazines and tricyclic antidepressants in treating pain of various neurotic origins, labelling these drugs ‘non-analgesic analgesics’. Taub3 used this combination successfully in treating PHN. A combination of a phenothiazine and a tricyclic antidepressant is now commonly used for treating chronic intractable pain of neuritic origin.4 It is particularly effective in treating sharp, ‘lightning’ or burning pain such as phantom limb pain,5 PHN, pain caused by a postoperative scar or failed laminectomy, atypical facial pain6 and diabetic peripheral neuropathy.7 Of all these syndromes PHN seems to respond to the combination best.

PHN has also been treated with amantadine hydrochloride,5 electrical stimulation,9 chlorprothixene,10 corticosteroids,11 triamcinolone-procaine injection12 and clomipramine.13 Considering the usual failure of analgesic drugs in the treatment of PHN and the incapacitating effect of this complication on patients, our results (89% success) are encouraging. The prompt onset of pain relief was unexpected, since the tricyclic antidepressants take longer to be effective in treating depression.

The pharmacological rationale for using a tricyclic antidepressant in combination with a phenothiazine is not clear. Amines such as noradrenaline, serotonin and dopamine may be neurochemical modulators of pain. The tricyclic antidepressants block the amine pump (E2-receptors) in the presynaptic nerve ending, which is claimed to be the most important mechanism for terminating adrenergic sympathetic transmission.14 Some also inhibit the re-uptake of serotonin. The phenothiazines, on the other hand, block dopamine receptors. Some, such as methotrimeprazine, have intrinsic analgesic effects; others also potentiate analgesia produced by standard analgesic drugs. There may therefore be some alteration in the amine content or availability in specific brain regions where pain modulation occurs. The phenothiazines most commonly used for treating PHN are members of the piperazine subclass such as perphenazine. Members of this group have the highest milligram potency and cause less sedation and fewer extrapyramidal effects than the aliphatic group (e.g. chlorpromazine), but they do produce more extrapyramidal reactions. We did not encounter any extrapyramidal symptoms in our patients.

We found it necessary to keep the patients on the optimal dosage for 2 - 3 months, gradually withdrawing the drug over the next 3 - 6 months. Whenever pain recurred during this period we increased the dose slightly and then tapered it off more gradually. We do not consider the side-effects encountered to be serious, particularly in view of the potential benefits. For many patients the side-effects appeared to be a welcome alternative to the pain they had suffered. Our results using the combination of amitriptyline and perphenazine in acute herpetic pain with the same qualities as PHN were gratifying.

We conclude that the use of a fixed-ratio combination of perphenazine and amitriptyline has an important place in the treatment of PHN and at least some severe cases of acute herpetic pain.

REFERENCES