Cimetidine in the Treatment of Herpes Zoster

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Herpes zoster can be a distressing event in the elderly, causing confusion and distress in the acute phase and incapacitating post-herpetic neuralgia in a high percentage of cases[1].

The preliminary observations of Van der Spuy *et al.*[2] suggested that cimetidine may have a beneficial effect in several herpes virus infections, including herpes zoster. In an uncontrolled open assessment of one patient, cimetidine relieved the pain and shortened the course of herpes zoster. A subsequent uncontrolled trial of cimetidine in 21 patients with herpes zoster produced encouraging results in all but three patients.

More recently, Mavligit and Talpaz[3] reported that cimetidine 300 mg q.d.s. for seven days produced a rapid improvement in the pain and pruritus of herpes zoster in four cancer patients whose immune systems were profoundly suppressed.

Herpes zoster is thought to be associated with a state of depressed cellular immune function[4]. It is theoretically possible for H_2 receptor antagonists such as cimetidine to modify cell-mediated immune responses since thymus dependent T-lymphocytes have been shown to possess H_2 receptors[5–7]. In addition to a possible direct anti-viral effect[2], cimetidine may augment the immune defences of the body which produce early control of the herpes zoster virus.

The present trial, more extensive than that of Van der Spuy *et al.*[2], was designed to establish whether cimetidine was effective in the treatment of herpes zoster. Since herpes zoster has a variable and unpredictable natural history, it was necessary for this study to be placebo controlled.

Patients

Sixty-three patients aged 27 to 92 years (mean 66.4 years) with herpes zoster, suitable to be treated as out-patients, entered the study. Of these patients 41 were female (mean age 67 years) and 22 were male (mean age 65 years). Local general practitioners and other hospitals in the Bolton area co-operated in recruiting suitable patients. Patients with herpes who had involvement of the ophthalmic division of the trigeminal nerve were not included in the study.

Patients with herpetic infections other than herpes zoster and those who had received cimetidine treatment for other diseases within the past month were excluded from the study, as were patients receiving specific anti-herpetic medications; calamine lotions (for local relief of discomfort) and analgesics such as aspirin and paracetamol were permitted. Pregnant or lactating patients, patients with severe renal impairment and those receiving oral anticoagulant therapy were also excluded from entry.

Methods

The study was conducted in accordance with the Declaration of Helsinki. The nature of the trial was fully explained to all patients before entry and their consent obtained. All patients were informed of their right to withdraw from the study at any time. The permission of the hospital ethical committee was obtained and the patients' general practitioners were informed by the investigator.

The diagnosis of herpes zoster was made entirely on clinical grounds. The infection was identified by the presence of erythema and/or vesicles corresponding to the unilateral distribution of a sensory nerve. In most patients, pain was experienced at the affected area. In those patients in whom herpes zoster was diagnosed on the basis of erythema and pain, vesicles subsequently developed within 48 hours of entry to the trial.

Patients were seen at the earliest possible stage of infection. At the initial visit the distribution, site and stage of the lesions and presence or absence of pain were recorded. Any medications for concomitant disease were noted. Patients were then randomly allocated in a double-blind manner to treatment with either cimetidine 200 mg t.i.d. and 400 mg nocte, or matching placebo tablets. Treatment continued for 28 days.

Patients were reviewed daily for the first two days and again at one and four weeks. At each review the distribution, site and stage of the lesions and presence or absence of pain were recorded as for the initial visit. The presence and distribution of any new lesions were also recorded. At the two and four week visits the presence or absence of complications was noted. At three months and six months, patients were assessed for development of com-

plications including post-herpetic neuralgia (defined as pain which outlasts the lesions by more than one month).

During the treatment period patients were requested to complete diary cards daily to record the presence or absence of pain and its duration.

Statistical Analysis

Demographic parameters (the number of days lesions and pain were present before the start of the trial) were compared between the two treatment groups using the Wilcoxon two sample rank-sum test. A chi-squared test was used to compare the incidence of healing of lesions and pain after one month of treatment. Two-tailed tests were used throughout.

Results

Forty-nine patients completed the one month's treatment period as planned; 24 of these patients (18 women, 6 men; mean age 65 years) received cimetidine and 25 patients (13 women, 12 men; mean age 63 years) received placebo treatment. Fourteen of the 63 patients who entered the study were excluded or withdrawn before completion of the treatment period. The reasons for patient withdrawal/exclusion were as follows: default (5 patients); ophthalmic herpes (5 patients); death which was unrelated to treatment (2 patients); inadequate records (2 patients).

The two treatment groups were comparable with respect to the duration of signs of infection (lesions and pain) before the start of the trial. The median number of days vesicles were present in the cimetidine group was three (1–7), compared to two (range 0.5–6) in the placebo group. The median number of days of pain before the trial in the cimetidine group was three (range 0.5–14), compared to five (range 0–12) in the placebo group. The stage of the lesions in the two treatment groups was roughly comparable at the start of the trial.

Efficacy of the treatments was compared by examining the incidence of healing of the vesicles and the incidence of pain at the end of the one month treatment period (Table 1).

Table 1. Efficacy of treatments compared by examining incidence of healing of vesicles and incidence of pain after 28 days' treatment. H = 100% healed. N = not healed. P = present. A = absent.

	Cimetidine	Placebo
Healing of lesions at Day 14	6H, 18N	6H, 19N
Day 28	18H, 6N	24H, 1N
Pain at Day 28	6A, 18P	15A, 10P
Incidence of post-herpetic neuralgia at		
Month 3	12A, 11P	17A, 8P
Month 6	16A, 9P	20A, 5P

No statistically significant difference between the effects of the two treatments on healing of vesicles was seen. Eighteen out of 24 (67 per cent) healed in the cimetidine group compared with 24 out of 25 (96 per cent) in the placebo group ($0.05 < P < 0.1$, in favour of placebo). A statistically significant ($P < 0.05$) difference between the incidence of pain after one month of treatment was found. A higher proportion of patients in the placebo group (15 out of 25, or 60 per cent) experienced no pain, compared with the cimetidine group (6 out of 24, or 25 per cent).

There was no statistically significant difference between the two treatment groups with respect to the incidence of post-herpetic neuralgia at 3 months and 6 months (Table 1). No clinically significant untoward events related to cimetidine therapy were reported by any patient.

Discussion

There is no evidence from the study data that cimetidine relieves the pain or accelerates the rate of healing of lesions in herpes zoster. This conclusion does not support the clinical observations of Van der Spuy *et al.*[2] and Hayne and Mercer[8]. It is possible, though unlikely, that the dosage of cimetidine (1.0 g/day) used in the present study was not sufficient. Van der Spuy *et al.*[2] reported that relief of pain was the main criterion for judging the success of treatment of herpes zoster with cimetidine (1.6 g/day for the first two days, followed by 1.0 g/day for five days). In our study only the incidence of pain at the beginning and end of treatment was examined statistically. It was not possible to compare the effects of cimetidine and placebo on the relief of pain throughout the period of treatment as only some of the patients completed the diary cards with a record of pain they had experienced.

Hayne and Mercer[8] claimed that cimetidine (1.8 g/day for $8\frac{1}{2}$ days) accelerated the rate of healing of lesions of one patient with herpes zoster, on the basis that the duration of the disease can be predicted from the length of time it takes for all the vesicles to erupt[9]. From our data it was impossible to determine the precise time taken for all the vesicles to erupt and therefore to predict the duration of the active phase for each patient. Neither could any effect of treatment on the duration of the active phase be assessed, since the time course of healing of the vesicles after they had crusted was recorded only at days 7, 14 and 28 of treatment and was not monitored between these visits. However, as there was no statistically significant difference between the two treatments given with regard to the number of patients with lesions which were healed, it is unlikely that cimetidine affected the rate of healing of the vesicles.

The discouraging outcome of this large controlled trial, unlike that of previous, smaller, uncontrolled trials[2,3,8], suggests that further trials of cimetidine in herpes zoster would not be worthwhile.

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Harveian Memorials

It must have been a long day's pilgrimage to rural Essex on St Luke's Day, 1883. On that day at Hempstead church the remains of William Harvey, lapt in lead, were transferred to a new sarcophagus inscribed 'The remains of William Harvey, discoverer of the circulation of the blood, were reverentially placed in this sarcophagus by the Royal College of Physicians of London in the year 1883'. Preceded by the vicar of Hempstead, the Rev. Mr Eustace, and his curate, the sarcophagus was borne into the church by Fellows of the College, followed by four members of the Harvey family, the President of the College, Sir William Jenner, robed and carrying the caduceus, and then the College officers, gowned, with Fellows of the College bringing up the rear. The procession went into the Harvey chapel to lay the sarcophagus on its final resting place. After a short service, with hymns sung by the village choir, the President placed in the sarcophagus a bound copy of Harvey's works sealed in a metal box and a scroll describing the event and lauding Harvey as a munificent benefactor of the College.

The College had been concerned with the state of Harvey's remains since the first report in 1847 that the lead coffin was damaged. In 1859 a deputation from the College found the coffin was half full of water and further damage was reported in 1878. On 28th January 1882 the tower of Hempstead church and part of the nave collapsed, causing further damage. The College forthwith appointed a committee to consider the matter. They rejected a suggestion that Harvey's remains should be reinterred in Westminster Abbey to join such distinguished Fellows as Thomas Willis, Richard Mead and Thomas Young, and suggested the ordering of an appropriate sarcophagus which was purchased for £155. As a matter of history the church at Hempstead was not fully repaired until 1961, the work being aided by substantial sums from the William Harvey Memorial Fund and the Harveian Society of London. The choice of St Luke's Day for the 1883 reinterment was made because for many years that had been the day for the Harveian Oration. Indeed the July Comitia in 1884 resolved that the Oration should henceforth be given on St Luke's Day.

The Harveian Oration and Dinner was, of course, instituted by Harvey. Old, infirm, rich and childless, he considered how he could benefit the College. He was the 'anonymous' donor of a library building and, after its ceremonial opening in 1656, the College elected Harvey as President. This offer was received and declined with perfect dignity and with the recommendation that Dr Prujean should continue as President; a recommendation speedily accepted. By an indenture of 21st June 1656, Harvey transferred his patrimonial estate at Burmarsh, Kent, to the College. From the proceeds of this he asked that the College, 'to maintain friendship', should at 'every meeting once a month' prepare a 'small collation' and that 'once every year' there should be 'a general feast for all the Fellows'. The idea of the feast comes before the Oration, as he laid down that 'on the day when such a feast be kept . . . some one person of the said College shall make an oration in Latin publicly'. He exhorted the orator to commemorate the College's benefactors and encourage others to follow their example and he also exhorted 'Fellows and Members to search and study out the secrets of nature by way of experiment'.

The first Harveian Oration was given in July 1656, only a month after Harvey's gift, by Dr Edward Emily, a physician to St Thomas's Hospital. This proved a disaster. In Comitia of 28th July 1656, Dr Emily 'was accused of having declaimed more bitterly than was proper against military matters, and also of disparaging the present rule of the Commonwealth'. Dr Emily affirmed that 'he had said nothing in a bad spirit'. However, Comitia decided that in future no such oration should be given in the College unless the President and Censors had read and approved the text one month before the oration was due to be given.

The College was anxious to remain on good terms with Cromwell's major-generals so the decision to let Emily go without rebuke but to introduce censorship of future orations must have been thought sufficient to ward off official displeasure. What remains puzzling is the choice of Dr Emily as the first Harveian Orator. At the start of the Civil War Emily had hinted in a letter that he sided with the Parliamentarians, so his oration suggests that he had become disillusioned by that cause. Emily's career showed no distinction and any promise of achievement went unfulfilled, as he died in November 1657.