Cimetidine in the Treatment of Herpesvirus Infections

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SUMMARY

In August 1977 a patient developed herpes zoster just before she commenced a course of cimetidine (Tagamet; Smith, Kline & French) for a chronic gastric ulcer. She experienced both rapid relief of the ulcer symptoms and, rather unexpectedly, dramatic relief of the herpetic pain and rapid disappearance of the eruption. On the basis of this observation cimetidine was prescribed to 21 patients with herpes zoster. The results continued to be encouraging in all but 3 patients. The trial was therefore extended to other herpesvirus infections. In all but 1 of 7 patients with herpes labialis the blisters were aborted, and in 1 patient with herpes keratitis the result was also encouraging, the attacks being markedly shortened in duration and reduced in frequency. The results of this preliminary trial warrant a systematic scientific inquiry into the potential role of cimetidine in the treatment of herpesvirus infection, as well as a study of the mechanisms involved.

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Cimetidine (Tagamet; Smith, Kline & French) is a potent H_2-receptor antagonist known for its efficient inhibition of both basal and stimulated gastric acid secretion by the parietal cells of the stomach. It has proved to be a very useful drug in the treatment of peptic ulceration. As the result of an observation by one of us (D.W.L.) that a patient with florid herpes zoster experienced rapid relief of pain and disappearance of the eruption within days of commencement of cimetidine therapy for gastric ulceration, cimetidine was subjected to further trial in patients with herpes zoster. The trial was extended to other herpesvirus infections. Experience gained with cimetidine in the treatment of 21 patients with herpes zoster, 7 with herpes febrilis, and 1 with herpes keratitis is reported here.

PATIENTS AND METHODS

The diagnosis of herpesvirus infections in this series was made entirely on clinical grounds. No supportive virus studies or antibody examinations were carried out. Cimetidine was prescribed to all patients on the day of referral. The dosage schedule was derived empirically from the standard regimen recommended for the treatment of peptic ulcer. For the first 2 days of treatment a daily dose of 1 600 mg was given, i.e. 400 mg with meals 3 times during the day and at bedtime. This was followed by 1 000 mg/d for 5 days (200 mg with meals and 400 mg at bedtime). The treatment period was limited to 1 week, largely because of the need to limit the cost of treatment. The above schedule was found satisfactory in most cases. The treatment period was extended to 1 month when there was a special need for the eradication of a very troublesome recurrent infection, for example in patient 1 in the herpes labialis group and in the patient with herpes keratitis. In patients with fever blisters a 2-day course of 1 600 mg/d appeared sufficient to abort the infection.

In patients with herpes zoster particular note was taken of the intensity of the pain and neuralgia, their analgesic requirements, the appearance of the rash, and the effect of cimetidine on these parameters.

RESULTS

None of the patients treated with cimetidine experienced any side-effects attributable to the drug. The results obtained are described separately for each infection category.

Herpes Zoster

Relief of pain formed the main criterion for success in the herpes zoster group. Fading of the erythema and early vesiculation were also considered significant, but when pustule formation and ulceration had occurred dramatic healing was not expected.

The clinical course of the patients treated is summarized in Table I. It will be noted that, on the basis outlined above, the results of cimetidine therapy in 21 patients with herpes zoster could be described as remarkable in 6, good in 12, and poor in 3. Some illustrative cases will be described more fully.

Case 1. A 51-year-old woman gave a history of disseminated lupus erythematosus of 20 years' duration, for which she was taking steroid maintenance therapy. She had also experienced symptoms attributable to an ulcer for a year, and a gastric ulcer was diagnosed on endoscopic examination. She consulted her physician (D.W.L.) in August 1977 because of a recurrence of the ulcer symptoms and a severe attack of herpes zoster of 3 days' duration at the level of T6 on the left side. The skin eruption was florid and angry looking, and the accompanying pain had become agonizing. Steroid therapy was continued, paracetamol was prescribed for the herpetic pain, and oral cimetidine 1 000 mg/d was commenced. Not only did her ulcer symptoms subside rapidly, but a remarkably rapid remission in the herpes zoster followed. The pain subsided completely within 3 days and the vesicular rash

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TABLE I. SUMMARY OF RESPONSE OF PATIENTS WITH HERPES ZOSTER TO TREATMENT WITH CIMETIDINE

Case	Age	Sex	Associated condition	Duration (days) before treatment		Distribution	Response to cimetidine		Grade
				Pain	Rash		Pain	Rash	
1	51	F	Disseminated lupus erythematosus, gastric ulcer	3	3	T6 (r)	Subsided completely within 3 days	Vesicles dry within 5 days	++
2	76	M	Jaundice (hepatitis)	?	1	T10 (l)	Patient confused, never a feature	Started drying after 2 days, dry within 1 week	+
3	44	F	Stage II breast cancer	4	4	C5 (r)	Eased after 3 days, little pain after 7 days, no residual neuralgia	Started drying after 3 days, dry after 7 days	+
4	71	M	Bronchitis, hypertension	7	1	T10 (l)	Eased after 1 day, only 2 minor bouts of neuralgia since	Obviously drying after 2 days, dry after 7	+
5	52	F	Stage II breast cancer	4	1	T7 (r)	Ceased for 3 days, then recurred without further response	New blisters formed after 3 days	0
6	45	F	None	2	2	T6 (l)	Mild, faded slowly over a period of 12 days	Blisters started drying almost the same day	++
7	59	M	Chronic renal failure, on peritoneal dialysis	0	1	T2 (r)	Pain started subsiding the day after treatment	Blisters confluent and pustular after 5 days, started clearing after 7 days, dry after 2 weeks	+
8	80	F	None	4	0	T7 (r)	Relief after 1 day, severe neuralgia started after 14 days and lasted 2 months	Blisters broke down, healed over a period of 1 month	0
9	67	F	None	2	14	T11 (l)	Considerable relief after 1 day, subsided after 10 days	Dry after 7 days	+
10	60	M	None	8	2	C4,5 (l)	Became worse as pustules formed, improved rapidly as pustules responded to co-trimoxazole	Became pustular after 2 days with scattered pustules on right side of body; rapid response to co-trimoxazole	+
11	79	F	None	10	7	T3 (r)	Definite relief within 3 days, odd twinge after 7 days	Gradual fading following commencement of treatment	+
12	67	F	Recurrent myocardial infarctions	0	4	C3,4 (r)	None	Gradual fading from commencement of therapy	+
13	38	F	Stage IV breast cancer with involvement of bone and liver	2	1	T9 (l)	No response — became worse while on cimetidine; immediate relief following two infusions of zoster-immune plasma	No apparent effect; vesicles became confluent, ruptured and healed over a period of 3 weeks	0
14	78	F	None	16	18	5th (r) supra-orbital	Almost total relief after 1 day	Vesicles dried and faded over a period of 12 days	+
15	50	M	None	4	2	T1 (l)	Partial relief after 2 days, subsided completely after 2 weeks	Blisters became purulent after 4 days, healed within 3½ weeks	+
16	62	F	None	12	2	L4 (l)	Considerable relief after 1 day, occasional twinge felt for 10 days	Drying and fading, well advanced after 2 days	++
17	70	M	None	17	10	L5 (r)	Considerable relief after 4 days, occasional ache since	Blisters dry after 4 days	+

TABLE I. SUMMARY OF RESPONSE OF PATIENTS WITH HERPES ZOSTER TO TREATMENT WITH CIMETIDINE (continued)

Case	Age	Sex	Associated condition	Duration (days) before treatment: Pain	Duration (days) before treatment: Rash	Distribution	Response to cimetidine: Pain	Response to cimetidine: Rash	Grade
18	63	F	None	1	5	T7 (r)	Became agonizing after 3 days on metronidazole, almost pain-free after 2 days on cimetidine, occasional twinge for 7 days	New blisters appeared while on metronidazole; drying and fading commenced 1 day after commencement of cimetidine therapy	++
19	13	M	None	4	2	T3 (l)	Partial relief after 3 days on cimetidine 800 mg, complete relief after 1 day on 1 600 mg	Some drying of lesions after 3 days on 800 mg, complete drying 1 day after increasing dosage to 1 600 mg	++
20	48	F	Advanced breast cancer with involvement of bone and pleura	4	0	T5 (r)	Pain disappeared within 2 days	Never developed fully, faded rapidly	++
21	48	M	None	5	4	T9 (r)	Remained severe while on griseofulvin; diminished rapidly within 3 days of commencing cimetidine	Pustular formation continued while on griseofulvin; cimetidine obviously did not affect the process of ulceration and healing	+

++ = remarkably rapid relief of pain, or prompt drying of the vesicles and fading of the rash.
+ = fairly definite relief of pain, or acceleration in the drying of vesicles and fading of the rash.
0 = no obvious effect on pain relief or disappearance of the rash.

dried completely and began fading within 3 days. The patient subsequently recalled that she had had herpes zoster at the same level (T6) but on the right side 20 years previously, and that this had taken 9 months to clear up.

It occurred to the attending physician that the cimetidine might have been responsible for this very remarkable recovery from a florid attack of herpes zoster. A further trial of cimetidine in other patients with herpes zoster was considered appropriate. It was perhaps fortunate that the history of the previous attack of herpes zoster became known only after the trial was well on the way; the dramatic remission might otherwise have been attributed (possibly correctly, at least in part) to acquired immunity following previous exposure to the herpes zoster virus.

Case 8. An 80-year-old woman presented with a 4-day history of nausea, vomiting and severe root pain and with a vesicular eruption at the level of T7 on the right side. The nausea and vomiting and the pain settled 1 day after the commencement of cimetidine therapy; the rash, however, which appeared to be unaffected by treatment, progressed through pustule formation, ulceration and healing over a period of 4 weeks. A fortnight after presentation the patient started complaining of pain in the distribution of the eruption. The pain was severe and lasted for approximately 2 months.

It is of interest to note the rapid subjective response of the pain and associated constitutional symptoms to cimetidine, whereas the rash, already far advanced, completed its natural course. The late appearance of neuralgia a fortnight after adequate control of the initial pain is one of the puzzling features of herpes zoster. Cimetidine was regarded as a failure in this patient, in spite of the very satisfactory primary response.

Case 21. A 52-year-old man developed severe pain at the level of T9 on the right side. When a vesicular rash appeared the next day, griseofulvin[1] 500 mg/d was prescribed. Five days later the rash had become florid, with marked erythema and pustule formation, and the pain remained intense. Cimetidine was substituted. Over a period of 3 days there was a marked relief of pain. The eruption progressed, apparently unaffected, through the stages of ulceration and healing over a period of 2 weeks.

Griseofulvin was used in this patient as an alternative and less expensive form of treatment,[1] but proved ineffective. Cimetidine produced good relief of pain, even though introduced after a delay.

Herpes Labialis

The common localized form of herpes labialis runs a fairly predictable course characterized by vesiculation, rupture of vesicles, crusting, and ultimate healing. The whole process is complete over a period of 7 - 12 days. Cimetidine was used in 4 patients with early localized vesiculation. Patient 1 was treated with cimetidine on 3 occasions (see report below). Patient 2 was treated twice: the first crop of blisters disappeared after 2 days on cimetidine 1 000 mg/d, and the second crop appeared 2 months later and took 8 days to heal after a 2-day course of cimetidine 800 mg/d. Patient 3 did not respond to cimetidine. In patient 4 the blisters were aborted within 24 hours of starting a 2-day course of cimetidine 1 600 mg/d.

Case 1. A 30-year-old woman gave a history of recur-

rent herpes labialis, which had affected either lip since the age of 10 years. The vesicles appeared practically every month, usually at the time of menstruation. The blisters were more extensive and lasted longer (approximately 14 days) than in most patients. In view of the particularly troublesome nature of the herpes infection, treatment with cimetidine was continued for a month. The vesicles with which she presented on 30 June 1978 disappeared within 2 days. On 23 October two small blisters recurred on the lower lip; cimetidine was once more prescribed in standard dosage for 1 week and the blisters again disappeared in 2 days. On 8 November a single vesicle appeared on the lower lip, but was promptly aborted by a 2 - day, 1 600 mg course of cimetidine. There has been no recurrence of blisters at the time of reporting 12 months later.

Experience with this patient clearly showed that individual crops of herpes labialis can be aborted promptly with cimetidine. Recurrences appeared to have become distinctly less frequent. It remains to be seen whether this is related to drug dosage, to duration of treatment, or to the booster effect of repeated courses.

A more extensive form of herpes labialis is often seen on the 2nd or 3rd day following whole-body hyperthermia, which is being used in patients with advanced cancer in our institution. It usually starts at or near the angle of the mouth, and as a rule spreads to involve the whole of both lips; otherwise it runs a course similar to localized herpes febrilis, extending over a period of 10 - 12 days. Cimetidine was prescribed in standard dosage for 1 week in 3 patients while the vesicles were still confined to the angle of the mouth. In all no further extension occurred and healing occurred within 3 - 4 days. We have no experience with the use of cimetidine in the treatment of the extensive herpes stomatitis encountered after cardiac and renal transplantation.

Herpes Keratitis

Cimetidine was used in 1 patient with herpes keratitis. The patient, a 36-year-old White woman, had been seen for the first time in January 1978. She gave a 10-year history of recurrent bouts of herpes keratitis with dendritic ulceration, affecting both eyes. She had had 3 courses of antiherpes vaccine, in 1972, 1974 and 1977 respectively. On each occasion the infection appeared to respond to vaccination. Both corneas were scarred as a result of recurrent infection and repeated carbolization. She had developed 3 bouts of keratitis with corneal oedema since January 1978. On each occasion she responded to idoxuridine drops over a period of a week to 10 days. Steroid eyedrops were prescribed in between attacks.

On 31 July 1978, after a recurrence of the infection, cimetidine was prescribed in a dosage of 1 600 mg/d for 5 days and 1 000 mg/d for 3 weeks. The keratitis and corneal oedema settled down within 5 days. On 11 September the keratitis flared up again. The attack subsided within 4 days of commencing a repeat course of cimetidine. On 15 January 1979 the keratitis flared up in the right eye. She commenced cimetidine and idoxuridine therapy the same day; 2 days later she was virtually symptom-free, but the steroid eyedrops were continued. The patient has had no further recurrences up to the time of reporting 9 months later.

Both the patient and her ophthalmologist were of the opinion that it was the addition of cimetidine which had cut short the duration of the recurrent attacks of keratitis and possibly even contributed to the following period of quiescence. Firm conclusions cannot be drawn from experience with a single patient, particularly in view of the unpredictable natural history of herpes keratitis and the simultaneous use of other forms of medication, but the results obtained were sufficiently encouraging to warrant a further trial of cimetidine in patients with this condition.

DISCUSSION

The results reported here are sufficiently encouraging to warrant further scientific study of the use of cimetidine in herpesvirus infections. In order to place observations of this kind beyond reasonable doubt it is desirable that further clinical trials should be accompanied by appropriate controls and confirmatory virus studies. Controlled trials will be particularly necessary in conditions with a variable and unpredictable natural history, such as herpes zoster and herpes keratitis. It is suggested that such studies should be extended to herpesvirus infections not reported here, such as herpes genitalis, herpes encephalitis, and disseminated herpes infections in immunosuppressed patients.

Details regarding dosage and the duration of therapy have to be established more precisely for each condition separately. In general, an initial loading dose of 1 600 mg/d for 2 days appears to be more satisfactory than smaller doses such as 800 or 1 000 mg/d. In herpes febrilis such a 2-day regimen appears to be all that is required to abort a crop of blisters. In patients with herpes zoster treatment was continued at a lower dosage (1 000 mg/d) for 5 days. Whether this was sufficient, or in fact necessary, remains to be established. In particularly troublesome and recurrent infections such as herpes keratitis and the occasional case of herpes febrilis, attempts at eradication of the infection, possibly by more prolonged treatment or by repeated booster doses, should be considered. This approach was used in fact in patient 1 in the herpes febrilis group and in the patient with herpes keratitis — both the recurrent attacks were shortened in duration and reduced in frequency. Further experience may define the relative importance of duration of treatment, dosage level, and booster doses in the control or eradication of recurrent herpesvirus infections more clearly.

Laboratory studies are required to explain the effect of cimetidine, which may have some direct antiviral effect as yet unknown. Alternatively, it may augment the immune defences of the body which produce early control of the offending virus. Evidence suggesting that an immune mechanism may be involved will be reviewed.

It has been established that thymus-dependent T lymphocytes have H_2-receptors.[3,4] Theoretically it is therefore possible for H_2-receptor antagonists such as cimetidine to modify cell-mediated immune responses. In a study of patients with duodenal ulcers, Avella *et al.*[5] demonstrated an augmented delayed hypersensitivity response to 4 antigens after 6 weeks' treatment with cimetidine. It was sug-

gested that the H_2-receptor antagonists produce this effect by stimulating the release of the migratory inhibitory factor. It has been demonstrated *in vitro* that histamine suppresses delayed hypersensitivity responses by H_2-receptor-induced release of the migratory factor.

The importance of immune mechanisms in the body's defence against herpesvirus infections is well known, and fits in well with the above findings. The studies of Rand *et al.*[6] of herpesvirus in cardiac transplant patients are particularly illuminating in this regard. They found that susceptibility to both herpes zoster and herpes simplex infections correlated closely with depressed cellular immune responses to the specific virus involved, as measured by lymphocyte transformation and interferon response to the killed virus. It is not unreasonable to expect that the corollary may also apply, viz. that a rapid recovery from a herpesvirus infection may be related to an augmentation of the cellular immune response.

Before an augmented cellular immune response can be accepted as a valid explanation for the antiviral activity of cimetidine, several other requirements have to be met: (*i*) other H_2-receptor antagonists such as burinamide and metiamide should have similar effects on herpesvirus infections; (*ii*) the time scale of the augmented response should match that of the antiviral effect observed; and (*iii*) H_2-receptor antagonists should prove effective to some degree in a wide range of virus infections in which the cell-mediated immune response plays a critical role.

The clinical consequences of an augmented immune response are difficult to predict. While it may be beneficial in some conditions, such as in herpesvirus infections, it may be harmful in others. Allograft rejection, for example, is basically a delayed hypersensitivity response, and could conceivably be encouraged by H_2-receptor antagonists. In fact, Primack[7] recorded two irreversible episodes of rejection in renal transplant patients, ending in death, which he attributed to cimetidine. Other workers,[8,9] however, have found that cimetidine had no effect on rejection or graft function. Until this issue has been clearly resolved by further prospective studies, cimetidine should be used with caution in transplant patients, whether it be prescribed with the more conventional purpose of controlling peptic ulceration or used for the control of herpesvirus infections in the immunosuppressed patient.

In conclusion, these preliminary observations strongly suggest that cimetidine has an antiviral effect in herpesvirus infections, certainly in herpes labialis. The natural histories of herpes keratitis and herpes zoster are too unpredictable to permit firm conclusions at this stage; nevertheless, the results are sufficiently encouraging to warrant further trials and to merit research into the nature of the apparent antiviral effect observed.

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NEWS AND COMMENT

CLOSTRIDIUM DIFFICILE INFLAMMATORY BOWEL DISEASE

We have recently referred to the role of *Clostridium difficile* in pseudomembranous colitis usually in association with antibiotic administration, but it now appears that this organism and its toxin may have a more extended role in chronic inflammatory bowel disease. Two papers in *The Lancet* (1980, **1**, 381 and 383) deal with this problem. The first report by LaMont and Trnka of Boston describes the finding of *Cl. difficile* toxin in the stools of 6 patients with chronic inflammatory bowel disease during a remission of symptoms. Three patients had a definite ulcerative colitis, 1 had Crohn's disease and the other 2 had a proctitis without pseudomembranes. When the toxin disappeared, the symptoms improved. In 5 patients oral vancomycin therapy was accompanied by distinct improvement, while symptoms abated in the other patient with steroids, sulphasalazine and bowel rest. The antibiotic did not of course cure the underlying chronic inflammatory bowel disease.

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In the second report from Bristol, Bolton *et al.* described the finding of *Cl. difficile* toxin in the stool of 9 out of 56 patients with diarrhoea. Out of these, 5 had severe inflammatory bowel disease and were receiving systemic steroids, 2 were on steroids for other conditions, and only 1 had been on antibiotics. Again, clearance of the toxin with vancomycin or metronidazole improved the clinical condition. The authors believe that the toxin is capable of damaging adult colonic mucosa and that its presence in an already diseased bowel may be one reason why the disease does not yield to standard therapy but improves on antibiotics to which *Cl. difficile* is sensitive. They believe that the toxin should be sought in those patients with inflammatory bowel disease in whom the condition is severe or unresponsive to standard therapy.

In an accompanying editorial the question is raised whether inflammation of the bowel caused by some other factor may favour colonization by *Cl. difficile* or whether some other influence permits the organism to multiply and produce toxin and thus inflame the bowel.