Oral Cimetidine and the Treatment of Verrucae

To the Editor:

Verrucae of any type are a difficult skin condition to treat effectively. Painful treatments and frequent recurrence are a source of stress for the patient and podiatric physician alike. A new treatment, however, shows promise in treating warts in children and adolescents.

Cimetidine is an H_2 receptor blocker used primarily to decrease histamine stimulation of gastric acid secretion from the parietal cells in the duodenal mucosa. But it will also act on H_2 receptors throughout the body, which includes H_2 receptors on a type of lymphocyte called the suppressor T cell (T_s) which is involved in the cell-mediated immune response against viral infections.

In an established viral infection, the major defense of the host system is cell-mediated immunity.[1] When a virus infects a cell, it changes the surface of the cell membrane by producing substances that act as antigens. T cells (lymphocytes) are then activated to fight the infection.

There are two forms of T cells, helper T cells and suppressor T cells. Helper T cells fight the viral infection by producing cytotoxic lymphokines which are toxic to viral-infected cells and which stimulate phagocytes. Suppressor T cells are involved in regulating the cell-mediated immune response by causing immunosuppression.[2] They turn off the cell-mediated immune mechanism. If the immunosuppression can be blocked, then theoretically, the activity of the helper T cells or other components of the immune system can be enhanced.

Although the response to the classic wart virus is primarily a cell-mediated one, there are some measurable changes in IgE, IgM, and IgA to the virus. These increased titres, however, do not necessarily mean that these antibodies are active in the elimination of the wart virus. They simply may have increased in response to viral particles once the virus is killed and the epidermal cell lyses.

There are more than 40 types of the human papillomavirus, which is composed of DNA. A change in DNA nucleotide sequence of the human papillomavirus causes antigenic differences which yields different types of clinical responses, so flat warts, plantar warts, or venereal warts can form.

What clinical evidence exists that says that this immune response is important in eliminating the human papillomavirus? First, patients with deficient cell-mediated immunity and those on chemotherapy or other forms of immunotherapy often develop warts. Second, lymphocytes are present in regressing warts. Third, delayed hypersensitivity, a cell-mediated immune response, develops in intradermally injected wart tissue.

Where does cimetidine fit into this cell-mediated immune response? Researchers have shown that in mice, with experimentally induced fibrosarcoma and mastocytoma, T_s produced by the tumors permitted the growth of these tumors, cimetidine selectively inhibits the antigen specific afferent acting T_s and may be used in the immunotherapy of tumors.[3] It inhibits the expression, and to a lesser extent, the induction of T_s *in vitro* so that they may actually cause regression of some tumors, similar to cyclophosphamide, the most potent T_s suppressor.[2]

Gifford et al[4] showed that mice receiving cimetidine had plasma levels similar to levels obtained in humans at doses of 300 mg every 6 hr. It is theoretically possible, therefore, that similar T_s suppression may occur in patients infected with human papillomavirus.

Researchers administering cimetidine at doses of 800 mg to 1,600 mg/day to 12 healthy volunteers without human papillomavirus infection, six male and six female, ranging in age from 24 to 33 years, found definite changes in the immune system as monitored in peripheral blood.[5] Initially, 800 mg/day was administered to the group for 7 days. After an interruption of 2 months, 1,600 mg/day was taken for 21 days. During both treatment periods, there was significant proliferation of lymphocytes. In the 800 mg/day group, there was a decrease in suppressor T-cell numbers. In the 1,600 mg/day group, there was a striking transformation of the entire immune system. Although T_s numbers increased slightly, helper T cells, macrophages, and B cells (which produce immunoglobulin) increased significantly.

According to Orlow and Paller[6], cimetidine has already been used to treat mucocutaneous candidiasis, herpes zoster, and other immune-altered skin diseases. Their work is the stimulus for this study. They treated 32 children (ages 3 to 16 years) with common and plantar warts present for at least 6 months with cimetidine at a dose of 25 to 40 mg/kg/day. By 2 months, the warts had entirely disappeared in 26 (81%) of the children. None had recurred, but the authors did not indicate how long they followed their patients. There were no side effects reported.

Method

The author's patients from 6 to 50 years old were first offered a variety of treatment options. Most had other treatments performed previously with no success (Table 1). Some warts had been present for more than 3 years. Doses of cimetidine ranged from 900 mg to 1,800 mg/day with the majority of patients taking 1,500 mg/day. The usual dosage was 300-mg tablets because of the cheaper cost (five 300-mg tablets cost $3.72/day *versus* $5.00/day for two 800-mg tablets). Now that generic cimetidine can be prescribed, the cost is expected to decrease considerably. Patients involved in this study were instructed not to use any other topical or oral treatment for their warts. Length of treatment varied from $2^1/_2$ weeks to $4^1/_2$ months.

Patients or their legal guardians were warned of potential side effects, with nausea, vomiting, and diarrhea being the most commonly reported. Cimetidine has antiandrogenic effects, so male patients were warned of the possibility of gynecomastia, diminished libido, and reversible sterility.[7] Decreased leucocyte counts (approximately 1/100,000 patients) including agranulocytosis (3/million patients) have been reported. Most of these reports were patients who had serious concomitant illnesses and received drugs and treatments known to produce neutropenia. Thrombocytopenia (3/million patients), and rarely cases of pancytopenia or aplastic anemia, also have been reported.[8] Cimetidine, however, is generally regarded as a safe drug with limited side effect potential.

Because it is a potent hepatic inducer, it interacts with a host of drugs, especially lidocaine, theophylline, oral anticoagulants, benzodiazepines, and narcotic analgesics.[9] No patient under 17 years was on any other prescription medication. There was no

Table 1. Treatment and Outcome

Patient	Sex	Age (Yrs)	Length of Time Warts Present Before Cimetidine (Months)	Previous Treatment	Cimetidine Dosage (Mg/day)	Length of Cimetidine Treatment (Months)	Number of Warts	Outcome
1	Female	13	2	Cryotherapy	1,500	2	1 (12 mm)	Complete resolution
2	Female	11	12	Acid	1,200	2	3	Complete resolution
3	Female	14	4	Unknown	1,500	2	3	Complete resolution
4	Female	13	31	Laser, office acid, outpatient acid	1,500	2	3	Complete resolution
5	Female	14	7	Office acid	1,500	$4^1/_2$	6	Complete resolution
6	Female	11	32	Office acid	1,200	1	9	Complete resolution
7	Male	6	7	Office acid	900	$^1/_2$	2	Complete resolution
8	Male	12	4	Unknown	1,800	$2^1/_2$	40	Complete resolution
9	Female	11	5	Outpatient acid	1,500	2	25	Complete resolution
10	Male	14	72	Outpatient acid	1,500	3	10	Complete resolution
11	Male	15	6	Outpatient acid	1,600	2	3	Complete resolution
12	Female	12	10	Outpatient acid	1,600	2	6	Complete resolution
13	Female	11	3	Outpatient acid	1,200	$1^3/_4$	4	All but one with complete resolution
14	Male	16	18	None	1,600	3	6	No change
15*	Female	16	10	Office acid, outpatient acid	1,500	2	5	Complete resolution
16	Male	39	17	Office acid, outpatient acid, cryotherapy	1,500	3	8	Complete resolution
17	Male	19	33	Office acid, outpatient acid, laser, cryotherapy	1,600	2	1	No change
18	Male	45	72	Office acid, laser, outpatient acid	1,600	2	Large mosaic	No change
19	Male	48	24	Office acid	1,500	2	3	No change
20	Male	17	36	Cryotherapy	1,500	$3^1/_2$	13	No change
21	Female	49	12	Office acid, outpatient acid	1,500	2	1	Complete resolution
22	Female	25	26	Office acid, laser, outpatient acid	1,800	2	2	Complete resolution
23	Male	50	36	Unknown	1,500	$3^1/_2$	6	No change
24	Female	21	14	Outpatient acid	1,600	2	20	No change

*Had recurrence of one wart 2 months after termination of treatment.

biopsy of wart tissue performed on any patient prior to enrollment in the study, but two patients had verrucae at previous invasive treatments.

It became clear early in the study that results were far more predictable in patients under the age of 17 years. In fact, there was a complete resolution of all warts in 12 of 15 patients (80%). Of the remaining three patients, one had 24 verrucae eliminated on one foot, with one wart persisting on the contralateral foot after 4 months of therapy. There was no change with two other patients with multiple lesions.

Patients older than 17 years did not fare as well, with complete resolution in only three of ten patients (30%). One of those cured voluntarily discontinued his first round of therapy after only 1 month because he had not noticed any results. Six months later, he agreed to retreatment at the same daily dosage and had complete resolution at 3 months.

In most patients, regardless of age, changes in the lesions began after 1 month of therapy. At this time, the wart tissue began to darken to a light brown or black color (Fig. 1). Most of the wart tissue was simply manually debrided at the end of therapy, but on a few occasions, the warts spontaneously disappeared (Fig. 2). If no visual change had occurred after 2 months of treatment, none of these verrucae would eventually be eliminated, regardless of the length of time therapy was continued.

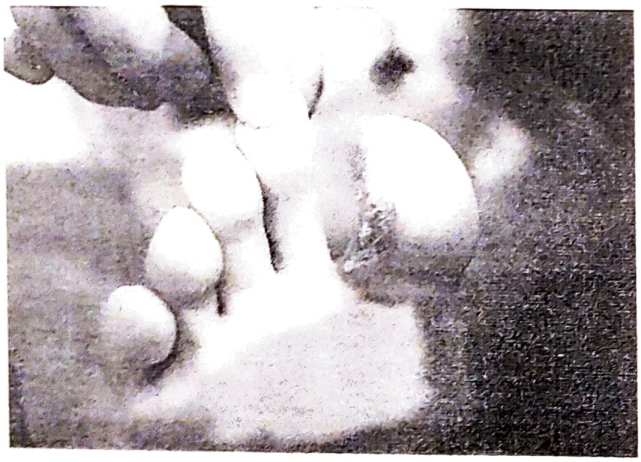

Figure 1. Three weeks after initiating oral cimetidine for verrucae on right hallux and second toe. Notice the hemorrhagic change and superficial tissue slough to both lesions.

Figure 2. Complete resolution of lesions after 8 weeks of cimetidine therapy.

No systemic side effects were reported. However, in the youngest patient, who was 6 years of age, therapy was discontinued after 17 days because of a local allergic reaction secondary to an apparent dissemination of the breakdown products into the lymphatic tissue with localized multiple erythematous streaks emanating from the warts. One patient has reported a single recurrence out of five warts. This occurred 2 months after terminating therapy, at which time no warts were seen clinically. No other patient has reported a recurrence. For most patients, it has been at least 8 months since treatment was discontinued.

Discussion

This clinical study raises a number of questions that need further research. First of all, why do patients under the age of 17 years respond to cimetidine, while those over 17 years do not? Is it caused by the difference in drug absorption and metabolism or the cell-mediated immune system in these two groups? Because of increased total weight, adults usually were taking cimetidine at doses of 25 mg/kg, while children could be maintained at 35 to 40 mg/kg and not exceed the daily dosage of 1,800 mg. Should cimetidine be taken at the higher doses per kilogram to be effective? The manufacturer does not recommend exceeding 1,800 mg/day.

Would nanitidine hydrochloride, another H_2 antagonist, yield similar results? Nanitidine hydrochloride has a somewhat better safety profile than cimetidine and might be more suitable. The next phase of this investigation would attempt to formulate a topical preparation of cimetidine which may eliminate some of the risks of oral dosing.

Conclusion

Oral cimetidine appears to be an effective, painless treatment for pedal verrucae with limited side effect potential. Doses of 25 to 40 mg/kg/day were effective in completely eliminating wart tissue in 80% of patients under 17 years and in 30% of patients older than 17 years. It is necessary at some point to conduct a double-blind cross-over study to elimi-