Cimetidine as a First-Line Therapy for Pedal Verruca

Eight-Year Retrospective Analysis

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Can cimetidine therapy effectively stimulate the body's immune response against warts? Several clinicians have anecdotally reported success using cimetidine against warts. Previous double-blind studies comparing cimetidine with placebo therapy have failed to statistically and scientifically corroborate those results. Between 1995 and 2002, 216 patients underwent an isolated course of oral cimetidine therapy for verruca plantaris. Our treatment outcomes closely parallel those obtained by other researchers. Cimetidine may be used as a safe, effective, lone treatment modality for verruca in all age groups. (J Am Podiatr Med Assoc 95(3): 229-234, 2005)

The treatment of pedal warts is diverse and has long perplexed clinicians. Multiple treatment modalities exist, which are associated with varying degrees of success, complications, recurrence rates, and morbidity. An ideal treatment should be highly effective and safe, be associated with a low recurrence rate, and cause minimal pain and morbidity. In 1995, the primary author (B.R.M.) observed an outcome dichotomy with a curettage/fulguration procedure performed for plantar warts on his two nieces. This provided the initial stimulus to search for additional verruca treatment options. One girl had a personal medical history of Crohn's disease and experienced two recurrences of plantar warts. Her sister, who had no significant medical history, underwent the same treatment course, which was successful without recurrence. The outcome dichotomy for these two siblings raised the question whether an association exists between autoimmune disorders and whether these disorders interfere with the host's immune response to viral infections.

Because cell-mediated immunity is the characteris-

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tic host defense mechanism against viral infections,[1] a MEDLINE search was performed to determine whether there was an association between warts and autoimmune disorders and whether any immune system enhancement therapy exists to eradicate resistant lesions. The search revealed that cimetidine had previously been reported to exhibit immunomodulatory activity through increased mitogen-induced lymphocyte proliferation and inhibition of suppressor T cell function at its histamine type 2 receptor site.[2] Griswold et al[2] also referenced several additional scientific studies that corroborate cimetidine's immunomodulatory capabilities. In 1993, Orlow and Paller[3] first used cimetidine to stimulate the body's immune response, successfully eliminating multiple resistant warts in 36 children (86%). That study provided the impetus for our adoption of the same treatment protocol for pedal warts. We now report our 8-year retrospective analysis of the use of cimetidine as an isolated treatment modality for pedal warts in children and adults.

Methods

All of the patients included in this study either used cimetidine as a lone, first-line therapy for pedal ver-

ruca or were administered the medication after undergoing previous unsuccessful treatments. (A table containing complete data for all participating patients may be accessed at the authors' private-practice Web site at http://www.footdocspc.com from the "Doctors Only" page or by contacting the primary author.) No concurrent treatment was used during the course of cimetidine therapy. Pediatric patients were given 25 to 40 mg/kg per day (most were given 30 mg/kg per day) in divided doses, in accordance with guidelines established by Orlow and Paller.[3] Adult doses averaged 20 mg/kg per day to avoid exceeding the 1,600-mg maximum daily cimetidine allowance. No patient exclusions existed with respect to age, past medical history, or pedal lesion locale or morphology.

Follow-up questionnaires were recovered from 169 (78%) of 216 patients a minimum of 15 months after cimetidine therapy cessation (Fig. 1). In the 47 study patients who did not provide a completed questionnaire, we witnessed visible, documented evidence of the success or failure of cimetidine. All remaining outcome parameters reviewed for the completed questionnaire patient group were also reviewed for this group, except for recurrence rate, which could not be accurately documented. Patients who did not complete questionnaires and whose results could not be thoroughly documented were eliminated from the study. Patients who did not achieve a successful therapeutic outcome because of failure to complete the mean successful treatment duration for their age group or because of noncompliance regarding prescribed dosing schedules were not included in the statistical analysis determining the treatment's success rate but were included in analysis of the adverse effects of cimetidine therapy. A successful therapeutic response was determined by the clinician's observation of complete restoration of skin lines coursing throughout the entire lesion's surface area, with complete elimination of symptoms. Pediatric age groups consisted of young (3–7 years), pre-pubescent (8–12 years), and pubescent (13–17 years) children to determine whether statistical variations existed for the various outcome parameters selected. Adults were arbitrarily divided into two groups to as-

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Cimetidine/Tagamet Questionnaire

(Please use back of form if additional space is needed.)

1. Approximately how long was the wart(s) present before starting treatment?

2. Were any other treatments tried, either before or in conjunction with cimetidine?

3. How long did you take cimetidine? What dose was taken and how often?

4. Was the cimetidine effective/ineffective (circle one) in *completely* eliminating the warts?

5. Was anything observed prior to their disappearance? If ineffective, were you compliant/noncompliant (circle one) in taking the medication?

6. Were there any side effects to cimetidine? If so, what were they?

7. Has there been any recurrence of the warts? If so, when did they reappear?

8. Would you have any reservation recommending this treatment? If so, why?

9. Do you or does anyone in your family have a history of autoimmune disorders, such as Crohn's disease, ulcerative colitis, rheumatoid arthritis, or lupus? Who?

Figure 1. Cimetidine therapy follow-up questionnaire.

certain whether advancing age affected the successful treatment outcome rate and other selected parameters.

Results

A total of 216 patients (90 males and 126 females) were administered oral cimetidine for pedal verruca: 180 were children (78 boys and 102 girls) and 36 were adults (12 men and 24 women) (Table 1). The treatment success rate for all age groups was 84.3%. In the pediatric groups, the combined success rate was 86.0%; in adults, the rate was 75.8%. Of the successful outcomes documented, 12 recurrences were observed after completion of cimetidine therapy (7.2%). Seven of the recurrences (5.0%) occurred in the pediatric group, and five of those seven were observed in the pubescent group. Five recurrences (20.0%) were observed in the adult group (Fig. 2). In two of the recurrent cases, a second trial of cimetidine therapy eradicated the recurrent lesions, with no additional recurrence observed. Fifteen of 180 children and 3 of 36 adults did not reach the mean successful treatment duration established for their respective age groups.

Thirty-four documented adverse events occurred in 33 patients, creating an overall adverse event rate of 15.7%. This statistic is in stark contrast with the minimal cimetidine adverse event observations of Orlow and Paller.[3] However, their series consisted of only 36 patients. Of the adverse events documented,

gastrointestinal upset predominated (21 reported events [10%]). Of these, 16 gastrointestinal complaints (7.4%) were significant enough to prevent treatment completion. The complete adverse event analysis is shown in Table 2.

The fastest therapeutic response to cimetidine therapy occurred within 1 week. The mean successful treatment duration was 6.1 weeks in children and 7.9 weeks in adults (Fig. 3). One sibling triad and 14 pairs of siblings were involved in this study. One triple and 13 double successful outcomes were observed in the 15 sibling groupings (93%). Twenty-seven patients had either a personal or a family history of autoimmune disease; cimetidine therapy was successful in 22 cases (81.5%). Thirteen patients previously underwent failed surgical excision/curettage. Cimetidine therapy successfully eradicated the recurrent lesions in 11 of those cases (84.6%). Nine patients achieved a successful therapeutic response despite using a reduced dosing schedule because of the medication's adverse effects, documented missed doses, or cognizant parental decision making that breached the dosing protocol. The longest symptom duration in which there was a successful response to cimetidine therapy was 150 weeks. In this patient, however, the warts recurred. Four patients experienced successful outcomes with a lesion duration of 100 weeks, without observed recurrence.

The greatest statistical gender differential occurred in the pubescent age group (13–17 years). In this group, 7 (28%) of 25 boys and only 4 (8%) of 49

Table 1. Characteristics of 216 Pediatric and Adult Patients Who Underwent Cimetidine Therapy for Pedal Verruca

Age (years)	Patients (No.) (Sex, M/F)	Completed Questionnaires (No.)	Adverse Effects/ Treatment Interrupted (No.)	Negative Outcomes/ <Mean Duration (No.)	Incomplete Treatment (No.)	Symptom Duration (weeks)	Treatment Duration (weeks)	Positive Outcomes/ Total Patients (No.)	Successes (%)	Recurrences (No. [%])
3–7	26 (13/13)	20	4/2	4/1	2	19.5	5.2	19/23	82.6	0
8–12	79 (39/40)	70	14/6	10/3	6	15.7	6.6	65/73	89.0	2 (3.1)
13–17	75 (26/49)	53	10/6	12/1	7	19.9	6.0	57/68	83.8	5 (8.8)
All pediatric patients	180	143	28/14	26/5	15	18.0	6.1	141/164	86.0	7 (5.0)
18–24	18 (6/12)	15	1/0	3/0	0	55	8.1	14/18	77.8	2 (14.3)
≥25	18 (6/12)	11	4/2	5/1	3	50	7.7	11/15	73.3	3 (27.3)
All adults	36	26	5/2	8/1	3	52.5	7.9	25/33	75.8	5 (20.0)
Total	**216**	**169**	**33/16**	**34/6**	**18**	**22.6**	**6.4**	**166/197**	**84.3**	**12 (7.2)**
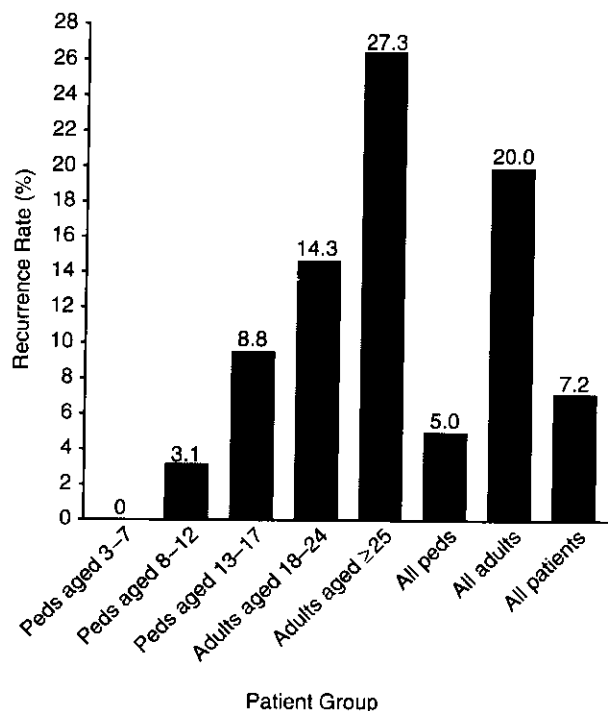
Figure 2. Pedal verruca recurrence rates after cimetidine therapy completion by group. Peds indicates pediatric patients.
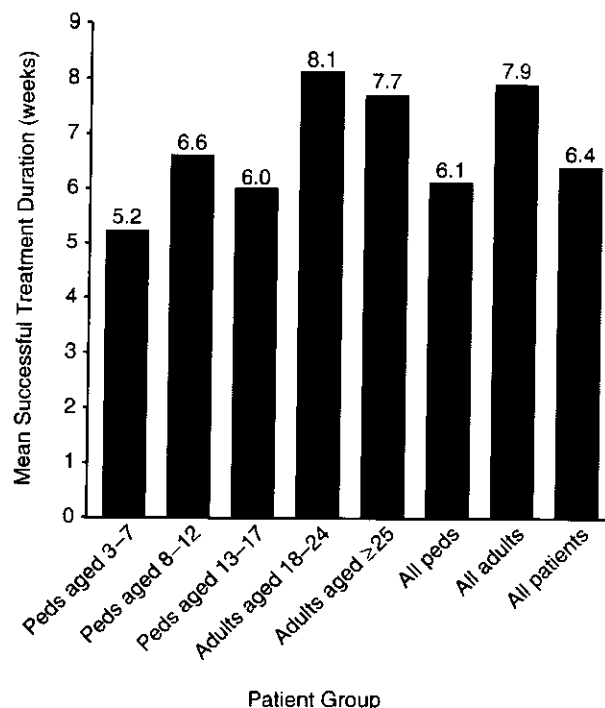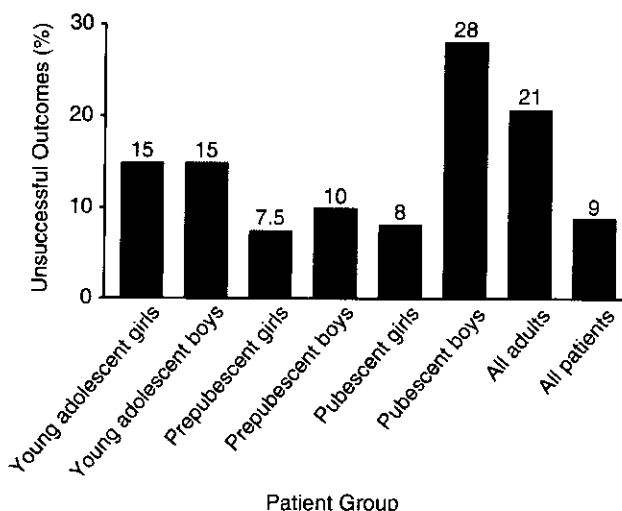

Figure 3. Mean successful cimetidine treatment duration by group. Peds indicates pediatric patients.

girls experienced unsuccessful outcomes (Fig. 4). Pediatric and adult lesion durations were plotted against total outcomes and treatment duration. For symptom duration plotted against successful outcomes, the adult-to-pediatric ratio was 2:1 (29.7:15.5), whereas a 3:1 ratio (88.6:28.2) was observed for unsuccessful outcomes (Fig. 5). For symptom duration

plotted against treatment duration, in the successful duration group, the adult-to-pediatric ratio was 2:1 (4.75:2.5), whereas a 16:1 ratio (34.3:2.3) was observed for the unsuccessful duration group (Fig. 6).

**Table 2. Adverse Effects of Cimetidine Therapy in 216 Pediatric and Adult Patients**

Adverse Effect	Events (No. [%])
Gastrointestinal complaints	21 (10)
Central nervous system complaints	8 (4)
Lethargy	4 (2)
Panic/spacey	2 (1)
Headache	2 (1)
Hematologic complaints	2 (1)
Cutaneous complaints	2 (1)
Pruritus	1 (0.5)
Dermatitis	1 (0.5)
Drug interactions	1 (0.5)
Total events	**34 (15.7)**
Total events causing premature treatment cessation	**16 (7.4)**

Figure 4. Unsuccessful cimetidine therapy outcomes by group.
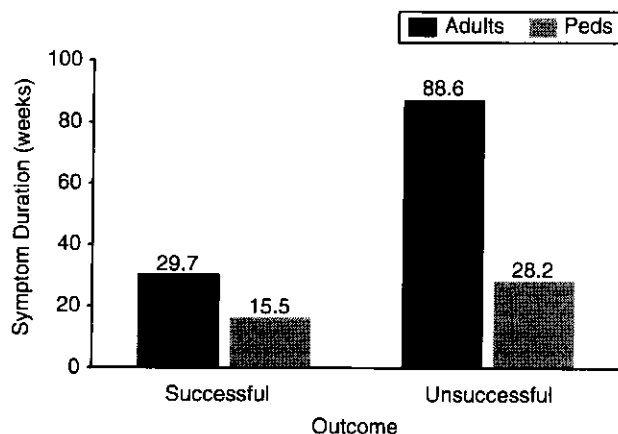
Figure 5. Symptom duration according to cimetidine therapy outcome. Peds indicates pediatric patients.
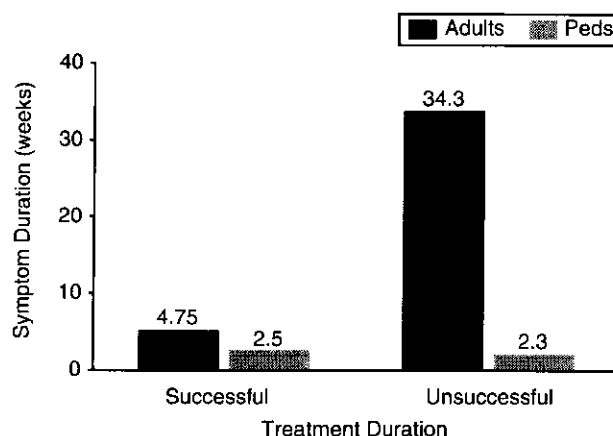
Figure 6. Symptom duration according to cimetidine treatment duration. Peds indicates pediatric patients.

Minimum follow-up for all patients who completed the questionnaire was 15 months after cessation of cimetidine therapy.

Discussion

It is nearly impossible to undertake a completely flawless anecdotal study. First, warts have been observed to spontaneously resolve within 2 years of onset.[4] Only a handful of patients in our study presented with lesion durations of 100 weeks or longer; thus it could be argued that some percentage of spontaneous lesion resolution could have occurred, thereby skewing the success rate toward a falsely higher percentage. Second, 47 patients (22%) did not return completed questionnaires after cimetidine therapy cessation and could not be traced, creating incomplete follow-up. Thus we could not determine that group's recurrence rate. Forty patients in that group completed their treatment course commensurate with the established mean successful treatment duration for their age group. Of these 40 patients, 32 (80%) had successful outcomes that were documented by a clinician. This success rate approximates that observed in the entire study (84.3%). Can it be extrapolated that the recurrence rate for this age group would parallel that observed in the completed questionnaire group? Last, cimetidine therapy's success rate was calculated as a function of a given individual's ability to complete the treatment course with respect to the mean successful treatment duration for that age group. Orlow and Paller[3] frequently observed successful responses 6 to 8 weeks after treatment initiation. However, in several of their cases the therapeutic response took considerably longer.

Would some of our unsuccessful treatment outcomes have reversed had the patients extended treatment duration beyond their age group's mean successful treatment duration? If so, then our successful outcome percentage may have been skewed in a falsely low direction. Similarly, in all but one patient we limited treatment duration to 12 weeks. The remaining patient insisted on extending treatment for an additional 4 weeks and subsequently experienced a successful outcome because of that extension. Would other patients in our series who initially did not respond to 12 weeks of therapy or less have enjoyed a similar fate?

Despite a small patient sample, the gender differential observed for reduced successful outcomes in pubescent boys at least raises the question whether active testosterone synthesis interferes with cimetidine's immunomodulatory suppressor T cell capabilities. Adults experienced four times as many recurrences as children. In two parameters, symptom duration plotted against unsuccessful outcomes and symptom duration plotted against treatment duration, the adult-to-pediatric ratio was significant (3:1 and 16:1, respectively). Why such a disparity? Could the lower cimetidine dosing in adults, necessitated to avoid exceeding toxic levels, have had such a great effect on cimetidine's immunomodulatory activity? Or is a child's immune system somehow more easily influenced and enhanced than an adult's? Although cimetidine's past anecdotal effectiveness against warts is well documented,[3, 5, 6] its success has not been statistically and scientifically substantiated through corroborative double-blind placebo-controlled studies.[7, 8] However, one double-blind study[7] did show a trend toward better therapeutic responses in younger sub-

jects. Seth Orlow, director of pediatric dermatology at the New York University School of Medicine and one of the treatment's originators, still successfully uses cimetidine against pediatric warts (Seth Orlow, personal communication, 2001), as do we. We also ask the same question that Mahoney[6] posed in his article: Can histamine type 2 antagonists other than cimetidine be used effectively to eradicate warts?

Conclusion

Our data suggest that cimetidine is a reasonably safe, successful, lone treatment modality for pedal verruca in all age groups. We believe that cimetidine can be used as a first-line therapeutic option. Because of our success with cimetidine, we significantly reduced the number of surgical excisions/curettages for resistant lesions, thus in many cases avoiding the physical and emotional morbidity associated with surgery. We hope that other clinicians who treat warts will begin to realize and appreciate cimetidine's immune system enhancement potential and successfully incorporate this treatment into their practices. From a medicolegal perspective, we believe that it is imperative to increase awareness of this off-label use of cimetidine. It should be noted that its use in children younger than 16 years and the dosage apparently required to achieve therapeutic responses against warts are not officially recommended. Therefore, we strongly advise that, before initiation of treatment, all clinicians either obtain informed consent or review educational material with patients and their parents on cimetidine's off-label use.

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