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Candicidin Treatment of Prostatism: A Prospective Double-blind Placebo-controlled Study

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Summary. The polyene macrolide candicidin was investigated in the treatment of benign prostatic hyperplasia (BPH). Forty-one unselected patients with BPH and prostatism were admitted to a prospective, douple-blind placebo-controlled clinical trial. Patients treated with 270 mg candicidin daily for 6 months had a significant decrease in residual urine and a significant increase in maximum flow rate after correction for differences in corresponding bladder volume. Symptoms improved significantly in both the candicidin and the placebo group but no differences in improvement were found between the two groups. The mechanism of the drug's effect is unknown and positive results are much less pronounced than those obtained with surgery. Candicidin appears valuable in the treatment of BPH patients who are a poor surgical risk.

Key words: Candicidin, Prostatism, Urodynamics.

Introduction

Since the median age of the population of the western world is increasing, the number of patients who will need prostatic surgery for benign prostatic hyperplasia (BPH) is rising. Many of these patients are poor surgical and anaesthetic risks, often because of ischaemic heart disease and chronic obstructive pulmonary disease, and therefore would benefit if effective nonsurgical treatment for prostatism were available. During recent years several nonsurgical approaches have been attempted, such as treatment with antiandrogens [12, 17, 24, 29], aldactone [5], dopaminergic agents [10], tadenan (an extract of African prune) [9], alpha-adrenergic blockers [4, 20], and intraprostatic phenol injections [7]. Most of these studies showed no improvements in symptoms or objective findings. In 1968 Gordon and Schaffner observed remarkable reductions in prostatic size in old dogs with histologically established prostatic hyperplasia following administration of candicidin and other polyene macrolide antimycotics (e.g., amphotericin B and nystatin) for 30 days [13]. The mechanism of action is still unknown but the effect must be exerted within the gastrointestinal tract because the absorption of these antimycotics is at best very poor. Possibly they interfere with both the absorption of exogenous cholesterol and the enterohepatic circulation of cholesterol, thereby lowering the serum cholesterol level. The effect of hypocholesterolemia might be a decrease in cholesterol content of the prostate gland and a decrease in androgen activity diminishing the prostatic size [13, 22, 27, 28].

In a pilot study Aalkjaer [1] found no effect of nystatin. Candicidin has been used in several open studies and the results have been favorable, with improvement in symptoms and urinary flow rate and decrease in residual urine and prostatic size, making surgery unnecessary in as many as 73% of the patients [15, 16, 19]. In a controlled clinical trial Sporer et al. [27] confirmed these results while Abrams [2] and Jensen et al. [14] found candicidin to be no more effective than placebo.

In the present prospective double-blind, placebo-controlled study we evaluated whether candicidin administered for 6 months to patients with BPH had any effect on symptoms, residual urine and urinary flow rate.

Materials and Methods

Patients consecutively referred for prostatism were randomly assigned to either a transurethral resection of the prostate (TURP) study, a no-TURP study, or this candicidin drug study. Forty-one patients were included and underwent detailed symptom analysis, physical examination including neurological examination, urinalysis, urine culture, routine blood chemistry, uroflowmetry and postvoiding residual urine determination. Cystoscopy was performed when indicated. To qualify for the study the patients had to be 45–75 years of age with a mean urinary flow rate (Qave) less than 10 ml/sec and a postvoiding residual urine of more than 30 ml. The symptoms of prostatism had to be unequivocal and an informed consent form signed. Exclusion criteria included concomitant medication that

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Table 1. Comparison of symptom scores and findings of uroflowmetry in the candicidin and placebo groups before initiation of treatment

	Symptom Scores			Uroflowmetry			Corrected		
	Total	Irritative	Obstructive	Voided vol. (ml)	Residual urine (ml)	Bladder vol. (ml)	Q_{max} ml x sec^{-1}	Q_{max} $ml^{0.5}$ x sec^{-1}	Q_{ave} ml x sec^{-1}
Candicidin									
Median	16	5	11	219	80	302	8.7	0.52	4.2
Range	12–22	3–9	7–14	130–335	30–375	160–568	3.0–18.8	0.15–0.96	1.3–9.1
Placebo									
Median	14	4	10	213	90	251	7.7	0.42	3.7
Range	9–19	1–8	5–13	81–548	30–350	111–898	3.7–28.5	0.27–1.26	1.4–9.4
Statistics	$p = 0.16$	$p = 0.17$	$p = 0.32$	$p = 0.90$	$p = 0.69$	$p = 0.95$	$p = 0.54$	$p = 0.59$	$p = 0.80$

might affect the effect of candicidin (e.g., antibiotics, adrenal and sex steroids, gonadotropic agents and alfa-adrenergic stimulators), instrumentation of the urethra within the last month before beginning of the trial, symptoms specific for lower urinary tract disorders other than BPH (e.g., neurogenic bladder dysfunction, bladder neck contracture, urethral stricture, carcinoma of the prostate and prostatitis), diabetes insipidus, insulin-requiring diabetes mellitus, hepatic, cardiac or renal failure, previous prostatic surgery, hematuria (more than 15 red blood cells/high power field), general illness or imminent need for prostatic surgery.

All symptoms were graded on a scale from 0 to 3. Symptoms comprising the irritative symptom score were urgency, diurnal frequency and nocturia; those comprising the obstructive symptom score were hesitancy, intermittency, impaired urinary stream, sensation of incomplete bladder emptying and terminal dribbling. For uroflowmetry the DISA mictiograph was used, while a 12 or 14F Foley catheter was employed for postvoiding residual urine determination. Terminology and definitions are in accordance with the prosposals of the International Continence Society except for the corrected maximum flow rate [3]. In order to make the maximum flow rate volume independent we used the following formula: corrected $Q_{max} = Q_{max}/\sqrt{\text{bladder volume}}$, bladder volume being the sum of voided volume and residual urine volume [11].

Following qualification for the study all patients underwent a single-blind placebo treatment for 1 month. Then they were stratified according to the severity of BPH, based on repeated residual urine determination and Qave, and were randomized to either the placebo or the candicidin group. This part of the investigation was double-blind. In the candicidin group the dosage was two capsules three times daily after meals, each capsule containing 45 mg candicidin (supplied by Merrell-National Laboratories, Cincinnati, Ohio, USA). The patients in the placebo group were given inactive capsules of identical appearance. During the study the patients were re-evaluated every month.

The data were analyzed by non-parametric statistical methods including the Mann-Whitney rank sum test and Wilcoxon's test for paired differences. *P* values less than 0.05 were considered significant.

Results

Eleven patients failed to complete the study. Four belonged to the placebo group and seven to the candicidin group. In the placebo group one patient developed hematuria because of a bladder tumor and subsequently had a TURP and resection of the tumor. One patient did not attend the monthly evaluations and later had a TURP. Two patients did not complete before the study was closed. In the candicidin group three patients did not attend final evaluation. Two patients complained of intractable nausea related to the candicidin ingestion, while one patient was eliminated from the study because of increasing symptoms and had a TURP, the microscopy revealing an unsuspected carcinoma of the prostate. Finally one patient died from an acute myocardial infarction.

Of the remaining 30 patients 17 were in the placebo group and 13 in the candicidin group. The median age in the two groups was 67 years (range 57–72) for the placebo group and 61 years (range 53–74) for the candicidin group, the difference being statistically insignificant ($p = 0.16$). Comparison of the two groups showed no significant differences in symptom scores, uroflowmetry data or residual urine either before initiation of treatment or after treatment for 4 months (Tables 1 and 2). However, after 6 months of treatment the residual urine was significantly lower in the candicidin group than in the placebo group. No differences were found in the maximum flow rate (Q_{max}), but when corrections were made for differences in bladder volume the corrected Q_{max} for the candicidin group was significantly higher than for the placebo group (Table 3).

Analyzing each group separately, we noted significant improvements in both irritative, obstructive and total symptom scores for the candicidin group, while the placebo group did not improve in irritative score. No objective improvements were found in the placebo group but the candicidin group improved in both residual urine and corrected Q_{max} when pretreatment data were compared to data obtained after treatment for 6 months (Table 4). More than 3 months after completing the study two patients from the candicidin group and four patients from the placebo group had a TURP performed because of increasing symptoms.

Table 2. Comparison of symptom scores and findings at uroflowmetry in the placebo and candicidin groups after 4 months of treatment

	Symptom Scores			Uroflowmetry			Corrected		
	Total	Irritative	Obstructive	Voided vol. (ml)	Residual urine (ml)	Bladder vol. (ml)	Q_{max} ml x sec^{-1}	Q_{max} $ml^{0.5}$x sec^{-1}	Q_{ave} ml x sec^{-1}
Candicidin									
Median	9.5	3	6	180	30	234	11.5	0.71	4.3
Range	6–13	1–6	2–10	53–640	5–200	110–653	3.5–22.3	0.33–1.09	1.9–10.8
Placebo									
Median	11	4	6	180	48	268	8.5	0.55	4.1
Range	1–18	1–7	0–14	76–681	14–450	144–831	3.5–20.3	0.23–1.05	0.7–10.0
Statistics	$p = 0.62$	$p = 0.35$	$p = 0.94$	$p = 1.00$	$p = 0.23$	$p = 0.41$	$p = 0.27$	$p = 0.29$	$p = 0.70$

Table 3. Comparison of symptom scores and findings at uroflowmetry in the placebo and candicidin groups after 6 months of treatment

	Symptom Scores			Uroflowmetry			Corrected		
	Total	Irritative	Obstructive	Voided vol. (ml)	Residual urine (ml)	Bladder vol. (ml)	Q_{max} ml x sec^{-1}	Q_{max} $ml^{0.5}$x sec^{-1}	Q_{ave} ml x sec^{-1}
Candicidin									
Median	9	3	6	145	15	171	8.8	0.66	3.5
Range	3–16	1–7	1–11	34–310	0–285	48–319	2.6–19.5	0.15–1.36	1.0–12.2
Placebo									
Median	10	4	6	188	65	289	7.3	0.49	3.8
Range	5–20	1–8	0–14	72–396	5–350	91–560	3.6–19.3	0.21–1.06	1.2–8.0
Statistics	$p = 0.38$	$p = 0.76$	$p = 0.26$	$p = 0.17$	$p = 0.02$	$p = 0.03$	$p = 0.42$	$p = 0.02$	$p = 0.86$

Table 4. Comparison of pre-treatment data to 4- and 6-months data in the placebo and candicidin groups separately

	Placebo		Candicidin	
	4 Months	6 Months	4 Months	6 Months
Total symptom score	S	S	S	S
Irritative score	NS	NS	S	S
Obstructive score	S	S	S	S
Voided volume	NS	S	NS	S
Residual urine	NS	NS	NS	S
Bladder volume	NS	NS	NS	S
Q_{max}	NS	NS	NS	NS
Corrected Q_{max}	NS	NS	NS	S
Q_{ave}	NS	NS	NS	NS

S = significant; NS = non-significant

Discussion

In the study of diseases like BPH, in which spontaneous improvements have been reported to occur in as many as two thirds of the patients [8], clinical trials must include a control group and neither the patients nor the physician may know whether the patient gets placebo or the drug under trial. It is therefore no surprise that the open studies by Kljucharev et al. [16] and Keshin [15] reported high success rates and that Abrams noticed improvement in voiding in more than 60% of patients in both the control and the candicidin groups [2]. Accordingly we found that both the control and the treated group noticed improvement in their obstructive and total symptom scores while the placebo group did not improve in irritative score as did the candicidin group. However, when the two groups were com-

pared before treatment and at 4 and 6 months after treatment, no statistically significant differences in symptoms were found.

The use of maximum flow rate in assessment of bladder outlet obstruction is widely accepted [23, 25, 26]. Maximum flow rate depends on urine volume, and it is well documented that when maximum flow rate is plotted versus the $\sqrt{\text{volume}}$, the graph approximates to a straight line, i.e., the ratio $Q_{max}/\sqrt{\text{volume}}$ is constant. Thus a minimum volume of 150–200 ml is not crucial [11, 21, 26]. The volume under consideration should be the bladder volume (the voided volume plus the residual urine) rather than the voided volume, because the latter will lead to overestimation of the voiding ability [26]. When analyzing our data no difference was found between Q_{max} in the placebo and candicidin group. However, there was a significant difference in bladder volumes after 6 months of treatment and when this difference was taken into consideration a significantly higher Q_{max} was revealed in the candicidin group. According to Castro et al. [6] this increase in maximum flow reflects an increase in the cross-sectional area of the urethra, provided no change in the intravesical pressure has occured. This implies that the prostate gland might have diminished in size during the treatment period. No attempt was made to estimate changes in prostatic size employing rectal palpation because of the inaccuracy of this method [18]. A significant decrease in residual urine was found after 6 months of treatment with candicidin, while the difference was insignificant after 4 months. Sporer et al. also found a significant decrease in residual volume [27], the explanation of this observation being unclear. These results indicate that to be effective in terms of objective variables, candicidin treatment should be extended to at least 6 months.

Although we found candicidin to have some effect the results do not compare to those following prostatic surgery. Nevertheless, treatment with candicidin might be justified in patients who are poor surgical risks and in patients who refuse well-indicated surgery for prostatism.

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