Part 1

PROSTAQUIL™

Chapter 1
BPH: VARIATION IN PROSTATE VOLUME AND VESICAL VOLUME; EFFECTS OF PROSTAQUIL™

LEDDA A., BELCARO G., DUGALL M.
IRVINE3 LABS, DEPT OR MED BIOMED SCIENCES, CH-PE UNIVERSITY, ITALY

INTRODUCTION

BPH (Benign Prostatic Hypertrophy) is a nonmalignant growth of the prostate. Symptoms include bladder outflow obstruction with weak urine stream, hesitancy, urinary frequency and urgency, nocturia, feeling of incomplete emptying, terminal dribbling, overflow or urge incontinence and incomplete urinary retention.

The diagnosis is made by digital rectal examination and ultrasound considering symptoms. Cystoscopy, ultrasound, urodynamics or other imaging studies may be used to define and quantify the problem and to exclude concomitant problems, including cancer.

With a prostate volume >30 mL and a high *American Urological Association Symptom Score* the prevalence of BPH (within the age range 55-74, in subjects without prostate cancer) is around 19%.
If voiding criteria (maximum urinary flow rate <10 mL/sec and a post-void residual urine volume >50 ml) are considered the prevalence is only 4%.
The prevalence of BPH increases from 8% in subjects between 31 and 40 years to 40-50% in men between 51 and 60 and to >80% in men older than 80 years (1,2).
At the moment, there is no definitive treatment (1). The treatment is generally symptomatic; 5-alfa reductase inhibitors, alfa blockers and surgical options are possible treatments.
However signs and symptoms may affect a large number of subjects, therefore costs and safety, considering the great number of possible procedures, are important issue. Several options may be considered. Initial mild, symptoms may benefit from milder drug/supplement management (Saw Palmetto (SP) or other supplements).
In most preparations of SP, fatty acids inhibit 5alfa-reductase opposing the conversion of testosterone to dihydrotestosterone. Most SP formulations tested in studies are hexane extracts of saw palmetto berries (with 80-90% essential fatty acids and phytosterols).
Strong evidence supports the use of SP to treat signs/symptoms of BPH (i.e.frequency) (1). Prostaquil™ (Alchem, capsules, 100 mg) includes Pygeum Extract, Saw palmetto oil, zinc, oxide and pumpkin seed oil.
Pygeum is one of the favourite leaves of the mountain gorilla. The plant has been used for fever, malaria, wound care, stomach pain, kidney disease and as an appetite stimulant. Pharma standard extracts of Pygeum, have been succesfully used for BPH.

This registry evaluated the management of initial symptoms of BPH in otherwise healthy subjects, using Prostaquil™ (Alchem, India) in a supplement registry (150 days).

Patients-Methods: subjects with BPH were included. The target of the registry was the supplementary management of initial, mild symptoms in subjects not using other drugs, who did not have previous surgical procedures or urinary retention and no significant infections in the 3 years before the registry.

STANDARD MANAGEMENT (SM) in subjects without surgical indications, with initial symptoms, is based on avoidance of anticholinergic, sympathomimetics, opioids.
Alfa-adrenergic blockers (terazosin, doxazosin, tamsulosin, alfuzosin) improve voiding; 5 alfa-reductase inhibitors (finasteride, dutasteride) tend to reduce prostate size.
In the treatment of BPH a combination of drugs is generally more effective than single treatments. Regular voiding, avoiding long periods sitting, regular exercise, regular hydration/drinking avoiding caffeine and spices, a diet with decreased sugar and NaCl are adviced.
In a second, supplement group, Prostaquil™ was used at the dosage 2 cp in the evening. The product includes Pygeum extract (100 mg) and Saw palmetto oil (35 mg). The evaluation forms for these patients was a modified IPSS (International prostate symptom score) adapted to the need of self-management and self evaluation.

REGISTRY: two groups were progressively formed: a control group using only SM (according to the Merck Manual) and another group using SM and the supplementation.

Table 1.1. Registry groups.

Group	Prostaquil™	Controls
Number	19	29
Days of follow up	166;7	182;4.7
Age	63.2:4	62.6;3.3
PSA <4 ng/mL	3.2	3.14
Creatinin levels	Normal	Normal
Prostatic volume (normal <30 mL)	39.4;5.5	39.3;3.1

Types of evaluation: a high-resolution ultrasound scanner (Preirus, Hitachi, Japan) was used to evaluate residual urinary volumes and prostate morphology; also PSA and routine blood tests (hematocrit and test of liver/kidney function, elecrtolytes) were used at inclusion and end-study.

RESULTS

The two resulting groups were comparable for age, symptoms distribution and ultrasound findings (both considering prostate volume and residual urinary volume). The days of

follow up were comparable. No side effects or tolerability problems were observed and compliance was optimal with more than 97% of the capsules correctly used.
Emptying, frequency, intermittency, urgency, weak flow, straining, nocturia were all significantly improved with Prostaquil™ ($p<0.05$); the improvement – evaluating any single item - was significantly superior to the improvement observed in controls ($p<0.05$).

The **most important target measurement** *(the residual vescical volume)* decreased for 54.5 ml with the supplement group (vs 29 ml in controls).
In the supplement group 4 out of 19 subjects had to use other drug (not more than 3 days) to control symptoms; in the control group 12 out of 29 patients used some other drug including anti-inflammatory agents or antibiotics ($p<0.05$).
Urinary bacterial contamination was absent at inclusion and at the end of the study.

Table 1.2. The main observation items measured in a visual analogue scale line.

		Prostaquil™		**Controls**	
	Score				
Symptoms	Range	Inclusion	**150 days**	Inclusion	150 days
Emptying	**(0-5)**	**3.4;0.4**	**1.2;0.4***	**3.3:0.2**	**2.7;0.4***
Frequency		3.5;1	1.4;0.4*	3.6;0.3	3.3;0.2*
Intermittency		**3.4;0.4**	**1.4;0.2***	**3.5;0.3**	**2.7;0.1***
Urgency		3;0.3	1.3;0.2*	2.9;0.2	2.8;0.2*
Weak flow		**3.6;0.1**	**1.9;0.2***	**3.5;0.2**	**2.9;0.1***
Straining		3.5;0.2	2.1;0.1*	3.6;0.2	3.1;0.2*
Nocturia		**3.4;0.1**	**1.4;0.2***	**3.4;0.2**	**2.8;0.4***
Residual vescical urinary volume in ml (method a + method b)/2		98.8;11	44.3;8*	97.2;3.3	68.2;6*

Volume formula:(4/3)*(pi)*(r1)*(r2)*(r3) where r1 = radius 1, r2 = radius 2, r3 = radius 3 are the radii of the three dimensions. In 3 dimensions, the volume inside a sphere/spheroid (ball-shape) is derived to be $V = \frac{4}{3}\pi r^3$ where r is the radius of the sphere and π is the constant pi. The formula is also derived using integral calculus, i.e. disk integration to sum the volumes of an infinite number of circular disks centered side by side along the x axis from $x = 0$ where the disk has radius r (i.e. $y = r$) to $x = r$ where the disk has radius 0 (i.e. $y = 0$).

DISCUSSION

Subjects with newly diagnosed BPH and initial or mild symptoms may try self-management of symptoms with a non-prescription supplement as the first step.
Pygeum and Saw Palmetto-derived compounds are considered good options, recognized, for long-term management and considered effective and safe. Long-term treatment with 5-alfa reductase inhibitors or alfa blockers – particularly used as the initial option - may expose patients to side effects and significant, potential interferences and interactions with other drugs.
In men taking finasteride significant worsening of ejaculatory function has been observed; also both doxazosin and finasteride may cause significant worsening in erectile function and cause other sexual problems (including alteration in libido).
Also *depression*, and *anxiety* have been observed. Rare side effects include breast tenderness and enlargement (*gynecomastia*) and *allergic* reaction. *Finasteride* is also associated with *intraoperative floppy iris syndrome* and *cataract* formation.
At present, there is very limited evaluation of the medical treatment of BPH.
Actually, medical treatment is limited and there is a very minor possibility of self-medication for patients with initial, limited and controllable symptoms. Most studies have been focusing on interventional and surgical treatments that generate much higher profits. Most studies on medical treatment are relatively old and population-limited. Studies on drug interactions are also limited or unsatisfactory. Medical treatment is basically considered a poor option by most patients and specialists.
Most urologists are not interested in treatment or managing BPH with drugs and therefore they have a minimal interest in supplements that may be a very significant option in countries where the medical services are limited or when there is no medical coverage.
The sexual aspects related to treatments and the potential advantage of Pygeum have not been studied with full or adequate attention. A number of evaluations have studied *Pygeum* in treating BPH, comparing it to a placebo rather than drugs. A review indicates that standard preparations may be a useful to control urinary symptoms in BPH, but larger, clinical studies are needed.

In conclusion, Prostaquil™, a new generation PS supplement – including Pygeum - may be an important option for self-management in most uncomplicated patients with BPH.

References

1. Kim EH, Larson JA, Andriole GL. Feasibility of an alternative option for the management of male lower urinary tract symptoms. J Urol. 2015 Sep 10. pii: S0022-5347
2. Romics I. Pharmacologic treatment of benign prostatic hyperplasia. Orv Hetil. 2003 Sep 14;144(37):1809-1422
3. Belcaro G, Dugall M, Luzzi R, Ledda A, Pellegrini L, Hosoi M, Errichi BM, Francis S, Cornelli U. Supplementary management of benign prostatic hypertrophy with Prostaquil™. An 8-week registry. Minerva Gastroenterol Dietol. 2015 Oct 22. [Epub ahead of print].