

Potassium Paraaminobenzoate (POTABA™) in the Treatment of Peyronie's Disease: A Prospective, Placebo-Controlled, Randomized Study

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Abstract

Purpose: The aim of this study was to investigate the effect of potassium paraaminobenzoate (Potaba™) in Peyronie's disease in a prospective, randomized, double-blind, placebo-controlled, multicentre study during a 12-months period of treatment.

Patients and methods: 103 patients with Peyronie's disease and a history <12 months, non-calcified plaques and without pre-treatment were included. 51 were randomized to potassium paraaminobenzoate, 52 to placebo receiving 4 × 3 g/day for 12 months. Follow-up was performed during the treatment period. Response has been defined as regression in plaque-size and/or reduction in penile curvature of at least 30%. Data analysis was focussed on 75 patients who completed the study [valid-cases (VC)].

Results: No severe adverse events occurred. Response rates were 74.3% on potassium paraaminobenzoate and 50.0% on placebo ($p = 0.016$). Mean plaque-size decreased from 259 mm² to 142 mm² in the treatment arm. In the placebo group, plaque-size aggravated from 259 mm² to 303 mm² after 6 months but improved slightly to 233 mm² after 12 months. Differences between the groups were significant ($p = 0.042$). Pre-existing curvature did not improve under the drug ($p = 0.066$) but comparing the development of new curvature or deterioration of pre-existing curvature under potassium paraaminobenzoate penile deviation remained stable. However, under placebo penile curvature deteriorated significantly in 32.5% of the cases ($p < 0.001$). No significant differences concerning decrease of pain could be observed between the two groups (82.6% vs. 77.3%).

Conclusions: The results of this study indicate a significant plaque-related effect of potassium paraaminobenzoate. There was no relevant difference with regard to improvement of pre-existing penile deviation. However, under potassium paraaminobenzoate a significant protective effect on deterioration of penile curvature could be demonstrated. Potassium paraaminobenzoate appears to be useful to stabilize the disorder and prevent progression of penile curvature.

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Keywords: Peyronie's disease; Potassium paraaminobenzoate; Double-blind multicenter study

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1. Introduction

Peyronie's disease is a localized disorder of connective tissue primarily affecting the tunica albuginea and surrounding erectile tissue [1]. Development of an inelastic, fibrotic plaque of "scar"-tissue usually located at the penile dorsum is associated with an excessive collagen deposition and disorders of elastic fibers. Clinically this results in a condition characterized by pain, penile curvature and loss of rigidity during sexual intercourse [1]. Peyronie's disease has two discernible clinical phases: An acute inflammatory phase characterized by pain, and a chronic phase with reduction of active inflammation and subsiding of pain [1]. Although the definite etiological pathogenesis of Peyronie's disease remains unknown patients may show an inherent predisposition to an excessive, fibrotic response to mechanical traumatic lesion of the tunica [2].

Potassium paraaminobenzoate (PotabaTM) appears to have both an anti-inflammatory and an anti-fibrotic effect due to stabilization of the tissue serotonin-monoamine oxidase activity and a direct inhibitory effect on fibroblast glycosaminoglycane secretion [3–5]. Historically, it has been used for the treatment of chronic inflammatory conditions associated with fibrotic alterations including dermatomyositis and scleroderma. In Peyronie's disease a "clinical" effect on penile plaques has been observed in non-controlled studies [6] and also in a preliminary controlled clinical trial [7] concerning plaque-size, penile pain, and even curvature. Due to the natural course of the disease with stable periods and the possibility of complete spontaneous resolution [8,9], investigators today accept the need to evaluate the potential benefit of such a conservative therapy approach in a placebo-controlled trial [10].

The aim of this study was to investigate the therapeutic effect of potassium paraaminobenzoate (PotabaTM) in Peyronie's disease in a prospective, randomized, double-blind, placebo-controlled, multicentre study over a 12-months period of treatment.

2. Patients and methods

This multicenter study (11 centers) was initiated by the principal investigator and approved by the ethics committees of all participating centers of the Peyronie's Disease Study Group of the Andrological Group of German Urologists. Patients were informed about questions related to the efficacy of conservative oral treatment of Peyronie's disease with potassium paraaminobenzoate (PotabaTM). Information was provided about research details and possible side effects of the drug. All patients agreed to

the double-blinded design of the prospective, placebo-controlled trial and gave written informed consent following accepted GCP-criteria. The study included 103 men (age mean 50 years, range 18–71 years) who presented with Peyronie's disease at different centers. Inclusion criteria were a case history of a maximum of 12 months, no prior treatment, and no evidence of calcified plaques. Diagnostic procedures included a standardized interview assessing painful erections with a graduated pain score (grade 0 = no pain, grade 1 = mild, grade 2 = moderate, grade 3 = severe pain), a history of cohabitation impairment and evidence of penile curvature. Evaluation of the plaque was performed on the fully stretched penis during flaccidity by palpation and measurement of the plaque-size in length and width (mm²) using a caliper and following a standardized, established protocol by all centers [11]. In cases with more than one plaque the size of each plaque was added up to one total plaque size. Ultrasound was applied to exclude calcifications. An erection test utilizing intracavernous injection of 10–20 µg (including redosing) prostaglandin E₁ (Schwarz Pharma, Monheim, Germany) and manual stimulation after the injection was performed to determine the objective curvature under full erection [11]. Measurement of penile curvature was performed using standardized photos taken during the pharmacoinjection test according to the Kelâmi technique. Reduced quality of erection was noted, classifying erectile response to intracavernous injection into 6 grades (E0 no response; E1 slight tumescence, no rigidity; E2 medium tumescence, no rigidity; E3 full tumescence, slight rigidity; E4 full tumescence, medium rigidity; E5 full erection) [12]. A validated symptomatic evaluation of erectile function with a standardized questionnaire [13] was not available at the time of study initiation. Laboratory examinations included hemoglobin, platelet counts, creatinine, and transaminases. Patients with a history of prior treatment, symptoms of more than 12 months duration, sonographic evidence of calcification, and/or no response to the intracavernous injection test were excluded. Further clinical exclusion criteria included evidence of diabetes mellitus, compensated nephropathy, and chronic gastric and bowel diseases. Examinations under therapy following the pre-treatment visit were scheduled at 1, 2, 3, 6, 9 and 12 months after onset of therapy including an erection test to determine changes of curvature.

Patients were randomly divided into 2 groups. The first group received 3 g potassium paraaminobenzoate (powder) 4 times daily, and the second group received placebo, respectively over the twelve months course of the study. The placebo powder was a mixture of potassium citrate, lactose, hydrous, and potassium chloride identical in colour and appearance to the active drug. Response was defined as full resolution or as reduction in plaque-size (product of length and width in mm²), and/or reduction in penile curvature of at least 30% in comparison to the initial evaluation. A minor goal of the study were alterations of penile pain under erection. Alterations of erectile function were only documented.

Statistical analyses was performed as specified by the study protocol. Student's *t*-test and Mann-Whitney's *U*-test were used as well as analyses of covariance for repeated measurements to compare means and medians, respectively, of continuous distributions. Categorical data were analyzed by means of χ^2 -test. The sample size was estimated prospectively to show significant superiority of verum compared to placebo with respect to response rates. With $\alpha = 0.05$, $\beta = 0.20$ and $\Delta = 30\%$ a minimum of 46 patients per group should complete the trial.

3. Results

3.1. Disposition of patients and baseline characteristics

In total, 103 patients participated in the study. In the ITT group (Intention To Treat, confirmed drug intake), 51 patients were treated with potassium paraaminobenzoate and 52 patients received placebo (Table 1). Baseline differences between the groups (Table 1) were not significant, and basic homogeneity of the tested groups could be assumed.

7 patients (13.7%) of the potassium paraaminobenzoate group and 4 men (7.7%) of the placebo group dropped out prematurely due to side effects: 4 patients each in the potassium paraaminobenzoate group (7.8%) and placebo group (7.7%) due to gastro-intestinal disorders. Additionally, one patient each in the potassium paraaminobenzoate group dropped out to pruritus, fever or chills. All other noted disorders resolved without any problems during the course of ongoing treatment. Thus, a causal relationship was unlikely. Clinically significant pathological laboratory values were not observed. Further 17 men (9 in the potassium paraaminobenzoate group versus 8 in the placebo group) had to be excluded due to not sufficient compliance during drug intake what means that the patient informed the physician that he did not take the

drug regularly. After exclusion of 28 men who prematurely terminated the therapy due to side effects ($n = 11$) or non-compliance ($n = 17$), altogether 35 patients of the potassium paraaminobenzoate group and 40 patients of the placebo group were included in the valid-case population resulting in 75 cases (VC-group). This differentiation between the ITT- and VC-population allows a proper statistical analysis despite the relatively high drop out rate over the treatment period of one year.

3.2. Clinical study outcome

The study outcome-defined as full resolution or reduction in plaque size and/or reduction in penile curvature of at least 30% - showed a statistically significant difference ($p = 0.016$) in favour of the potassium paraaminobenzoate group (26 of 35 patients, 74.3%) versus placebo (20 of 40 patients, 50.0%). Concerning plaque size measurement of this parameter indicated a significant reduction under potassium paraaminobenzoate with the largest differences found after 3, 6 and 9 months (Fig. 1). The treatment effects in the study period were significant ($p = 0.042$).

There were no relevant differences between potassium paraaminobenzoate and placebo with regard to improvement of preexisting penile deviation ($p = 0.066$) (Table 2). Starting from the baseline, however, there was a higher rate of deterioration detectable in the placebo group (Table 2). In the 13 patients with an initial straight penis none developed a deviation under potassium paraaminobenzoate. But 6 out of 8 patients (75%) under placebo developed a new penile curvature (Table 2). This difference was significant

Table 1

Demographic and other baseline characteristics

Parameter	Potassium paraaminobenzoate ($n = 51$)	Placebo ($n = 52$)
Age (years)	49 (18–70)	53 (24–71)
Duration of Peyronie's disease [months; median (range)]	6 (1–12)	6 (1–12)
Number of plaques		
1	44 (86.3%)	43 (82.7%)
2	5 (9.8%)	6 (11.5%)
3	1 (2.0%)	2 (3.8%)
4	1 (2.0%)	1 (1.9%)
Plaque-size [mm^2 ; means \pm SEM]	264.1 \pm 36.6	259.8 \pm 28.8
Penile curvature	45 (88.2%)	43 (82.7%)
Pain during erection		
no	18 (35.3%)	21 (40.4%)
mild	16 (31.4%)	12 (23.1%)
moderate	14 (27.5%)	14 (26.9%)
severe	3 (5.9%)	5 (9.6%)
Cohabitation impaired or impossible	31 (60.8%)	38 (73.1%)
No rigidity, reduced tumescence (E0, E1, E2)	1 (2.0%)	3 (5.8%)
Other fibrotic diseases ^a	12 (23.5%)	16 (30.8%)

^a Predominantly Dupuytren's contracture.

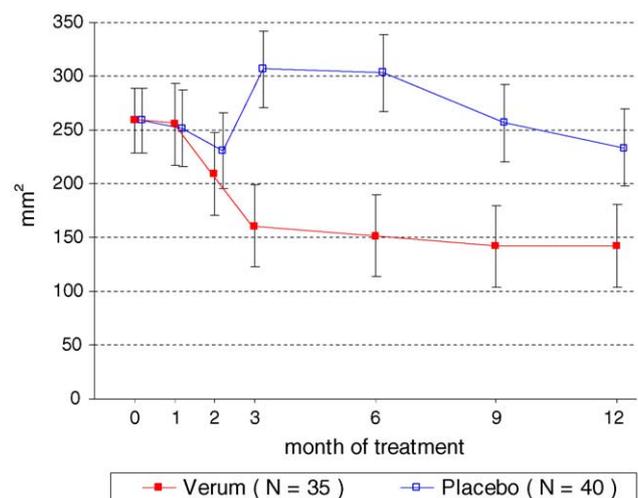


Fig. 1. Baseline adjusted means (\pm SEM) of the penile induration (valid cases). Note: one-sided p -values of t -test for adjusted means (months): 0.530 (1), 0.341 (2), 0.003 (3), 0.002 (6), 0.015 (9), 0.042 (12); treatment factor of the ANCOVA: $p = 0.042$ two-sided, interaction of month and treatment: $p = 0.004$.

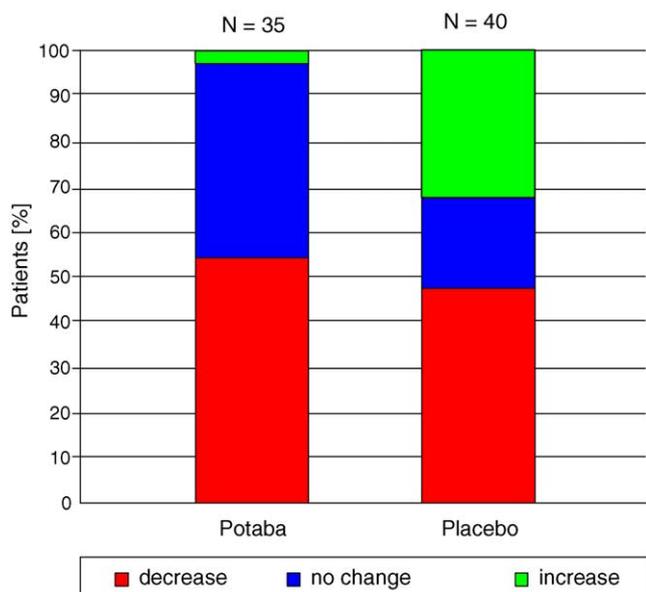


Fig. 2. Response concerning penile curvature in the valid cases.

Table 2

Outcome of penile curvature (Valid cases: $n = 75$; χ^2 -test, Fisher's test)

	Potassium Paraaminobenzoate ($n = 35$)	Placebo ($n = 40$)
Preexisting penile deviation	$N = 30$	$N = 32$
decrease	19 (63.3%)	19 (59.4%)
no change	10 (33.3%)	8 (18.8%)
increase	1 (3.3%)	7 (21.9%)
Initial straight penis	$N = 5$	$N = 8$
stable	5 (100.0%)	2 (25.0%)
new curvature	0 (0%)	6 (75.0%)
Total number of deterioration of penile curvature	1/35 (2.9%)	13/40 (32.5%)

($p = 0.021$). Comparing new development or deterioration of penile deviation in both groups, one out of 35 men (2.9%) of the potassium paraaminobenzoate group indicated progression versus 13 out of 40 men (32.5%) under placebo (Fig. 2). This difference was significant ($p = 0.001$).

Table 3

Changes of erectile quality according to the erection score ranging from E0 to E5

Erection score (E0–E5)	Potassium Paraaminobenzoate ($N = 35$)		Placebo ($N = 40$)	
	Pre-treatment n (%)	Posttreatment n (%)	Pre-treatment n (%)	Posttreatment n (%)
E0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
E1	0 (0%)	0 (0%)	0 (0%)	3 (7.5%)
E2	1 (2.8%)	0 (0%)	1 (2.5%)	1 (2.5%)
E3	2 (5.7%)	2 (5.7%)	4 (10.0%)	1 (2.5%)
E4	8 (22.9%)	7 (20.0%)	7 (17.7%)	10 (25.0%)
E5	24 (68.6%)	26 (74.3%)	28 (70.0%)	25 (62.5%)

Incidence of painful erections rapidly subsided in both groups. The improvement rates reached 82.6% under potassium paraaminobenzoate, not significantly different to 77.3% under placebo. With regard to erectile quality as parameter of sexual dysfunction no differences were observed (see Table 3).

4. Discussion

A causal drug therapy is not available yet due to the uncertain etiopathology of Peyronie's disease [1]. Unfortunately, basic studies describing the mode of action for drug treatment of Peyronie's plaque are lacking [1,10]. Only for colchicine animal data do demonstrate a decreased TGF- β protein expression as a result of drug application [14]. Recently, the effects of colchicine, Prostaglandin E₁, verapamil and α -interferon have been investigated in cell culture models. This study demonstrated an inhibitory effect in varying degrees depending on the type of substance and its concentration [15].

The antifibrotic and antiinflammatory mechanisms of potassium paraaminobenzoate on skin fibroblasts have been investigated especially under cell culture conditions. These studies have demonstrated that potassium paraaminobenzoate increases oxygen consumption and inhibits the secretion of mucopolysaccharide and glycosaminoglycane by the cells [4,16]. Other investigators explain the potential anti-inflammatory effect of the drug by metabolization of activated granulocytes at the site of inflammation providing some experimental evidence that potassium paraaminobenzoate may be helpful in retarding abnormal fibroblast proliferation [17]. A further unsolved problem that needs to be addressed is the lack of knowledge regarding significant tissue levels of orally taken drugs within the plaque. Recent data using local or electromotively provided transdermal use of verapamil demonstrate contradictory results. While administration as a gel failed to achieve significant levels inside the plaque [18], in 71.5% of the specimen after

electromotive drug administration significant levels of the drug could be detected [19]. These studies highlight the unsolved pharmacokinetic problem of absorption and local bioavailability for all oral drug applications.

Regarding these limitations, it seems vital that drug therapy - the first option for many experts counseling patients with Peyronie's disease has to be clinically assessed under controlled conditions. Unfortunately, a proven effect on pain, penile curvature and plaque size has generally not been demonstrated in a randomized, placebo-controlled, double-blinded study design for any orally applicable substance [10]. Zarafonitis and Horrax were the first to describe an improvement of pain, curvature and plaque-size under potassium paraaminobenzoate [3]. These findings were confirmed in a recent study by Carson [6]. However, all these data are the result of non-controlled studies and did not consider the natural history of the disease with periods of improvement and gradual spontaneous resolution [8,9]. An European investigator group published the preliminary results of a prospective double-blinded controlled study on potassium paraaminobenzoate including 41 patients in 1983 [7]. Although there was a trend towards improvement of the symptoms under potassium paraaminobenzoate, differences concerning penile pain, erectile failure, and plaque size were not significant [7]. In our study we observed a response rate of 50.0% in the placebo group and 74.3% in the potassium paraaminobenzoate group. The response rate to placebo seems remarkably high compared to the verum group. This could perhaps be explained by the natural course of the disease with response rates in 13% regarding all symptoms [8] or on plaque size in up to 71% in an older study [21]. This underlines the importance of placebo controlled studies. In a placebo controlled trial on tamoxifen response rates for placebo of 25% for plaque size, 42% for curvature and 75% for penile pain have been observed [22].

However, a significant plaque-related effect using potassium paraaminobenzoate in comparison with placebo was evaluable in our study resulting in a decrease of plaque-size hypothetically reducing the scarification segment as one cause of curvature [20]. Furthermore, our data do provide evidence for a distinct "protective" effect of potassium paraaminobenzoate concerning the formation of new penile deviation or progression of curvature under therapy. It seems that potassium paraaminobenzoate may be able to stabilize the disease

preventing deterioration of penile curvature. This would be of high value for the patients for two reasons: In cases with a plaque without penile deviation the development of curvature could be avoided under administration of the potassium paraaminobenzoate. Moreover, the progression of pre-existing curvature seems to be influenced positively. Nevertheless, distinct penile curvature cannot be improved.

In this study painful erections were not influenced by the drug compared with the natural history in the placebo group. Unfortunately, with initiation of the study an objective assessment of erectile function, e.g. with a standardized questionnaire [13] was not available. The effect of the drug on hampered sexual intercourse could not be proven.

The drop-out rate due to non-compliance that became evident in both groups was remarkable although the incidence of predominant gastrointestinal side effects was similar under potassium paraaminobenzoate and placebo. Even though the rate of these side effects is much lower than in the first randomized trial 25 years ago with a drop-out rate of 25% in the potassium paraaminobenzoate group and 19% in the placebo group [7]. Our experience with non-compliant men provide some evidence that the powder application with an inconvenient taste and the amount of drug intake contribute to this unfavourable outcome.

There is no doubt that spontaneous improvements do occur ranging from 3.8 to 13% of all cases [8,9]. That is why potential effects of oral drug therapy have to be evaluated critically under placebo-controlled conditions [10]. The results of our study demonstrate a significant improvement of plaque size but no improvement of manifest curvature. However, a significant protective effect on the development of new penile curvature and inhibition of progression of penile deviation could be observed under potassium paraaminobenzoate.

5. Conclusion

Oral treatment with potassium paraaminobenzoate (PotabaTM) resulted in a significant effect on plaque size in this randomized, placebo-controlled study but no improvement of manifest penile deformity was evident. However, potassium paraaminobenzoate can prevent the development and further progression of penile curvature.

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Editorial Comment

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There are a few drawbacks on the currently available medical therapies for Peyronie's disease. The first concerns the low level of scientific evidence upon which the administration of the majority of compounds is based. Several non surgical treatment options for Peyronie's disease have gained a massive popularity despite their scientific background is often supported by studies at best non randomised and uncontrolled. There are only a few randomised well conducted studies whose statistical conclusions are sometimes limited by the small number of patients recruited.

Another limitation often encountered in studies addressing a treatment option for Peyronie's disease is the absence of a placebo arm. Data reported by patients with a Peyronie's disease history lasting from 1 to up to 5 years showed that the disorder self-resolved in 14% of cases and remained unchanged in 47% [1]. In one of the few controlled studies available [2], in which Tamoxifen was compared to placebo, a 46% rate of reduction in penile deformity was recorded in the placebo arm. Additionally, it is well known that spontaneous improvement of Peyronie's disease related penile pain usually occurs within 6 months as the inflammation settles [3]. The picture is further con-

fused by the absence of a precise knowledge in the pathogenesis of Peyronie's disease, an essential prerequisite for a rationale therapeutic approach.

Up to the advent of the current study, *Potassium paraaminobenzoate (Potaba)* had been widely employed as a treatment option for Peyronie's disease based on its hypothetical ability of decreasing the fibrogenesis [3]. For many years, the only literature report coming out in a Medline search on this compound had been represented by a retrospective and uncontrolled review of 32 patients treated for 3 months with 12 g of Potaba powder daily and followed for 8 to 24 months. An improvement of penile angulation had been subjectively reported in 18 out of 31 patients, with a complete resolution in 8 patients and a decrease in plaque size in 18 of 32 patients [4]. Given these figures, the authors should be congratulated for providing additional scientific evidence on the use of this oral medication for Peyronie's disease through a rigorously conducted study. Moreover, the overall 50% response rate in the placebo arm as well as the lack of efficacy of Potaba for penile pain leads to the obvious conclusion that many of the treatments currently in use for Peyronie's disease, whose efficacy has only been assessed with case studies, could simply be ineffective.

After reading this elegant paper two questions may be raised. One, mentioned by the authors themselves in the discussion, relies on the limitations in the measure-

ments of the treatment end points in Peyronie's disease, in particular the penile curvature. Even if the photograph of an erected penis following intracavernous injection of vasoactive drugs is a widely accepted objective method to assess post-treatment curvature changes, psychological factors may negatively affect pharmacological erection in a clinical setting, thus making this technique poorly reproducible [5]. I wonder whether the subjective patient's opinion may provide more relevant clinical information in a double blind placebo controlled setting. The other question concerns the clinical relevancy of the reported beneficial effects of Potaba. For instance, is the statistical significant reduction in plaque size and the preventive effect on penile curvature observed in the present study outweighed by such a demanding treatment schedule (four times a day for one year)? The reader may be left

with the impression that the use of Potaba in clinical practice is still a controversial issue . . .

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