Nitric Oxide Based Influence of Nitrates on Micturition in Patients with Benign Prostatic Hyperplasia

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Background: Nitric oxide (NO) is involved in the physiologic regulation of smooth muscle relaxation in the prostate. Organic nitrates act as NO donors. In this prospective open study we prove the influence of orally given nitrates on micturition.

Methods: Thirty-two patients underwent a urological medical check-up prior to starting nitrate medication for cardiovascular disease. We examined peak flow rates, residual urine, IPS-score, PSA level and prostate volume. Exact inclusion and exclusion criteria were defined. Fifteen patients suffered from obstructive symptoms, 17 patients reported no subjective micturition problems. Urological re-evaluation was performed two weeks and three months after nitrate medication.

Results: A significant improvement of peak urinary flow rates (+3.1 ml/s; p<0.05), IPS score and significant decrease of residual urine volume (−22 ml; p<0.05) were found in the symptomatic patients. No significant changes of micturition parameters were found in asymptomatic patients. PSA levels and prostate volumes did not change in either groups.

Conclusions: Organic nitrates influence micturition parameters in patients with obstructive benign prostatic hyperplasia. This might be explained by the known mechanism of NO donation (smooth muscle relaxation) of nitrates. More functional controlled studies are necessary to describe the grade of influence of nitrates on the prostate. Concomitant oral medication with nitrates must be considered as a relevant bias factor on BPH in future clinical studies.

Introduction

During the past few years nitric oxide (NO) has been found to be a fundamental biological messenger mediating neurotransmission, smooth muscle relaxation and vasodilatation in various organs [1, 2, 3]. In the male genit al tract the bladder neck, prostate, vas deferens, seminal vesicle and corpus cavernosum were found to have high levels of CA⁺-dependent nitric oxide synthase (NOS) activity [4]. NO plays an important role in the autonomic innervation of all compartments of prostatic tissue [1, 5]. Recently Bloch et al.
showed that in obstructive benign prostatic hyperplasia the nitrinerigic innervation is reduced as compared to that in normal prostate tissue [6]. A decrease of NO release subsequently causes an increase of smooth muscle tone, as shown by electrical field stimulation in the human and canine prostate [5]. Therefore NO may play an important role in the dynamic obstructive component of benign prostatic hyperplasia. It is possible that the α-adrenergic innervation may be antagonized by non-adrenergic non-cholinergic (NANC) induced relaxation mediated by NO [6, 7].

There is no clinical study demonstrating the influence of NO donors on the human prostate. The importance of nitrovasodilators as pharmacological tools in the treatment of cardiovascular diseases or congestive heart failure has been well known since 1867 [8]. Many patients are treated with oral nitrates in the form of isosorbid dinitrate or glyceryl trinitrate [8, 9]. Nitrovasodilators act as donors of NO which leads to vasodilatation. In many studies the importance of NO in regulating basal tone in resistance vessels has been demonstrated [8, 9, 10].

The influence of vasodilators like isosorbid dinitrate on micturition has so far not been examined. We assessed the influence of organic nitrovasodilators on micturition parameters in this prospective study.

**Patients and methods**

Between May 1997 and June 1998 we examined 35 male patients who were referred to us by a cardiologist for routine urological check-up. These were performed in a urological office before starting a long-term oral treatment with isosorbid dinitrate (60–120 mg/day). The nitrates were prescribed after an external cardiological examination by a cardiologist for clinical forms of ischaemic heart disease (e.g. stable or unstable angina, congestive heart failure). All patients were under outpatient cardiological control to monitor the nitrate medication and effect.

A primary urological evaluation of the micturition parameters was performed on all patients by the measurement of peak uroflow, residual urine volume, prostate volume determined by transrectal ultrasound (TRUS) and symptom score (IPSS questionnaire). The inclusion and exclusion criteria for the study are listed in Table 1.

No patient suffered from insulin dependent diabetes. Four patients had concomitant medication with antihyperlipidaemic agents and four patients were treated with low dose acetyl salicylate.

A urological re-evaluation was performed two weeks and three months after initiation of nitrate medication. Two weeks after nitrate medication uroflow and sonographic residual urine volume were examined. Three months after nitrate medication measurement of uroflow, residual urine, TRUS, symptom score and PSA were repeated. No urological medication (e.g. phytotherapeutic agents, 5-alpha-reductase inhibitors or α-agonists) were prescribed during this period. All urological examinations were performed by the same investigator.