bladder and detrusor hyperreflexia (1). We conducted the first placebo-controlled study to investigate the short-term efficacy and safety of oral temiverine in the treatment of urinary frequency, urgency, and urge incontinence. To obtain information on dose–response relationships, two dosage schemes with increasing doses were compared.

Methods: The study enrolled 220 patients with urodynamically confirmed bladder overactivity, increased frequency of micturition (at least 8 micturitions per 24 hours), and symptoms of urgency and/or urge incontinence (at least one episode per 24 hours). After a run-in period of one to two weeks, the study participants were randomly allocated into three parallel groups. One group (N=72) received placebo tablets twice daily throughout the study; the low-dose group (N=76) receivec oral temiverine 5 mg twice daily for two weeks, followed by 10 mg twice daily for another two weeks; and the high-dose group (N=72) received 10 mg of temiverine twice daily for two weeks, followed by 20 mg twice daily for another two weeks. Both the participants and investigators were masked to the treatment allocation. The participants visited the study site at the beginning and end of the run-in period and after two and four weeks of treatment. At the end of the run-in period, before the clinic visit at two weeks, and at the end of the study the participants recorded their daily and nightly micturition frequency, including the number of incontinence episodes, on five consecutive days and volume voided during two of those five days. Adverse events reported by the participants were recorded at each clinic visit. A 12-lead electrocardiogram and blood samples for monitoring liver and kidney function and serum electrolytes were obtained before treatment, after two weeks of treatment, and at the end of study treatment. The study was conducted in urology and gynecology clinics in Denmark, Finland, Norway, Sweden, and the UK.

Results: After four weeks' treatment, the mean frequency of micturition decreased by 1.6 (14%) and 1.9 (15%) micturitions in the high- and low-dose groups of temiverine, respectively, while the corresponding decrease in the placebo group was 1.5 (12%) (P=0.53, baseline-adjusted analysis of variance). Voided volumes increased by 9%, 11%, and 5% in the high-dose, low-dose, and placebo groups. In patients with urge incontinence at baseline (72% of participants), the mean number of incontinence episodes decreased by 42%, 30%, and 24%, respectively, in the high-dose temiverine, low-dose temiverine, and placebo recipients (P=0.19). At the end of treatment, 52%, 49%, and 39% of the high-dose temiverine, low-dose temiverine, and placebo recipients, respectively, reported improvement in their bladder condition compared with baseline. Dry mouth was the most common adverse event, reported by 25% in the high-dose group, 8% in the low-dose group, and 6% in the placebo group. The incidence of headache was slightly lower in the active treatment groups than placebo, while the rates of occurrence of fatigue, abnormal vision, dyspepsia, nausea, and influenza-like symptoms were comparable in all groups. No electrocardiographic changes were observed; a clinically meaningful increase in liver enzymes was observed in one patient in the low-dose temiverine group.

Conclusions: In the dose range studied, temiverine is safe and well tolerated but does not appear to be efficacious in the short-term treatment of symptomatic bladder overactivity.

Reference: (1) Randomized double-blind study to compare clinical efficacy of temiverine and propiverine for unstable bladder and detrusor hyperreflexia. Neurourol Urodynam 1997;16(5):345–6.

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THE EFFECT OF NITRIC OXIDE ON ACETYLCHOLINE RELEASE IN FEMALE RABBIT BLADDER

Aims of Study

The parasympathetic nervous system plays an important role in the function of the lower urinary tract (1). A major neurotransmitter for physiological bladder contraction is acetylcholine (ACh) released from prejunctional parasympathetic nerve endings. Furthermore, nitric oxide (NO) is widely known to play an important role in function of lower urinary tracts. In the urethra, NO is a major neurotransmitter for relaxation response, however the role of NO on bladder smooth muscle is still unknown. Recently, there are

some reports that NO prejunctionally inhibits ACh release from cholinergic nerves endings in several smooth muscles (2,3), but there is no information available on the effects of NO on ACh release in bladder smooth muscles. Therefore, using microdialysis procedure (4) and high-performance liquid chromatography (HPLC) with electrochemical detection (ECD), we evaluated the effects of NO on ACh release and contractile response induced by electrical field stimulation (EFS) in rabbit bladder smooth muscles.

Methods

Four-month-old female New Zealand white rabbits weighing 3.0 kg were killed by exsanguination after intravenous administration of sodium pentobarbital. The bladder was removed and dissected free from connective tissue and vaginal wall. Uniform longitudinal strips of the posterior wall of the bladder dome were prepared. The microdialysis probe (O-P 100-10, Eicom, Kyoto, Japan) was inserted through the muscle strip, and the inlet cannula of the prove was connected to a microinfusion syringe pump. Ringer (pH 7.4) containing 100 μM physostigmine sulfate was continuously perfused at a rate of 2 μl/min. These muscle strips were suspended in 20 ml thermostatically controlled organ baths filled with modified Krebs-Henseleit solution. Each muscle strip was connected to a force displacement transducer, and isometric forces were recorded. EFS (supramaximun voltage, pulse duration 0.5 ms, frequency 5 Hz (low) and 20 Hz (high), train of pulse 2 sec and stimulation interval 2 min) was applied to muscle strips, and tension developments were recorded.

The dialysate from microdialysis probe during EFS was collected, and a volume of 10 μl was injected into the ACh assay system. The amount of ACh in the dialysate fraction was measured by HPLC with ECD as reported proviously (4). The effect of pretreatment with L-NNA (NOS inhibitor) on the contraction and ACh release induced by EFS was evaluated.

Results

ACh releases and EFS-induced contractions in the low and high frequency stimulations were 2.48 ± 0.45 pmol/g, 3.68 ± 0.36 g, and 8.12 ± 2.42 pmol/g, 5.03 ± 0.79 g, respectively. In the low frequency stimulation, the pretreatment with L-NNA (100 μM) caused significant increases in ACh release (7.85 ± 1.62 pmol/g) and the contraction (4.21 ± 0.51 g). While, in the high frequency stimulation, the pretreatment with L-NNA did not significant effects on the contraction and ACh release.

Conclusions

The data suggest that there may be a mechanism inhibiting ACh release from cholinergic nerve endings mediated by NO in rabbit bladder smooth muscles, which contributes to the bladder function.

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