Functional studies: Strips of detrusor muscle (6 x 2 mm), were suspended in organ baths containing Krebs-Henseleit solution, continuously bubbled with 95% O_2 and 5% CO_2. After 60 min equilibration, the isolated detrusor strips were exposed to 100 μM carbachol (maximum contraction). Concentration-response curves to NKA and carbachol were constructed by discrete addition of drug to the preparation. Responses were measured in g tension and were also expressed as percent of maximum response.

Results

Immunohistochemical studies: In the bladder mucosa, moderate numbers of small fibres immunoreactive for NKA and SP were localised near the urothelium and around blood vessels. In the lamina propria, small fibres were associated with small arteries and arterioles. In the detrusor muscle, NKA- and SP-immunoreactive fibres were rather sparse, and ran parallel to the muscle bundles.

Functional studies: Exogenously applied carbachol (1 nM – 100 μM) and NKA (1 nM – 10 μM) caused concentration-dependent contractions in detrusor muscle strips. A maximum contraction of 2.5 ± 0.3 g (n=36) was evoked by 100 μM carbachol, whereas NKA evoked a maximum contraction of 2.1 ± 0.3 g (59 ± 4 % of the maximum response; n=31) at 10 μM, with corresponding pD_2 values 5.84 ± 0.07 and 7.09 ± 0.09, respectively. No differences in smooth muscle contractility with respect to age or sex were observed.

In the UTI-group, the maximum response to carbachol was 2.9 ± 0.3 g (n=26), whereas the maximum response in non-UTI-patients only reached 1.6 ± 0.3 g (n=10; $p<0.05$; Fig 1A). Corresponding pD_2 values were 5.89 ± 0.08 and 5.70 ± 0.13, respectively. No differences in responses to NKA were observed between the two groups, and the responses were 2.1 ± 0.3 g (58 ± 5%; n=25), and 2.6 ± 1.4 g (76 ± 15 %; n=6; Fig 1B), respectively.

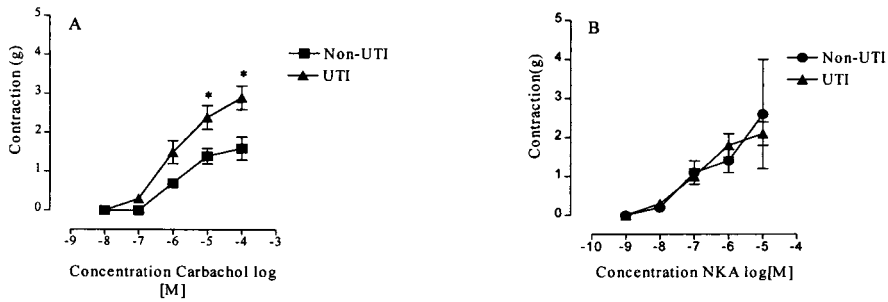

Figure 1. Graph showing responses to (A) carbachol and (B) NKA in child detrusor in children with and without a previous history of urinary tract infection (UTI). The difference in contractility in response to carbachol is statistically significant ($p<0.05$).

Conclusions

No differences in responses to NKA were observed between detrusor strips from with children with or without a history of UTI. However, carbachol produced a significantly larger contractile response in children with a history of UTI compared with uninfected children, indicating possible alterations in muscarinic receptor characteristics. The relatively sparse distribution of NKA-like immunoreactive nerve fibres in the detrusor was surprising in view of its potent contractile effect upon this muscle in vitro: thus its physiological role in micturition remains incompletely understood. The presence of NKA and SP immunoreactive fibres around blood vessels suggests a possible function of these neuropeptides in control of local blood flow.

References

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SHORT-TERM EFFICACY AND SAFETY OF TEMIVERINE IN THE TREATMENT OF BLADDER OVERACTIVITY—A RANDOMIZED CLINICAL TRIAL IN ADULT MEN AND WOMEN

Aims of Study: Temiverine, a new agent with anticholinergic and calcium channel antagonistic properties, has been found, in uncontrolled and active-drug controlled studies, clinically useful for the treatment of symptomatic unstable

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.

The study was sponsored by Orion Corporation Orion Pharma, Espoo, Finland.

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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