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NICORANDIL, A KATP CHANNEL OPENER AND NITRIC OXIDE DONOR, WAS EFFECTIVE IN THE TREATMENT OF URINARY FREQUENCY – A RANDOMISED CLINICAL TRIAL

Hypothesis / aims of study
Overactive bladder is a common health problem with negative effect on quality of life for both sexes. Detrusor instability contributes to the increased urinary frequency. Currently, muscarinic antagonists are considered the first-line therapy for treating overactive bladder. However, their significant adverse effects often limit their clinical use. The ideal treatment of bladder overactivity involves the selective inhibition of involuntary bladder contraction without altering the normal micturition reflexes. The ATP-sensitive K+-channel (K_{ATP} channel) openers have been proposed as a possible alternative to the anticholinergic drugs. Experimental studies have shown that K_{ATP} channel openers have been shown to inhibit unstable bladder contractions without affecting the normal voiding reflex (1). However, an unacceptable level of hypotension at effective doses hampers their clinical utility. Nicorandil, which has a unique feature as a K_{ATP} channel opener and nitric oxide donor, has been used for angina quite safely for a long time (2). The purpose of this study was to evaluate the efficacy of nicorandil, a K_{ATP} channel opener and nitric oxide donor, in the treatment of urinary frequency.

Study design, materials and methods
This preliminary single centre study included a 2-week single-blind placebo run-in, a 4-week double-blind placebo-controlled active treatment phase. The institutional review board approved the current study. Men and women with urinary frequency > 10 times per day were enrolled after obtaining the informed consent and were randomized to receive placebo or nicorandil during the study period of between November 2004 and November 2005. The dose of Nicorandil was increased step wisely from 5 mg once daily to 15 mg thrice daily in 2 weeks. Fifteen mg of nicorandil was the typical dosing used for the treatment of angina in Japanese. The primary end point was mean urination times per 24 hrs.

Results
Nicorandil produced statistically significant improvements in voids/24 h vs. placebo (mean voids/24 h; at base line to at the end of study, nicorandil: 12.5+2.0 to 11.7+2.7 p=0.044, n=10, placebo: 13.6+2.9 to 13.5+2.7 p=0.86, n=12). The effect of nicorandil was more prominent in the reducing urinary frequency during the daytime. Quality-of-life outcomes supported the efficacy results. IPSS significantly improved by nicorandil but not by placebo (mean IPSS score; at base line to at the end of study, nicorandil 14.7 to 11.25 p=0.032, placebo 16.9 to 15.1 p=0.14). BII improved in the both group (mean BII score; at base line to at the end of study, nicorandil 7.3 to 5.0 p=0.0057, placebo 6.4 to 5.4 p=0.021). There were no serious treatment-related adverse events.

Interpretation of results
In this preliminary study, nicorandil had a modest effect on reducing the urinary frequency and improving IPSS.

Concluding message
Nicorandil has been used safely for the treatment of angina. From the results of this study, further evaluation in large-scale phase III studies to examine the effect of nicorandil in subjects with overactive bladder is warranted.

References
1. J Urol. 1989;141:637–640
2. Lancet. 2002;359:1269-75

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