

HCT 1026- A NOVEL TREATMENT FOR URGENCY?

Aims of Study

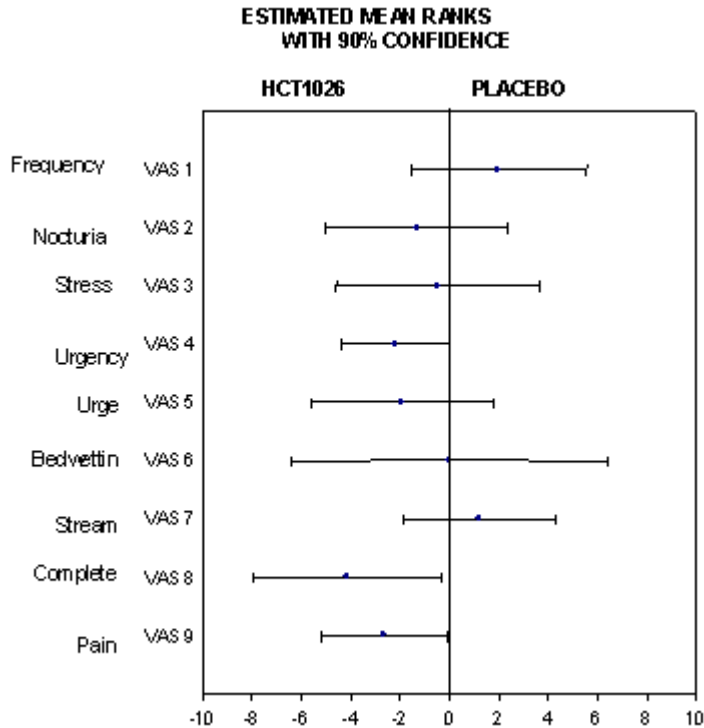
The human bladder is innervated by neuropeptide-containing sensory nerves which transmit sensations of bladder fullness, urgency and pain. Increased afferent activity caused by prostaglandins can induce involuntary bladder contractions in some patients. The L-arginine/nitric oxide (NO) pathway has a role as a neurotransmitter causing direct relaxations of the detrusor smooth muscle. As this pathway and prostaglandins seem to be partly involved in the pathogenesis of detrusor instability, it was of interest to evaluate the effect of HCT1026 (a new, proprietary flurbiprofen nitro-derivative) for this indication. HCT1026 is thought to combine the analgesic and anti-inflammatory effects of flurbiprofen with the smooth muscle relaxant effect of the NO moiety. HCT1026 was shown to be more potent than flurbiprofen in inhibiting carbachol-induced bladder strip contractions in vitro (1). In two models of acetic acid bladder dysfunction in conscious rats, HCT1026 was slightly more effective than flurbiprofen in increasing bladder volume and reducing micturition pressure (1). Phase I trials showed good safety and acceptability, potent prostaglandin inhibition and reduced gastric toxicity by means of gastroscopic evaluation (1, 2). In a pilot phase IIa study in patients with neurogenic bladder, an improvement in urodynamic parameters and clinical symptoms was observed (3). In the light of these data, a proof of concept study was designed to assess the efficacy and acceptability of HCT1026 in those women who complain of urgency and frequency with or without incontinence.

Methods

A 2 centre randomised double-blind placebo controlled cross-over study. All women with symptoms of urgency and frequency were eligible for inclusion. There were a large number of exclusion criteria, which made recruitment difficult. No power calculation was performed as this was a proof of concept study. Before participating in the study women were asked to fill in a pre screening diary. The study period lasted 6 weeks with a single blind run in week prior to the two double blind treatment weeks, where the women received either 100mg HCT1026 or placebo twice a day. The efficacy of the treatment was assessed objectively with frequency volume charts, visual analogue scores and cystometry. Although the latter was carried out in one centre only. The safety was assessed using a medical examination including pulse and blood pressure, a full blood count, clinical chemistry, urinalysis and reported adverse events. Ethical approval was obtained and all women were asked to sign informed consent.

Results

31 women were included in the study, 6 dropped out after screening and 25 were randomised to receive medication. 4 failed to complete the study as a result of adverse events. Objective results showed a significant reduction in urgency and pain in the HCT 1026 group when compared to placebo (Anova model for 2 period cross over design after rank transformation) see below.



There were no significant differences between cystometric parameters or the various parameters addressed by the frequency volume chart when HCT 1026 was compared to placebo. There were two severe adverse events, one woman complained of rectal bleeding although this was not confirmed clinically and one woman had an episode of hypertension. There were no significant differences between the adverse events in the placebo group and the HCT 1026 group.

Conclusions

HCT 1026 is an exciting new drug which may have a role to play in the treatment of the overactive bladder. It is encouraging that there were so few adverse events. As a result of this further studies are planned particularly looking at its use in women with interstitial cystitis, sensory urgency and other painful bladder syndromes.

References

1. NicOx internal report
2. Donnelly M.T., Stack W.A., Courtauld E.M., Garlick N., Del Soldato P., Hawkey C.J. Nitric oxide donating flurbiprofen (HCT1026) causes less endoscopic damage in healthy volunteers than flurbiprofen. British Society of Gastroenterology - 1997.
3. Costa P., Perrouin-Verbe B., Rouays-Mabit H., Turlan J.L. Effects of an new drug, HCT1026, in patients with neurogenic bladder overactivity. International Urogynecology Journal - Vol. 11 Suppl 1, 2000. This study was supported by an educational grant from NicOx