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THE EFFECT OF DARIFENACIN ON NEUROGENIC DETRUSOR OVERACTIVITY IN PATIENTS WITH SPINAL CORD INJURY.

Aims of Study

Anticholinergic agents are important in the management of neurogenic detrusor overactivity (NDO) in patients with spinal cord injury (SCI). Common side-effects resulting from organ non-selectivity, such as dry-mouth, constipation and tachycardia, limit their clinical use [1] . Bladder contraction in normal individuals is mediated mainly by the M3 muscarinic receptor [2], however following neurological injury the role of the M_2 receptor may be of increased importance [3]. Darifenacin, a novel antagonist selective for the M_3 muscarinic receptor, has been shown to demonstrate bladder selectivity, and has been studied in relation to idiopathic detrusor overactivity [4]. Provocation studies are useful in the assessment of treatment modalities for NDO [5]. The aim of this study was therefore to assess the ability of darifenacin to suppress provoked unstable bladder contractions in patients with spinal cord injury.

Methods

A randomised, placebo-controlled, double-blind crossover study was performed. 8 patients (all male) were included in the study. All patients were more than one year post-injury; 6 had a thoracic-level lesion, and 2 had cervical-level lesions (one of which was incomplete). Patients received no drugs to treat incontinence or any medication with anti-cholinergic properties in the week prior to the study. Each patient attended for two urodynamic sessions, separated by a washout time of 3 days or more. Randomisation determined whether the drug (darifenacin 6mg i.v. in 5% mannitol) was given on the first or second occasion. Placebo consisted of a 5% mannitol infusion without darifenacin.

Bladder filling was performed at 15 ml/min to establish the volume at first unstable contraction. 50-100ml was then withdrawn, and infused rapidly (at approximately 20 ml/sec) to produce an unstable contraction. Three sets of provocations were performed for each time interval. The intervals were 30 minutes pre-dose, 30 minutes post-dose and 90 minutes post dose. For each unstable contraction, the area under the pressure-time curve (AUC, $cmH_20.sec$) was automatically calculated by a data-acquisition program.

Results

Provocation tests reliably produced unstable bladder contractions The intravenous administration of darifenacin resulted in a significant reduction in the AUC attributable to unstable bladder contractions compared to placebo. The statistical significance was greater at 90 minutes post-dose ($p = 0.001$), compared to that seen at 30 minutes post dose ($p = 0.005$), using a paired t-test. A typical individual response is shown in Figure 1.The mean values and standard errors for the 8 patients are shown in Figure 2.

Figure 1: Example of an individual response to darifenacin

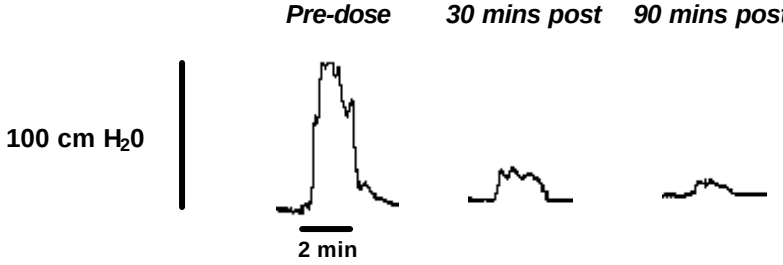
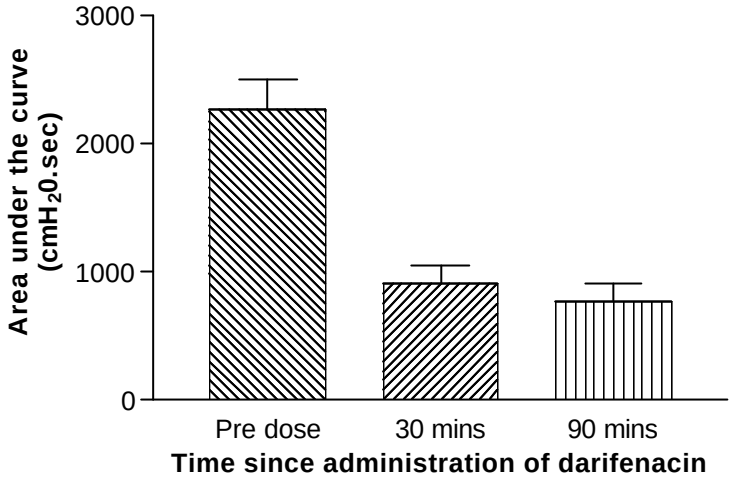


Figure 2: The effect of darifenacin on provoked unstable bladder contractions



Conclusions

Darifenacin given as a single intravenous dose is capable of suppressing unstable provoked bladder contractions attributable to neurogenic detrusor overactivity in spinal cord injury patients. This is the first study reporting the effects of this novel M_3 receptor antagonist on the lower urinary tract in patients with spinal cord injury, and would suggest a clinical role for the oral preparation of darifenacin.

Additionally, this study reinforces the role of provocation-based studies in assessing new putative treatments for neurogenic detrusor overactivity in spinal cord injury.

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