448

Stöhrer M[1], Mürtz G[2], Kramer G[3], Warnack W[4], Primus G[5], Strugala G[2]
1. *University Essen, Dept. of Urology and Paediatric Urology,* ***2.*** *APOGEPHA Arzneimittel GmbH,* ***3.*** *Bennebroek, Holland,* ***4.*** *Hagenow, Germany,* ***5.*** *Graz, Austria*

EFFICACY AND TOLERABILITY OF PROPIVERINE HYDROCHLORIDE EXTENDED RELEASE COMPARED TO IMMEDIATE RELEASE IN PATIENTS WITH NEUROGENIC DETRUSOR OVERACTIVITY

Hypothesis / aims of study

The aim of this study was to evaluate the efficacy and tolerability of propiverine hydrochloride extended release (ER) compared to propiverine hydrochloride immediate release (IR) in patients with neurogenic detrusor overactivity with respect to urodynamic parameter. Reflex volume was assessed as primary, other urodynamic measures as secondary parameters.

Study design, materials and methods

The study was conducted double-blind, double-dummy, randomized, multicentre, multinational (phase III) administering propiverine hydrochloride ER 45 mg s.i.d. or propiverine hydrochloride IR 15 mg t.i.d. Male or female Caucasian patients aged ≥ 18 and ≤ 70 years of age with proven neurogenic detrusor overactivity (NDO) and a reflex volume ≤ 250 mL were included. Urodynamic and clinical outcome parameters were assessed at baseline (V1) and after a scheduled treatment period of 21 days (V2). Reflex volume, defined as urodynamically assessed volume at first uninhibited detrusor contraction, served as primary efficacy outcome (reference 1). Primary study objective was to demonstrate non-inferiority of propiverine ER compared to propiverine IR, defined as a treatment group difference of ≤ 25mL in change from baseline of reflex volume (PP-population). If no uninhibited detrusor contractions occurred, the maximum cystometric capacity was imputed for reflex volume. Secondary efficacy outcomes were also assessed urodynamically: leak point volume, maximum detrusor pressure, and bladder compliance (reference 2). All urodynamic parameters were assessed by the respective investigators of the six study centres and by an independent expert, whose values were taken as results. Adverse events and treatment-related adverse events were assessed as tolerability outcomes.
An interim analysis was planned following the recruitment of 60 patients. In each group 33 patients were screened for inclusion, randomized and treated.

Results

The demographic characteristics of the 66 patients were in accordance with the disease investigated (41.4 and 40.9 years of age, respectively; 22 male and 11 female and 19 male and 14 female, respectively). The time since manifestation of neurogenic impact (7.5 and 5.4 years), type (traumatic, stroke, inflammable, degenerative) and level of neurogenic impact (suprasacral or suprapontine) were balanced between both treatment groups.
Primary efficacy parameter: Reflex volume improved by 102.0 mL in the propiverine IR group (V1: 100.9, V2: 202.9) and by 90.5 mL (V1: 89.8, V2: 180.3) in the propiverine ER group. The mean treatment group difference was -12.4 mL with a 95% confidence interval ranging from -58.9 to 34.0 mL. The one-sided p-value for the test against the hypothesis “ER-IR≤-25mL” was 0.2952 and the study was not continued.
Secondary efficacy parameter: Leak point volume (mL) increased by a comparable extent in both groups (propiverine IR: V1: 124.1, V2: 228.6, difference 104.4; propiverine ER: V1: 106.7, V2: 204.3, difference 97.5). Maximum detrusor pressure (cm H_2O) decreased by a comparable extent in both groups (propiverine IR: V1: 66.1, V2: 42.4, difference -20.0; propiverine ER: V1: 67.0, V2: 43.7, difference -20.0). Also, bladder compliance (mL/cm H_2O) improved comparably in both groups (propiverine IR: V1: 56.5, V2: 114.8, difference 58.3; propiverine ER: V1: 52.1, V2: 85.0, difference 32.9). Post void residual increased by a comparable extent (+17.6 mL IR, + 17.0 mL ER) in both groups. The percentage of patients presenting with incontinence was reduced in the propiverine IR group from 79.3% to 65.5%, and in the propiverine ER group from 80.6% to 41.9%.

Tolerability: 48.5% of the patients in the propiverine IR group, and 36.4% of the patients in the propiverine ER group experienced at least one adverse event, the incidence of treatment-related adverse events was 42.2% and 36.4%, respectively. Typical anticholinergic adverse events were stated more often under propiverine IR compared to ER (dry mouth: 24.2% vs 27.3%; gastrointestinal motility disorders: 9.1% vs 3.0% and accommodation disorder 6.1% vs 0%).

Interpretation of results

The primary objective of this study, to demonstrate non-inferiority of propiverine ER compared to propiverine IR, defined as a treatment group difference of ≤25mL in change from baseline of reflex volume, was not achieved. But the reflex volume and the secondary, also urodynamically assessed efficacy parameters demonstrated comparable improvements of both galenic formulations with respect to improved leak point pressure, decreased maximum detrusor pressure and improved bladder compliance. Therefore, from a clinical point of view, it can be assumed that both galenic formulations, propiverine IR 15 mg t.i.d. and propiverine ER 45 mg s.i.d., exert comparable clinical effects. The urodynamically demonstrated improvements comply well with improvements documented in other studies conducted in patients with neurogenic detrusor overactivity (reference 3). However, the clinically assessed parameter of incontinence favoured propiverine ER, because this treatment group achieved higher continence rates. This finding might be indicative of a more stable drug exposure to the propiverine ER compared to the propiverine IR formulation.
With respect to tolerability superiority of propiverine ER compared to propiverine IR was demonstrated for the overall rate of adverse events and the treatment-related adverse events.

Concluding message

This study documented propiverine hydrochloride extended release (45 mg s.i.d.) and propiverine hydrochloride immediate release (15 mg t.i.d.) being equieffective in patients with neurogenic detrusor overactivity from a clinical point of view, despite not achieving the statistical aims. With respect to tolerability the ER formulation was superior to the IR formulation.

References

1. Stöhrer M. Goepel M. Kondo A. et al. The Standardisation of Terminology in Neurogenic Lower urinary Tract Dysfunction. Neurourology and Urodynamics. 1999; 18:139-158
2. Abrams P. Cardozo L. Fall M. et al. The Standardisation of Lower urinary Tract Function: Report from the Standardisation Sub-committee of the International Continence Society. Neurourology and Urodynamics. 2002; 21:167-178
3. Stöhrer M. Mürtz G. Kramer G. Propiverine compared to oxybutynin in neurogenic detrusor overactivity – results of a randomized double-blind, multicenter study. European Urology. 2007; 52: 235-242

Specify source of funding or grant	**Unrestricted educational grant of APOGEPHA Arzneimittel GmbH, Dresden, Germany**
Is this a clinical trial?	**Yes**
Is this study registered in a public clinical trials registry?	**Yes**
Specify Name of Public Registry, Registration Number	**EudraCT, 2004-001275-19**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**Yes**
Specify Name of Ethics Committee	**Ethikkommission der Sächsischen Landesärztekammer, 01076 Dresden, Germany**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**