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EFFICACY, TOLERABILITY AND SAFETY OF PROPIVERINE HYDROCHLORIDE IN COMPARISON TO OXYBUTYNIN IN CHILDREN WITH NEUROGENIC DETRUSOR OVERACTIVITY – A MULTICENTER OBSERVATIONAL COHORT STUDY

Hypothesis / aims of study
Children suffering from neurogenic detrusor overactivity are treated with antimuscarinics and (clean) intermittent catheterisation to achieve a low intravesical pressure situation and / or continence. Oxybutynin presents the current standard for antimuscarinics in children and is registered in most countries world-wide. However, limited tolerability, both in adults and children, has been reported, thus increasing continuously concerns about the applicability of oxybutynin, especially in the paediatric population. A much more favourable tolerability profile compared to oxybutynin has been reported for propiverine in children suffering from non-neurogenic conditions (1). For neurogenic detrusor overactivity the results of propiverine-treated-children encompassed limited patient numbers only, which were evaluated in one retrospective and another prospective study (2). Therefore, this study aims at a comparative assessment of efficacy, tolerability and safety of propiverine (Mictonetten®) and oxybutynin in children with neurogenic detrusor overactivity aged 1–18 years.

Study design, materials and methods
In a comparative multicenter (14 centers) study 255 children with neurogenic detrusor overactivity were evaluated retrospectively: 199 with myelomeningocele (MMC), 46 with spinal cord injury. All children had been treated with antimuscarinics (127 propiverine, 128 oxybutynin). Mean age at treatment initiation was 7.18 years in the propiverine group, and 7.98 years in the oxybutynin group. Due to the retrospective character of this analysis baseline values of urodynamic and clinical parameters were not homogeneous.

Results
The clinically most relevant efficacy outcome parameter, maximum detrusor pressure (p_{det}), either assessed at the end of the storage phase or during emptying, was on average significantly reduced in both treatment groups: propiverine pre 59.8 cm H_20, post treatment 36.7 cm H_20; oxybutynin pre 65.2 cm H_20, post treatment 54.9 cm H_20. These treatment differences were highly significant, favouring propiverine. Individual reductions of p_{det} were assumed to be clinically relevant either if values below 40 cm H_20 were achieved or if a reduction of at least 50 % compared to pre-treatment values manifested under medication: Correspondingly, 74 % of the propiverine group compared to 50 % of the oxybutynin group attained these success criteria, defined as primary outcome. Thus, a significantly more effective treatment response of propiverine compared to oxybutynin was documented in the total population, mainly due to an enhanced response of children with MMC to propiverine. Improvements in p_{det} corresponded to the secondary outcomes, both other urodynamic and clinical parameters: Continence was achieved to a comparable extent (7.7% pre, 31.6 % post propiverine treatment, 20.8 % pre, 50.4 % post oxybutynin treatment).

In 17/26 cases of both treatment groups, affected with severe gradings of vesicoureterorenal reflux prior to antimuscarinic treatment, and being classified as stage III-V according to Parkkulainen, an abolishment or downgrading of reflux manifested.

Daily doses were on average increased during the treatment period: in the propiverine group from 16.7 mg/day to 20.9 mg/day (equivalent to 0.7 mg/kg body weight/day), in the oxybutynin group from 9.8 mg/day to 13.6 mg/day (equivalent to 0.47 mg/kg body weight/day). The

presented results were achieved after treatment periods of 695 (propiverine) and 499 days (oxybutynin) on average.

Propiverine was better tolerated than oxybutynin in the total study population (9.40 % versus 17.46 % adverse events overall), in children with myelomeningocele it was significantly better tolerated. No serious adverse events occurred.

Interpretation of results

To the best of our knowledge this study, evaluating antimuscarinics comparatively, comprises the most extensive number of children suffering from neurogenic detrusor overactivity. The primary goals in these children, a low intravesical pressure situation during storage and emptying phase as well as continence, could be achieved in both treatment groups. However, MMC children responded more favourably to propiverine compared to oxybutyin. One may hypothesize that this is due to the additional calcium-channel-modulating effects of propiverine, surpassing antimuscarinic effects, as in-vitro-studies of bladder strips showed differences between MMC and non-MMC patients (3).

The superior tolerability profile of propiverine compared to oxybutynin was confirmed also in neurogenic detrusor overactivity of children.

Concluding message

This study demonstrates both a superior tolerability and a more effective reduction of maximum detrusor pressure of propiverine compared to oxybutynin in children with neurogenic detrusor overactivity, especially in those with myelomeningocele. We hypothesize that the more pronounced effects of propiverine are due to its dual mode of action, antimuscarinic and calcium-channel-modulating. However, further research is warranted to elucidate the underlying mechanisms.

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FUNDING: APOGEPHA Arzneimittel GmbH