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Propiverine Compared to Oxybutynin in Neurogenic Detrusor Overactivity – Results of a Randomized, Double-blind, Multicenter Clinical Study

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FVC, frequency volume chart
ITT, intention to treat
PP, per protocol

Abstract

Objectives: To compare the efficacy and tolerability of propiverine and oxybutynin in patients with neurogenic detrusor overactivity.
Methods: Patients were eligible, if at least 18 years of age and suffering from neurogenic detrusor overactivity. Eligibility also required a maximum cystometric capacity less than 300 ml. After a one-week run-in period, propiverine 15 mg t.i.d. or oxybutynin 5 mg t.i.d. were administered for 21 days. As primary efficacy outcomes urodynamic parameters were assessed. As tolerability outcome the percentage of patients with newly manifesting anticholinergic adverse events was taken.
Results: 131 patients were recruited at 20 study centers. The maximum cystometric capacity (ml) was increased significantly in the propiverine group from 198 (±110) to 309 (±166), and in the oxybutynin group from 164 (±64) to 298 (±125). Similarly, maximum detrusor pressure during the filling phase (cm H_2O) was lowered significantly in the propiverine group from 56.8 (±36.2) to 37.8 (±31.6), and in the oxybutynin group from 68.6 (±34.5) to 43.1 (±29.2). No significant differences resulted between treatment groups.

Anticholinergic adverse events were reported less frequently in the propiverine compared to the oxybutynin group (63.0% versus 77.8%). Dryness of the mouth, the most frequent adverse event, was reported significantly less (47.1% versus 67.2%; $p = 0.02$) in the propiverine compared to the oxybutynin group.
Conclusion: Propiverine and oxybutynin are equally effective in increasing bladder capacity and lowering bladder pressure in patients with neurogenic detrusor overactivity. The trend for better tolerability of propiverine compared to oxybutynin achieved significance for dryness of the mouth.

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1. Introduction

The efficacy of oxybutynin has been well established over almost three decades of clinical experience, both in idiopathic [1,2] and neurogenic detrusor overactivity [3]. However, therapeutic efficacy is associated with a high incidence of adverse events, up to 80% with oral administration [4], typically anticholinergic in nature (e.g. dry mouth, constipation, drowsiness, blurred vision), often dose-limiting, in some cases necessitating premature treatment discontinuation. A recent review and metaanalysis of anticholinergics by Chapple et al. [5] concluded oxybutynin immediate release was not well tolerated. Despite being an efficacious drug of first choice in patients suffering from this condition, the poor tolerability of oxybutynin necessitated the search for alternative drugs. This applies especially to neurogenic detrusor overactivity, which often requires higher dosages [6] for suppressing involuntary detrusor contractions during the filling phase. Tolterodine is also of proven efficacy, but it too is not freely available in some countries, notably Australia and NZ.

Propiverine hydrochloride (referred to in the following as propiverine) is one of the few drugs recommended for the treatment of detrusor overactivity by the International Consultation on Incontinence [4]. It comprises a neurotropic and a musculotropic mode of action, thus inducing antimuscarinic effects as well as effects on the calcium-influx and calcium-homeostasis [7]. Most of the propiverine studies have focussed so far on patients suffering from idiopathic detrusor overactivity [8–10], and demonstrated the beneficial effects of its dual mode of action. In a dosage-optimizing study of spinal cord injured adults Mazur and coworkers [11] recommended 15 mg propiverine t.i.d. as adequate dosage in most patients. Subsequently, Stöhrer et al. [12] proved the efficacy of propiverine (15 mg t.i.d.) compared to placebo over a treatment period of 14 days by documenting urodynamic improvements.

Therefore the aim of this study was to compare the efficacy and tolerability of propiverine and oxybutynin in patients suffering from neurogenic detrusor overactivity.

2. Patients and methods

This multinational, double-blind, comparative trial was conducted at 20 study centers specialized in neurourology. Ethical approval was obtained at each center. All patients gave written informed consent, and the study was conducted in accordance with the declaration of Helsinki.

2.1. Patients

Patients were eligible, if at least 18 years of age and suffering from a known neurological disorder and had demonstrable detrusor overactivity at urodynamic assessment. Maximum cystometric capacity was restricted to 300 ml. Patients were excluded if they had other genitourinary tract anomalies (e.g. infravesical obstruction, ectopic ureters, hypospadias, fistulas, anomalies of the urethra, epispadias), a post void residual >15% of the bladder capacity, acute infections of the genitourinary tract, or clinically relevant diseases of the kidneys. Further exclusion criteria were abnormal liver, gastrointestinal tract or cardiovascular system function, metabolism disorders (e.g. diabetes mellitus, diabetes insipidus), pre-existing medical contraindications for anticholinergics (e.g. megacolon, achalasia, respective cardiac or ocular disorders like tachyarrhythmias of hemodynamic significance, angina pectoris, glaucoma, myasthenia gravis). Patients were also not eligible, if having participated in any other study with an investigational drug within at least one month prior to inclusion in this study, or if concomitant treatment, possibly interfering with the trial medication, was applied.

2.2. Study design

After a one-week run-in period patients were randomized (1:1) using random permuted blocks with a computer-generated randomization list prepared by a trial-independent statistician. Patients received either oral propiverine 15 mg t.i.d. or oxybutynin 5 mg t.i.d. (double-dummy technique with matching placebos) for 21 days. No dose adjustment of the trial medication was allowed during the study. Oxybutynin immediate release was chosen, because oxybutynin extended release was not yet commonly available at the planning for this study. Trial drugs of identical appearance covered 28 days, thus guaranteeing sufficient medication even in those cases with possibly prolonged treatment periods. Medication was pre-packaged according to the randomization list, and a multiple of the block size was distributed to each study center. The investigators at each center had to allocate individual treatment by assigning subject numbers in consecutive order.

Efficacy assessment, conducted prior to and after 21 days of treatment, comprised maximum cystometric capacity, maximum detrusor pressure during filling phase, and detrusor compliance as urodynamic parameters. Residual urine was assessed after having performed urodynamics, either by catheterization or by ultrasound. All methods, definitions and units of this study conform to the standards recommended by the International Continence Society, except when specifically noted [13].

Furthermore, the patients completed 5-day bladder diaries prior to treatment and at treatment termination. Secondary efficacy outcomes were 24-h micturition frequency, 24-h incontinence episodes and mean volume voided/micturition in the per-protocol-population.

The primary tolerability outcome was the percentage of patients with newly manifesting typical anticholinergic adverse events in both treatment groups.