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

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**Abstract**
**Objective of the study:** Efficacy and tolerability of propiverine extended-release (ER) compared to immediate-release (IR) were evaluated in patients with neurogenic detrusor overactivity (NDO).
**Patients and methods:** Propiverine ER 45 mg s.i.d. or IR 15 mg t.i.d. were administered in patients with proven NDO in a randomized, multicentre, double-blind study. Urodynamic and clinical outcomes were assessed at baseline (V1) and after 21 days of treatment (V2): reflex volume served as primary, leak point volume and maximum detrusor pressure as secondary efficacy outcomes, treatment-related adverse events as tolerability outcomes.
**Results:** Sixty-six patients were enrolled with demographic and clinical characteristics representative for the investigated disease. Reflex volume (mL) increased significantly in the propiverine IR (V1: 100.9, V2: 202.9) and in the propiverine ER (V1: 89.8, V2: 180.3) group, no significant intergroup difference resulted. Leak point volume (mL) increased, and maximum detrusor pressure (cm $H_2O$) decreased significantly in both groups without significant inter-group differences. The percentage of patients presenting with incontinence was reduced by 13.8% in the propiverine IR and by 38.7% in the propiverine ER group, evidencing ER to be significantly superior to IR. Treatment-related adverse events manifested in 42.2% and 36.4% following propiverine IR and ER, respectively.
**Conclusions:** The urodynamic efficacy outcomes demonstrated both galenic formulations to be equieffective. However, following propiverine ER 45 mg s.i.d. significantly higher continence rates compared to propiverine IR 15 mg t.i.d. were achieved, possibly indicative of more balanced plasma-levels. A trend for superior tolerability outcomes of propiverine ER compared to IR was demonstrated.

**Keywords**
neurogenic detrusor overactivity, antimuscarinics, propiverine, adults

**Introduction:**
Antimuscarinics are widely used in overactive bladder (OAB) / idiopathic detrusor overactivity (IDO), but also in neurogenic detrusor overactivity (NDO). So far only immediate-release (IR) formulations of oxybutynin [1, 2, 3], propiverine [3, 4] and trospium chloride [2, 5] were investigated with respect to placebo- and comparator-controlled studies in NDO. However, due to the necessity of increased doses in patients with NDO compared to IDO it is difficult to outbalance efficacy and tolerability, since inacceptable adverse events could be a limiting factor [6].

Consecutively, extended-release (ER) formulations of antimuscarinics have been developed assuming that more stable plasma concentrations will introduce constant efficacy over time. Moreover, smoothening of serum concentrations by administering ER formulations also improves the tolerability of antimuscarinics by avoiding high peak serum concentrations, expected to be associated with the manifestation of adverse events, as shown in pharmacokinetic studies of oxybuytnin [7] and tolterodine [8]. Treatment outcomes have been improved by introducing ER formulations in OAB / IDO, e.g. different doses of oxybutynin ER [9], propiverine ER 30 mg [10], tolterodine ER 4 mg [11], and trospium chloride ER 60 mg [12]. Unequivocally, these studies have shown comparable efficacy combined with an improved tolerability profile for ER formulations in OAB / IDO.

However, in NDO controlled clinical studies of ER formulations of antimuscarinics in adults were lacking so far, despite the assumed clinical advantages associated with well-balanced plasma concentrations, inducing continued efficacy over time and a more favourable adverse event profile by minimizing peak-trough-level-fluctuations. As additional rationale not only a slower drug release but also a reduced formation of active metabolites in the colon can be taken into account for ER formulations of propiverine HCl (in the following abbreviated as propiverine) [13]: CYP3A4 and ABCC2, the major variables in pharmacokinetics of propiverine, are less expressed in the colon, an additional absorption site for propiverine released from the ER formulation in more distal parts of the intestinal tract, whereas the absorption of IR formulations of propiverine is localised in more proximal parts [13].

Improved convenience of ER formulations is expected to have positive implications with respect to compliance and quality of life in these chronic patients, most of them suffering from spinal cord injury. Oral applications of ER formulations are preferable to intravesical instillations, because this mode of delivery is detrimental due to logistic problems, necessitating multiple catheterisations and transport of auxiliary measures during journeys and holidays. These potentially beneficial aspects of the propiverine ER 45 mg s.i.d. formulation with respect to tolerability and patient convenience inaugurated clinical research, aiming at the special demands of chronic patients with NDO, such as intervals of dosing. The galenic properties of this innovative ER formulation of propiverine have been published recently [14]. The aim of this study was to evaluate the efficacy of propiverine ER 45 mg s.i.d. compared to propiverine IR 15 mg t.i.d. in patients suffering from NDO with regard to key urodynamic parameters, and, tolerability.

**Materials and methods:**

Study design: The phase III study was conducted in a double-blind, double-dummy, randomised, multinational, parallel group design at six European study centres specialised in neurourology. Study conduct was in accordance to the declaration of Helsinki and Good Clinical Practice Guidelines, patients had to give written informed consent. The study is registered in the clinical trial register (EudraCT number 2004-001275-19).

Propiverine was either administered in capsules as ER 45 mg s.i.d. or in coated tablets as IR 15 mg t.i.d. over a treatment period of 21 days. The double-dummy technique of medication guaranteed a blinded randomisation to one of the two application forms. A period of seven days preceded the treatment period, during which medication interfering with the trial medications, such as antimuscarinics, parasympathomimetics, ß-sympathomimetics, spasmolytics, neuroleptics, and tricyclic antidepressants, were not allowed. Randomisation was conducted at the baseline visit (V1) applying a ratio of 1:1 and a block size of four.

The following key inclusion criteria had to be fulfilled: (i) female and male Caucasian patients ≥ 18 and ≤ 70 years of age; (ii) NDO proven as occurrence of reflex detrusor contractions; (iii) reflex volume of ≤ 250 mL. The key exclusion criteria comprised: (i) multiple sclerosis; (ii) increased post void residual; (iii) acute urinary tract infection; (iv) anomalies, radiation or surgery of the lower urinary tract; (v) contraindications for antimuscarinics; (vi) cardiac insufficiency; (vii) botulinum toxine treatment within the last 12 months.

Outcomes: Urodynamic and clinical outcome parameters were assessed at baseline (V1) and after a scheduled treatment period of 21 days (V2): the change from V1 to V2 in reflex volume, defined as urodynamically assessed volume at first uninhibited detrusor contraction, served as primary efficacy outcome [15]. In case of non-occurrence of uninhibited detrusor contractions during filling cystometry reflex volume was imputed by maximum cystometric capacity.

Secondary efficacy outcomes were also urodynamically assessed according to the guidelines of the International Continence Society [16]: maximum detrusor pressure and leak point volume, defined as infused volume at first leakage. In case of non-occurrence of leakage during filling cystometry leak point volume was imputed by maximum cystometric capacity as a conservative measurement. The following filling cystometry standards had to be fulfilled: transurethral access with 8 Charriére 2-lumen perfusion catheter, 10 Charriére balloon rectal tube catheter, physiological sodium chloride as filling medium with 38°C temperature, 20 mL/min filling rate, and maximum filling volume of 400 mL. Lubricants without any local anaesthetics were allowed to be used, if necessary. All urodynamic parameters were assessed by the investigators of the study centres and by an independent reviewer, highly experienced in assessing urodynamic results. These values were taken as results in order to

guarantee a standardized analysis across all study centres. Incontinence was assessed by asking the patients about the number of episodes per 24 hours at V1 and V2.

Adverse events, its intensity (“mild”, “moderate”, “severe”) and its relationship to the trial medication (“certain”, “probable”, “possible”, “unlikely”, “conditional”, “not assessable”) were assessed as tolerability outcomes. A final evaluation of the tolerability of the medication by the investigators and the patients was conducted at the end of the study period according to the four categories “very good”, “good”, “moderate”, and “poor”. Laboratory assessments and post void residual in patients with spontaneous voiding were determined at V1 and V2.

Statistical analysis: The primary efficacy outcome was defined as change in reflex volume from V1 to V2 as determined in the per-protocol-population using an analysis of covariance (ANCOVA) model with treatment groups and baseline values as explanatory variables. Non-inferiority of propiverine ER compared to propiverine IR was tested with a non-inferiority margin of ≤ 25mL in reflex volume from V1 to V2. Statistical information on reflex volume, a parameter not been used previously as outcome measure in clinical studies, was missing: Therefore, a two-stage adaptive test design with interim analysis was planned as proposed by Bauer and Köhne [ 17]; an overall one-sided significance level of α=0.025 was stipulated. This interim analysis, planned after enrolment of 60 patients, allowed for both sample size adjustments for the second recruitment period or for discontinuation of the study (confidence interval 95%). Premature study discontinuation after interim analysis could either be evoked due to demonstration of non-inferiority after enrolment of 60 patients or due to futility to finalize the study with a clinically reasonable patient number. The secondary urodynamic outcome parameters in the intention-to-treat- and in the per-protocol-population were analysed by applying the above mentioned ANCOVA model. Furthermore, all efficacy parameters were analysed by using descriptive statistics.

**Results:**

Patient population characteristics: The allocation of the 66 enroled patients with respect to the safety-, intention-to-treat-, and per-protocol-population is given in table 1, demographic and baseline characteristics are given in table 2 and 3, respectively. Almost all patients were treatment-naïve.

Efficacy - primary efficacy outcome parameter: Reflex volume improved by 102.0±85.2 mL in the propiverine IR and by 90.5±92.1 mL in the propiverine ER group, evidencing a significant increase within both treatment groups, and non-significant intergroup differences (p=0.59; table 4). 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. This p-value was in the a priori defined range (0.0102<p-value<0.5) for which the interim analysis neither showed non-inferiority nor futility to demonstrate non-inferiority. Assuming a significance level of $alpha_2$=0.013 for the second period of patient enrolment according to the applied algorithm [17] and ß=0.2 as type II error rate altogether 938 evaluable patients per group (i. e. per-protocol) would have been to be included. The estimated number of almost 2.000 patients and the extremely low incidence rate of NDO impeded study continuation in a realistic time and budget frame, resulting in termination of the study.

Efficacy - secondary efficacy outcome parameters: Leak point volume increased significantly in both treatment groups without significant inter-group difference (table 4). The same applied for maximum detrusor pressure (table 4).

The evaluation of urodynamic traces by the central reviewer differed not relevantly from the evaluation of the local investigators, irrespective of the investigated parameter analysed. Therefore, the presented results are restricted to the per-protocol-analysis of the urodynamic expert.

Most interestingly, the improvements of all key urodynamic parameters, additionally calculated as change in percentage, are almost identical across both treatment groups (table 4).

Continence: The percentage of patients presenting with incontinence was reduced in the propiverine IR group from 79.3% to 65.5% (-13.8%; p=0.125), and in the propiverine ER group from 80.6% to 41.9% (-38.7%; p=0.0005) following treatment. These results are indicative of statistical significance in the propiverine ER group only, and, moreover, of a statistical significant inter-group difference (p=0.041).

Tolerability: 16/33 (48.5%) of the patients in the propiverine IR group, and 12/33 (36.4%) of the patients in the propiverine ER group experienced at least one adverse event (table 5). The number of patients presenting with gastrointestinal disorders, nervous system disorders, and eye disorders of both treatment groups is given in table 5. Treatment-related adverse events manifested in 14/33 (42.2%) patients of the propiverine IR and in 12/33 (36.4%) patients of the propiverine ER group. With respect to severity four patients (12.1%) of the propiverine IR group and two patients (6.1%) of the propiverine ER group experienced a severe adverse event, out of which two adverse events (6.1%) of the propiverine IR group and one adverse event (3.0%) of the propiverine ER group were treatment-related. Serious adverse events or adverse events necessitating dose reductions of medication or premature withdrawal did not manifest in either treatment group. No clinically significant abnormalities of laboratory values were observed.

Overall tolerability was assessed both by investigators and patients. In general, the patients rated the tolerability worse in comparison to the investigators: 23 (71.9%) versus 26 (78.8%) of the patients rated the tolerability as “very good” or “good”, nine (28.1%) versus seven (21.2%) of the patients as “moderate” or “poor” in the propiverine IR and ER group, respectively.

Post void residual increased in the propiverine IR group by 17.6±34.2 mL (V1: 9.7±10.9, V2: 27.3±37.5) and in the propiverine ER group by +17.0±31.3 mL (V1: 12.0±29.5, V2: 28.9±36.6).

No safety concerns arose with respect to incidence rates of overall adverse events, its severity, laboratory parameters, and vital signs (blood pressure, heart rate) across both treatment groups.

**Discussion:**

The primary objective, demonstrating non-inferiority of propiverine ER compared to propiverine IR, was not achieved in this study. This is mainly due to the limited number of patients enroled, reflecting that NDO is a rare disease, affecting only 500 out of 1.000.000 subjects. Consecutively, the recruitment of almost 2.000 patients, as requested according to the interim analysis, was not a feasible option. Nevertheless, reflex volume and secondary urodynamically assessed efficacy parameters, leak point volume and maximum detrusor pressure, demonstrated comparable improvements for both galenic formulations, statistically significant and clinically relevant. Interestingly, the values for maximum detrusor pressure were almost identical at baseline in both groups. Moreover, almost identical pressure reductions by approximately 23 cm $H_2O$ were achieved in both treatment groups for this key urodynamic parameter, used in most placebo- and active-controlled studies as primary efficacy outcome. This reduction in pressure is comparable to the values reported in studies administering propiverine 15 mg t.i.d. in NDO: maximum detrusor pressure was reduced by approximately 19 and 27 cm $H_2O$, respectively [3, 4]. Therefore, from a clinical point of view it can be concluded that the key objective in these patients, protecting the upper urinary tract by the “conversion of an overactive, high-pressure bladder into a low-pressure reservoir” [6] was achieved by both galenic formulations.

The urodynamically assessed bladder capacity outcomes, reflex volume and leak point volume are interdependent. An increase by approximately 90-100 mL, both for reflex volume and leak point volume, following either propiverine IR or ER, is in accordance with an increase by approximately 104 [4] and by 110 mL [3] for cystometric capacity following propiverine 15 mg t.i.d. Moreover, the improvements in these key parameters, paralleled by a substantial decrease in maximum detrusor pressure, confirm previous results for propiverine, oxybutynin, and trospium chloride, the antimuscarinics most intensively investigated in the therapeutic indication of NDO [2, 3, 4, 5].

One of the most striking findings of this study is that the percentage of patients achieving continence is significantly higher in the propiverine ER (+38.7%) compared to the propiverine IR (+13.8%) group. These results may be thought to be contradictory to the urodynamically assessed parameters maximum detrusor pressure and maximum cystometric capacity, both showing no inter-group differences. Obviously, the timing of the urodynamic assessment and the timing of administering study medication has to be considered: However, it is not feasible to request for adjusting the timing of urodynamic assessment to the expected time profile of plasma-levels. Therefore, urodynamic assessment might have been performed in one patient possibly at the peak, in another patient possibly at the trough-level of the individual serum-levels of propiverine and its metabolites, in most patients timing was most probably at random. Consecutively, urodynamic results do not necessarily translate into continence findings. We argue that, contrary to the conventional urodynamic assessment, the evaluation of incontinence reflects to a much greater extent the variations in plasma-levels. Moreover, also the fact that the standard deviations of the key urodynamic parameters reflex

volume, leak point volume and maximum detrusor pressure are unequivocally lower in the ER compared to the IR group stresses a higher variability in the IR group. These results are in accordance with the pharmacokinetic findings of even more balanced plasma-levels following propiverine ER compared to IR. This possible inconsistency of our urodynamic and clinical findings could be elucidated by performing ambulatory urodynamics over 24 hours instead of conventional urodynamics. However, this proposal presents not yet a feasible option, limited by the intention of restricting invasiveness in our patients and limited by the fact that standardisation of methodology is still missing for ambulatory urodynamics. Moreover, in the case of propiverine the serum concentration of the main metabolite M-5 is to be expected significantly reduced by about 10% during treatment with propiverine ER [13]. Due to the lower intrinsic activity of M-5 in comparison to propiverine and their different modes of action [18] this may result in improvements of the safety and efficacy, as was speculated earlier [13]. Future research should address this issue, not investigated in other studies so far, whether more balanced profiles of plasma-level following ER in comparison to IR formulations are associated with higher continence rates.

Aiming at steady plasma-levels, minimising peak-trough-fluctuations ("spikes and waves") is an important goal for further optimizing treatment outcomes. The efficacy outcomes with respect to improved continence rates, and the tolerability outcomes, highlighting a trend for a superior tolerability profile of propiverine ER compared to IR, give some hints for having also achieved an even more sustained and balanced drug release over 24 hours following propiverine ER. However, pharmacokinetic issues were not in the focus of this study, because avoiding invasiveness necessitated to do without determining plasma-levels. Therefore, the interface of pharmcokinetics and pharmacodynamics was not evaluated in this study. Taking into account the pharmacological profile of propiverine it can be assumed that metabolites, possessing strong antimuscarinic properties, have contributed to the efficacy of propiverine: According to Yokota et al. [19] antimuscarinics are especially effective in NDO, as the contribution of cholinergic transmission to detrusor contraction is considerably increased, whereas the purinergic component is decreased in comparison to OAB/IDO.

The potentially beneficial implications of improved continence rates following propiverine ER with respect to quality of life were not investigated. However, this is a drawback of all studies investigating NDO, focussing primarily on the key objective of detrusor pressure reduction as surrogate parameter for avoiding secondary, potentially lethal complications of the upper urinary tract [6, 15]. Nevertheless, according to results of studies in OAB/IDO, investigating the interdependence between continence and quality of life, the improvement of continence is associated with improved quality of life [20].

The expectation of further optimising treatment outcomes by introducing a 45 mg ER formulation of propiverine was fulfilled: Clinically comparable efficacy of both formulations associated with a trend of improved tolerability of the ER compared to the IR formulation is documented in the overall rate, the rate of treatment-related adverse events, and in the tolerability assessments (table 5). Both in patients with NDO and in those patients with OAB/IDO, in which higher antimuscarinic doses are necessitated, propiverine ER 45 mg will enlarge the therapeutic options. In consistency with the presented study results a more favourable tolerability profile of the 30 mg ER in comparison to the 15 mg b.i.d. IR formulation of propiverine was also demonstrated in patients suffering from OAB [10]. Adverse events were reported less frequently in both treatment groups of the presented study compared to other studies investigating propiverine IR 15 mg t.i.d. in NDO [3], adverse events being reported spontaneously, not actively provoked.

The promising results were achieved following a treatment period of only 21 days. Most studies in NDO were restricted to treatment periods of 14-21 days, a period sufficient to demonstrate onset of efficacy [3, 4, 5]. Results with respect to longer treatment periods are almost lacking in NDO. However, it is well-known from studies conducted in OAB/IDO that efficacy is further improved following treatment periods beyond 2-4 weeks [20]. Investigating the long-term effects of antimuscarinics in adults suffering from NDO is also an urgent issue for future research, because most patients are exposed to life-long antimuscarinic treatment.

Can the merits of the ER formulation of propiverine ER 45 mg s.i.d., within the therapeutic armamentarium of NDO already be assessed ? Can positive implications of this innovative galenic formulation on quality of life, patient convenience, patient compliance and adherence rates be assumed ? Future research should address, whether ER compared to IR formulations are superior with respect to the following issues: (1) The superior continence rates following ER compared to IR formulations need to be further elucidated. (2) Unfortunately, pharmacoeconomic studies have not been conducted in NDO. However, at least in patients with OAB pharmacoeconomic studies have

shown more favourable patient compliance (74.3% vs. 60.9%) and adherence rates (115 days vs. 60 days) following ER compared to IR formulations of antimuscarinics [21]. Other studies [22] confirmed pharmacoeconomic advantages of ER compared to IR formulations in OAB patients for persistence over 1 year (15.3% vs. 6.5%), switch rates of (16.5% vs. 19.4%), and adherence rates (36.1% vs. 14.8%) to antimuscarinics. These issues are of paramount importance, especially in patients suffering from NDO, requiring life-long medication in order to avoid lethal sequelae.

In summary, this newly introduced galenic formulation of propiverine is distinctly preferable to other antimuscarinics, such as oxybutynin IR, which exerts a less favourable tolerability profile. However, comparative studies of oxybutynin ER and propiverine ER in NDO are lacking. A comparative study of the respective IR formulations documented the superiority of propiverine IR 15 mg t.i.d. compared to oxybutynin IR 5 mg t.i.d. with respect to tolerability [3]. Therefore, propiverine ER 45 mg s.i.d. is an antimuscarinic meeting the merits of an ER formulation applied once-daily associated with improved tolerability. This option is also less invasive compared to botulinum toxine injections, effective, but still off-label, presenting the consecutive 2$^{nd}$ step in the internationally acknowledged management algorithm in cases non-responsive to antimuscarinics [23].

**Conclusions:**
The urodynamic outcome parameters of this study demonstrated propiverine ER 45 mg s.i.d. and IR 15 mg t.i.d. to be equieffective in patients with NDO from a clinical point of view. The key clinical efficacy outcome, continence, and the tolerability outcomes, highlighting a trend for a superior tolerability profile of propiverine ER compared to IR, give indirect evidence for having achieved a more sustained drug release over 24 hours following propiverine ER. Future clinical practice still has to proof the merits of the presented innovative 45 mg ER galenic formulation of propiverine.

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Abbreviations:
ANCOVA analysis of covariance
ER extended release
IDO idiopathic detrusor overactivity
IR immediate release
ITT intention to treat
NDO neurogenic detrusor overactivity
OAB overactive bladder
PP per protocol

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