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Stöhrer M[1], Mürtz G[2], Madersbacher H[3]
1. *Urology and Paediatric Urology, University of Essen, Germany,* ***2.*** *APOGEPHA Arzneimittel GmbH,* ***3.*** *Neurology, University Hospital, Innsbruck, Austria*

NEUROGENIC DETRUSOR OVERACTIVITY IN ADULTS: A REVIEW OF THE EFFICACY, TOLERABILITY AND SAFETY OF ORAL ANTIMUSCARINICS

Introduction: Recently published reviews on antimuscarinics (AM) focus on idiopathic detrusor overactivity (IDO) and overactive bladder (OAB) [1]. This is also true for the latest Cochrane report on AM [2]. Studies on neurogenic detrusor overactivity (NDO) were either not included or not analysed separately, despite the fact that AM alone or in combination with intermittent catheterisation (IC) are the first-line treatment for NDO [3]. In this context it is important to realise that the aim of AM treatment in NDO is different compared to IDO as detrusor pressure in the storage and emptying phase is crucial for these patients: Its normalisation by AM is an important issue and demands urodynamic investigations before and during treatment as follow-up. This is in contrast to studies for IDO, in which improvement of the key symptoms, urgency with or without incontinence, frequency and nocturia are of paramount importance. Therefore, the aim of this review is to analyse the efficacy of AM in NDO with special reference to the detrusor pressure. To the best of our knowledge this is the first ever conducted review of AM in NDO.

Materials and methods: The review is based on a comprehensive search of all major literature bases and the abstract books from important conferences such as AUA, EAU, ICI, ICS and IMSOP / ISCOS during 1980 - 2009. There were no restrictions on the inclusion of publications by language, publications in languages other than English were included, if an abstract in English or German was available. Studies conducted with darifenacin, fesoterodine, oxybutynin, propiverine, solifenacin, tolterodine, and trospium chloride were reviewed. Our review is restricted to orally administered AM, because data on other modes of delivery, such as patches or intravesical application, are scarce in NDO of adults. Each of the AM was applied at various doses and dosing intervals.

Results: Placebo-controlled dose-finding studies in NDO were conducted only with propiverine, trospium chloride, and tolterodine, recommending 15 mg t.i.d. for propiverine, and 20 mg b.i.d. for trospium chloride. For tolterodine 1 or 2 mg b.i.d. were recommended as standard dose. However, superiority of tolterodine over placebo could not be demonstrated for the investigated urodynamic parameters.

The very first placebo-controlled study in NDO demonstrated the superior efficacy of oxybutynin 5 mg t.i.d. compared to placebo. Also for trospium chloride 20 mg b.i.d. statistically significant superiority over placebo was shown in terms of urodynamic parameters. Improved therapeutic responses were achieved, if flexible daily doses (90 - 135 mg) compared to standard doses of trospium chloride were applied. Flexible dosing of oxybutynin was investigated in another study, which demonstrated improved efficacy and tolerability of doses up to 30 mg following a prospective 12-week dose titration. The efficacy of propiverine 15 mg t.i.d. compared to placebo was evaluated in spinal cord injured patients: maximum cystometric bladder capacity increased significantly, paralleled by a significant decrease of maximum detrusor contractions. Other investigators demonstrated either a combined high dose of two AM or combining oral and intravesical AM as a feasible option for improving clinical results.

Time to onset of efficacy was determined in a study, which showed effects on detrusor overactivity as early as 0.5 hours following single doses of 2 mg tolterodine. Darifencin so far only has been investigated with respect to single intravenous doses, but not with respect to therapeutic oral doses. Solifenacin and fesoterodine up to now have not presented any study results in NDO.

Comparative studies of different AM or of different galenic formulations of the same AM have been undertaken: significantly larger increases in maximum cystometric bladder capacity were shown for oxybutynin compared to propantheline. Self-selected dosing of AM, in some cases exceeding the recommended doses, improved efficacy and tolerability, as demonstrated in a comparative trial of oxybutynin and tolterodine. Equieffectivity of trospium choride 20 mg b.i.d. and oxybutynin 5 mg t.i.d. following a treatment period of two weeks was shown. As efficacy is also dependent on tolerability the following results regarding tolerability are presented: with respect to severe gradings of dryness of the mouth trospium chloride was superior to oxybutynin. Also for propiverine a more advantageous tolerability profile compared to oxybutynin was shown, whereas propiverine and oxybutynin were equally effective. Recently, the equieffectiveness of the immediate (15 mg t.i.d.) and the extended (45 mg s.i.d.) release formulation of propiverine following 3 weeks of treatment was presented: reflex volume, leak point volume, and maximum detrusor pressure, as defined by the ICS, were evaluated as outcome parameters.

According to this review the overall incidence rates of adverse events (50% - 94%) as well as the incidence rates of dryness of mouth (17% - 67%) showed broad ranges, even if the same AM was administered. Adverse events seemed to be primarily dependent on the method of evaluation, such as spontaneous reporting or eliciting adverse events by questioning the patients.

Discussion: In NDO, contrary to IDO and OAB, no remarkable placebo effects were demonstrated following placebo treatment, which is not surprising, as most of the studies were conducted in spinal cord injured patients. With respect to NDO only oxybutynin, propiverine and trospium chloride were evaluated in placebo-controlled studies, tolterodine only with regard to one dose-finding study. These AM demonstrated a decrease of maximum detrusor pressure by 30 % - 40 %, paralleled by an increase of maximum cystometric bladder capacity by 30 % - 40 %, in some studies even more remarkable improvements resulted. The clinical effects were not only dependent on the AM and the dose applied, but also impacted by the respective

baseline values: effects were more pronounced in patients with a lower cystometric bladder capacity or higher detrusor pressure at treatment initiation. Moreover, detrusor contractility, a risk factor for the upper urinary tract, also normalized following AM treatment. Darifenacin, fesoterodine, and solifenacin so far have published only very limited or no data at all on these issues.

Future studies should aim at incorporating not only urodynamic, but also the crucial clinical parameters, e.g. achievement of continence between catheterisations. Moreover, the effects of AM on quality of life, for which only scarce data are available in NDO, should be investigated further. Despite the fact that most patients with NDO are on AM medication life-long, unfortunately, long-term data were primarily assessed for IDO.

Incidence rates of adverse events, especially dryness of the mouth, are dependent on the AM, its respective dose, and on the method of evaluation: adverse events manifested more often, if prompted questioning elicited adverse events compared to spontaneous reporting. Despite doses comparably higher in studies investigating NDO vs. IDO the incidence rates of adverse events did not show remarkable differences, presumably due to the younger age of the patient populations investigated in NDO.

Conclusions: A review of studies administering AM in NDO of adults is presented. Only oxybutynin, propiverine and trospium chloride are sufficiently investigated in NDO with respect to evidence-based criteria. Maximum detrusor pressure is lowered by 30 % - 40 %, paralleled by an increase of maximum cystometric bladder capacity of 30 % - 40 %. Long-term outcome studies are urgently requested. Moreover, those AM not evaluated in NDO up to now, should undergo adequate research.

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