

## ANTIMUSCARINICS IN CHILDREN: IS ITS USE IN CHILDREN EVIDENCE-BASED?

**Aims of study:** The aim of this review was to evaluate the existent evidence for the use of antimuscarinics in children with respect to neurogenic detrusor overactivity (NDO), and idiopathic detrusor overactivity (IDO) / overactive bladder (OAB). Furthermore, pharmacokinetic and dose-finding studies in children were analyzed.

**Study design, materials and methods:** Medline was searched for all trials performed with antimuscarinics in children from 1979 - 2009. Studies were included, if antimuscarinics were administered in children suffering either from NDO or from IDO / OAB. The efficacy parameters in NDO comprised especially urodynamic measurements, in IDO / OAB mostly clinical parameters were assessed. In NDO most of the studies administered oral formulations of antimuscarinics combined with intermittent catheterisation, some studies applied intravesical formulations. Furthermore, tolerability and safety parameters were evaluated.

**Results:** Altogether 48 open-label and randomized studies of both oral and intravesical galenic formulations of antimuscarinics were evaluated. For NDO, 26 studies were analysed. The conducted pharmacokinetic studies with oxybutynin, and tolterodine suggested no strong relationships between plasma levels and clinical effects. For darifenacin only one open-label pharmacokinetic study in NDO was reported. Dose-finding studies in IDO / OAB resulted in the following dose recommendations: 0.2 - 0.3 mg/kg bodyweight/day for oxybutynin, 0.8 mg/kg bodyweight/day for propiverine, 1 - 2 mg/day for tolterodine, and 10 - 25 mg/day for trospium chloride. These studies were conducted either in NDO, or in IDO / OAB.

Historically, oxybutynin has been authorized in children, despite presenting only limited evidence. In clinical studies investigating NDO oxybutynin was administered either orally or intravesically: According to a study review following intravesical administration of oxybutynin maximum cystometric capacity was increased from 43 mL up to 100 mL (+21.5% up to +100%), pressure at maximum capacity was decreased by 7.0 up to 26.2 cm H<sub>2</sub>O (-11.1% up to -47%). Incontinence episodes improved by 61% up to 83%. Only one placebo-controlled study and few open-label studies investigated orally applied oxybutynin, either administered as immediate or extended release formulation. Efficacy results following oral application were comparable to those achieved following intravesical application.

In NDO for orally applied propiverine results of one open-label retrospective, one prospective study, however both with limited patient numbers, and one study with active control, enrolling 255 children and adolescents, were reported: the urodynamically assessed efficacy of propiverine proved to be at least comparable to oxybutynin. Orally applied tolterodine was investigated in one open-label, and one comparative study, assuming equivalence of tolterodine and oxybutynin, however based on 16 children only. For fesoterodine, solifenacin, and trospium chloride no studies in NDO were reported.

Evidence with respect to long-term application of antimuscarinics has been reported for intravesically applied oxybutynin, orally applied propiverine, and tolterodine in NDO. In IDO / OAB only one open-label study reported long-term data following tolterodine treatment.

For IDO / OAB 22 studies were analysed in our review. Superior efficacy of oxybutynin compared to measures combining education, instructions on a voiding regimen, bladder diaries, and treatment of constipation and urinary tract infections was not proven with respect to clinical outcomes. Placebo-controlled studies for oxybutynin do not exist so far. Tolterodine did not show superior efficacy compared to placebo in two multi-centre studies. Propiverine could proof superior efficacy compared to placebo in one multi-centre study: The primary, clinically assessed efficacy parameter, voiding frequency, decreased significantly (-2.0 for propiverine versus -1.2 episodes for placebo; p=0.0007). Furthermore, a significant increase in voided volume (+31.4 mL versus +5.1 mL), and a significant decrease in incontinence episodes (-0.5 versus -0.2) as secondary parameters, were documented. One open-label study showed efficacy for propiverine in children with IDO / OAB. A comparative retrospective study of propiverine versus oxybutynin proved propiverine to be at least as effective as oxybutynin. For trospium chloride a placebo-controlled dose-finding study was reported, the only study in IDO / OAB not only evaluating clinical, but also urodynamic outcomes: with respect to overactive detrusor contractions a decrease by 54.3% was reported. Furthermore, volume at first detrusor contraction increased by 71.4%. For darifenacin, fesoterodine, and solifenacin no paediatric studies in IDO / OAB were reported.

Due to the limited number of studies with placebo or active control in children comparative evaluations of the tolerability of antimuscarinics are limited: In 225 children with NDO the tolerability of oral and intravesical oxybutynin was compared, claiming intravesical administration as the more safe and better tolerated galenic formulation. However, cognitive impairment also occurred following intravesical treatment of oxybutynin. The issue of adverse events of the CNS has been extensively addressed in open-label studies. However, a comparative evaluation of the adverse events profile across antimuscarinics in children focussing especially the CNS is still lacking. In a placebo-controlled trial 23% treatment-related adverse events for propiverine compared to 20% for placebo were reported. A head-to-head comparative trial documented lower incidence rates for propiverine (3.9%) compared to oxybutynin (16.3%). However, the retrospective evaluation of incidence rates of adverse events must be considered as a potential source of bias. In the two placebo-controlled trials of tolterodine 57% and 42% adverse events following tolterodine, and 54% and 42% adverse events following placebo were reported. For trospium chloride treatment-related adverse events were reported in 8% without evaluating tolerability in the placebo-group.

**Interpretation of results:** In children with NDO mostly open-label studies have been conducted for evaluating the efficacy of antimuscarinics. Nevertheless, the assessed urodynamic parameters demonstrated normalisation of maximum detrusor pressure and maximum cystometric capacity, thus convincingly demonstrating efficacy.

In children with IDO / OAB tolterodine did not prove efficacy in placebo-controlled studies, the proof of efficacy of oxybutynin is still lacking. Despite these drawbacks, open-label studies suggest at least oxybutynin as an effective treatment option. So far, only propiverine demonstrated its efficacy in a placebo-controlled study, which fulfilled statistical criteria. Trospium chloride proved its efficacy in a placebo-controlled study, which, however, due to a limited number of enrolled patients, did not meet statistical criteria.

Consecutively, according to the International Consultation on Incontinence oxybutynin, tolterodine, and trospium chloride were consistently evaluated with 3 C, the level of evidence and grade of recommendation given for propiverine in children was 1 B / C. In future research studies for other antimuscarinics (e.g. darifenacin, fesoterodine, and solifenacin) should be inaugurated in order to evaluate their respective potential in the paediatric population.

**Concluding message:** In adults suffering from NDO or IDO / OAB antimuscarinics are well documented with respect to efficacy and tolerability. In children, however, evidence-based studies are still limited and vary widely across these compounds. This fact is associated with different levels of evidence and grades of recommendation for oxybutynin (3 C), propiverine (1 B / C), tolterodine (3 C), and trospium chloride (3 C) awarded by the International Consultation on Incontinence.

#### References

1. available on request from correspondence author

<b><i>Specify source of funding or grant</i></b>	<b>None</b>
<b><i>Is this a clinical trial?</i></b>	<b>No</b>
<b><i>What were the subjects in the study?</i></b>	<b>NONE</b>