

Is tolterodine as effective as oxybutynin in overactive bladder caused by spinal cord injury?

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Abstract: Abstract: In neuro-urological practice the immediate release oxybutynin - the extended release one has become available in Italy only in 2010 - is usually considered more effective than the immediate release tolterodine in the treatment of overactive bladder caused by spinal cord injury. But in literature there is no a clear evidence, mainly for lack of papers on this topic.

We reviewed records of patients with spinal cord injury from January 1996 and June 2009. We found 16 patients (11 males and 5 females, mean age 43.5 years, range 22-67) that switched the antimuscarinic treatment from one drug to the other one having been checked by videourodynamic examinations during the assumption of each drug. The drugs were assumed at the usual dosages (tolterodine 2 mg twice a day and oxybutynin 5 mg twice or three times a day with an average of 12.5 mg). The efficacy of the antimuscarinics has been estimated clinically, based on the micturition diaries, and instrumentally, based on the modifications of the urodynamic parameters. Oxybutynin has resulted more effective than tolterodine at the recommended dosage for 75% of patients with detrusor-sphincter dyssynergy caused by sovrasacral spinal cord injury. Videourodynamic studies showed an increase of cystometric bladder capacity and a decrease of detrusor pressure in comparison with tolterodine. The statistical comparison between the two averages relative to maximal detrusor pressure and bladder cystometric capacity determined by using the "Student test for data joined to a tail" has turned out meaningful for $p < 0,01$.

Key words: Antimuscarinics; Neurogenic bladder; Spinal cord injury; Urodynamics

INTRODUCTION

Many neurourologists consider oxybutynin (OX) more effective than tolterodine (TL) in the treatment of the overactive bladder caused by the sovrasacral spinal cord injury (SCI) in the picture of the detrusor-sphincter dyssynergy (DESD). In DESD the antimuscarinics are usually used to abolish detrusor contractions in order to permit voidings by clean intermittent catheterism (CIC). However, in literature there is no a clear and well established evidence although these drugs were mainly compared in idiopathic overactive bladder or in a few and different types of neurogenic overactive bladder.¹⁻⁸

In Italy the extended release OX has become available only in 2010. On the other hand the immediate release OX is still nowadays the main antimuscarinic agent used for neurogenic bladder as the generic drug is dispensed free of charge by the National Health System to the SCI patients. Therefore we reviewed the records of the SCI cases referring to our departments in order to identify the patients who switched the immediate release antimuscarinic therapy - from TL to OX or otherwise - and who underwent videourodynamic studies during the assumption of each drug.

MATERIALS AND METHODS

Between January 1996 and June 2009 16 patients have met our inclusion criteria: they should have been treated in different times with OX and TL, they should have undergone urodynamics during the assumption of each drug and the urodynamic examination should have been performed at least 2 month after the beginning of the assumption of each antimuscarinic agent (see tab. 1).

All the patients presented DESD caused by at least a two year stabilized sovrasacral SCI and all of them had to change the therapy in use: 11 patients discontinued OX, and changed with TL, for comparison of side-effects (moderate/severe dry mouth in 10 patients and tachycardia in 1) while in 5 subjects TL assumption was interrupted, and re-

placed by OX, as TL wasn't effective in the cure of the urinary incontinence. The drugs were assumed at the usual dosages: TL 2 mg twice a day and OX at the dose of 5 mg twice or three times a day (average of 12.5 mg/die).

Thirteen patients voided by self-CIC while 3 women, at the beginning treated with TL, voided by reflex micturitions. The videourodynamic examination was carried out at least 2 months after the assumption of each drug (range 2-13 months, mean 3.8) and it was performed in the lytotomic position using one double-lumen transurethral catheter 6 Ch and one rectal probe. Iodinated contrast medium was infused at a flow rate of body weight/4 ml/min and a Medtronic Duet system was used. Urinary sterility and regularity of urinary tracts by ecography were checked previously. For all patients the micturition diaries of 4 days were available.

The effectiveness of the therapies has been estimated: a) clinically, based on the micturition diaries and on the urinary leakages; b) instrumentally, based on the modifications of the urodynamic parameters.

A "t of Student for data joined to a tail" test was applied to compare the different values of maximum cystometric capacity and maximal detrusor pressure during treatments with OX and TL. Statistically significant difference was accepted for $p < 0.05$.

TABLE 1. Patients' features

	M	F	tot
patients n.	11	5	16
age at lesion	37,1(22-61)a.	30,1(23-62)a.	34,9(22-62)a.
age at observation	45,6(26-64)a.	38,6(24.64)a.	43,4(24-64)a.
cervical level	2	1	3
thoracic level	9	4	13

RESULTS

Clinical data

In 12 patients (75%) OX improved the storage bladder symptoms in comparison with TL: 9 of them complained urinary incontinence only during the therapy with TL while 3 patients were incontinent with both the drugs but the urinary leakages worsened during the treatment with TL. Also the voided volumes increased during the treatment with OX (9-46% more than with TL, with an average of 26%).

Four patients were unchanged with both the drugs and 2 of them, complaining urinary leakages, underwent detrusorial injections of botulinum toxin.

OX caused complete urinary retention in 2 women that previously voided by reflex micturitions.

Urodynamics data

All the patients showed DESD with normal compliance and hypo-anesthesia of the bladder. None showed vesicoureteral reflux or major radiological alterations.

The average maximum cystometric capacity was 253 ± 126 ml with TL against 323 ± 111 ml observed during OX treatment: therefore OX increased the maximum cystometric capacity of 80 cc (38%) in average, respect to TL. All the values are shown in fig. 1. The statistical comparison between the two averages executed with the test "t of Student for data joined to a tail" has turned out meaningful for $p < 0,01$.

The maximal detrusor pressure was reduced by OX: from an average of 43.5 ± 24.4 cm H₂O with TL to an average of $31.2 \pm 16,7$ (range 0- 53 cm H₂O less, mean 12.3 corresponding to a mean percentage decrease of 19% - see fig. 2). The statistical comparison between the two averages executed with the test "t of Student for data joined to a tail" has turned out meaningful for $p < 0,01$.

In 4 patients (25%) urodynamic data were the same during both the therapies.

In conclusion a situation of low-pressure bladder – assuming a cut-off for maximal detrusorial pressure < 30 cm during cystometry – has been reached in 9 patients during OX treatment and in 4 subjects during TL therapy.

DISCUSSION

There exists only limited literature on the use of antimuscarinics in patients with neurogenic incontinence.

The overactive bladder caused by sovrasacral SCI is a suitable model to compare the effects of antimuscarinic drugs since the detrusor contraction is reflex in such patients and it is not influenced by psychological inhibition. But, on the other hand, it is really problematic to compare antimuscarinics in randomised or prospective trials in such patients for ethical reasons.

OX generally causes a significantly higher incidence of adverse events than TL^{4,7,10} and this feature have been greatly underlined in last years. Especially the frequent dry mouth induced by OX, reported in 30-60% of cases based on different series, has led to find alternative drugs and TL has been the molecule more used in 1990s, even though few studies proved its efficacy in neurogenic overactive bladder.^{2,6,11}

In a randomised study including 33% SCI patients, Van Kerrebroeck and all showed that TL was more effective than placebo in treating the symptoms of overactive bladder and that the therapeutic effect was dose-dependent.¹

Later only Ethans² compared OX and TL in 10 patients with neurogenic overactive bladder – in 7 of them caused by SCI – but in self-selected doses regimen. He reported that the efficacy of TL was comparable to OX in enhancing bladder volume, improving continence and cystometric bladder capacity but OX presented a worse side effect profile (dry mouth). In this study larger doses of TL have been used to achieve this effect: TL twice daily at the average dose of 8 mg has been compared with OX twice daily at the usual average dose of 12.5 mg.

Further Horstmann³ suggested to double TL and trospium chloride doses in neurogenic overactive bladder not responding to the usual dosages. Two doses of extended release TL, 4 mg and 8 mg respectively, were compared and a significant amelioration of urodynamic parameters with the higher dosage was observed.

In the last years Cameron⁴ and again the group of Horstman⁵ proposed to combine two or more antimuscarinics in neurogenic bladder resistant to monotherapy.

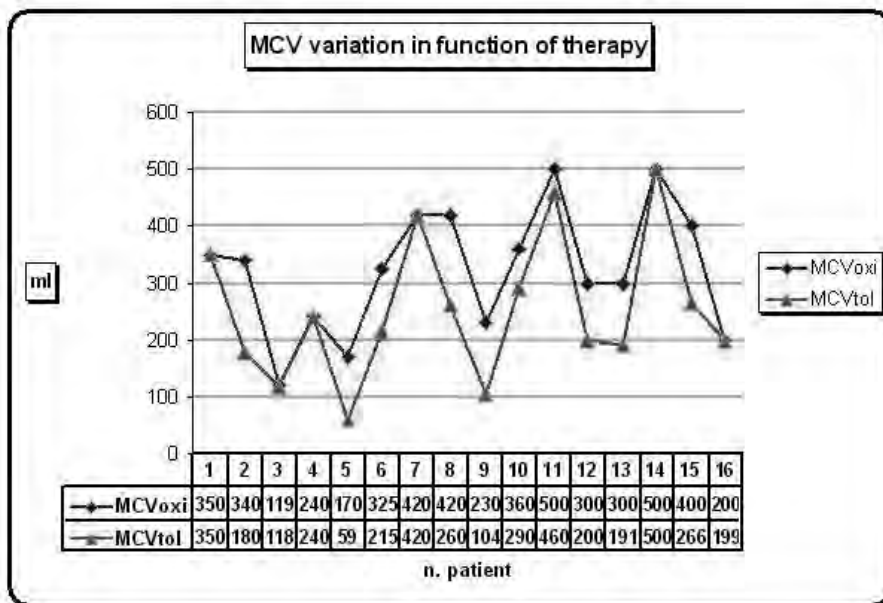


Figure 1. – Maximum cystometric capacity (MCV) for any patient in consecutively treatment with oxybutynin and tolterodine.

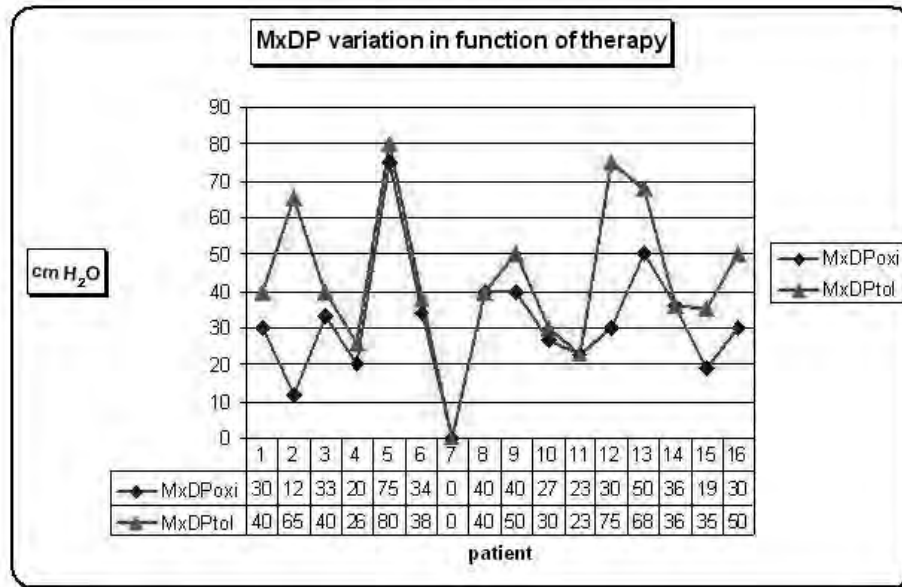


Figure 2. – Maximum detrusor pressure (PMax) for any patient in consecutively treatment with oxybutynin and tolterodine.

Many SCI patients referring to our neuro-urological departments assume OX and most of them are satisfied. We reviewed all our records and we found a little and homogeneous group of sacral SCI patients who assumed in different times the immediate release forms of TL and OX at usual dosages and who were checked instrumentally during both the therapies. Even though the usual methodological and ethical limits in studies regarding SCI patients – the studies are mainly retrospective and based on a small number of patients – the higher efficacy of OX was observed in 75% of cases both clinically – disappearance of urinary incontinence and enhancing voided volumes – than instrumentally with a mean increased of 38% as regard the cystometric bladder capacity and a mean percentage decrease of 19% of maximum detrusor pressure. Therefore the usual dosage of TL shouldn't be used in overactive bladder due to SCI except than in patients who void by reflex micturitions in a safe way and in whom a reduction of urgency is searched (but low dosages of OX could also be used in these rare situations). In our opinion in case of adverse events caused by OX it is better to prescribe trospium chloride or detrusorial injections of botulinum toxin rather than TL.

CONCLUSIONS

The immediate release OX is still the reference antimuscarinic drug in SCI patients in Italy as its effectiveness is well-supported by daily activity and the literature.

In our experience OX has proven to be more effective than the immediate release form of TL for 75% of SCI patients with detrusor-sphincter dyssynergy.

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