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ORIGINAL ARTICLE

Are oxybutynin and trospium efficacious in the treatment of detrusor overactivity in spinal cord injury patients?

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Objectives: To evaluate the efficacy of anticholinergic agents in the treatment of neurogenic overactive bladder (NOAB) and neurogenic detrusor overactivity (NDO) in spinal cord injury (SCI) patients on clean intermittent catheterisation (CIC).
Methods: Chronic suprasacral SCI patients on CIC presenting with at least one urinary leakage a day were included. Urodynamics and voiding diaries were performed at baseline and 1 month follow-up. In case of NDO at baseline, an anticholinergic drug was prescribed.
Results: The 231 SCI patients presented with one to five urinary leakages per day (mean 2.1). Urodynamics showed NDO in all patients. A new anticholinergic treatment was started in all, either in monotherapy (134 patients) or in association with the existing anticholinergic drug (oxybutynin + trospium bitherapy, 97 patients). The mean maximum bladder capacity significantly increased from 225 to 441 ml, and the mean involuntary detrusor contractions (IDC) significantly decreased from 67 to 41 cm H_2O. Only 75 SCI patients (32%) were fully continent. However, 25 out of these 75 patients showed persistent NDO, with amplitudes of IDC above 40 cm H_2O in 12 patients. Incontinence was still found in 156 SCI patients (67%), with an average of 1,2 leakages a day. In 100 patients, amplitudes of IDC remained above 40 cm H_2O. There was no statistical difference between patients on anticholinergic monotherapy or bitherapy at follow-up.
Conclusion: Anticholinergic treatment is not always satisfactory in terms of control of NDO and rarely allows full continence. Urodynamic follow-up is mandatory in all patients, even in those showing clinical continence.
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INTRODUCTION

The quality of life of patients presenting with spinal cord injury (SCI) is frequently impaired by lower urinary tract dysfunction. In supra-sacral SCI lesions, neurogenic overactive bladder (NOAB) is common, with symptoms including urgency, with or without urge incontinence, frequency and nocturia.[1] Patients with NOAB are often found to have neurogenic detrusor overactivity (NDO), an urodynamic observation characterised by involuntary detrusor contractions (IDCs) during the filling phase that is either spontaneous or provoked.[2] Amplitudes of IDC greater than 40 cm H_2O pose a threat to the upper urinary tract.[3]

Oral antimuscarinic agents have been widely used as first-line treatment for patients with NDO. However, they are ineffective in some patients and are often associated with bothering side effects such as dry mouth, constipation and blurred vision.[2,4]

The clinical and urodynamic efficacy of anticholinergic agents in SCI patients has been evaluated in a limited number of studies.[5–9] They all showed a significant decrease in the number of leakages per day with improved quality of life. Urodynamic testing showed significant improvement in maximum bladder capacity (BCmax) and significant reduction in amplitudes of IDC. However, these were mainly short-term studies, using different evaluation criteria, with different drugs at flexible doses. Surprisingly, patients presenting with daily leakages and persistence of IDC (as high as 35 mm Hg) could still be considered as good results.

In a large population of chronic SCI patients on clean intermittent catheterisation (CIC) presenting with NOAB, we systematically assessed the efficacy of anticholinergic agents at 1 month's follow-up, with strict clinical and urodynamic criteria.

MATERIALS AND METHODS

We conducted a retrospective and monocentric study, over a period of 33 months (from January 2007 to November 2009).

Inclusion criteria were chronic (>6 months) suprasacral SCI patients on CIC presenting with at least one urinary leakage a day. Patients could be either on one anticholinergic agent in monotherapy (oxybutynin or trospium at therapeutic doses), or not. Exclusion criteria were symptomatic urinary tract infection, bladder or renal stones, history of intradetrusor botulinum toxin or pressure sore presence. Patients already on two anticholinergic drugs for the bladder were also excluded.

Urodynamic testing was performed in each patient at baseline. In case of NDO, an anticholinergic drug was systematically prescribed at therapeutic dose. When an anticholinergic treatment was initiated, either oxybutynin or trospium was used in monotherapy. In those patients already on anticholinergic agent, another anticholinergic drug was associated, so as to have an association of oxybutynin + trospium, each at therapeutic dose. Therapeutic doses used for these patients are in accordance with French recommendations, with oxybutynin at 15 mg per day (taken as 5 mg orally three times daily), and trospium chloride at 40 mg per day (20 mg orally twice daily).

A control urodynamic testing was then performed in these patients at 1 month follow-up.

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All urodynamic testings at baseline or follow-up were preceded by a 72-h voiding diary and by a urine culture test. Appropriate antibiotic treatments were given for at least 2 days before testing. At baseline, routine exams also included creatinine blood level and clearance test on 24-h urine sample, kidneys and bladder ultrasound (to eliminate a local urologic complication).

All experiments were performed with the patient in the supine position. Intravesical and sphincter pressures were measured with a fluid-filled, CH 8, triple lumen catheter; the abdominal pressure was measured with a fluid-filled rectal balloon. Cystometries (50 ml min^{-1}) were carried out in each patient with saline at room temperature with a Geyre Electronic 2500C (MMS) equipment. Bladder filling was stopped in the presence of detrusor contraction exceeding 10 cm H_2O, sensation of urgency or up to 600 ml.

The urodynamic output measures were the BCmax and the amplitude of IDC, according to the International Continence Society terminology.[1] We defined the urodynamic balance as the combination of BCmax greater than 400 ml and amplitude of IDC lower than 20 cm H_2O. The clinical balance was defined as the absence of leakage between the CIC (that is, complete continence).

Two groups of patients were constituted, according to the clinical balance: fully continent (group 1) or not (group 2).

Data were analysed using the SPSS software (IBM, USA, http://en.wikipedia.org/wiki/SPSS). Averages, medians and s.d.'s were calculated for quantitative variables, whereas simple frequencies and relative frequencies (percentages) were calculated for categorical variables.

To compare the mean values of our independent series, the Student's *t*-test was used after verification of the factor F of Snedecor homogeneity of variances. The significance of the test was set at 0.05.

RESULTS

Two hundred and thirty-one SCI patients hospitalized in our rehabilitation centre were included. The clinical data are reported in Table 1. The severity of lesion is defined according to the ISCoS/ASIA Impairment Scale as AIS A (complete, no sensory or motor function is preserved in the sacral segments), AIS B (incomplete, sensory but not motor function is preserved below the neurological level and includes the sacral segments), AIS C and D (incomplete, partial motor function preserved).[10]

All patients presented with an upper motor lesion syndrome with exaggerated reflexes at the perineum. Urinary incontinence was managed either with urinary sheaths or incontinence pads in all patients.

One hundred and thirty-four patients were on one anticholinergic drug in monotherapy at baseline: 112 patients were on oxybutynin 15 mg per day and 22 on trospium chloride 40 mg per day.

Baseline

All patients ($n = 231$) showed clinical imbalance, with one to five urinary leakages per day (mean 2.1 per day).

Urodynamic testings showed NDO in all patients. The BCmax ranged from 80 to 550 ml (mean 225 ml), with most patients ($n = 172$) having BCmax lower than 300 ml. The mean amplitude of IDC ranged from 21 to 140 cm H_2O (mean 67 cm H_2O), the large majority of patients ($n = 189$) having amplitudes above 40 cm H_2O.

A new anticholinergic treatment was started in all patients, either in monotherapy (134 patients) or in association with the existing anticholinergic drug (oxybutynin + trospium bitherapy, 97 patients).

Follow-up

Urodynamic testings were performed between day 21 and day 46 (mean 1 month (Tables 2 and 3).

Table 1 Characteristics of the patients

	All (n = *231*)	*Tetraplegic* (n = *62*)	*Paraplegic above T12* (n = *32*)	*Paraplegic below T12* (n = *137*)
Age (years)	38.4 ± 14.0	35.4 ± 10.9	40.5 ± 16.2	39.2 ± 14.5
Evolution (months)	87.7 ± 102.8	71.9 ± 71.4	89.2 ± 137.2	94.4 ± 105.4
Sex				
Men	195	58	21	116
Women	36	4	11	21
Motor neuron lesion				
Upper	231	62	32	137
Lower	0	0	0	0
Severity of lesion	172 AIS A 59 AIS B/C/D	32 AIS A 30 AIS B/C/D	20 AIS A 12 AIS B/C/D	120 AIS A 17 AIS B/C/D

Table 2 Urodynamic data in all patients

	BCmax		*IDC*	
	Baseline	*Follow-up*	*Baseline*	*Follow-up*
Group 1 (fully continent)	236 ml	463 ml	63 cm H_2O	25 cm H_2O
75 SCI (32.4%)	+ 227 ml ($P<0.01$)		− 38 cm H_2O ($P<0.01$)	
Group 2 (incontinent)	211 ml	292 ml	75 cm H_2O	55 cm H_2O
156 SCI (67.5%)	+ 81 ml ($P<0.01$)		− 20 cm H_2O ($P<0.01$)	
All	225 ml	441 ml	67 cm H_2O	41 cm H_2O
231 SCI	+ 216 ml ($P<0.01$)		− 26 cm H_2O ($P<0.01$)	

Abbreviations: BCmax, maximum bladder capacity; IDC, involuntary detrusor contraction; SCI, spinal cord injury patients.

Table 3 Urodynamic data in the fully continent group

	BCmax			*IDC*		
	Baseline		*Follow-up*	*Baseline*		*Follow-up*
50 SCI (21.6%)	255 ml		480 ml	58 cm H_2O		0 cm H_2O
		+225 ml ($P<0.01$)			−58 cm H_2O ($P<0.01$)	
25 SCI (10.8%)	217 ml		446 ml	68 cm H_2O		50 cm H_2O
		+229 ml ($P<0.01$)			−18 cm H_2O ($P<0.01$)	

Abbreviations: BCmax, maximum bladder capacity; IDC, involuntary detrusor contraction; SCI, spinal cord injury patients.

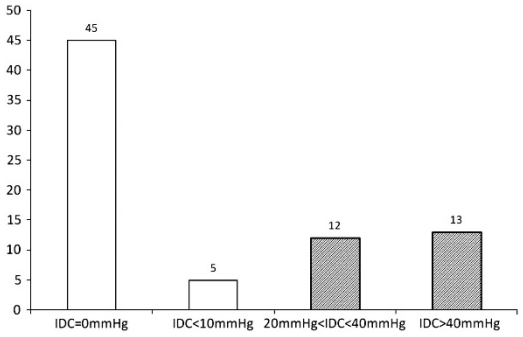

Figure 1 IDC in continent SCI patients. IDC, involuntary detrusor contraction; SCI, spinal cord injury patients.

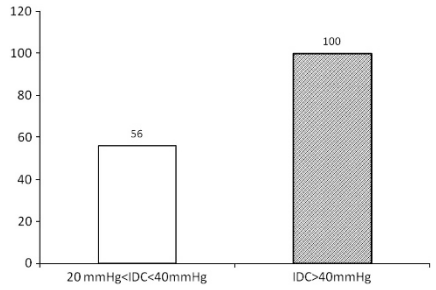

Figure 2 IDC in incontinent SCI patients. IDC, involuntary detrusor contraction; SCI, spinal cord injury patients.

The mean BCmax significantly increased by 216 ml (from 225 to 441 ml, $P<0.01$), and the mean amplitude of detrusor contractions significantly decreased by 26 cm H_2O (from 67 to 41 cm H_2O, $P<0.01$). However, only 75 SCI patients were fully continent (group 1), whereas 156 patients were not (group 2).

No relations were found between the changes in urodynamic parameters (BCmax and amplitude of IDC) and the level of injury ($P=0.88$), or between the type of anticholinergic therapy (mono- or bitherapy) and urodynamic balance ($P=0.35$). Out of the 97 SCI patients who had an anticholinergic bitherapy, 13 presented with detrusor hypoactivity (BCmax greater than 500 ml, NDO absent or with amplitudes of less than 10 cm H_2O).

Oxybutynin and trospium were significantly more effective in patients with an incomplete SCI lesion ($P=0.04$), and a shorter time since injury ($P=0.02$).

We did not systematically assess the importance or the prevalence of anticholinergic side effects; however, 30 out of the 97 SCI patients on anticholinergic bitherapy reported an increase of dry mouth and constipation.

Group 1. At 1 month's follow-up, clinical balance (full continence) was found in 75 SCI patients (32%). They had an average of 1,6 leakages a day (from 1 to 4) at baseline. Urodynamic balance was found in 50 patients (21% of our cohort) with a significant increase in the mean BCmax of 225 ml ($P<0.01$). Detrusor contractions were absent in 45 patients and present with less than 10 cm H_2O in five others). Thirteen out of these fifty patients were on anticholinergic bitherapy. By contrast, 25 patients (10% of the cohort) showed clinical but not urodynamic balance (Figure 1). The mean BCmax significantly increased by 229 ml ($P<0.01$), whereas the mean amplitudes of IDC significantly decreased by18 cm H_2O ($P<0.01$). In 12 patients, amplitudes of IDC still remained above 40 cm H_2O. Four out of these 25 patients were on anticholinergic bitherapy.

Group 2. At follow-up, incontinence (clinical imbalance) was still found in 156 SCI patients (67%; Figure 2), with an average of 1,2 leakages a day (versus 2,3 leakages at baseline, $P=0.03$). They all showed persistent NDO. The mean BCmax significantly increased by 81 ml ($P<0.01$), whereas the mean amplitudes of IDC significantly decreased by 20 cm H_2O ($P<0.01$). In 100 patients, amplitudes of IDC still remained above 40 cm H_2O.

Eighty out of these 156 patients were on anticholinergic bitherapy.

DISCUSSION

The main findings of this study are as follows:

- in patients with suprasacral SCI lesions, urinary leakage is always related to NDO;
- oxybutynin and trospium are significantly effective in raising BCmax and decreasing amplitudes of IDC;
- there were no significant differences between anticholinergics in mono- or bitherapy.

However,

- on oxybutynin and trospium, only 32% of patients are fully continent;
- clinical balance (absence of leakage) is not predictive of urodynamic balance, as one-third of the fully continent patients showed persistent IDC.

Management of NOAB and NDO aims to reduce upper urinary tract complications and to improve the quality of life of each individual. It also promotes their ability to engage in sexual activities. The risk for upper tract damage is far greater in patients with SCI

than in patients with progressive neurological diseases such as multiple sclerosis, even when these diseases are associated with severe disability and spasticity.[11] Risk factors for upper urinary tract deterioration in patients with suprasacral SCI include high-pressure storage (poor compliance), high detrusor leak-point pressure (>40 cm H_2O), chronic bladder overdistension and vesicoureteral reflux with infection. However, as lower detrusor leak-point pressures have also been shown to be a risk factor,[12] all patients with SCI should undergo baseline urodynamic studies.

CIC associated with pharmacological treatments allow a complete and regular bladder emptying and limit the risk of incontinence.

When necessary, anticholinergic drugs are first-line treatments to increase bladder capacity and reduce the amplitude of detrusor contractions.[13] They are associated with significant side effects because of their action on nonspecific muscarinic receptors:[14,15] symptoms such as dry mouth, constipation and blurred vision are common and not well tolerated and may explain why this treatment is often discontinued.[9,13,16,17] This is an additional bias to evaluate their real effectiveness. At the time of the study, oxybutynin and trospium were the only anticholinergic drugs fully licensed and refunded in France, tolterodine being licensed but not refunded.

The combination of two anticholinergic drugs is often necessary to optimize their effectiveness. Amend *et al.*,[5] in a prospective study, showed that bitherapies associating tolterodine + oxybutynin, tolterodine + trospium or oxybutynin + trospium were more effective than any anticholinergic monotherapies, with no significant increase in side effects. In our study, 97 SCI patients were on oxybutynin + trospium, whereas 134 were on a single anticholinergic drug (oxybutynin or trospium). The clinical and urodynamic changes were not related to the type of therapy (mono- or bitherapy).

To reduce the side effects, oxybutynin can be used at lower dosages with the same efficiency,[6,11,18,19] either in intravesical instillation or on transcutaneous application (patch). However, these methods are not marketed in France.

Studies showing clinical or urodynamic improvements on anticholinergic medication in SCI patients are few. In a prospective study over 4 weeks and involving 27 neurological patients (including 21 SCI patients), Amend *et al.*,[5] compared three different associations of anticholinergic drugs. The group associating oxybutynin + trospium showed clinical improvement with significant reduction in the number of leakages per day (from 8.6 to 1.3), and significant urodynamic improvement on BCmax (from 170 to 412 ml) and compliance (from 15–33 ml cm^{-1} H_2O). It should be noted that the urodynamic balance was defined as IDC lower than 40 cm H_2O and BCmax greater than 300 ml, the clinical balance as less than two leakages per day. Madersbacher *et al.*[9] showed a significant improvement in BCmax, compliance and reduced IDC amplitudes in 95 SCI patients on oxybutynin or trospium. Kim *et al.*[8] assessed 109 SCI patients on oxybutynin, and observed a significant decrease in leakages, a significant increase in compliance and decrease in detrusor contractions.

Our study in 231 SCI patients confirms these results, showing a significant increase in BCmax (from 225 to 441 ml) and a significant decrease in the mean amplitudes of the IDC (from 61 to 41 cm H_2O). We further asserted that, although dramatic improvements in urodynamic data were observed in the group of 75 SCI fully continent patients, these changes were significant but far less impressive in the group of 156 incontinent patients, 125 patients having a BCmax lower than 400 ml and 100 patients an IDC greater than 40 cm H_2O.

Whereas it is important to show the improvement on urodynamic data, as it implies a reduced risk in upper tract deterioration, results of a study on anticholinergic drugs cannot rely on quantitative data only. Full continence in everyday life is another major goal that allows a better quality of life. This qualitative result is achieved in only 75 out of our 231 SCI patients, which cannot be considered as satisfactory.

Our study further stresses the importance of urodynamic testing for two different reasons. First, we observed a remaining NDO in 25 out of the 75 SCI patients who were fully continent, meaning that follow-up cannot solely rely on clinical balance. Second, we showed that urodynamic data were predictive of the results of an anticholinergic treatment, with poor responder having smaller BCmax and stronger IDC amplitudes at baseline.

Finally, as clinical and urodynamic balance on anticholinergic medications is only obtained in a minority of patients (21%), alternative treatments must be sought. For the last 10 years, intradetrusor injection of botulinum toxin type A has proved its efficiency in achieving these goals.[2] This treatment received official approval to market in France in 2011 and can be fully refunded. It is now considered as thes second-line treatment for these patients, either for clinical or urodynamic imbalance.

LIMITATIONS

All urodynamics were performed at a medium filling rate of 50 ml min^{-1}, whereas 20 ml min^{-1} is advocated by the ICS.[1] Fast filling (>100 ml min^{-1}) is considered to be provocative of detrusor overactivity and tends to produce lower bladder capacity in non neurogenic patients.[20] The influence of filling rates on urodynamic data has been rarely studied in SCI patients. In 16 patients presenting with uninhibited neurogenic bladder, repeated cystometries were performed at varying filling rates from 10 to 90 ml min^{-1}.[21] This resulted in no change in BCmax or amplitudes of IDC in the majority of patients, even though a decreased BCmax could be found in a smaller number of them ($n=4$); the amplitudes of IDC could also vary in some (increase in 4, or decrease in 4). It was concluded that the rate of filling is of less importance as long as one and the same rate is used in the same experiments, which was the case in this study.

CONCLUSION

Our study confirms the efficacy of anticholinergic treatments on quantitative urodynamic parameters. However, from a qualitative point of view, these results are not satisfactory, as only 75 SCI patients (32%) were completely dry, which remains one of the main goals for patients on CIC.

We further showed that the follow-up of patients on anticholinergic drugs cannot rely solely on the clinical balance. This strongly supports the necessity of systematic urodynamic follow-up in the weeks following the start of any new anticholinergic treatment. In case of clinical or urodynamic imbalance, second-line treatments should be proposed, such as intradetrusor injections of botulinum toxin A.

DATA ARCHIVING

There were no data to deposit.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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