OXYBUTYNIN CHLORIDE IN THE TREATMENT OF FEMALE IDIOPATHIC BLADDER INSTABILITY

Results from double blind treatment

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SUMMARY

The Authors carried out a random double-blind trial on 30 patients affected by idiopathic urge incontinence with oxybutynin chloride (15 mg/die) and placebo for two 20 day therapeutical cycles. The 24 patients who completed the trial oxybutynin chloride induced statistically significant effects – compared to placebo too – both on the subjective symptoms (reduction or disappearance of the urgency in 14 cases – 60.8% – and of urge incontinence in 16 cases – 76.1%) and on the objective symptoms showed by cystomanometry (increased bladder capacity at the FD and VSD in 14 and 15 cases, respectively; absence of involuntary contraction in 9 cases and normal or reduced detrusor pressure at the VSD in 13 out of 16 cases).

Improvements, though less significant, were also obtained with the placebo.

Bladder instability is a common cause of urinary incontinente, its main symptoms being pollakiuria, urgency, urge incontinence and nocturia. It may be caused by known neurological troubles (like multiple sclerosis) or obstructive pathologies (like prostatic hypertrophy in men) but bladder instability is very often idiopathic, probably due to the absence of cortical inhibition of the detrusor activity ([1, 2]).

Different therapeutical approaches have been proposed to treat bladder instability: surgery ([3]), bladder distension ([4]), pharmacological treatment ([1]) and – particularly for idiopathic instability – biofeedback techniques ([5]).

In fact their results have always been rather variable.

Oxybutynin chloride has proven to be one of the most effective substances ([6, 7]); it is an antispastic drug acting on smooth muscles and inhibiting the action of acetylcholine on these muscles without any anticholinergic effects on neuromuscular junctions or ganglia of the autonomic nervous system ([8, 9, 10]).

It is effective both on subjective symptoms (urgency, urge incontinence, pollakiuria) and on instability showed by cystomanometry (increased bladder capacity, less acute and frequent non-inhibited detrusor contractions, etc.) ([7]).

This study reports results from a random double-blind treatment with oxybutynin chloride and placebo carried out on 30 patients affected by 'idiopatic' urge incontinence.

MATERIAL AND METHODS

Between September 1980 and December 1982 297 patients affected by urinary incontinence came to the out-patients' urodynamics center of the 5th Obstetric-Gynecological Clinic of Milan University. Among 63 of them (21.2%), affected by bladder instability, according to the definition by the International Continence Society ([11]), we choose 30 cases presenting either idiopathic bladder instability (24 cases) or 'sensorial' urge incontinence (6 cases) diagnosed in

Table 1. — *Total micturition frequency (24 cases).*

	Pre-treatment	Oxybutynin chl.	Placebo
Normal	14	23	20
Patological	10	1	4
Mean	6.52	4.54	5.73
Sx	2.19	1.61	1.80
		p<0.001	p n.s.
		p<0.01	

Table 2. — *Pathological micturition frequency (10 cases).*

	Oxybutynin chl.	Placebo
Normal	9	6
Pathological	1	4
	p<0.001	p<0.02
	p n.s.	

our center between November 1981 and November 1982.

In view of the characteristics of the drug patients affected by heart or liver diseases, moderate or high blood pressure or glaucoma were excluded. The patients' age ranged between 36 and 70 years (average 51.5).

This group included both patients traeated previously and unsuccessfully with different drugs and untreated cases.

6 out of 30 patients did not carry through this study due to intercurrent disease (1 case), withdrawal of therapy (3 cases) or allergy (2 cases).

Urodynamic data are not available for 2 of the 24 patients who carried the treatment through.

Before the treatment began and at the end of each cycle all patients underwent accurate general and specific to incontinence history, gynecologic and neurologic examinations of the perineal area and lower limbs and filled the clinical form used in our center.

Prior to treatment, complete urine examination and urinocolture were carried out in all cases whereas cystoscopy was carried out only when recurrence of previous urinary infections was observed (12 cases).

The treatment consisted of 2 random therapeutical cycles in double-blind of drug and placebo, lasting 20 days each and separated at least by a 10-day wash-out. The drug was taken in 3 daily doses adding up to 15 mg.

Before the treatment began and on the final day of each cycle the patients underwent H_2O cystomanometry with 50 ml/min infusion speed and provocative tests by fits of coughing and postural changes.

Bladder instability (increased in detrusor pressure $\geqslant$ 15 cm H_2O) was observed in 17 patients (out of the 22 whose urodynamic data were available) while "sensorial" urge incontinence was diagnosed in 5 cases (in 2 of which previous cystomanometry had shown non-inhibited detrusor contractions).

The following subjective symptoms were taken into account:

1) day-time urinary frequency (7 being the normal threshold);
2) urgency;
3) urge incontinence;
4) nocturia.

The following cystomanometric parameters were considered:

1) volume at which the FD (first desire of voiding) was felt;
2) volume at which the VSD (very strong desire of voiding) was felt;
3) detrusor pressure at the VSD (v.n. < 15 cm H_2O);
4) filling volume when the first non-inhibited contraction occurred.

The following hematochemical tests were carried out prior to and at the end of the treatment to assess the systemic tolerability of the drug: complete blood count, blood glucose, BUN, creatininemia, total bilirubinemia, SGPT, SGOT, alkaline phosphatase.

Moreover, at the end of each therapeutic cycle all side-effects, their acuteness and time of onset were reported on a clinical file.

The significance of the results obtained was assessed by two-directional Student's "t" test with paired data.

RESULTS

Tables 1-4 show the data concerning subjective symptoms (frequency, urgency,

Table 3. — *Urgency (24 cases).*

	Pre-treatment	Oxybutynin chl.	Placebo
Absent	1	9	1
Weak	—	5	9
Strong	23	9	13
		p<0.001	p n.s.
		p<0.01	

Table 4. — *Urge incontinence (24 cases).*

	Pre-treatment	Oxybutynin chl.	Placebo
Absent	3	12	6
Weak	—	4	3
Strong	21	5	12
		$p<0.001$	$p<0.005$
		$p<0.01$	

urge incontinence) reported by the patients before the treatment and after taking the drug and placebo. Graph 1 shows the average micturition frequency. Table 2 makes a particular distinction between the patients whose pre-therapy micturition frequency was positively pathological (=7) and the others.

It is worth noting that while the drug had always statistically significant effects on all these parameters the placebo influenced significantly only pathological frequency and urge incontinence. Drug and placebo effects differed significantly on 3 out of the 4 parameters examined. Nocturia (4 cases) disappeared in all patients, whether treated with drug or placebo (no statistical evaluation was made given the very few cases).

Regarding objective data tables 5-9 and graph 2 show the results achieved. Clearly the effects of oxybutynin chloride are always very significant, also if compared with the placebo in 3 out of the 4 parameters considered. Therefore the cystomanometry confirmed the reliability of the favourable results reported subjectively by the patients.

Systemic tolerability of the drug was excellent without any significant changes in hematochemical parameters. Two of the 30 original patients showed allergies.

Side-effects (tab. 10) – mainly strong xerostomia whether or not associated with

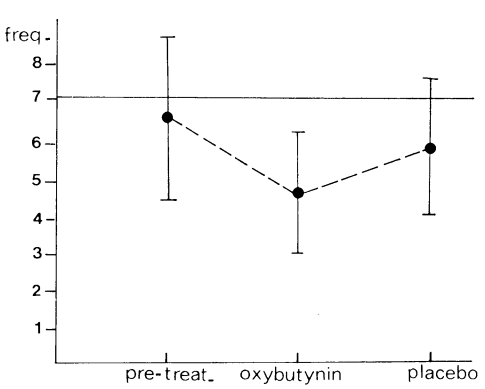

Fig. 1. — Urinary frequency (mean and DS).

Table 5. — *F.D. (22 cases).*

	Oxybutynin chl.	Placebo
Improved	14	13
Unchanged or worsened	8	9
Pre-treatment mean cc 118	166 (+41%)	135 (+14%)
	$p<0.01$	p n.s.
	$0.025>p>0.02$	

Table 6. — *V.S.D. (22 cases).*

	Oxybutynin chl.	Placebo
Improved	15	11
Unchanged or worsened	7	11
Pre-treatment mean cc 231	286 (+24%)	229 (=)
	$0.01>p>0.005$	p n.s.
	$p<0.01$	

Table 7. — *1st contraction (15 cases).*

	Oxybutynin chl.	Placebo
Absent	9	5
Improved	2	5
Unchanged or worsened	5	6 *
	$0.05>p>0.025$	p n.s.
	p n.s.	

* 1 case appeared with placebo.

Table 8. — *Detrusor pressure at the V.S.D. (16 cases).*

	Oxybutynin chl.	Placebo
Normal	10	6
Reduced	3	2
Unchanged or worsened	4 *	9 *
	$p<0.001$	$0.02>p>0.01$
	$0.02>p>0.01$	

* 1 case appeared during treatment.

gastroenteric troubles (nausea, gastralgia) and/or vision troubles – appeared in some patients from the very beginning of the treatment. In 6 cases the dose was consequently decreased to 10 mg/die without any apparent reduction of the clinical effectiveness.

However quite a few patients reported side-effects also following administration of placebo.

DISCUSSION

In a large majority of cases the pharmacologic treatment of bladder instability has dealt merely with symptoms and even in the field of subjective symptoms (urgency, urge incontinence, pollakiuria, etc.) results have varied widely.

Keeping patients 'dry' during the period of therapy is undoubtedly important but urodynamic tests have often shown no real objective improvement and incontinence has reappeared at the end of the treatment just as often.

Table 9. — *Objective data (22 cases).*

FD cc			VSD cc			1st Contraction cc			Detr. pressure VSD cm H_2O		
Pre-treat.	Oxyb.	Plac.	Pre-treat.	Oxyb.	Plac.	Pre-treat.	Oxyb.	Plac.	Pre-treat.	Oxyb.	Plac.
60	+ 40	−20	380	+ 50	−230	60	—	40	58	12	28
50	+100	+80	120	+ 80	+ 60	—	—	—	8	8	12
100	+220	+50	400	− 25	−150	400	—	—	40	12	4
160	+ 40	−10	250	+ 0	+ 20	—	—	—	4	8	4
50	+ 90	+60	100	+240	+ 50	50	340	110	32	20	52
250	+ 0	+20	420	− 20	− 70	420	400	350	40	20	40
100	+130	+10	250	+100	+ 0	250	—	—	34	10	12
30	+ 0	+30	100	+ 80	+ 70	—	200	170	10	20	20
140	− 60	−20	250	− 70	− 50	—	—	—	12	4	7
30	+ 70	+90	50	+ 80	+100	40	—	120	36	8	28
40	+ 90	+20	200	+ 50	+ 20	—	—	—	8	6	8
70	+130	+90	150	+150	+100	250	—	—	16	6	9
170	+ 10	+30	380	+ 30	− 30	—	—	—	8	4	8
150	− 70	+ 0	200	−100	− 20	150	100	180	40	24	40
150	+ 30	−70	350	+ 50	− 50	150	—	80	20	8	24
150	+130	+50	200	+180	+ 50	200	—	—	20	8	6
150	− 30	−50	200	+120	+120	200	—	260	15	6	24
100	+ 50	+20	150	+ 50	+ 30	150	150	180	24	24	24
200	+ 0	−50	270	+ 50	+ 30	290	350	—	15	15	8
80	− 20	−20	150	− 20	+ 0	150	60	80	20	26	28
200	+ 60	+50	310	− 10	− 10	—	—	—	16	10	8
180	+ 0	+ 0	220	+ 10	+ 10	220	—	180	44	8	60

Table 10. — *Side effects.*

	Oxybutynin chl.	Placebo
Xerostomy	22	8
Vision troubles	10	5
Nausea	10	4
Cephalalgia	9	8
Gastralgia	7	6
Tachycardia	4	—
Vertigo	2	4
Asthenia	2	—
Retention of urine	1	—
Constipation	1	—

In a wide review of the literature Cardozo *et al.* [1] report success of therapies using various drugs in 18% to 63% of cases while Meyhoff [12] reports 65% success with emepronium and Jarvis [13] 56% with flavoxate + imipramine association.

More encouraging results have so far been achieved by using drugs to support, initially, biofeedback or bladder re-training treatments. Both the percentage of success [13, 14, 15, 16] and the lasting objective remission [17] have been improved.

Frewen [14], for instance, reports 82% success with anticholinergic drugs associated with bladder re-training; Fantl [16] reports success in 30 out of 35 patients with propantheline associated with bladder drill.

Oxybutynin chloride has shown greater therapeutical effectiveness than all these drugs, notably as far as subjective troubles are concerned, while objective improvements have been slightly less significant: Moisey *et al.* [18] report objectively detected favourable results in 39% of cases.

In our opinion our data are among the most significant to be found in the literature particularly as regards objective results. Besides reduction or disappearance of urgency of voiding in 14 cases (60.8%) and urge incontinence in 16 (76.1%)

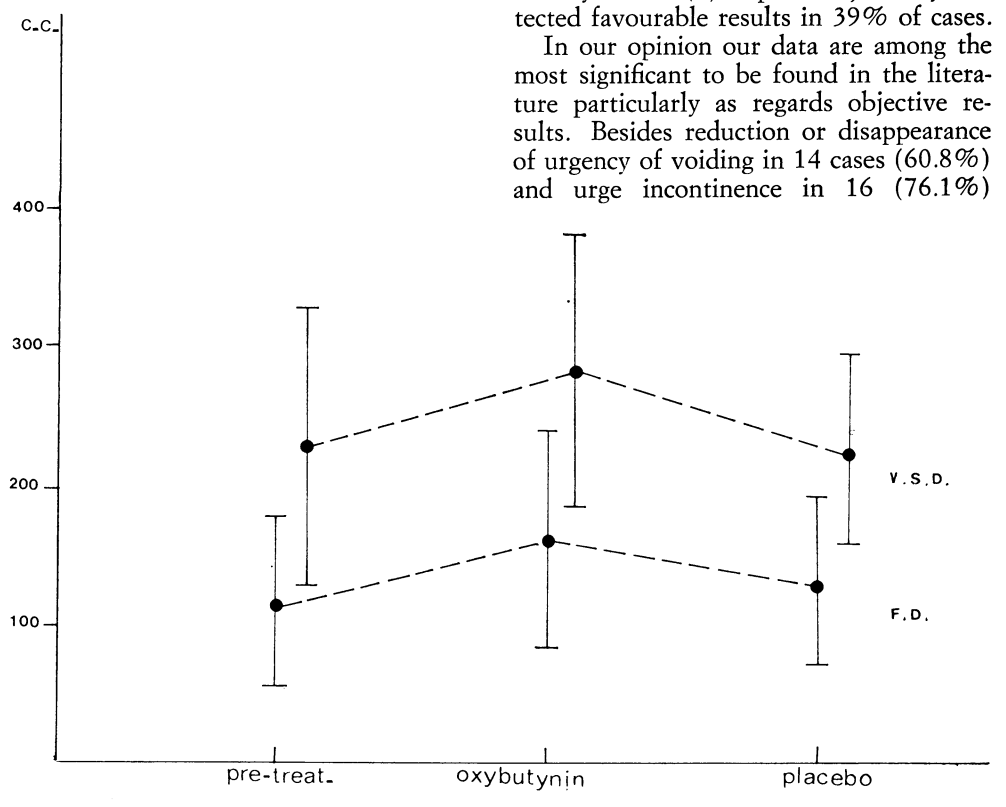

Fig. 2. — F.D. and V.S.D. (mean and DS).

– both statistically significant data – cystomanometry showed improved bladder capacity at the FD and VSD in 14 and 15 cases and normal of reduced detrusor of involuntary contractions in 9 out of 15 cases and normal or reduced detrusorial pressure at the VSD in 13 out of 16 cases (all statistically significant data).

Remission of symptoms started at the very beginning of the therapy occurring even in those patients who had been previously unsuccessfully treated with other drugs.

It is fair to recall, however, that the placebo too caused improvements, though less significant, which stresses the importance of psychological factors to the etiopathogenesis of idiopathic bladder instability.

However the difference between the effects of the drug and those of the placebo was statistically significant in 6 out of 7 parameters.

As regards long-term outcome, 6 out of 9 patients cured with oxybutynin chloride and followed-up are still symptom-free whereas three have resumed the therapy.

Side-effects were rather strong though well tolerated by most patients, and dose reductions were needed in 6 cases only. Furthermore the intensity of these side-effects decreased as treatment went on and some of them were reported following administration of placebo too.

Apparently dose reductions do not entail decreased therapeutical effectiveness.

In our opinion oxybutynin chloride is a satisfactory alternative to previously proposed pharmacologic treatments of idiopathic bladder instability given its favourable effects both on subjective symptoms and on objective parameters and despite its treating merely symptoms, in many cases, and causing rather strong side-effects. The best current option, therefore, is probably a temporary association of this drug with bladder re-training and biofeedback techniques, notably in cases of weak or moderate urge incontinence ([5, 13, 16]).

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