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INTRAVESICAL ELECTROMOTIVE ADMINISTRATION OF OXYBUTYNIN IN PATIENTS WITH DETRUSOR HYPERREFLEXIA UNRESPONSIVE TO STANDARD ANTICHOLINERGIC REGIMENS

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ABSTRACT

Purpose: About 15% to 20% of patients with detrusor hyperreflexia do not benefit from oral oxybutynin regimens, frequently because of unpleasant side effects. Several reports indicate that intravesical oxybutynin is effective in many of these patients but there are some who still fail to respond.

Materials and Methods: A select group of 10 adults with detrusor hyperreflexia unresponsive to standard oral and intravesical oxybutynin regimens were treated at weekly intervals with 5 mg. oxybutynin orally, or 5 mg. oxybutynin in 100 ml. intravesically for 60 minutes of passive diffusion and for 30 minutes with 5 mA. electrical current. Each treatment (plus oral placebo and 2 intravesical controls) was associated with an 8-hour, full urodynamic monitoring session, and periodic blood and bladder content sampling.

Results: There was no significant objective improvement with oral or intravesical passive diffusion oxybutynin. Conversely there was significant improvement in 5 of 6 objective urodynamic measurements with intravesical electromotive oxybutynin. Plasma profiles were a single peak and decay following oral oxybutynin and 2 distinct peaks with intravesical passive diffusion and electromotive oxybutynin. Area under the curve for intravesical passive diffusion were 709 ng. per 8 hours versus oral 1,485 ($p < 0.05$) versus intravesical electromotive 2,781 ($p < 0.001$). Bladder content samples confirmed oxybutynin absorption. Oral oxybutynin caused anticholinergic side effects in 7 of 10 patients. There were no side effects with intravesical passive diffusion or electromotive administrations.

Conclusions: Accelerated intravesical administration results in greater bioavailability and increased objective benefits without side effects in previously unresponsive patients compared with oral and intravesical passive diffusion oxybutynin administration.

KEY WORDS: reflex, abnormal; cholinergic antagonists; administration, intravesical

Clean intermittent catheterization combined with oral anticholinergic agents is standard therapy in spinal cord injured patients with detrusor hyperactivity and/or detrusor-sphincter dyssynergia.[1] Several studies have shown that intravesical instillation of oxybutynin is effective in many patients who are unresponsive to or cannot tolerate the drug orally.[2,3] However, the effectiveness of intravesical oxybutynin has proved variable and somewhat unpredictable with patient selection, evaluation criteria, drug concentration and dwell time of instillation affecting interpretation of results. Drug penetration into bladder wall tissues and drug concentrations at the target site (detrusor) are important determinants of efficacy [4] but passive transport of drugs across the urothelium is complex and not easily defined. Many factors, including pressure gradients, time of exposure, partition coefficient, molecular weight and configuration, pH, degree of ionization and urinary output, interact to produce different transport rates. Although its relatively low molecular weight (394 daltons) is only a minor diffusive impediment, oxybutynin (hydro) chloride in solution is ionized and, in general terms, electrical charge inhibits transport through tissues. Therefore, the degree of ionization is critical and depends on the pH of the solution and pKa of oxybutynin.

Recruitment of electrokinetic forces accelerates drug administration rates across biological membranes and into underlying tissues. The term electromotive drug administration describes transport of all water soluble drugs under the influence of an electrical field and, unlike passive diffusion, is most effective when dealing with an ionized drug in which the rate of drug transport is proportional to the intensity of the applied electrical current which largely overrides all other variables.[5]

Following initial laboratory studies describing passive diffusion and electromotive transport rates of oxybutynin,[6] we define the urodynamic effects and pharmacokinetics of oxybutynin in specially selected spinal cord injured patients with detrusor hyperreflexia who received oral, intravesical passive diffusion and intravesical electromotive single doses of the drug. Both sets of measurements are correlated to the

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TABLE 1. *Patient demographics and preliminary urodynamic evaluation*

Pt. No.—Sex—Age	Lesion Level	Disease Duration (mos.)	Bladder Capacity (ml.)	Bladder Compliance (ml./cm. H2O)	Uninhibited Detrusor Contraction Threshold (ml.)	Uninhibited Detrusor Contraction Max. Amplitude (cm. H2O)	Uninhibited Detrusor Contraction Duration (secs.)	Leak Point Pressure (cm. H2O)
1— M — 22	T12	13	230	22	178	44	312	41
2— F — 45	C6	84	124	27.5	110	50	84	47
3— F — 31	T12	16	150	33	99	61	306	56
4— F — 28	T5	37	133	30	120	53	78	50
5— M — 22	C6	14	130	25	124	70	36	63
6— M — 17	T2	18	153	29	145	64	48	59
7— F — 28	T9	36	122	16	113	57	54	55
8— M — 35	C7	23	167	37	148	84	114	77
9— M — 55	T5	44	140	15	136	66	24	61
10— M — 23	T10	21	206	32	191	93	90	86

method of administration, therapeutic efficacy and anticholinergic side effects.

MATERIALS AND METHODS

Oxybutynin. The prescribed oral formulation consisted of 5 mg. oxybutynin chloride tablets. Oxybutynin chloride for intravesical instillations was analyzed with high-pressure liquid chromatography (HPLC) and was >99% pure. Oxybutynin solution was prepared by dissolving the crystals in sterile water to obtain 1 l. 5 mg./ml. stock solution that was sterile filtered, and 1 ml. aliquots were placed in autoclaved ampules protected from light and stored at −20C until use.[6] Stability of the solution was verified by analyzing oxybutynin ampules at various intervals. Urodynamic studies were performed using a 16-channel system and electromotive drug administration with a current generator, catheter electrodes and dispersive skin electrodes to complete the circuit. HPLC analyses were performed with a system supplied with a reversed phase C18 column.

Patient characteristics. Of 143 patients with detrusor hyperreflexia treated at our medical centers 23 did not respond or suffered intolerable side effects to standard anticholinergic regimens, including intravesical passive diffusion oxybutynin. Of these unresponsive patients 6 men and 4 women 17 to 55 years old, with spinal cord injury, American Spinal Injury Association impairment scale A,[7] were enrolled in our study (table 1). All patients provided written informed consent and the protocol was approved by the ethics committee of the institutions. There were no alcoholics or smokers and none was taking oral contraceptives. All patients had detrusor hyperreflexia or detrusor-sphincter dyssynergia and urinary incontinence, and were on clean intermittent catheterization regimens. Inclusion criteria were unacceptable detrusor activity suppression (clinical and urodynamic) by oral and intravesical passive diffusion oxybutynin, intolerable systemic side effects from oral oxybutynin, bladder capacity 120 ml. or greater and no vesicoureteral reflux.

Preparation and evaluation for inclusion. Anticholinergic medications were suspended for 1 month before evaluation, and often by the patients. Urinary tract infections were appropriately treated and all patients were free of infection during the study. Urodynamic criteria for inclusion followed International Continence Society standards, and detrusor hyperreflexia and striated sphincter dyssynergia were defined according to these standards.[8] Table 1 summarizes patient demographics and preliminary (before study) urodynamic evaluations.

Drug administration techniques. Either 5 mg. oxybutynin chloride orally or an identical placebo tablet was ingested immediately before the relevant urodynamic session began. With all intravesical instillations the bladder was drained, slowly flushed with 150 ml. water and drained again, and then 100 ml. solution (37C) of either sodium chloride 0.9% (control) or 5 mg. oxybutynin in sodium chloride 0.45% was instilled and the relevant urodynamic session began immediately thereafter. Electromotive drug administration comprised a 5 mA. pulsed current (2.5 KHz.) applied via a catheter electrode of positive polarity (anode) to the intravesical solution for a dwell time of 30 minutes and the bladder was then drained. With passive diffusion (no current applied) dwell time was 60 minutes followed by drainage.

Urodynamic studies. The urodynamic procedures started in the early morning, and the subjects were well hydrated and had taken no solid food since the previous evening meal. Each session lasted 8 hours and each patient underwent a total of 6 such sessions (suitably spaced), which incorporated 6 different drug and placebo/control administrations. The sessions were performed in randomized order and were double-blinded insofar as patients and attending staff were unaware of the nature of the oral administrations (oxybutynin or placebo tablets) or the intravesical instillations (oxybutynin/sodium chloride 0.9%). Specifically, each urodynamic procedure was dedicated to baseline oral placebo, 5 mg. oxybutynin orally, control 100 ml. sodium chloride 0.9% intravesically with passive diffusion for 60 minutes, 5 mg. oxybutynin in 100 ml. sodium chloride 0.45% intravesically with passive diffusion for 60 minutes, control 100 ml. sodium chloride 0.9% intravesically with electromotive drug administration for 30 minutes and 5 mg. oxybutynin in 100 ml. sodium chloride 0.45% intravesically with electromotive drug administration for 30 minutes. During these 8-hour sessions the patients were maintained supine at constant room temperature (22C) with continuous recording of the frequency, amplitude and duration of hyperreflexic episodes and urinary leakage. At 4 and 8 hours the bladder was drained and the volume was measured.

Pharmacokinetic studies. Blood samples (10 ml.) were drawn before, and 0, 5, 15, 30, 45, 60, 90, 120, 180, 300 and 480 minutes after oxybutynin administration. Samples were collected in heparinized tubes, cooled in an ice bath and centrifuged at 1,500 g. for 10 minutes. Plasma was separated, protected from light and stored at −20C before analysis. During intravesical passive diffusion and electromotive of oxybutynin administration samples of the bladder contents were taken at 5, 15, 30, 45 and 60 minutes, and 5, 15 and 30 minutes, respectively. After the instillation period (60 and 30 minutes) the solution was drained and measured, and a further aliquot was taken for analysis.

Oxybutynin assay. A HPLC assay of oxybutynin was used for analysis of plasma and urine samples. To 1 ml. plasma samples we added acetonitrile in a ratio 1:0.5 (volume per volume) and 1 mM. tris hydrochloride buffer, pH 9.4 (200 μl. per sample ml.), and extracted twice with hexane in a ratio 1:2 (volume per volume) for 10 minutes. The hexane layer obtained after centrifugation at 500 g. for 5 minutes, was back extracted into 0.1 mM. hydrochloride. After centrifugation the aqueous layer was separated, freeze-dried and stored at −20C until analysis. For urinalysis, a 0.1 ml. sample was

TABLE 2. *Urodynamic studies of uninhibited detrusor contractions*

Procedure	Mean ± SEM of 10 measurements			
	No.	Duration (secs.)	Amplitude (cm. H2O)	Max. Amplitude (cm. H2O)
Oral placebo	33.6 ± 7.2	99.0 ± 114.6	35.1 ± 3.3	64.1 ± 9.0
Oral oxybutynin	25.0 ± 6.2	56.0 ± 28.3	33.1 ± 4.2	60.5 ± 10.2
Control in 100 ml. sodium chloride 0.9% intravesically with passive diffusion	27.4 ± 6.2	67.2 ± 50.8	34.0 ± 4.2	65.4 ± 9.2
5 Mg. oxybutynin in 100 ml. sodium chloride 0.45% intravesically with passive diffusion	21.9 ± 7.8	57.4 ± 34.5	31.4 ± 3.3	58.2 ± 8.8
Control in 100 ml. sodium chloride 0.9% intravesically with electromotive drug administration	35.6 ± 9.0	66.5 ± 56.7	31.7 ± 2.7	57.0 ± 7.3
5 Mg. oxybutynin in 100 ml. sodium chloride 0.45% intravesically with electromotive drug administration	9.2 ± 3.7	26.5 ± 23.1	21.8 ± 5.7	35.7 ± 10.5
p Value	0.0006	0.0936	0.0034	0.0049

extracted twice with 1.0 ml. chloroform and then the organic layer was mixed and processed in the same way as the plasma samples. External standard and calibration curves were obtained using aqueous solutions of oxybutynin. The limit of detection was 1.0 ng./ml. of sample. All analyses were performed in duplicate. The pH of 5 mg. oxybutynin chloride in 100 ml. sodium chloride 0.45%, was measured. During electromotive the voltage across the entire circuit was recorded. Vital signs, Holter electrocardiogram and side effects were recorded during all urodynamic sessions.

Data analysis. Data are presented as the means plus or minus standard error of the mean (SEM) of 10 observations per group. Kinetic parameters (elimination half lives and constants), exponential decays, regression analysis and areas under the curve were calculated using commercially available software. Urodynamic data, intravesical residual volume and urinary leakage were analyzed by commercial software. For urodynamic studies a pressure of 15 cm. water and duration of 15 seconds were the arbitrary limits of uninhibited detrusor contractions analyzed, and 40 cm. water was the cutoff value between low and high pressure uninhibited detrusor contractions.[8] Differences among group means were analyzed by repeated measures analysis of variance and the degrees of freedom for the F statistics were corrected.[9] Significance was assumed at $p < 0.05$.

RESULTS

Urodynamics studies. Table 2 enumerates uninhibited detrusor contractions and the dependent variables of number, duration, amplitude and maximum amplitude in the 10 patients. There were no significant differences among baseline oral placebo, the 2 intravesical controls, oral oxybutynin and intravesical passive diffusion oxybutynin. Electromotive oxybutynin resulted in a significant decrease in the number, amplitude and maximum amplitudes compared with all other sessions. Figure 1 displays maximum detrusor pressure amplitudes at cumulative times in the 10 patients. Figure 2 displays detrusor pressure tracings recorded during the 6 urodynamic sessions in 1 patient.

Table 3 enumerates intravesical residual volumes and number of leakages from 0 to 4 and 4 to 8 hours in the 10 patients. There were no significant differences between residual volumes resulting from the first 5 urodynamic sessions. Electromotive oxybutynin resulted in significantly greater intravesical residual volumes compared with those following all other sessions. There were significantly fewer episodes of urinary leakage following electromotive oxybutynin as compared with those of all other sessions.

Pharmacokinetics. Figure 3 displays plasma levels of oxybutynin following oral administration, intravesical passive diffusion and intravesical electromotive. Figure 4 demonstrates the area under the curve values during 480 minutes of the 3 administration methods. Peak plasma concentrations (7.82 ± 1.8 ng./ml.) were reached at 90 minutes after oral administration, and thereafter levels decayed by first order kinetics with a half-life of 61 minutes and $\beta = 0.0114$ (area under the curve value was 1,485 ± 200 ng.). Peak plasma concentrations (4.7 ± 0.24 ng./ml.) were observed within 60 minutes following intravesical passive diffusion, and subsequently there was a second peak (3.0 ± 0.35 ng./ml.) at 180

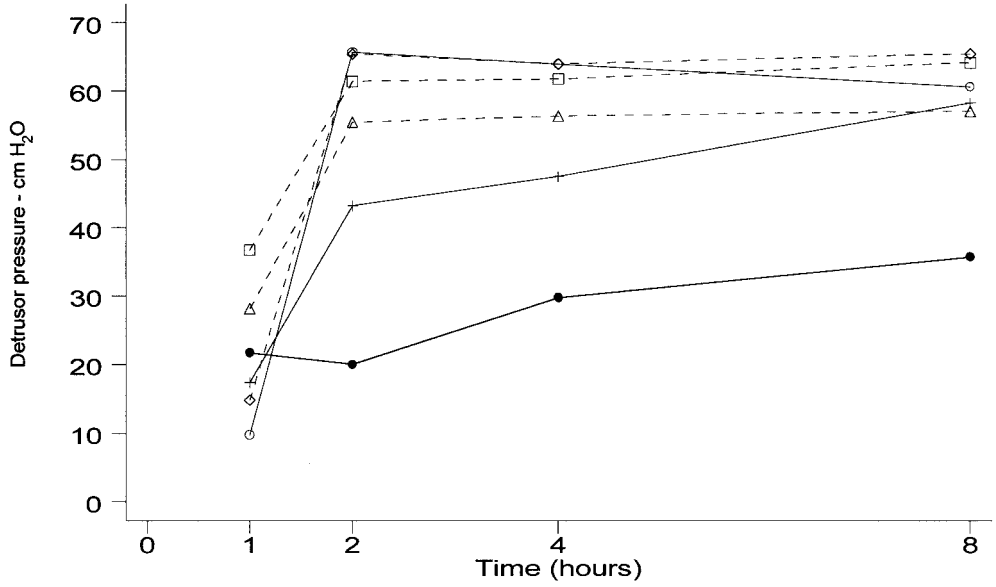

FIG. 1. Mean amplitude of maximum detrusor contractions at cumulative times of 0 to 1, 0 to 2, 0 to 4 and 0 to 8 hours. □ — □, oral placebo. o—o, oral oxybutynin. ◇—◇, passive diffusion/sodium chloride. +—+, passive diffusion oxybutynin. Δ—Δ, electromotive/sodium chloride. ●—●, electromotive/oxybutynin.

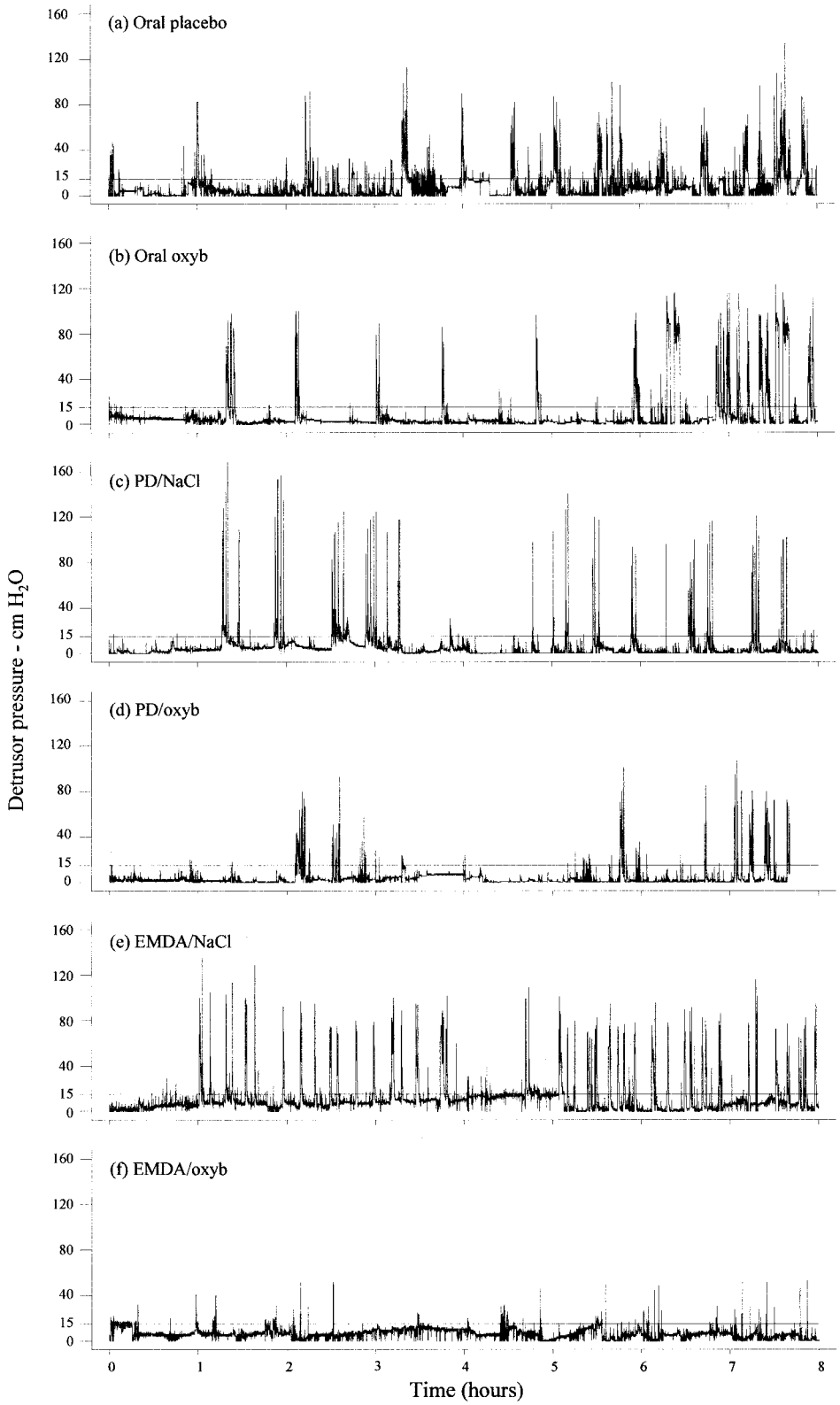

FIG. 2. Example of urodynamic tracings during all 6 urodynamic sessions in patient 6. *oxyb*, oxybutynin. *PD/NaCl*, control in 100 ml. sodium chloride 0.9% intravesically with passive diffusion. *PD/oxyb*, 5 mg. oxybutynin in 100 ml. sodium chloride 0.45% intravesically with passive diffusion. *EMDA/NaCl*, control in 100 ml. sodium chloride 0.9% intravesically with electromotive drug administration. *EMDA/oxyb*, 5 mg. oxybutynin in 100 ml. sodium chloride 0.45% intravesically with electromotive drug administration.

minutes. The area under the curve value was 709 ± 64 ng., which was significantly lower ($p < 0.05$) than that after oral administration. Intravesical electromotive drug administration (5 mA.) resulted in a plasma profile somewhat similar to that obtained after passive diffusion with the first peak at 60 minutes and a second peak at 300 minutes. There was a sharp increase in bioavailability, with area under the curve levels of 2,781 ± 314 ng. ($p < 0.001$ versus oral and intravesical passive diffusion routes).

A corrective factor was applied to oxybutynin concentra-

TABLE 3. *Urodynamic studies of intravesical residual volumes and number of urinary leakages*

Procedure	Mean ± SEM of 10 measurements			
	Residual Volumes 0–4 Hrs. (ml.)	Residual Volumes 4–8 Hrs. (ml.)	Urinary Leakages 0–4 Hrs. (No.)	Urinary Leakages 4–8 Hrs. (No.)
Oral placebo	33 ± 5.2	39 ± 8.5	6.8 ± 1.1	8.2 ± 1.2
Oral oxybutynin	31 ± 8.3	34 ± 6.5	3.3 ± 0.7	7.5 ± 1.4
Control in 100 ml. sodium chloride 0.9% intravesically with passive diffusion	37 ± 6.0	30 ± 6.2	6.4 ± 0.4	6.7 ± 0.7
5 Mg. oxybutynin in 100 ml. sodium chloride 0.45% intravesically with passive diffusion	41 ± 6.0	39 ± 6.5	3.9 ± 1.6	6.5 ± 1.1
Control in 100 ml. sodium chloride 0.9% intravesically with electromotive drug administration	34 ± 7.2	37 ± 4.6	8.1 ± 1.7	8.0 ± 1.6
5 Mg. oxybutynin in 100 ml. sodium chloride 0.45% intravesically with electromotive drug administration	163 ± 41	198 ± 47	1.4 ± 0.9	2.3 ± 1.1
p Value	0.0068	0.0039	0.0004	<0.0001

tions in intravesical samples to eliminate the measured volume effect of inflowing urine in each patient. Using these transformed values, the decay of oxybutynin concentration with passive diffusion is shown in figure 5. The best fit ($r = 0.9999$) is a 2-phase exponential decay equation, $y = 23.59^{-0.016x} + 26.24,^{-0.219x}$ with a phase of rapid absorption and half-life of 3.2 minutes, followed by a second slower phase half-life of 43 minutes. Electromotive administration resulted in a different profile and the kinetic model that best describes ($r = 0.9998$) the disappearance rate of oxybutynin is a 1-phase exponential decay equation, $y = 45.99^{-0.435x} + 3.871$), with an estimated half-life of 1.6 minutes (fig. 5). The pH of 5 mg. oxybutynin chloride in 100 ml. sodium chloride 0.45% was 6.19 units. Mean voltage plus or minus SEM at beginning and end of treatments was 7.4 ± 0.2 and 5.9 ± 0.2 for intravesical sodium chloride 0.9%, and 9.0 ± 0.2 and 7.3 ± 0.3 for intravesical oxybutynin sodium chloride 0.45%.

Clinical tolerance. There were no adverse changes in pulse rate or blood pressure, nor were there any arrhythmias during the urodynamic sessions. Following oral oxybutynin anticholinergic side effects were reported by 7 patients, including dry mouth (4), nausea (3), headache (3) and blurred vision (2). There were no such side effects following either mode of intravesical administration. Transient erythema of the skin underlying the dispersive electrodes occurred after all electromotive procedures.

DISCUSSION

Following its initial formulation in the early 1960s oxybutynin was rapidly accepted into clinical practice for its modest, direct action spasmolytic properties and potent antimuscarinic activity on detrusor muscle.[10] There is also a local anesthetic effect, approximately twice that of lidocaine.[11] Although in widespread clinical use, reports involving comparative studies of the pharmacological actions, clinical effects, side effects and pharmacokinetics of oxybutynin administered by different routes are sparse probably because there is no readily available, sterile aqueous formulation.

Oral oxybutynin results in high plasma levels of N-desethyl oxybutynin,[12] a pharmacologically active metabolite that exhibits lower relative plasma levels following intravesical oxybutynin,[13] and substantially contributes to anticholinergic effects.[10] Several groups have conducted investigations with intravesical oxybutynin in adults[2,14] and children.[13,15–17] With the variations in patients, intravesical dosages and volumes, and schedules for plasma measurements, no consistent pharmacokinetic pattern emerged from these studies. However, with 1 noteworthy exception,[18] all investigators made the 2 encouraging observations that intravesical administration often provided subjective and objective clinical benefits, and the unpleasant side effects of oxybutynin were either decreased or absent.

Our study consisted of a homogeneous group of adults who had a common etiology for detrusor hyperreflexia, were unresponsive to standard anticholinergic regimens, including intravesical oxybutynin, taking no anticholinergic medications and were free of infection. Essentially, the study was designed to determine whether 1) accelerated intravesical administration of oxybutynin provided objective benefits in these previously unresponsive patients, 2) the results could be correlated with plasma levels and intravesical uptake of oxybutynin and 3) the presumptive benefits could be achieved without intolerable side effects. The 3 questions were answered in the affirmative but the investigations raised puzzling issues, for some of which there are no ready explanations.

The pharmacokinetic profile of oral oxybutynin is similar to that of other investigators,[12,13] and yet the profiles following intravesical oxybutynin in our study are unique compared with any reported so far.[2,13,16] The initial peak at about 1 hour with secondary peaks at 3 hours (passive diffusion) and 5 hours (electromotive) are suggestive of storage and delayed release but there is nothing to indicate where or by what mechanism this phenomenon might occur. The area under the curve values following the 2 modes of intravesical oxybutynin agree with the respective transport rates demonstrated in earlier laboratory experiments.[6] In the present study electromotive delivered about 90% of intravesical oxybutynin content within 30 minutes and passive diffusion delivered about 80% in 60 minutes (fig. 5) with indirect confirmation provided by initial peak plasma levels appearing after 1 hour in our and other studies.[13,16] Considering the total quantities absorbed, the area under the curve differential (about 4:1) following the 2 methods of intravesical administration is large and merits further consideration.

The pH of 5 mg. oxybutynin hydrochloride in 100 ml. sodium chloride 0.45% was 6.19 units. With pKa 6.96 (tertiary amine) the ratio of ionized-to-nonionized oxybutynin (ionized oxybutynin/nonionized oxybutynin) was about 6:1. This dynamic situation provides ample ionized oxybutynin for electromotive, and probably supplies sufficient nonionized oxybutynin for significant passive transport of these nonionized molecules whose diffusion into the bladder wall is unimpeded by electrical charge. Cytochrome P450 isozymes in the endoplasmic reticulum are widely distributed throughout the body, and it is conceivable that the urothelium is included. Following oral administration of oxybutynin certain P450 enzymes in the liver and gut wall metabolize (first pass) about 80% to 90% of the drug to desethyl oxybutynin.[12,13] Following intravesical passive diffusion administration the peak plasma level ratios and their timing of oxybutynin and desethyl oxybutynin, as reported by Buyse et al,[13] indicate that the postulated P450 enzyme systems in the bladder wall metabolize a maximum of 50% to 65% of the drug. Their superficial location facilitates oxybutynin transport by helping maintain its concentration gradient and, furthermore, some of the desethyl oxybutynin and other metabolites diffuse down its concentration gradient back into the bladder cavity. However, oxybutynin accelerated by electromotive drug administration would rapidly saturate the sparse population compared with the liver of P450 enzymes and allow them considerably less time to regenerate. Therefore, a significantly larger quantity of oxybutynin, absolute

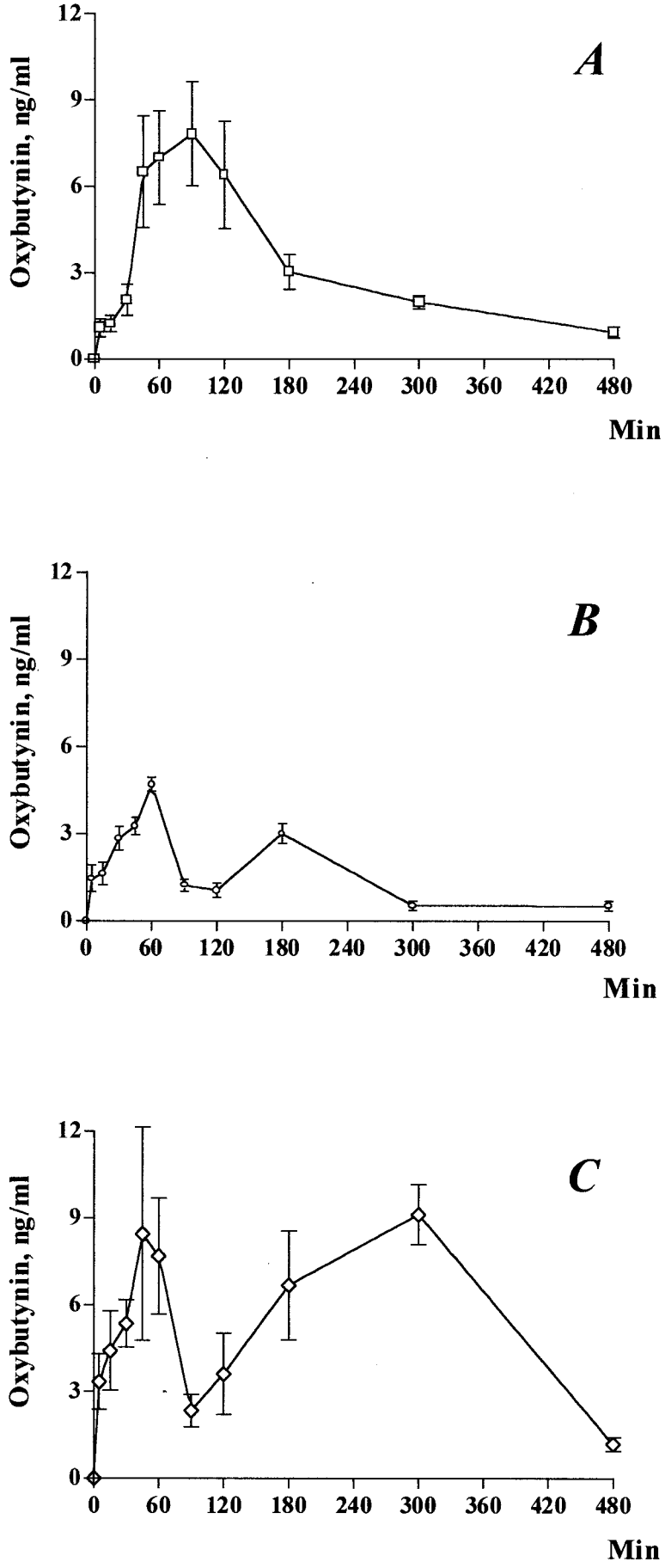

FIG. 3. Plasma oxybutynin levels following administration of 5 mg. oxybutynin chloride orally (*A*) by intravesical passive diffusion (*B*) and by intravesical electromotive drug administration (*C*). Data are mean ± 1 SEM of 10 measurements per time point.

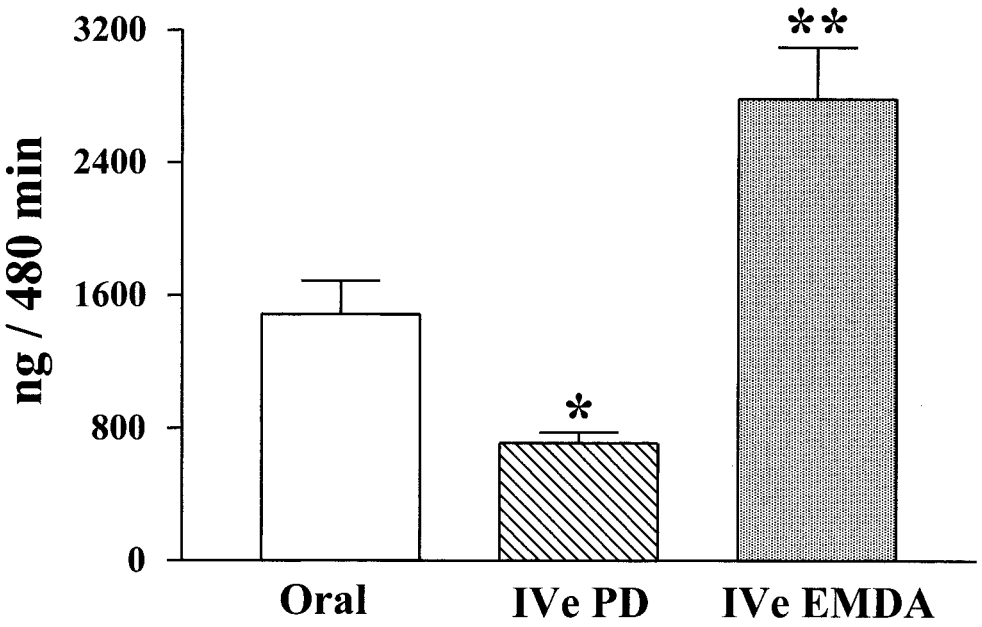

FIG. 4. Comparison of plasma oxybutynin area under curve values following administration of 5 mg. oxybutynin chloride orally, by intravesical passive diffusion (*IVe PD*) and by intravesical electromotive drug administration (*IVe EMDA*). Data are mean ± 1 SEM of 10 measurements per group (*p <0.05, **p <0.01 versus area under curve following oral administration).

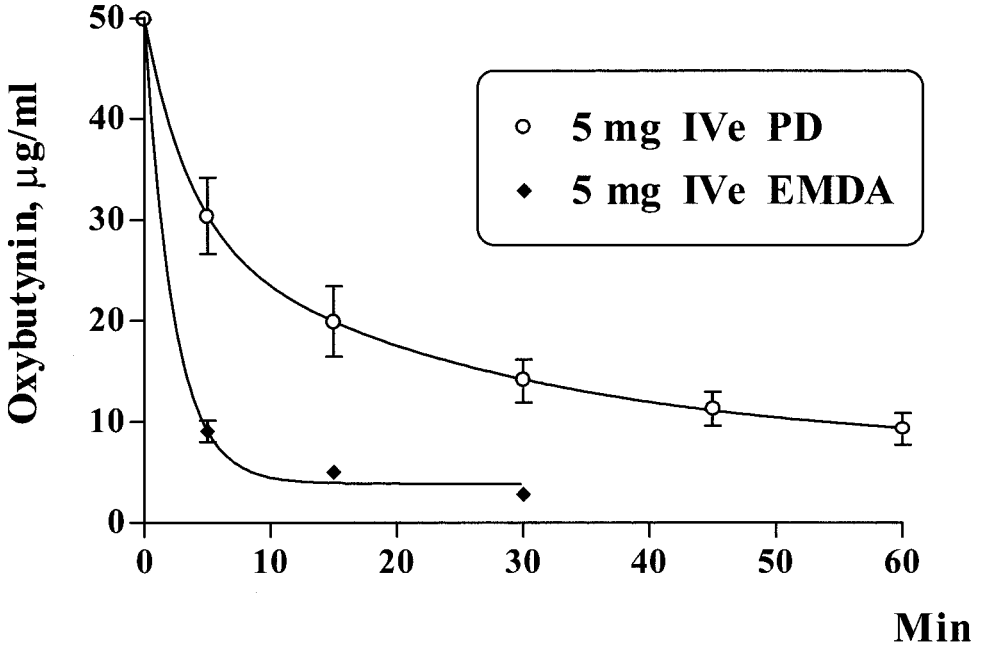

FIG. 5. Decay of intravesical oxybutynin concentrations initially 5 mg. in 100 ml., during passive diffusion for 60 minutes (*IVe PD*) and electromotive drug administration for 30 minutes (*IVe EMDA*). Data are mean ± 1 SEM of 10 measurements per time point.

and relative to desethyl oxybutynin, enters the circulation and is reflected in the greater peak and area under the curve plasma levels.

With hindsight measurements of desethyl oxybutynin in plasma and bladder contents would have helped resolve the situation but only in part. It has been assumed that with intravesical administration the reduced plasma desethyl oxybutynin to oxybutynin ratio is somehow responsible for a reduction in side effects while maintaining therapeutic efficacy.[13] If so, the precise mechanism is obscure. Laboratory experiments by Waldeck et al demonstrated that the antimuscarinic actions of oxybutynin and desethyl oxybutynin on human detrusor and parotid gland were similar indeed.[10] In purely quantitative terms the therapeutic effects and side effects are a function of the arithmetic sum (amounts) of oxybutynin and desethyl oxybutynin. Therefore, if therapeutic effects are sustained and side effects are diminished in the clinical setting, these same investigators made it clear that additional unknown factors must be responsible.[10]

There is also the issue of a localized effect with intravesical oxybutynin inferred indirectly by Madersbacher and Knoll[2] and emphasized by Buyse et al.[13] In our study intravesical passive diffusion administered 3 to 4 mg. oxybutynin in 60 minutes, implying that the tissues of 30 to 40 gm. bladders were potentially exposed to high concentrations (75 to 125 μg./gm.), which should result in profound relaxation of detrusor muscle. As this did not occur, the unsatisfactory explanation is that the drug was taken up by the venous col-

lecting system before reaching the underlying muscle layers. There is also a possible local anesthetic effect. In the majority of hyperspastic bladders C fibers assume the role of mechanoreceptors and constitute the afferent arm of a localized, hyperactive reflex arc.[19] The submucosal plexus containing the majority of vesical C fibers is superficially situated, and intravesical administration could well supply sufficient quantities to anesthetize the fibers in many patients and, thus, induce some detrusor relaxation, an effect that has been observed with intravesical lidocaine.[20] Following this line of reasoning, only patients unresponsive to intravesical passive diffusion were included in the study, so that accelerated administration with electrical current was required to induce the putative local anesthetic effect.

CONCLUSIONS

A select group of 10 adults with detrusor hyperreflexia unresponsive to all standard anticholinergic therapy underwent evaluation of urodynamics, pharmacokinetics and side effects of oxybutynin administered by different routes and techniques. Oral oxybutynin provided no objective benefits, and caused side effects and a conventional plasma profile. Intravesical oxybutynin with passive diffusion provided no objective benefits, and caused no side effects and a singular biphasic plasma profile displaying less bioavailability (area under the curve) than oral oxybutynin. Intravesical oxybutynin with a small electrical current provided objective benefits, and caused no side effects and a biphasic plasma profile that displayed greater bioavailability than oral oxybutynin.

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REFERENCES

1. Perkash, I.: Long-term urologic management of patients with spinal cord injury. Urol Clin North Am, **20:** 423, 1993
2. Madersbacher, H. and Knoll, M.: Intravesical application of oxybutynin: mode of action in controlling detrusor hyperreflexia. Eur Urol, **28:** 340, 1995
3. Szollar, S. M. and Lee, S. M.: Intravesical oxybutynin for spinal cord injury patients. Spinal Cord, **34:** 284, 1996
4. Mohler, J. L.: Relaxation of intestinal bladders by intravesical oxybutynin chloride. Neurourol Urodyn, **9:** 179, 1990
5. Fontanella, U. A., Rossi, C. A. and Stephen, R. L.: Bladder and urethral anaesthesia with electromotive drug administration (electromotive): a technique for invasive endoscopic procedures. Br J Urol, **79:** 414, 1997
6. Di Stasi, S. M., Giannantoni, A., Massoud, R. et al: Electromotive administration of oxybutynin into the human bladder wall. J Urol, **158:** 228, 1997
7. Ditunno, J. F., Young, W., Donovan, W. H. et al: The international standards booklet for neurological and functional classification of spinal cord injury. Paraplegia, **32:** 70, 1994
8. Stöhrer, M., Goepel, M., Kondo, A. et al: The standardization of terminology in neurogenic lower urinary tract dysfunction with suggestion for diagnostic procedures. Neurourol Urodyn, **18:** 139, 1999
9. Huynh, H. and Feldt, L. S.: Estimation of the Box correction for degrees of freedom from sample data in randomized block and split-plot designs. J Educ Stat, **1:** 69, 1972
10. Waldeck, K., Larsson, B. and Andersson, K. E.: Comparison of oxybutynin and its active metabolite, N-desethyl-oxybutynin, in the human detrusor and parotid gland. J Urol, **157:** 1093, 1997
11. Lish, P. M., Labudde, J. A., Peters, E. L. et al: Oxybutynin: a musculotropic antispasmodic drug with moderate anticholinergic action. Arch Int Pharmacodyn Ther, **156:** 467, 1965
12. Hughes, K. M., Lang, J. C. T., Lazare, R. et al: Measurement of oxybutynin and its N-desethyl metabolite in plasma, and its application to pharmacokinetic studies in young, elderly and frail elderly volunteers. Xenobiotica, **22:** 859, 1992
13. Buyse, G., Waldeck, K., Verpoorten, C. et al: Intravesical oxybutynin for neurogenic bladder dysfunction: less systemic side effects due to reduced first pass metabolism. J Urol, **160:** 892, 1998
14. Brendler, C. B., Radebaugh, L. C. and Mohler, J. L.: Topical oxybutynin chloride for relaxation of dysfunctional bladders. J Urol, **141:** 1350, 1989
15. Greenfield, S. P. and Fera, M.: The use of intravesical oxybutynin chloride in children with neurogenic bladder. J Urol, **146:** 532, 1991
16. Massad, C. A., Kogan, B. A. and Trigo-Rocha, F. E.: The pharmacokinetics of intravesical and oral oxybutynin chloride. J Urol, **148:** 595, 1992
17. Amark, P., Eksborg, S., Juneskans, O. et al: Pharmacokinetics and effects of intravesical oxybutynin on the paediatric neurogenic bladder. Br J Urol, **82:** 859, 1998
18. Palmer, L. S., Zebold, K., Firlit, C. F. et al: Complications of intravesical oxybutynin chloride therapy in the pediatric myelomeningocele population. J Urol, **157:** 638, 1997
19. De Groat, W. C., Kawatani, M., Hisamitsu, T. et al: Mechanisms underlying the recovery of urinary bladder function following spinal cord injury. J Auton Nerv Syst, suppl., **30:** S71. 1990
20. Higson, R. H., Smith, J. C. and Hills, W.: Intravesical lignocaine and detrusor instability. Br J Urol, **51:** 500, 1979