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# INTRAVESICAL OXYBUTYNIN: MODE OF ACTION ASSESSED BY PASSIVE DIFFUSION AND ELECTROMOTIVE ADMINISTRATION WITH PHARMACOKINETICS OF OXYBUTYNIN AND N-DESETHYL OXYBUTYNIN

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ABSTRACT

Purpose: A proportion of patients with detrusor hyperreflexia who are unresponsive to oral oxybutynin often benefit from intravesical oxybutynin instillation. To our knowledge the precise mode of action of this method is obscure.

Materials and Methods: In 12 patients with detrusor hyperreflexia who were previously unresponsive to oral and intravesical passive diffusion of 5 mg. oxybutynin we administered 5 mg. oxybutynin orally as well as increased doses of 15 mg. oxybutynin intravesically with passive diffusion and with 15 mA. associated electric current. Each administration mode per patient was associated with an 8-hour urodynamic monitoring session during which oxybutynin and N-desethyl oxybutynin plasma levels, and intravesical oxybutynin uptake were measured.

Results: A dose of 5 mg. oxybutynin orally induced no urodynamic improvement with an area under the plasma concentration time curve of combined N-desethyl oxybutynin plus oxybutynin of 16,297 ng./8 hours and an area under the curve ratio of N-desethyl oxybutynin-to-oxybutynin of 11:1. Passive diffusion oxybutynin resulted in 12 mg. oxybutynin intravesical uptake and significant improvement in 3 of 8 urodynamic measurements, although the area under the curve of combined N-desethyl oxybutynin plus oxybutynin was only 2,123 ng./8 hours and the N-desethyl oxybutynin-to-oxybutynin ratio was 1.1:1.0. Electromotive administration of oxybutynin resulted in almost complete intravesical uptake of the 15 mg. dose, significant improvement in all 8 urodynamic measurements and an increased oxybutynin level versus oral and passive diffusion, although the area under the curve of combined N-desethyl oxybutynin plus oxybutynin was 4,574 ng./8 hours and the N-desethyl oxybutynin-to-oxybutynin ratio was inverted at 1.0:1.4. The oral dose of 5 mg. oxybutynin caused anticholinergic side effects in 8 of the 12 patients. Neither intravesical passive diffusion nor electromotive administration caused side effects with an uptake of 12 and 15 mg., respectively.

Conclusions: A large proportion of intravesical oxybutynin is sequestered, probably in the urothelium. Intravesical oxybutynin administration confers therapeutic benefits via localized direct action within the bladder wall.

KEY WORDS: bladder, spinal cord injuries, cholinergic antagonists, pharmacokinetics.

In an earlier study we reported that intravesical administration of 5 mg. oxybutynin accelerated by electric current or electromotive administration provided objective urodynamic improvement in a select group of patients who did not respond to 5 mg. oxybutynin given orally or by intravesical passive diffusion.[1] These results correlated with the rapid intravesical uptake and increased systemic bioavailability of oxybutynin attained by electromotive means, which is pharmacologically rational. However, certain unanticipated features were difficult to explain.

Oral oxybutynin conferred no objective clinical benefits on urodynamics and caused anticholinergic side effects in 7 of 10 patients. Electromotive administration conferred objective benefits and yet significantly increased plasma oxybutynin caused no side effects in any patients, which is pharmacologically irrational. Also, the 2 techniques of intravesical administration were associated with a biphasic oxybutynin plasma profile in which there was a second peaks hours after the bladders had been drained of the instillation, implying some form of storage and release of oxybutynin. However, our study provided no indication of where or by what mechanism this phenomenon occurred.

With hindsight the lack of N-desethyl oxybutynin measurement was a limitation of the series. Such measurement should help to resolve the unexplained findings described. Furthermore, we anticipated that plasma profiles of this pharmacologically active metabolite[2] and oxybutynin combined with measurements of intravesical oxybutynin absorption would help to resolve another issue. To our knowledge the precise mechanism by which intravesical oxybutynin exerts its therapeutic effect is obscure. Localized direct action within the bladder wall is a recurring consideration[3] but uncertainty remains.[4]

Therefore, we enrolled the same 10 patients plus an additional 2 with the same characteristics in a similar study of the administration of oxybutynin orally and intravesically via electromotive and passive diffusion, involving urodynamic studies and the measurement of intravesical oxybuty-

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nin absorption and plasma levels. There were 2 variations. N-desethyl oxybutynin was also determined in all plasma samples, and intravesical oxybutynin and electric current intensity were increased to magnify and/or reveal further differences versus oral administration.

## MATERIALS AND METHODS

Materials and methods have been described previously in detail.[1]

*Chemicals.* N-desethyl oxybutynin and dicyclomine analyzed by high pressure liquid chromatography were greater than 99% pure. All other chemicals and drugs were analyzed as previously described.[1]

*Patient characteristics.* We enrolled in our study 7 male and 5 female patients 17 to 55 years old with spinal cord injury and neurogenic bladder dysfunction due to upper motor neuron lesions. All cases were classified as American Spinal Injury Association impairment scale A with detrusor hyperreflexia and detrusor-sphincter dyssynergia. All patients were on a clean intermittent catheterization regimen. An oral dose of oxybutynin of up to 15 mg. daily had resulted in unacceptable detrusor activity suppression and/or intolerable side effects. Intravesical administration of 5 and 10 mg. oxybutynin by passive diffusion in 9 and 3 patients, respectively, had resulted in neither benefits nor side effects. Importantly all patients were free of urinary tract infection at urodynamics. This study was approved by the ethics committee at our institutions and all patients provided written informed consent.

*Drug administration techniques.* Patients ingested 5 mg. oxybutynin chloride and placebo orally in tablet form. For intravesical administration a 100 ml. 0.9% sodium chloride solution serving as the control or 15 mg. oxybutynin in 0.45% sodium chloride were instilled at 37C. Electromotive administration involved a 15 mA. electric current applied via a catheter electrode to the intravesical solution for 30 minutes, after which the bladder was drained. Intravesical administration was performed by passive diffusion with drainage at 60 minutes.

*Urodynamic studies.* At the 6, 8-hour urodynamic sessions performed at weekly intervals 6 modes of drug and placebo administration were continuously monitored. Administration was done in random and double-blind fashion with respect to identity of oral placebo or oxybutynin tablets and intravesical control or oxybutynin solution (tables 1 and 2). In addition to uninhibited detrusor contraction components, bladder compliance was recorded from 0 to 4 and 4 to 8 hours with passive detrusor pressure peaks greater than 15 cm. water (uninhibited detrusor contractions) excluded from analysis. In addition, we determined post-void residual volume and the number of urinary leakage episodes.

*Pharmacokinetic studies.* We obtained 11 blood samples for oxybutynin and N-desethyl oxybutynin measurement during each 8-hour urodynamic session (fig. 1). Intravesical samples (1 ml.) were obtained at specified intervals for measuring oxybutynin concentration (Ct) (fig. 2). At the completion of electromotive diffusion at 30 minutes and passive diffusion at 60 minutes the bladders were drained. Bladder volume (Vt) included the original 100 ml. infusion (Vo) plus urine. When assuming a constant rate of urine inflow, the measured oxybutynin concentration was normalized to its concentration (Co) in the original 100 ml. volume using the formula, $Co = Ct \times Vt/Vo$. The small volume of the intravesical samples was safely ignored. Intravesical uptake of oxybutynin was calculated from the final transformed oxybutynin concentration in samples obtained when the bladders were drained (fig. 2).

*Assay of oxybutynin and N-desethyl oxybutynin.* The extraction procedure of oxybutynin and N-desethyl oxybutynin has been reported in detail.[2,5] Briefly, reverse phase high performance liquid chromatography of oxybutynin and N-desethyl oxybutynin was performed to analyze the samples. A dicyclomine internal standard of 100 $\mu$l. 1 $\mu$g./ml. in water, acetonitrile at a ratio of 1:0.5 volume per volume and 1 mM. tris-HCl buffer, pH 9.4 (200 $\mu$l./ml. sample) were added to 1 ml. plasma samples and extracted twice with hexane at a ratio of 1:2 volume per volume for 10 minutes using a glass tube and horizontal shaker. After centrifugation at 500 $\times$ gravity for 5 minutes the hexane layer obtained was back extracted into 0.1 M. HCl (0.12 ml./ml. sample) by slight shaking for 10 minutes. After centrifugation the aqueous layer was separated, freeze-dried and stored at $-20$C until analysis.

*Data analysis.* The number, duration, amplitude, maximum amplitude of uninhibited detrusor contractions, bladder compliance, intravesical post-void residual urine volume and episodes of urinary leakage were analyzed using random effects models, assuming compound symmetry among repeat observations in an individual. Pharmacokinetic data are presented as the mean plus or minus standard error of mean (SEM) of 12 observations per group. Kinetic parameters (elimination half-life and constants), exponential decay, regression analysis and area under the curve were calculated using commercially available software with significance considered at $p < 0.05$.

## RESULTS

*Urodynamic studies.* Table 1 shows uninhibited detrusor contractions with the dependent variables in the 12 patients, namely number, duration, amplitude, maximum amplitude and bladder compliance. Compared with oral placebo as the baseline value oral oxybutynin had no significant influence on uninhibited detrusor contractions or bladder compliance, while passive diffusion oxybutynin induced a significant decrease in the number of uninhibited detrusor contractions only and electromotive oxybutynin induced highly significant improvement in all 4 uninhibited detrusor contraction variables as well as in bladder compliance. Table 2 shows intra-

TABLE 1. *Uninhibited detrusor contractions and bladder compliance*

| Procedure | Mean Contractions (95% CI) | | | | Mean ml./cm. Water Compliance (95% CI) | |
|---|---|---|---|---|---|---|
| | No. | Sec. Duration | Cm. Water Amplitude | Max. Cm. Water Amplitude | 0–4 Hrs. | 4–8 Hrs. |
| Oral: | | | | | | |
| Placebo | 34.7 (21.3–47.1) | 97.1 (59.4–138.5) | 36.3 (26.8–43.8) | 65.8 (43.6–84.5) | 86.2 (44.4–128.0) | 105.5 (71.1–139.8) |
| Oxybutynin | 26.3 (12.9–33.7) | 57.1 (17.4–99.5) | 33.1 (24.9–41.4) | 62.3 (41.3–81.9) | 103.1 (61.3–145.0) | 97.5 (63.2–131.8) |
| Passive diffusion: | | | | | | |
| Sodium chloride | 29.5 (16.2–41.4) | 77.4 (27.6–106.7) | 35.0 (25.8–42.2) | 66.5 (45.3–85.9) | 105.0 (63.2–146.8) | 119.4 (85.1–153.8) |
| Oxybutynin | 23.6 (10.5–36.9)* | 51.7 (13.8–94.1) | 30.6 (22.4–38.9) | 55.4 (35.3–75.1) | 134.8 (92.9–176.6) | 143.9 (109.5–178.2) |
| Electromotive: | | | | | | |
| Sodium chloride | 35.6 (22.9–48.5) | 95.2 (55.4–134.9) | 37.7 (27.7–40.6) | 63.7 (42.1–83.3) | 104.7 (72.9–56.3) | 117.4 (83.0–151.7) |
| Oxybutynin | 8.9 (0–22.4)† | 23.2 (0–62.7)‡ | 19.4 (11.2–27.6)† | 36.1 (15.7–56.6)‡ | 171.0 (129.2–212.8)† | 154.3 (119.9–188.6)‡ |

* Versus placebo $p < 0.01$.
† Versus placebo $p < 0.001$.
‡ Versus placebo $p < 0.05$.

TABLE 2. *Intravesical post-void residual urine volume and number of urinary leakage episodes*

| Procedure | Mean Ml. Post-Void Residual Urine Vol. (95% CI) | | Mean No. Leakage Episodes (95% CI) | |
|---|---|---|---|---|
| | 0–4 Hrs. | 4–8 Hrs. | 0–4 Hrs. | 4–8 Hrs. |
| Oral: | | | | |
| Placebo | 32.3 (0–67.3) | 34.1 (0–72.7) | 7.3 (5.4–9.6) | 7.8 (5.8–10.5) |
| Oxybutynin | 35.6 (1.7–71.4) | 39.1 (0–78.2) | 5.3 (3.5–7.6) | 7.5 (5.1–9.9) |
| Passive diffusion: | | | | |
| Sodium chloride | 30.1 (0–64.7) | 33.5 (0–75.8) | 7.2 (5.1–9.3) | 7.9 (6.1–11.0) |
| Oxybutynin | 41.6 (6.2–75.6) | 40.2 (0–80.4) | 3.9 (2.1–5.9)* | 5.2 (3.7–7.6)† |
| Electromotive: | | | | |
| Sodium chloride | 29.8 (0–62.3) | 27.3 (0–60.8) | 7.9 (6.1–10.4) | 8.1 (6.7–11.6) |
| Oxybutynin | 205.4 (170.9–239.9)‡ | 250.6 (209.1–292.1)‡ | 1.4 (0–3.1)‡ | 2.3 (0–4.7)‡ |

* Versus placebo $p < 0.01$.
† Versus placebo $p < 0.05$.
‡ Versus placebo $p < 0.001$.

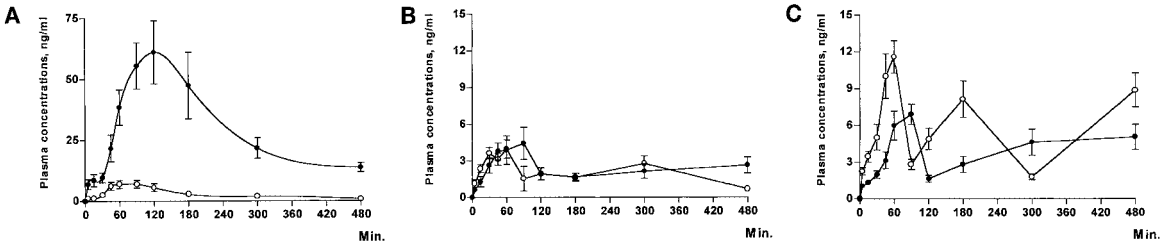


FIG. 1. Mean plasma oxybutynin (open circles) and N-desethyl oxybutynin (filled circles) ±1 SEM of 12 measurements per time point after oxybutynin administration. *A*, 5 mg. oxybutynin orally. *B*, intravesical passive diffusion of 15 mg. oxybutynin. *C*, electromotive administration of 15 mg. oxybutynin.

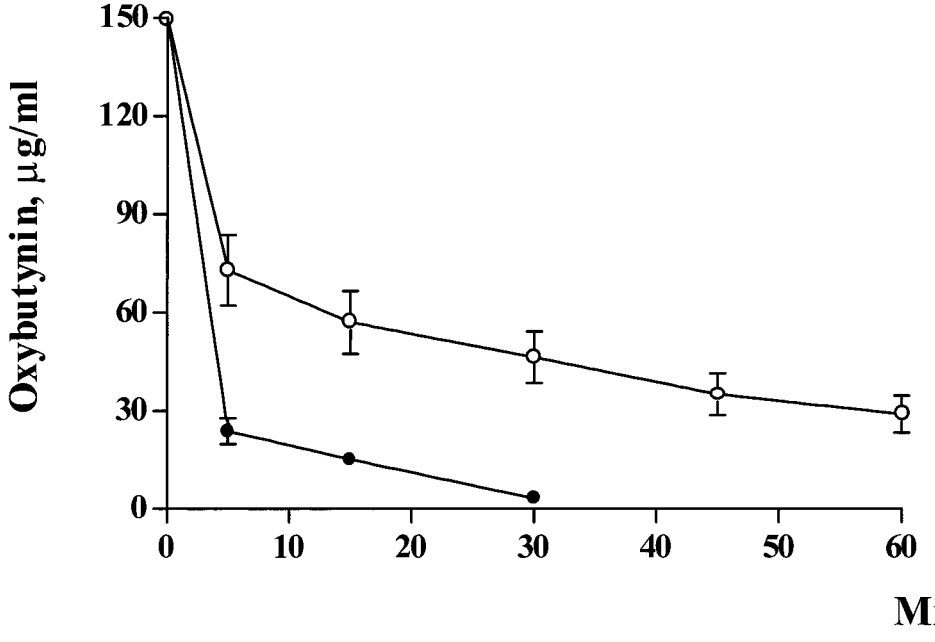


FIG. 2. Mean decay of oxybutynin concentration ±1 SEM of 12 measurements per time point in 100 ml. bladder instillation initially containing 15 mg. oxybutynin Open circles indicate passive diffusion. Filled circles indicate electromotive administration.

vesical post-void residual urine volume and the number of urinary leakage episodes from 0 to 4 and 4 to 8 hours in the 12 patients. Oral oxybutynin had no effect, passive diffusion oxybutynin significantly decreased urinary leakage and electromotive oxybutynin caused significantly greater intravesical post-void residual urine volume and significantly fewer episodes of urinary leakage.

*Pharmacokinetics.* Figure 1 shows plasma oxybutynin and N-desethyl oxybutynin after 5 mg. oral oxybutynin, passive diffusion of 15 mg. oxybutynin and electromotive diffusion of 15 mg. oxybutynin with 15 mA. electric current. Figure 3 shows all area under the plasma concentration time curve values for 480 minutes. After oral administration the mean maximum concentration of 7.0 ± 1.6 ng./ml. oxybutynin and 61 ± 13 ng./ml. N-desethyl oxybutynin occurred at 90 and 120 minutes for area under the curve values of 1,387 ± 178 ng. and 14,910 ± 2,425 ng., respectively (versus all other N-desethyl oxybutynin area under the curve values $p < 0.001$). The area under the curve ratio of N-desethyl oxybutynin-to-oxybutynin was 11:1. With passive diffusion oxybutynin peaked initially at a mean of 4.0 ± 0.7 ng./ml. at 60 minutes and peaked again at 2.8 ± 0.6 ng./ml. at 300 minutes. N-desethyl oxybutynin peaked at a mean of 4.4 ± 1.3 ng./ml. at 90 minutes, decreased to a nadir at 180 minutes and then increased slightly for up to 480 minutes. Mean area under the curve values were 990 ± 110 and 1,133 ± 232 ng., respectively, with an area under

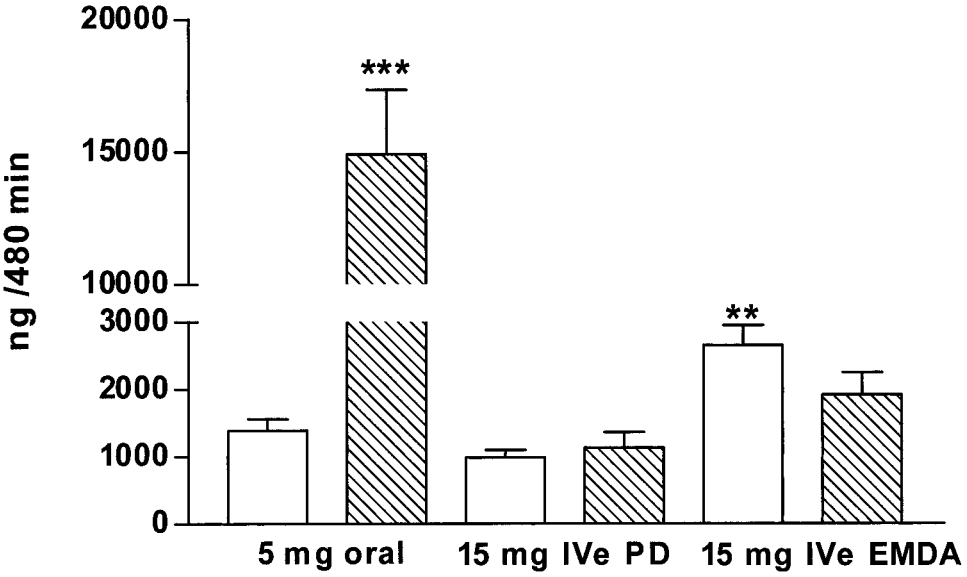


FIG. 3. Mean area under curve values of oxybutynin (open bars) and N-desethyl oxybutynin (hatched bars) after 5 mg. oxybutynin orally, intravesical passive diffusion (*IVe PD*) of 15 mg. oxybutynin and electromotive administration (*EMDA*) of 15 mg. oxybutynin. Double asterisks indicate $p < 0.01$ and triple asterisks indicate $p < 0.001$ versus comparable measurements.

the curve ratio of N-desethyl oxybutynin-to-oxybutynin of 1.1: 1.0. After electromotive administration oxybutynin achieved peak 1 at a mean of 11.6 ± 1.3 ng./ml. at 60 minutes, peak 2 at 8.1 ± 1.5 ng./ml. at 180 minutes and peak 3 at 8.8 ± 1.4 ng./ml. when the final blood specimen was obtained at 480 minutes. N-desethyl oxybutynin peaked at a mean of 6.9 ± 0.8 ng./ml. at 90 minutes, decreased to a nadir at 120 minutes and then increased slightly for up to 480 minutes. The mean oxybutynin area under the curve value was 2,654 ± 294 ng. (versus area under the curve of oral oxybutynin $p < 0.01$) and the N-desethyl oxybutynin area under the curve value was 1,920 ± 327 ng. The area under the curve ratio was inverted at a ratio of N-desethyl oxybutynin-to-oxybutynin of 1:1.4.

Intravesically for passive diffusion the best fit was provided by 2-phase exponential decay using the formula, $y = 72.1-0.015x + 77.5-0.86x + 0.09$ ($r2 = 1$). For electromotive administration the tentative equation involved 1-phase exponential decay using the formula, $y = 108.9-0.211x + 39.7$ ($r2 = 0.997$). Intravesical uptake derived from the transformed concentrations at the times of bladder drainage for passive diffusion and electromotive administration of oxybutynin was 12 and 14.8 mg., respectively.

*Side effects.* There were anticholinergic side effects in 8 of 12 patients after oral oxybutynin administration. There were no such side effects after either mode of intravesical administration.

## DISCUSSION

In our earlier study we stated or implied that the superior urodynamic results of intravesical electromotive oxybutynin were achieved because of the increased systemic bioavailability attained by this technique, as demonstrated by the plasma area under the curve.[1] Our current results indicate that this assumption is no longer tenable. The pharmacokinetics of oral oxybutynin were unremarkable according to plasma peak and decay curves with a maximum concentration ratio of N-desethyl oxybutynin-to-oxybutynin of approximately 9:1 and an area under the curve ratio of approximately 11:1, similar to the results of others.[2,4] The oral dose caused side effects without urodynamic improvement and resulted in a combined mean area under the curve value of oxybutynin plus N-desethyl oxybutynin that exceeded by 4-fold that after intravesical electromotive administration, although the latter method resulted in highly significant improvement in all 10 urodynamic measurements without side effects. The superior plasma oxybutynin level achieved by electromotive administration may imply that oxybutynin is relatively specific for detrusor M.3 receptors with resultant therapeutic and absent side effects. However, this remote possibility was negated by the laboratory studies of Waldeck et al, who observed that the actions of oxybutynin and N-desethyl oxybutynin on detrusor muscle and the parotid gland are almost identical, that is therapeutic and side effects of the 2 agents should be indistinguishable.[6] Furthermore, although our previous study showed that passive diffusion of 5 mg. oxybutynin was ineffective in our select patients, increasing the dose to 15 mg. resulted in the beginning of a therapeutic effect with improvement in 3 of 10 urodynamic measurements, while the peak and area under the curve of plasma oxybutynin was lower than that of oral oxybutynin. The logical conclusion incorporating these facts is that intravesical oxybutynin exerts its therapeutic effect by direct localized action within the bladder wall, probably through local anesthesia of the afferent arm of a reflex arc[7] and possibly via a small degree of diffusion down to the M.3 receptors in the detrusor.

Oxybutynin was retained in the bladder for 60 minutes during passive diffusion and 30 minutes during electromotive administration with absorption of about 12 and 15 mg., respectively, before the bladders were drained. Blood sampling to determine the plasma level commenced immediately at instillation and continued for 8 hours, resulting in a combined oxybutynin plus N-desethyl oxybutynin mean plasma area under the curve of 2,123 and 4,574 ng./8 hours for passive diffusion and electromotive administration, respectively. However, the mean corresponding combined area under the curve after 5 mg. oxybutynin orally was 16,297 ng./8 hours, indicating that only about 1 to 2 mg. oxybutynin entered the circulation in the 8-hour period after intravesical instillation. Therefore, a large proportion of oxybutynin administered intravesically was sequestered somewhere within the bladder wall. With absent complete flaccidity the detrusor is an improbable site for storing quantities in mg. The region of the lamina propria is a possible candidate but the most likely site is the urothelium, which has no direct blood supply.

The multiple peaks in plasma oxybutynin after intravesical administration were originally attributed to an unknown

storage and release phenomenon. In our study we identified a probable storage site but not the release component. Increasing intravesical oxybutynin from 5 to 15 mg. and current intensity from 5 to 15 mA. transformed an unexplained 2-peak plasma profile to an inexplicable 3-peak profile at up to 8 hours of measurement. N-desethyl oxybutynin showed an initial peak, a trough and then indicated continuing and possibly increasing oxybutynin metabolism from 2 to 8 hours, which helped little. Although it is not possible to state how long therapeutic quantities of oxybutynin and possibly N-desethyl oxybutynin remained stored in excess of 8 hours, the situation implies at least 1 intriguing clinical corollary. Short-term intravesical treatment days or weeks in duration often achieve gratifying results with few side effects. However, unless the dose is adjusted long-term therapy months or years in duration likely saturates urothelial storage capacity and then side effects become prominent, as reported by Palmer et al.[8]

## CONCLUSIONS

In patients with detrusor hyperreflexia unresponsive to standard anticholinergic regimens 5 mg. oxybutynin orally conferred no objective urodynamic benefits and caused side effects. Intravesical instillation of 15 mg. oxybutynin with passive diffusion resulted in 12 mg. uptake and some urodynamic improvement, while electromotive administration caused 15 mg. uptake and marked urodynamic improvement. Neither intravesical mode caused side effects and each resulted in a much lower mean area under the curve of plasma oxybutynin plus N-desethyl oxybutynin than oral oxybutynin. Therefore, the clinical benefit of intravesical oxybutynin instillation is the result of localized direct action within the bladder wall. Applying intravesical electric current enhances this effect. We postulate that a large proportion of intravesical oxybutynin is sequestered in the urothelium.

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