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Intravesical electromotive administration of oxybutynin: from laboratory to clinical field

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†Robert L. Stephen leaves us with the memory of an inspiring teacher, scientist, colleague and friend. We sorely miss him.

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INTRODUCTION

Following its introduction in the early 1960's (Brit pat. 940, 540), oxybutynin was rapidly accepted into clinical practice for its modest, direct-action spasmolytic properties and potent antimuscarinic activity on detrusor muscle (1). There is also a local anesthetic effect, approximately twice that of lidocaine (2). In spite of its widespread clinical use, comparative studies on the pharmacological actions, clinical effectiveness, side-effects and pharmacokinetics of oxybutynin administered by different routes, are scarce.

Clean intermittent catheterization (CIC) combined with oral anticholinergic agents is the standard treatment in patients suffering from spinal cord injury, presenting with detrusor hyperactivity and/or detrusor-sphincter dyssynergia (3). Several studies have shown that intravesical (i.v.) instillation of oxybutynin is an effective treatment in many patients who are unresponsive to, or cannot tolerate, the drug given by the oral route (4). However, the effectiveness of i.v. oxybutynin has proven variable and somewhat unpredictable, with patient selection, evaluation criteria, drug concentration and dwell time of instillation affecting the interpretation of results. Drug absorption through the bladder wall tissues and drug concentrations at the target site (detrusor) are important determinants of efficacy (5) but passive diffusion (PD) of drugs across the urothelium is complex and not easily defined. Many factors including pressure and concentration gradients, time of exposure, partition coefficient, molecular weight and chemical structure, pH, degree of ionization and urinary output rate all 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 upon the pH of the so-

lution and the pKa of oxybutynin according to Henderson-Hasselbach equation.

Recruitment of electrokinetic forces accelerates drug administration rates across biological membranes and into underlying tissues. The term "electromotive drug administration" (EMDA) describes transport of all water soluble drugs under the influence of an electric field and, unlike PD, is most effective when dealing with an ionized drug, where the rate of drug transport is proportional to the intensity of the applied electric current which largely overrides all other variables (6). Our group has gained a large experience in the last years working on pre-clinical and clinical models of EMDA; the present paper essentially resumes the work carried out by us on EMDA concept applied to oxybutynin-based treatments.

LABORATORY STUDIES

While various methods are reported in the literature for extraction and/or determination of oxybutynin in biological fluids (7) and pharmaceuticals (8) e.g. gas chromatographic-mass spectrometric analysis or reversed-phase ion-pair liquid chromatography, a detailed methodology to evaluate oxybutynin concentrations in tissues has never been standardised. Therefore, our very first step in oxybutynin studies was to develop a sensitive and selective method to determine tissue concentration of oxybutynin in human bladder wall samples, after passive delivery or electromotive administration, based on tissue extraction and drug analysis (9). Various approaches were evaluated to achieve optimal conditions for tissue extraction of oxybutynin. Tissue extraction was attempted after (a) no homogenization, (b) homogenization by a tissue grinder with Teflon piston, (c) ultrasonic homogenization, (d) rotor/stator type homogenizer in aqueous or aqueous/organic solutions, and (e) stainless steel blade assembled homogenizer in aqueous or aqueous/organic solutions. The latter approach allowed simultaneous sample homogenization and extraction, and reduced the amount of tissue remaining in the homogenizer assembly; this method was selected for sample preparation. High performance liquid chromatography (HPLC), equipped with a diode-array spectrophotometric detector, an electrochemical detector and reversed-phase column, was used to determine the tissue concentration of oxybutynin.

The subsequent laboratory study (10) was undertaken to establish an appropriate tissue pharmacokinetic model, in order to compare concentrations and delivery rates of oxybutynin in the human bladder wall after either PD or EMDA, and to evaluate the effects of EMDA on tissue morphology and viability as well as on oxybutynin structure. A two-chamber polyvinylchloride diffusion cell was used for oxybutynin delivery to bladder tissues. Sections of normal bladder wall tissue were obtained from informed patients undergoing radical cystectomy for bladder cancer. During each paired experiment, tissues from a single patient were fixed between the two chambers of a diffusion cell with a mirror-like central window of 1 cm in diameter. Urothelial areas were exposed to the donor compartments and serosa to the receptor compartments. Oxybutynin 9 mg was dissolved in 200 ml NaCl solution 0.45%, the pH was measured, and then the solution was divided into two volumes of 100 ml (oxybutynin 4.5 mg in NaCl solution 0.45%) which were placed in paired PD and EMDA donor compartments. The receptors compartments were filled with 100 ml NaCl solution 0.9%. In EMDA experiments an anode was placed in the donor compartment and a cathode in the receptor compartment. The electrodes were connected to the current generator and experiments were performed with pulsed DC of 5 mA for 15 min. No electric current was applied in PD control experiments. Oxybutynin tissue contents were assessed by high-pressure liquid chromatography. Tissue viability and morphology and oxybutynin stability were assessed by trypan blue exclusion test,

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tissue pH, histological analysis, and mass spectrometry analysis. Twelve paired experiments were performed using 24 bladder wall tissue samples from 12 different patients. The mean quantities of oxybutynin found into bladder wall samples after EMDA (8.69±4.52 μg) significantly exceeded the respective amounts achieved following PD (2.02±1.75 μg), as did mean tissue concentrations (3.84±2.22 μg/gm vs 0.87±0.78 μg/gm). The mean fluxes of oxybutynin in EMDA (0.73±0.38 μg/cm^2/min) and PD (0.16±0.14 μg/cm^2/min) experiments are directly derived from the total quantities administered. Interpretation of coefficient of variation clearly highlights the greater variability when oxybutynin is transported by PD (89.78 vs 57.85%, p=0.0006). All sections of tissue processed demonstrated negative staining of epithelial, subepithelial and muscle cells, thus indicating viability of the tissues throughout the time of experiments. All tissue samples examined were morphologically consistent with normal urothelial, subepithelial and muscle cells. There was no histological evidence of mucosal or bladder abnormality. Mass spectral analysis of oxybutynin samples showed no structural modification after EMDA. The dramatic improvement of oxybutynin diffusion through the bladder wall observed in vitro under EMDA conditions provided a robust rationale to extend our studies to the clinical setting.

CLINICAL STUDIES

The urodynamic effects and pharmacokinetics of oxybutynin were defined in a selected population of spinal cord injured patients with detrusor hyperreflexia who received single doses of the drug by oral or i.v. route. Both sets of measurements were correlated to the method of administration, therapeutic efficacy and antimuscarinic side-effects (11). A selected group of 10 adults with detrusor hyperreflexia unresponsive or who suffered intolerable side-effects to standard oral and i.v. passive diffusion of oxybutynin were enrolled in this study. Either 5 mg oxybutynin or an identical placebo tablet was given orally immediately before the relevant urodynamic session began. With all i.v. instillations the bladder was drained and then 100 ml solution of either NaCl 0.9% (control) or 5 mg oxybutynin in NaCl 0.45% was instilled and the relevant urodynamic session began immediately thereafter. EMDA comprised a 5 mA pulsed current applied via a catheter electrode of positive polarity (anode) to the i.v. solution for a dwell time of 30 min and the bladder was then drained. With PD (no current applied) dwell time was 60 min followed by drainage. Each urodynamic session lasted 8 hrs 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-blind insofar as patients and attending staff were unaware of the nature of the oral administration (oxybutynin or placebo tablets) or the i.v. instillations (oxybutynin/NaCl 0.9%). Specifically, each urodynamic procedure was dedicated to (a) baseline oral placebo, (b) 5 mg oxybutynin orally, (c) control 100 ml NaCl 0.9% i.v. with PD for 60 min, (d) 5 mg oxybutynin in 100 ml NaCl 0.45% i.v. with PD for 60 min, (e) control 100 ml NaCl 0.9% i.v. with EMDA for 30 min and (f) 5 mg oxybutynin in 100 ml NaCl 0.45% i.v. with EMDA for 30 min. During these 8-hr sessions the patients were maintained supine at constant room temperature with continuous recording of the frequency, amplitude and duration of hyperreflexic episodes and urinary leakage. At 4 and 8 hrs the bladder was drained and the volume was measured. Blood samples were drawn before, during and after oxybutynin administration. During i.v. PD and EMDA of oxybutynin, administration samples of the bladder contents were taken. After the instillation period (30 and 60 min) the solution was drained and measured and a further aliquot was taken for analysis. HPLC assay of oxybutynin was used for analysis of plasma and urine samples. Vital signs, Holter electro-

cardiogram and side-effects were recorded during all urodynamic sessions.

The analysis of uninhibited detrusor contractions and the dependent variables of number, duration, amplitude and maximum amplitude in 10 patients showed no significant differences among baseline, oral placebo, the 2 i.v. controls, oral oxybutynin and i.v. PD oxybutynin. EMDA oxybutynin resulted in a significant decrease in the number ($p=0.0006$), amplitude ($p=0.0034$) and maximum amplitude ($p=0.0049$) compared with all other sessions. There were no significant differences between residual volumes resulting from the first 5 urodynamic sessions. EMDA oxybutynin resulted in significantly greater i.v. residual volumes measured from 0 to 4 ($p=0.0068$) and 4 to 8 ($p=0.0039$) hrs, compared with those following all other sessions. There were significantly fewer episodes of urinary leakage recorded from 0 to 4 ($p=0.0004$) and 4 to 8 ($p<0.0001$) hrs following EMDA oxybutynin as compared with those of all other sessions. In pharmacokinetics studies peak plasma concentrations (7.82±1.8 ng/ml) were reached at 90 min after oral administration, and thereafter levels decayed by first order kinetics with a half-life of 61 min and $\beta=0.0114$; area under the curve (AUC) value was 1,485±200 ng). Peak plasma concentrations (4.7±0.24 ng/ml) were observed within 60 min following i.v. PD, and subsequently there was a second peak (3.0±0.35 ng/ml) at 180 min. The AUC value was 709±64 ng, which was significantly lower ($p<0.05$) than that after oral administration. I.v. EMDA (5 mA) resulted in a plasma profile somewhat similar to that obtained after PD with the first peak at 60 min and a second peak at 300 min. There was a sharp increase in bioavailability, with AUC levels of 2,781±314 ng; ($p<0.001$ vs both oral and i.v. PD routes). A corrective factor was applied to oxybutynin concentrations in i.v. samples to eliminate the effect of inflowing urine in each patient. Using these transformed values to calculate the decay of oxybutynin concentrations, with PD the best fit ($r=0.9999$) was a 2-phase exponential decay equation: $y = 23.59^{-0.016x} + 26.24^{-0.219x}$ with a phase of rapid absorption, half-life of 3.2 min, followed by a second slower phase, half-life of 43 min. EMDA resulted in a different profile and the kinetic model which best described ($r=0.9998$) 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 min. Thus, the application of electrical stimulation shifted the type of drug absorption from a 2-phase to a 1-phase exponential kinetic profile; the physical meaning of this shift is that the rate of absorption of oxybutynin under PD conditions is more rapid at the beginning of treatment and tends to decrease as long as i.v. concentrations decrease; this is consistent with a first-order kinetics. On the contrary, electrical stimulation overrides this mechanism and absorption has a constant rate throughout the time, according to a zero-order kinetics.

There were no adverse changes in pulse rate or blood pressure, nor were there any arrhythmias, during all urodynamic sessions. Following oral oxybutynin, anticholinergic side-effects were reported in 7 patients. Interestingly, there were no such side-effects following either mode of i.v. administration. Transient erythema of the skin underlying the dispersive electrodes was present following all EMDA procedures.

In the previous study we demonstrated that i.v. administration of oxybutynin 5 mg accelerated by electric current (electromotive) provided objective urodynamic improvement in a selected group of patients who did not respond to oral oxybutynin 5 mg or to PD i.v. oxybutynin 5 mg (11). These results correlated with the rapid i.v. uptake and increased systemic bioavailability of oxybutynin attained by EMDA, which is pharmacologically rational.

We also observed that oral oxybutynin conferred no objective urodynamic benefits and caused anticholinergic side-effects in 70% of patients; EMDA conferred objective benefits, yet the significant increases in oxybutynin plasma levels caused no side-effects in any of the pa-

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tients, an observation that is hard to explain on a rational basis. Also, both techniques of i.v. administration gave rise to biphasic oxybutynin plasma profiles with the second peaks occurring hours after bladders had been drained of their instillations, which suggested some sort of blood-vesical recycling; however, the studies provided no indication as to where or by what mechanism this phenomenon occurred.

With hindsight, the lack of N-desethyl oxybutynin measurements was a deficiency in the investigation and their inclusion should help resolve the above unexplained findings. Furthermore, the present investigators anticipate that plasma profiles of this pharmacologically active metabolite (7) and of oxybutynin, combined with measurements of i.v. oxybutynin absorption, will help resolve the following issue. The precise mechanism whereby i.v. oxybutynin exerts its therapeutic effect is obscure; a localized direct action within the bladder wall is a recurring consideration (12) but the uncertainty remains (13).

Therefore, 12 spinal cord injury patients with neurogenic bladder dysfunction, unresponsive to oral and i.v. oxybutynin and on CIC regimen, were recruited for similar studies: administration of oxybutynin orally and i.v. with both EMDA and PD; urodynamic studies and measurement of i.v. oxybutynin absorption and plasma levels (14). There were two variations: 1) N-desethyl oxybutynin levels were also measured in all plasma samples and 2) i.v. quantities of oxybutynin were increased as were electric current intensities so as to magnify and /or reveal further differences from oral administration.

Five mg oxybutynin chloride or placebo tablets were given by the oral route. For i.v. administration a 100 ml solution (37°C) of either NaCl 0.9% (control) or oxybutynin 15 mg in NaCl 0.45% was instilled. EMDA involved a 15 mA electric current applied via a catheter-electrode to the i.v. solution for 30 minutes and the bladder was then drained; with i.v. administration by PD, drainage was after 60 minutes.

Similar to the previous study, there were six 8-hr urodynamic sessions at weekly intervals, with continuous monitoring of six modes of drug and placebo administration applied randomly and double blind with respect to the identities of oral placebo/oxybutynin tablets and i.v. control/oxybutynin solutions. In addition to uninhibited detrusor contraction (UDC) components (number, duration, amplitude and maximum amplitude), bladder compliance was recorded from 0-4 and 4-8 hrs as were residual volumes and the number of urinary leakages.

Blood samples for oxybutynin and N-desethyl oxybutynin measurements were drawn during each 8 h urodynamic session. I.v. samples were withdrawn at specified time intervals for measurement of oxybutynin concentrations. On completion of EMDA (30 min) and PD (60 min), bladders were drained, with their volumes (Vt) comprising the original 100 ml infusion (Vo) plus urine. Assuming a constant rate of urine inflow, the measured oxybutynin concentrations were normalized to their concentrations (Co) in the original 100 ml volumes: $Co = Ct \bullet Vt/Vo$. I.v. uptake of oxybutynin was calculated from the final transformed oxybutynin concentrations in samples taken when bladders were drained.

The extraction procedure of oxybutynin and N-desethyl oxybutynin has been reported in detail (3, 6) and a reverse-phase HPLC assay of oxybutynin and N-desethyl oxybutynin was used for analysis of samples.

As compared to oral placebo (baseline), oral oxybutynin had no significant influence on UDC or bladder compliance; PD oxybutynin induced a significant reduction in the number of UDC only. EMDA oxybutynin induced a highly significant improvement in all 4 UDC variables and in bladder compliance. Oral oxybutynin had no effect on i.v. residual volumes and number of leakages; PD oxybutynin significantly reduced urinary leakage; EMDA oxybutynin resulted in significantly

greater i.v. residual volumes and in significantly fewer episodes of urinary leakage.

Following oral administration, peak plasma concentrations of oxybutynin and N-desethyl oxybutynin (7.0±1.6 ng/ml and 61±13 ng/ml) occurred at 90 and 120 min. The respective AUC values were 1,387±178 ng and 14,910±2,425 ng ($p<0.001$ vs all other N-desethyl oxybutynin AUC values). The AUC N-desethyl oxybutynin/oxybutynin ratio was 11/1. With PD, oxybutynin levels displayed an initial peak (4.0±0.7 ng/ml) at 60 min and a second peak (2.8±0.6 ng/ml) at 300 min; N-desethyl oxybutynin peaked (4.4±1.3 ng/ml) at 90 min, fell to a nadir at 180 min, then increased slightly out to 480 min. The AUC values were 990±110 and 1,133±232 ng respectively; the AUC N-desethyl oxybutynin/oxybutynin ratio in this case was 1.1/1.

Following EMDA, oxybutynin levels displayed an initial peak (11.6±1.3 ng/ml) at 60 min, a second peak (8.1±1.5 ng/ml) at 180 min and a third peak (8.8±1.4 ng/ml) on the last blood draw at 480 min; N-desethyl oxybutynin peaked (6.9±0.8 ng/ml) at 90 min, fell to a nadir at 120 min, then increased slightly out to 480 min. The oxybutynin AUC value was 2,654±294 ng ($p<0.01$ vs AUC oral oxybutynin) and N-desethyl oxybutynin AUC value was 1,920±327 ng. The AUC ratio was inverted, with N-desethyl oxybutynin/oxybutynin= 1/1.4.

Looking at the kinetic of oxybutynin disappearance from the i.v. compartment, for PD the best fit ($r^2=1$) was supplied by a 2-phase exponential decay: $y= 72.1^{-0.015x} + 77.5^{-0.86x} + 0.09$. For EMDA the tentative equation was a one-phase exponential decay: $y = 108.9^{-0.211x} + 39.7$ ($r^2=0.997$). I.v. uptake derived from the (transformed) concentrations at the times of bladder drainage: PD/oxybutynin= 12.0 mg; EMDA/oxybutynin= 14.8 mg. These results confirmed the finding from our previous study that EMDA can cause a shift from first-order to zero-order kinetic in drug absorption.

Again, there occurred anticholinergic side effects in 67% of patients following oral oxybutynin administration, whereas there were no such side-effects following either mode of i.v. administration.

DISCUSSION

Little is known about the pharmacokinetics of i.v. oxybutynin. Previous clinical studies focused on the concentration-time profiles of oxybutynin in the systemic circulation during i.v. therapy and have ignored the pharmacokinetics at the target site (12, 15). The current approach with i.v. oxybutynin is to instill the drug using an empirically-based dosage regimen and dwell time. Although these regimens have produced some favorable clinical effects, the highly variable responses rate suggests that improvement is possible. Target site exposure is crucial in achieving optimal i.v. therapy, because detrusor muscle cells and their muscarinic receptors located in the bladder wall must receive adequate oxybutynin concentrations.

Following initial laboratory studies describing PD and EMDA transport rates of oxybutynin (10), in the earlier clinical study (11) it was either stated or implied that the superior urodynamic results with i.v. electromotive oxybutynin were achieved because of increased systemic bioavailability (plasma AUC levels) attained with this technique. The results in the following clinical study (14) demonstrate that this assumption is no longer tenable.

The pharmacokinetics of oral oxybutynin were unremarkable: plasma peak and decay curves with C_{max} ratio N-desethyl oxybutynin/oxybutynin ~9/1 and AUC ratio ~11/1, similar to those of other investigators (7, 13). The oral dose caused side-effects without urodynamic improvement and resulted in a combined AUC oxybutynin + N-desethyl oxybutynin mean value which exceeded that following i.v. electromotive fourfold, yet electromotive administration resulted in highly signifi-

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cant improvement in 10/10 urodynamic measurements without side-effects. The superior plasma oxybutynin levels achieved with electromotive may imply that oxybutynin is relatively specific for detrusor M_3 receptors with resultant therapeutic effects and absent side-effects; however, this remote possibility is negated by the laboratory studies of Waldeck et al. (1) who demonstrated that the actions of oxybutynin and N-desethyl oxybutynin upon detrusor muscle and parotid gland are almost identical, that is, therapeutic effects and side-effects of the two agents should be indistinguishable. Notwithstanding, it clearly appears from our experience that higher levels of N-desethyl oxybutynin are associated to much lower tolerability; this phenomenon, albeit unexplained at present, should be taken into due account when choosing the route of administration for oxybutynin treatment.

Although our previous studies showed passive diffusion oxybutynin 5 mg to be ineffective in these select patients, increasing the dose to 15 mg resulted in commencing therapeutic effect with improvement in 3/10 urodynamic measurements, yet peak and AUC plasma levels of oxybutynin were actually lower than those achieved with oral oxybutynin. The logical conclusion which incorporates all the above facts is that i.v. oxybutynin exerts its therapeutic effect by a direct localized action within the bladder wall, probably through local anesthesia of the afferent arm of a reflex arc (16) 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 min during passive diffusion and 30 min during electromotive administration with absorption of about 12 and 15 mg respectively, then the bladders were drained. Blood draws for plasma levels started immediately upon instillation and continued for 8 hrs, resulting in combined oxybutynin + N-desethyl oxybutynin plasma AUC mean values of 2,123 ng/8h for passive diffusion and 4,574 ng/8h for electromotive administration. However, the corresponding combined AUC mean value following oxybutynin 5 mg taken orally was 16,297 ng/8h, which indicates that only about 1-2 mg of oxybutynin entered the circulation over an 8-hr period following the i.v. instillations. Therefore, a large proportion of oxybutynin administered i.v. is sequestered somewhere within the bladder wall. In the absence of total flaccidity the detrusor is an improbable site for storage of milligram amounts, 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 oxybutynin plasma levels following i.v. administrations were originally ascribed to an unknown storage and release phenomenon (11). The present studies have identified a probable storage site but have not assisted with the "release" component. Increasing the i.v. oxybutynin amount from 5 to 15 mg and the current intensity from 5 to 15 mA transformed an unexplained twin peak plasma profile to an inexplicable triple peak profile out to 8 hrs of measurements. N-desethyl oxybutynin levels displayed an initial peak, a trough and then indicated continuing (and possibly increasing) oxybutynin metabolism from 2-8 hrs, which helped very little. Although it is not possible to state how long therapeutic quantities of oxybutynin (and possibly N-desethyl oxybutynin) remain stored in excess of 8 hrs, the situation implies at least one intriguing clinical corollary. Short term (days, weeks) i.v. treatments will often yield gratifying results with few side-effects. However, unless dosages are adjusted, long-term therapy (months, years) will likely saturate the urothelial storage capacity and then side-effects will become prominent, a postdiction reported by Palmer et al. (17). There is also the issue of a localized effect with i.v. oxybutynin, inferred indirectly by Madersbacher et al. (2), emphasized by Buyse et al. (13) and confirmed by DeWachter and Wyndaele (18).

An additional, or alternative, explanation to the phenomenon of multiple plasma peaks after i.v. oxybutynin administration involves the theoretical model of plasma-vesical recycling. Indeed, it clearly appears that oxybutynin is massively metabolized to N-desethyl oxybutynin through hepatic first-pass effect, as it occurs after oral administration of the drug. When first-pass effect is avoided, as in the case of i.v. administration, far less N-desethyl oxybutynin is generated. Thus, larger amounts of parent drug are available for renal excretion, and concentrate in the urinary compartment. Under the conditions adopted in our studies, oxybutynin excreted in urine can therefore be re-absorbed from the bladder and return into the systemic circulation. The fact that oxybutynin passes across the bladder wall twice or trice during a single experimental session would increase the local effects on detrusor muscle, thus explaining the higher clinical efficacy of i.v. administration, EMDA in particular.

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