Electromotive Delivery of Mitomycin C into Human Bladder Wall

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ABSTRACT

The aim of this investigation was to establish an appropriate tissue pharmacokinetic model to compare concentrations of mitomycin C (MMC) in the human bladder wall after either passive delivery or electromotive administration (EMDA) and to evaluate the effects of EMDA on tissue morphology and MMC structure.

Tissue sections of human bladder were inserted into two chamber cells with urothelium exposed to donor compartments containing MMC (10 mg in 100 ml of 0.24% NaCl solution) and an anode and with serosa exposed to receptor compartments containing 100 ml of 0.9% NaCl solution and a cathode. Fourteen paired experiments (“current 5 mA/no current”) were conducted over 15 min; MMC tissue content was assessed by high-pressure liquid chromatography. Tissue viability and morphology and MMC stability were assessed by trypan blue exclusion test, tissue pH, histological analysis, and mass spectrometry analysis.

MMC concentrations were increased, and variability in drug delivery rate was reduced in all tissue in samples exposed to electric current. Tissues were viable and undamaged histologically, and no MMC structural modification was observed.

In conclusion, EMDA enhances administration of MMC into viable bladder wall tissue and reduces the variability in drug delivery rates.

INTRODUCTION

The most frequently diagnosed bladder tumors are superficial transitional cell carcinomas: carcinoma in situ (stage Tis), papillary lesions confined to the urothelium (stage Ta), and stage T1 invading the lamina propria (1). TUR² is the routine initial diagnostic and therapeutic step in management. Recurrence rates following TUR alone are reported as varying from 30 to >90% of cases (2) and progression to muscle invasion as 4–30% (3). The probability of recurrence and the unpredictability of progression have led to widespread use of intravesical therapies with cytotoxic and immunotherapeutic agents (4, 5). The main advantage of these methods is that little systemic uptake of drug occurs, while optimal contact between the tumor or tissue at risk and drug is obtained. The goals of intravesical therapy are to eradicate any existing tumor, to decrease the frequency of recurrences or new occurrences of disease, and to avoid the cost and morbidity of further surgery.

MMC is a favored chemotherapeutic agent used for this purpose. In patients with superficial bladder tumors, adjuvant intravesical MMC therapy has been shown to decrease the recurrence rate within 12 months by 2–43%, and Ta tumors appear to respond more favorably than T1 (6). Previous studies investigated the pharmacokinetics in MMC concentrations required for a cytotoxic effect on histocultures and Francesco Micali

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MMC is a favored chemotherapeutic agent used for this purpose. In patients with superficial bladder tumors, adjuvant intravesical MMC therapy has been shown to decrease the recurrence rate within 12 months by 2–43%, and Ta tumors appear to respond more favorably than T1 (6). Previous studies investigated the pharmacokinetics in superficial bladder cancer patients during intravesical therapy (7), the MMC concentrations required for a cytotoxic effect on histocultures of patient bladder transitional carcinoma (8), and the penetration of MMC in dog and patient bladders (9, 10). These data suggest that intravesical MMC treatment of cancer cells located in the deeper tissues of the bladder wall is inadequate. This may be due to reduced tumor sensitivity to the drug or to lower drug concentrations at target sites beyond the urothelium. Moreover, it is hypothesized that enhancement of MMC instillation therapy may be achieved by increasing MMC penetration across the urothelium, emphasizing the importance of the mucosa as a barrier to drug absorption (8).

Various electrokinetic phenomena can be recruited to accelerate drug administration across biological membranes and into underlying tissues. At least three such phenomena involved in electromotive transport are iontophoresis, electro-osmosis/electrophoresis, and electroporation.

Iontophoresis is the accelerated flux of ions (J) down their coulombic gradients induced by an electric field and is given mathematical expression by the equation:

\[ J(mol/sec) = \frac{I}{|z| \times F}, \]

where \( I \) is the current in amperes, \(|z|\) is the absolute valency of the ions, and \( F \) is Faraday’s constant. Transposing:

\[ J(mg/min) = \frac{60 \times I \times M}{|z| \times F}, \]

where \( I \) is now milliamperes (mA), and \( M \) is the molecular weight. For a specific ion (D) in a solution of ions,

\[ \frac{dD}{dt(mg/min)} = \frac{60 \times I \times M}{|z| \times F} \times tr, \]

where \( tr \), the transference number, is the fraction of total current used in transporting D and is always less than unity. As described by the above equations, the actual drug concentration is immaterial; within limits this is true, but if ionic concentrations are too low to conduct a specified current effectively, this leads to undesirable polarization and hydrolytic effects.

Electro-osmosis/electrophoresis is used to describe the current-induced convective flow of water in association with ions, which can accelerate the transport of ionized molecules down coulombic gradients, nonionized polar molecules (11), and ionized molecules against their coulombic gradients (12). MMC is nonionized at pH levels used clinically (5.0–8.0 units; Ref. 13), but some preparations contain NaCl as an excipient. When these vials are dissolved in water, the NaCl conducts current, and the polar, nonionized MMC is administered by electro-osmosis.

Electroporation implies increasing the permeability of biological membranes under the influence of an electric field, which promotes increased transport rates down concentration gradients (14).

Because of the multiple electrokinetic forces involved, the term electromotive drug administration (EMDA) was coined to describe accelerated drug transport under the influence of an electric field (15).

The present investigation was designed to: (a) establish an appropriate tissue pharmacokinetic model to compare quantities and con-
centrations of MMC in the human bladder wall after either PD or EMDA; (b) determine the effect of EMDA on tissue morphology and viability; and (c) determine the effect of EMDA on MMC.

MATERIALS AND METHODS

Chemicals. MMC was supplied in 10-mg vials (Kyowa Italiana Farmaceutici, Milan, Italy). The internal standard was porfiromycin (American Cyanamid, Pearl River, NY). HPLC analyses showed that MMC and porfiromycin were >99% pure. HPLC solvents and reagents were obtained from Sigma-Aldrich (Milan, Italy).

Apparatus. A two-chamber polyvinylchloride diffusion cell, developed in our laboratory, was used for MMC delivery to bladder wall tissue samples (Fig. 1). The current generator and silver spiral electrodes were supplied by Physion (Mirandola, Italy). The pH values of tissue and MMC solutions were measured using a model 1001 pH meter (Sentron, Roden, The Netherlands) supplied with a flat 1020 pH/T probe. The HPLC system consisted of a programmable solvent delivery system (model 120701, Science Marketing International, Ltd., Gloucester, United Kingdom); an automated injector (WISP 710B, Water Associates, Milford, MA) or a manual injector (model 7725, Rheodyne, Cotati, CA); a wavelength UV detector with 254- and 365-nm filters (model 200354, Science Marketing International, Ltd.); and an integrator (model 717, Axxiom Chromatography, Inc., Calabalas, CA). Tissue weights were determined with a precision of 0.1 mg on a Gibertini E42 balance (Gibertini Elettronica, Novate, Milan, Italy). Tissue samples were homogenized at room temperature with a biohomogenizer Blendor 7012F (Waring Products Division, Hartford, CT). Protein determination was performed using the Beckman DU-40 spectrophotometer (Beckman Instruments, Arlington Heights, IL).

Harvesting of Tissue Samples. From informed patients undergoing radical cystectomy for bladder cancer, full-thickness tissue sections were obtained. No patient had received prior radiotherapy or chemotherapy. The surgical technique was modified to maintain blood supply for as long as possible (10), and after the bladder was removed, two full-thickness tissue specimens (each 2 cm²) were excised within 5 min from visually cancer-free bladder wall that had not been scarred by previous transurethral resection. Perivesical fat was removed, and the serosal surface was exposed. The samples were placed in a cell culture medium (1 X DMEM, HyClone Europe, Cramlington, United Kingdom) at 4°C and transported to the laboratory in an average time of 25 min.

Experimental Protocol. During each paired experiment, tissue samples were placed on polysvinylchloride support mesh with a central window of 1 cm in diameter and fixed between the compartments of the diffusion cells. Urothelial areas of 0.78 cm² were exposed to the donor compartments, and the serosal layers were exposed to the receptor compartments. Twenty mg of MMC (with 480 mg of NaCl) were dissolved in 200 ml of bidistilled H₂O, the pH was measured (see Table 2, column labeled “Initial”), and the solution was divided into two volumes of 100 ml (10 mg of MMC in 0.24% NaCl solution), which were placed in paired PD and EMDA donor compartments. The receptor compartments were filled with 100 ml of 0.9% NaCl solution. In EMDA experiments, an anode was placed in the donor compartment, and a cathode was placed in the receptor compartment. The electrodes were connected to the current generator, and experiments were performed with pulsed direct current of 5 mA at 2500 Hz for a duration of 15 min. No electric current was applied in PD control experiments. The pH of the donor compartments was measured after each experiment (post-PD and post-EMDA, Table 2). Shortly after each experiment, 1-ml samples of all donor and receptor compartment solutions were withdrawn, and MMC concentrations were determined. All experiments were performed in an average time of 30 min, so that the total time between removal of the bladder and completion of the experiment was ~60 min.

Measurements of MMC in Tissues. Tissue samples were blotted with absorbent paper to remove unabsorbed drug solution and immediately trimmed, weighed, and collected in 50-ml nalgene tubes with 5 ml of 10 mM Tris-HCl (pH 9.0) and 300 mg of silica gel 60–80 mesh for chromatography. Porfiromycin (25 μg/ml solution in sterile H₂O) and ethyl acetate (10 ml/g of tissue) as an extraction solvent were added. All samples were homogenized at room temperature for 60–120 sec and centrifuged at 3000 X g for 10 min. An antioxidant solution consisting of 2[3]-t-butyl-4-hydroxyanisole (400 mg/ml) and 2-ter-butyl-4-methylphenol (250 mg/ml) was added to the supernatant. After centrifugation, the samples were evaporated in a speed-vac and stored at 4°C. The samples were reconstituted in 50 μl of HPLC mobile phase, and 25 μl were injected. HPLC was performed using a reversed-phase C18 column (RP-18, 250 X 4.6, 5 μm, Brownlee Laboratories, Norwalk, CT) with an aqueous mobile phase containing 15% acetonitrile and 30 mM phosphate buffer (pH 7.0). The solvent flow rate was 1 ml/min, and UV detection was 365 nm. The elution volumes for MMC and porfiromycin were 8.0 and 12.3 ml, respectively. The limit of detection was 10 ng/ml of sample.

Protein Determination. The protein content of the first five paired tissue samples was determined after MMC extraction. The aqueous phase remaining after extraction was heated in a 100°C water bath for 30 min to remove residual extraction solvent. The samples were diluted to 2.5 ml with 0.9% NaCl solution and made alkaline with 1 ml of NaOH 5N. Samples were incubated overnight at 37°C. The protein concentration was determined in an aliquot of the clear solution by the Coomassie blue method (Sigma kit 610, Sigma-Aldrich; Ref. 16).

An additional five series of experiments to determine bladder wall cell viability, urothelial barrier integrity, pH, and histological characteristics of tissues were carried out with multiple samples harvested from single bladders and transported to the laboratory under the same conditions as those described previously. The following procedures were used.

Trypan Blue Exclusion Test. Before (untreated samples) and after (post-PD and post-EMDA) each experiment, tissue sections of approximately 0.5 cm² were excised and incubated in 0.04% trypan blue in DMEM for 1 h at room temperature in a rotation chamber. Control samples were fixed in buffered formalin for 2 h and then stained by 0.4% trypan blue. After incubation, tissues were washed in 152 mM phosphate buffer (pH 7.3), placed in Cryomatrix compound with 10% polyvinyl alcohol and 4% polyethylene glycol (Shandon, Ltd., Astmoo, United Kingdom), and frozen in liquid nitrogen; 30-μm sections were cut with a cryostat, mounted in 40% glycerol in 152 mM phosphate buffer (pH 7.3), and studied by Axioskop microscopy (Zeiss, Jena, Germany). Blue- to pale blue-labeled cells within the tissue were considered nonviable, whereas unlabeled cells were regarded as viable.

pH of Tissue. The pH in tissue samples, at the urothelial and serosal surfaces, was measured before and after each experiment. The critical value was placed at pH 7.0 units. The average pH at each level was calculated and used for data analysis.

Histological Analyses. Before (untreated samples) and after (post-PD and post-EMDA) each experiment, tissue sections of approximately 0.5 cm² were excised and incubated in 0.04% trypan blue in DMEM for 1 h at room temperature in a rotation chamber. The microscopic sections, stained with H&E, were examined in random sequence, and the reviewer was blinded as to the group. To avoid bias during examination of wall thickness, each microscopic section was arbitrarily divided into approximately equal quadrants by lines intersecting at 90°. Micrometer measurements were made wherever a line crossed the tissue sample, for a total of eight examinations per sample. At X 100, all tissue layers...
(urothelium, subepithelial connective tissue, and muscle layers) were inspected for cytological changes.

**Voltage Measurement.** During each of the above EMDA experiments, the voltage across the entire circuit (leads, electrodes, MMC solution, tissue sample, and receptor compartment solution) was measured.

**Mass Spectrometry Analysis.** The samples of MMC obtained before and after EMDA were examined by positive ion fast-atom-bombardment mass spectrometry in m-nitrobenzyl alcohol. Observations were with a multiple quadrupole instrument (VG Quattro, Fisons, Inc., Manchester, United Kingdom) scanning over m/z 160 + 360 at 0.66 s/decade, resolution power 1000.

**Data Analysis.** Descriptive parameters (mean, SD, and CV) were calculated for tissue weight (g), MMC per wet tissue unit (µg/g), flux MMC (µg/cm²/min), and initial and post-PD and post-EMDA pH values in the donor compartments. The differences between variable measurements of MMC delivery were assessed by Wilcoxon signed rank test for the null hypothesis that the two methods of administration produce the same results at a significance level of 5%.

**RESULTS**

**MMC Concentrations in Tissues.** MMC concentrations were standardized to wet tissue weights because this method measured both unbound and reversibly bound MMC distributed in extra- and intracellular compartments. Furthermore, in our experience as well as that reported by others (17), the standardization of MMC concentrations relative to tissue weight showed a lower variability than standardization relative to other parameters, such as tissue protein content.

The results are shown in Table 1. The mean concentration of MMC transported into bladder wall by EMDA (21.5 µg/g) significantly exceeded the concentration achieved by PD (3.4 µg/g), which is mirrored by the respective calculated fluxes (5.5 µg/cm²/min versus 0.9 µg/cm²/min).

Measurements of MMC in the donor compartments showed no significant differences, and they were not sufficiently sensitive to permit mass balance studies. No MMC was detected in the receptor compartments.

**pH of the Donor Compartments.** The pH values of MMC in all 28 donor compartments initially and postexperimentally are shown in Table 2. The initial mean value (6.55 units) differs significantly from post-PD (mean 6.32) and post-EMDA (mean 6.36).

**Trypan Blue Exclusion Test.** All of the tissue sections processed demonstrated negative staining of urothelial cells, subepithelial connective tissue, and muscle cells, indicating viability of tissues throughout the course of the experiments (Fig. 2). All of the cell layers of the control sections fixed in buffered formalin and then incubated in trypan blue were intensely stained by the dye.

**Tissue pH.** The average pH of tissues before experiments was 7.28 units (range, 7.19–7.44; SD, 0.10; CV, 1.4%). Postexperimentally, there were no significant differences in the pH values of tissues in PD (mean value, 7.15; range, 7.09–7.23; SD, 0.05; CV, 0.8%; P = 0.053) and EMDA (mean value, 7.15; range, 7.09–7.22; SD, 0.05; CV, 0.7%; P = 0.063). Moreover, no significant difference was observed between post-PD and post-EMDA pH tissue values (P = 0.683).

**Histological Findings.** All of the tissue samples examined were morphologically coherent, with orderly urothelial cells, subepithelial connective tissue, and muscle layers. There was no histological evidence of mucosal or bladder wall abnormality (Fig. 2).

**Voltage Measurements.** The potential difference across the complete circuit was measured (n = 5) as 3.5 ± 0.3 V (range, 3.1–3.9 V).

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**Table 1** Tissue concentrations of MMC µg/g wet tissue weight

<table>
<thead>
<tr>
<th>Tissue weight (g)</th>
<th>MMC µg/g wet tissue</th>
<th>Flux MMC µg/cm²/mina</th>
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<tbody>
<tr>
<td><strong>PD</strong></td>
<td><strong>EMDA</strong></td>
<td><strong>PD</strong></td>
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<tr>
<td>1</td>
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<tr>
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<td>3.213</td>
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<tr>
<td>13</td>
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</tr>
<tr>
<td>14</td>
<td>3.315</td>
<td>3.233</td>
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<tr>
<td><strong>Total</strong></td>
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</tr>
<tr>
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<tr>
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</tr>
<tr>
<td><strong>CV (%)</strong></td>
<td>9.0</td>
<td>8.4</td>
</tr>
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</table>

* Flux of MMC calculated by incorporating surface area of urothelium exposed to donor compartments.
Fig. 2. Photomicrographs of urothelium and subepithelial tissue of bladder wall samples that underwent trypan blue exclusion test (A, C, and E) or were stained with H&E (B, D, and F). The figure shows representative sections of control samples (A and B), post-PD (C and D), and post-EMDA (E and F).

Mass Spectrometry Data. Mass spectral analysis of MMC samples showed no chemical modification after EMDA (Fig. 3).

DISCUSSION

In patients with multifocal recurrent disease, the probability of recurrence after TUR and the possibility of stage progression have led widespread use of intravesical therapy (4–6). Controlled clinical trials show that, compared with patients treated by surgery alone, those receiving adjuvant intravesical chemotherapy of thiotepa, MMC, or doxorubicin have a reduced short-term incidence of tumor recurrence, although the benefit with intravesical chemotherapy is highly variable, ranging from −3 to 41% for thiotepa, 1 to 43% for MMC, and 5 to 39% for doxorubicin (18). Pharmacokinetic studies in patients with superficial bladder cancer demonstrate large intra- and intersubject variability in the target site exposure to MMC during intravesical therapy (7). In dogs, inhibitory concentrations are achieved in the urothelium (Ta tumors) in 100% of cases, in the lamina propria (T1 tumors) in 20%, and within the muscle layer (T2 tumors) in ~17% (8). One in vitro chemosensitivity study with human bladder tumors showed that MMC concentrations of 16, 25, and 43 g/ml are needed to produce a 90% inhibition of the labeling index in Ta, T1, and T2 tumors, respectively (9). Pharmacokinetic data in patients who received intravesical MMC therapy at the time of radical cystectomy showed nearly identical kinetic parameters in human compared with dog bladders (10). The lower efficacy of intravesical MMC therapy in invasive tumors compared with superficial tumors is due in part to the ineffective drug concentration in the deep tissues (7–9) and to higher drug concentration needed to inhibit the deeper tumors (19). The degree of drug penetration in the superficial and deeper tissues and the drug concentrations at various tissue depths in the bladder wall are therefore important determinants of therapeutic efficacy.

A major objective of the present study was to establish an appropriate diffusion model across a homogeneous barrier to study the transport of MMC into human bladder wall sections and to assess cell viability and stability of MMC under the chosen experimental conditions. Studies of this nature possess inherent logistical and technical
difficulties: limited availability of samples, transport of bladder tissue in a viable state, provision of an appropriate method of tissue homogenization to achieve optimal conditions for complete extraction of drug, avoiding the enzymatic and nonenzymatic degradation of MMC, and repeated standardization of HPLC columns to ensure accurate, reproducible measurements.

The experiments possess several interesting features. Standardization of HPLC columns with additional steps to prevent oxidation of MMC, although tedious, is not unique. However, use of viable, normal human bladder wall in a two-chambered cell to test transurethelial drug administration rates by different techniques is unique in the field of urology. The advantages of this approach are that the relatively small size of the tissue samples, the absence of a confusing influx of urine (volume and electrolytes), and lack of blood supply all reduce variability and permit a more accurate assessment of drug administration techniques. Obviously, the disadvantage is that each of the cited advantages removes the process one step further from clinical reality. The low voltages (3–4 V) used are clinically innocuous; the majority of current generators available in the United States for iontophoretic drug delivery are powered by 9–12-V batteries (20), and their circuitry can enhance this to as much as 60 V. Two recent articles describe intravesical EMDA of drugs with application of 15 mA current (21, 22), which would require approximately 25–30 V to complete the circuit through the highly resistive stratum corneum to the dispersive electrode sited on the skin.

Under the experimental conditions used, there is little doubt that EMDA-MMC enhances the administration rate of the drug and assists in its penetration through the urothelial barrier. This is intriguing because MMC is essentially nonionized in the pH range used, and therefore, accelerated transport was not induced by classical iontophoresis. The MMC crystals used in these experiments were supplied admixed with (ionized) NaCl (240 mg/10-mg vial), and it was postulated that electro-osmosis/electrophoresis would accelerate administration of MMC, which proved to be the case. The small observed differences between initial (mean 6.55 units) and postexperimental (mean 6.32 units post-PD and mean 6.36 units post-EMDA) pH values in the MMC solutions (Table 2) do not appear to be of pharmacological relevance.

We emphasize that neither the total nor relative quantities of MMC measured in these experiments will relate to levels obtained with clinical application of EMDA-MMC; the intensity of applied current will be greater, but surface areas will be increased by at least 100-fold (an intravesical volume of 100 ml exposes a surface area of ~105
cm$^2$), and the thickness of the distended bladder wall will be decreased.

A combination of a well-equipped laboratory and a well-organized “harvesting” team has demonstrated that the little-known electrokinetic phenomenon of electro-osmosis/electrophoresis reduces the variability and enhances administration rates of MMC 7-fold, compared with passive diffusion, into viable human bladder wall; the applied electric current causes no histological damage to tissue and no chemical modification of MMC. These interesting results are reason for further investigation using an analogous approach in an animal model to verify its applicability in vivo.

ACKNOWLEDGMENTS

Dr. Robert L. Stephen assisted with the electrochemistry. Prof. Massimo Castagnola provided guidance in the development of the pharmacokinetic model. Dr. Giuseppe D’Arcangelo performed mass spectrometry analyses. We thank Drs. Giuseppe O. Mele, Antonia Silecchia, Michele Valitutti, Marco Bitelli, and Angelo Mancini for help and support during the course of these studies, and Alessandra Giacomini for expert secretarial assistance.

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Cancer Res 1997;57:875-880.

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