

#1348. Concentration-Depth Profiles of Mitomycin-C in the Human Bladder Wall After Passive Diffusion, Thermochemotherapy, and Electromotive Drug Administration.

G. Leprini, R. Massoud, S. Dolci, P. Navarra, C. Verri, F. Torelli, F. Angelini, S.M. Di Stasi.

Depts of Surgery/Urology, Clinical Biochemistry, and Cell Biology, Tor Vergata University, Rome; Institute of Pharmacology, Catholic University, Rome; Operative Unit of Urologic Oncology, Policlinico Casilino, Rome; Italy

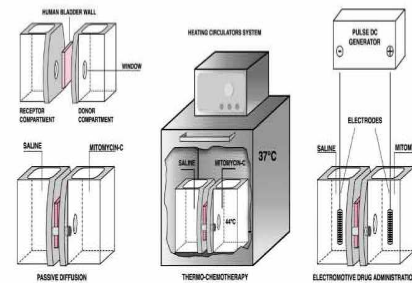
Objectives

- Device-assisted intravesical mitomycin-C (MMC), including electromotive drug administration (EMDA) and thermo-chemotherapy (TC), shows promise and offers the prospect of greater efficacy than passive diffusion (PD).
- Integration of drug delivery with tissue pharmacokinetics data provides a means to rational design of intravesical treatments.
- The objectives of these investigations were to compare concentration-depth profiles of MMC in the bladder wall after PD, TC and EMDA.

Materials and Methods

- During each experiment, three full thickness sections of viable human bladder wall were placed between the two chambers of individual diffusion cells, with urothelium exposed to donor compartments containing 40 mg of MMC in 100 ml water and with serosa-facing receptor compartments containing 100 ml of 0.9% NaCl solutions.
- Fifteen paired experiments were conducted over a 30 min period.
 - In TC experiments, the two chamber cells were placed in a 37 °C incubator with the donor compartments filled with heated MMC solutions at 44°C.
 - 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 direct current of 23 mA.
 - No electric current or hyperthermia were applied in PD control experiments.
- Bladder wall sections were cut serially into 40-mm slices parallel to the urothelium, the tissues were homogenized and supernatants analyzed by high-performance liquid chromatography for MMC concentration.

Diagram of experimental model for MMC delivery into bladder wall tissue samples



Concentration-depth profiles of MMC in bladder wall tissues following PD, TC or EMDA

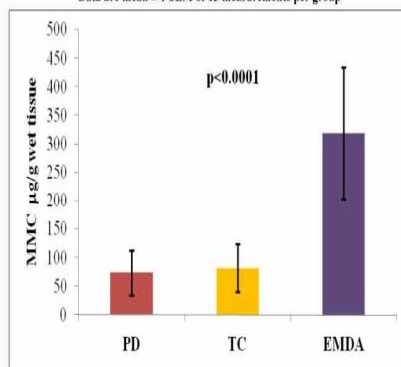
µg of MMC/mg of wet tissue ± SEM of 15 replicates per group

	PD	TC	EMDA	p value
Urothelium (80-200 µm)	53.06 ± 8.24	58.27 ± 8.82	207.99 ± 23.44	<0.001
Lamina propria (200-1200 µm)	18.09 ± 2.14	20.93 ± 3.20	85.34 ± 5.88	<0.001
Muscle layer (1200-4000 µm)	2.12 ± 0.33	2.42 ± 0.30	24.89 ± 3.64	<0.001

Non significant differences were found between PD and TC

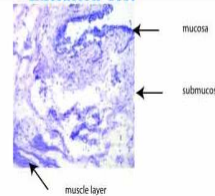
Comparison of Tissue MMC Area Under Curve Values Following PD, TC and EMDA

Data are mean ± 1 SEM of 15 measurements per group



Photomicrographs of Urothelium and Lamina Propria of Bladder Wall Samples Underwent Trypan Blue Exclusion Test

Exclusion Test



Conclusions

- EMDA significantly enhances MMC transport into all of the layers of the bladder wall, compared to both PD and TC.
- TC had no effect whatsoever on MMC transport into bladder wall tissues compared to PD.
- There is no evidence reported in existing literature of measurable specific action of both temperature and MMC in TC to our knowledge (what does what?).
- Further investigation in this respect may be necessary to clarify this important issue according to the results of our investigation.

