Introduction
to Electromotive Drug
Administration

EMDA®

Conventional administration of drugs for urologic pathologies is either by the systemic route or via intravesical instillation and subsequent passive diffusion into the urothelium. The well documented concerns with systemic administration are the small quantities of drug locating at the site of disease and side effects which are occasionally severe. The problems associated with conventional intravesical instillation are the slow rate of diffusion across the tightly knit urothelium and a fundamental inability to control the rate of drug administration.

Now, a controllable method for delivery of drugs into the bladder wall and prostatic urethra has been developed by PHYSION®. It comprises a non/invasive, painless local drug administration which provides greater clinical efficacy than does passive diffusion yet without the side effects seen with systemic administration.

EMDA® utilises an electrical current to impart an accelerated, directional (towards the tissue) movement of ionized drugs in an intravesical solution, which results in greater quantities of drugs being delivered to greater tissue depths than is achievable by passive diffusion. Furthermore, the rate of drug administration is fully controllable simply by varying the intensity of the electric current.
EMDA®
in bladder and prostate

EMDA®
a proven reliable drug delivery system
Therapeutic drug levels in the bladder and prostate are limited by toxic levels in other vital organs: kidneys, liver, heart, CNS, bone marrow.

Systemic side effects may be unpleasant, dangerous, or even lethal, as in the case of anticancer drugs.
Passive intravesical diffusion of drugs overcomes some of the inherent weaknesses of systemic administration, in that it achieves higher localized drug levels and less toxicity. But in the case of the bladder, one of the most impermeable of mammalian membranes, the rate of drug absorption during passive instillation has led to unacceptably long dwell times and variable drug levels at the pathogenic site. This, in turn, has led to the failure of a significant proportion of treatments, due to the unpredictable nature of drug dosages.

EMDA®, on the other hand, overcomes the problems associated with both systemic and local passive administration. In EMDA®, PHYSION® has successfully integrated all of the electrokinetic forces involved in drug transport. And, unlike any other form of conventional urologic drug administration, the physician controls the rate of drug administration simply by varying the intensity of the electric current.

- Iontophoresis: describes the active transport of ionized molecules into tissues by application of an electric current of appropriate polarity through a solution containing the ions to be delivered (For example: lidocaine).

- Electro-osmosis: describes the active transport of non-ionized solutes associated with the bulk transport of water that occurs with iontophoretic transport of other, ionized solutes. (For example: mitomycin C).

Using these mechanisms, it is possible to transport electrochemically almost any soluble drug, ionized or non-ionized. It is the integration of these two phenomena across a broad range of treatments that makes EMDA® so versatile and valuable to the urologist.
MECHANISM OF PASSIVE DIFFUSION

Photomicrographs of bladder wall sections of living dogs

Passive diffusion of methylene blue


Graphic representation of the passive diffusion mechanism
Photomicrographs of bladder wall sections of living dogs

EMDA® of methylene blue


Graphic representation of active transport with EMDA®
SYNOPSIS

LOCAL ANESTHETIC DRUGS
- Lidocaine (naropine 1,5)
  - biopsy/TURBT; BNI; TUIP

With more than 1500 treatments as a cover for invasive procedures reported in peer reviewed literature and a conservative 10.000 for routine procedure (oral communications), it can be stated that EMDA®/local anesthesia:
- provides adequate pain relief in 85-90% of patients
- has demonstrated no serious side effects; with an incidence < 0.3%
- is well accepted by 85% of patients
- may be performed as an outpatient procedure
- incurs less medical expense than the use of standard anesthetic techniques


LOCAL ANESTHETIC + ANTI-INFLAMMATORY DRUGS
- Lidocaine (and epinephrine) + dexamethasone
  - cystodistension for:
    - Urgency Frequency Syndrome (UFS)
    - [Syn: Interstitial Cystitis (IC)]

EMDA® local anesthesia and dexamethasone followed by cystodistension in patients with UFS has the following beneficial features:
- by any criterium the procedure of cystodistension itself is successfully achieved in almost 100% of patients
- approximately 50% of patients have durable (> 2 months) relief of symptoms
- no serious side effects have been reported
- it is always an outpatient procedure; ~ 1 hour of the patient's time
- patient preference for EMDA® as opposed to general anesthesia is marked.

SYNOPSIS

CANCER LOCALISING AGENTS

• Methylene blue + lidocaine (and epinephrine), Hexvix
  - localisation and resection of tumors

Cancerous tissue are less electrically resistive than normal tissues. Therefore, electrical current focuses on malignant regions and intravesical EMDA® of colored dyes stains cancerous regions more heavily than normal tissue. Thus:
  • EMDA®/methylene blue promotes significant penetration of dye into submucosa and muscularis layers
  • EMDA®/methylene blue promotes visibly deeper staining of cancerous urothelium as compared to normal urothelium

2. Fontanella UA, Rossi CA, Stephen RL. Localisation of bladder cancers with electric current and methylene blue. Abstract 16th World Congress on Endourology; NYC 1998.

CANCER TREATMENT DRUG

• Mitomycin C (MMC)
  - intravesical EMDA® therapy

intravesical EMDA®/anti-cancer drugs has intriguing prospects:
  • electro-osmosis of non-ionized MMC accelerates transports rates into tissues 6-7 fold as compared to passive diffusion
  • treatment times are reduced (20-25 min)
  • clinical studies with EMDA®/MMC in high risk bladder cancer are compelling

SYNOPSIS

CANCER LOCALISATION AND TREATMENT

- Mitoxantrone (+ local anesthetic drugs)
  - localization and resection of tumors

The combination of a colored anti-cancer agent and local anesthesia provides localisation and chemotherapy of cancerous areas, plus anesthetic cover for biopsy/TURBT; initial clinical studies show that:

- intravesical EMDA®/mitoxantrone causes visibly deeper staining of cancerous urothelium
- there is adequate anesthesia for biopsy/TURBT.


HYPERSPASTIC BLADDER: DRUGS

- Oxybutynin

Intravesical oxybutynin reputedly causes less side effects than an equivalent oral dose. Laboratory and clinical investigations have demonstrated that:

- EMDA® accelerates oxybutynin transport into the bladder wall
- EMDA®/oxybutynin temporarily relieves bladder spasms in most patients
- EMDA®/oxybutynin has a long term (week) beneficial effect in a few patients


- Capsaicin preceeded by local anesthesia

Intravesical capsaicin confers long term benefits upon the majority of patients with hyperspastic bladders but side effects, pain and/or sympathetic dysreflexia, are pronounced. EMDA®/local anesthesia prior to intravesical capsaicin:

- renders the procedure almost pain-free
- eliminates bladder spasms associated with treatment.


INFECTIVE RECALCITRANT CYSTITIS

- Netilmicin; gentamycin and other antibiotics

Infection in recalcitrant cystitis is usually subdued but rarely eliminated by conventional courses of antibiotics, however:

- Intravesical EMDA® antibiotics eliminates infection in 60-70% of patients with recalcitrant bacterial cystitis
- duration of freedom from infection is not yet clear
- treatment schedule remains tentative.

• While continuing to improve products and expand the clinical applications for electromotive drug delivery, PHYSION® makes available a singular service. Any drug or agent can be evaluated by PHYSION® for its electrochemical characteristics, clinical effects and side effects. Treatment protocols are created by PHYSION® after this assessment.

• As new protocols and indications are sure to be introduced, PHYSION® has organized an information service of all relevant studies for dissemination of data among clinicians. PHYSION® is committed to new applications, new drug, and new electrode designs and welcomes potential investigators.

• A complete bibliography (available on request), has been compiled to support the scientific base and the clinical features and benefits of EMDA®.
The **PHYSIONIZER® 30 MINI** is the most sophisticated and versatile machine available for electromotive drug administration. Powered by disposable batteries, it possesses a dedicated microprocessor which has operating instructions in five languages stored within it.

The **PHYSIONIZER® 30 MINI** incorporates the following features:
- Output current waveform is either pulse or dc.
- The intensity of output current is controlled by the operator (0-30 mA) with an accuracy within 1% ±0.2 mA of the readout.
- Maximum output voltage is 55 V dc.
- Numerous safety mechanisms, all designed to operate in a “fail safe” mode should there be any failure of any component.
- Several alarm system to warn the operator of low batteries, poor electrical connections; and the like.
- A minor “teaching program”, leading the operator through a sequential series of steps in order to implement a treatment.

Distributed by:
**PHYSION® S.r.l.**
The CE-DAS® UROGENICS® catheter electrode series is designed so that the intravesical section emitting electrical current lines along the diameter of a distended bladder, ensuring uniform distribution of electric current and thus, uniform drug delivery into the surrounding bladder wall. The catheter-electrodes are available in three types:

- **CE-DAS® UROGENICS®/Ag 9701**: The catheter section from the balloon to the tip is perforated by three pairs of holes thereby exposing the intravesical drug solution to the spiral electrode contained within the catheter. This equipment is used for all therapies confined solely to the bladder wall.

- **CE-DAS® UROGENICS®/Ag 9608c**: This catheter-electrode, for use in male patients only, is perforated by multiple holes running from the region of the prostatic urethra to the intravesical tip of the catheter. It is employed for all drugs to be delivered to the bladder and prostatic urethra and for administration of local anesthetic drugs in all procedures involving the passage of rigid endoscopes into the bladder.

- **CE-DAS® UROGENICS®/Ag 9903**: This catheter-electrode, for use in male patients only, is perforated by three pairs of holes in correspondence of the prostatic urethra. It is employed for all drugs to be delivered to the prostate and prostatic urethra.
The **dispersive electrode** is made of a stainless steel grid sandwiched between layers of non conductive absorbent cellulosic foam and covered with suede. A couple of dispersive electrodes placed upon a layer of ECG gel covering an area of unblemished, thoroughly degreased with alcohol skin on the abdomen permits application of dc 15-30 mA for 15-45 minutes with minimum to absent thermal damage to the skin.

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## LIST OF PRODUCTS

System consists of a current generator, catheter-electrodes and accessories. The system components are designed to function interdependently.

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<td>PHYSIONIZER 30 N2 current generator for EMDA 0-30 mA</td>
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<td>CT-DAS/500 Ag transcutaneous electrode 5 cm² for EMDA andrological therapies</td>
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Manufacturer
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• Notified Body: IMQ - Istituto Italiano del Marchio di Qualità
• Notified Body Number: 0051