

Intravesical electromotive drug administration

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ABSTRACT. "Iontophoresis" is the common term used to define the active transport of ionic molecules across biologic tissues under the influence of an electric field. The term "electro-osmosis" defines the subsequent transport of the solvent. The term "electrophoresis" indicates the transport of a solution and a solute, by means of an electric current, independently of the electric charge of the solute. The three terms: iontophoresis, electro-osmosis and electrophoresis are now usually included in the following few words: "Electromotive Drug Administration" (EMDA), and indicate the phenomena involved in drug transport across the biologic membranes, with the application of an electric current. In urology, EMDA has been used in different fields of application, as uro-oncology, neuro-urology, andrology and infective urological diseases. All the studies conducted, showed that EMDA is more effective than intravesical passive drug diffusion, without inducing any local or systemic side-effects. The basic premises of EMDA, as a greater knowledge of physical and chemical properties of the bladder wall and a more comprehensive knowledge of the drug employed, allow us to perform a non-empiric intravesical treatment. Repeatability of the results is one of the major concerns, which makes this methodology a really scientific treatment modality.

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INTRODUCTION

"Iontophoresis" is the common term used to define "the active transport of ionic molecules across tissues under the influence of an electric field" (1).

The intuition to use electric current to allow trans-cutaneous drug penetration is probably due to Veratti in 1747 (2). The concept of iontophoresis was described for the first time in the middle of the 18th century; however, only after the experiment by

Leduc in 1908, the researchers realized the importance of the differences between positive and negative ions and adopted this technique for therapeutic uses. In the latest years, iontophoresis has been used for local anesthesia of the skin (3), to administer corticosteroids to joints and to tendons involved in inflammatory processes (4), and for regular transcutaneous administration of drugs (5). One of the most interesting use of this technique is the local administration of pilocarpine to cause sweating in the diagnosis of the cystic fibrosis (6).

MAIN PRINCIPLES

1. The drugs to administer should be ionised and present in aqueous solution (water, hydrogel);
2. Positive ions are driven back from the anode and the negative ones are driven back from the cathode in the underneath tissues;
3. The total quantity of the transported ions is directly proportional to the total electric current applied, corresponding to the product of the power for the time:

$$\sum J_i \text{ oc } It$$

4. The transport of specific ions by means of an electric current is proportional to the product of concentration for the mobility and for the charges (valence) of a specific ion, and inversely proportional to the concentrations, mobility and valences of all the other ions present in the solution.
5. The transport of ions by means of an electric current is described by the equation of Nernst-Planck, establishing as follows: when there are both a concentration gradient and an electric field, the ionic flow is the linear sum of the flows that would derive from the following relation:

$$J_i = - D_i \frac{\Delta C_i}{\Delta x} + D_i \frac{z e E C_i}{K T}$$

where D_i is the coefficient of diffusion, C_i is the difference of the ionic concentration on a distance x ; z is the valence and e is the electron charge of the ion. E is the electrical field, K is the constant of Boltzmann and T is the temperature. The first expression on the right of the equation is the First Law of Diffusion by Fick within a solution. Among these five principles, the latter (5) is the most important. Another important aspect is the administration of the drug and that of its solvent by iontophoresis, and the comparison that can be made with the administration of the same drug and its solvent by injections. The concentrations of drugs in ampoule is rarely higher than 4-5%, because when the drug is injected in tissues (contrary to the injection in bloodstream), the hypertonic solutions (>5%) could dissect and damage the tissue at the level of the injected sites. For this reason the majority of solutions are composed for 95% by a solvent (water), with drug and some excipients up to 100%.

With the iontophoresis, the ionised molecules are injected with a small quantity of water accompanying the ionised drugs, producing a water film surrounding the ionised molecules themselves. This phenomenon is known as "electro-osmosis".

ELECTRO-OSMOSIS AND ELECTROPHORESIS

The iontophoresis is the transport of polar charged ions by Coulomb attraction (or repulsion); the electro-osmosis is the subsequent transport of the solvent. These two phenomena lead to a third transport modality: the "electrophoresis". If an electric field is applied to a solution containing ions and electric flows, a part of water joins the ions movement. If in the same solution there are not completely ionised solutes, small quantities of these solutes will be transported with the movement of the water. This phenomenon is called electrophoresis and can be defined as the transport of a solution and of a solute by

means of an electric field, independently on the electric charge of the solute. It also can be identified as: "entrainment of the solvent".

The three terms: iontophoresis, electro-osmosis and electrophoresis are now usually included in the following few words: "Electromotive Drug Administration" (EMDA).

THE BLADDER

The bladder is basically a container whose physiologic function is to keep great quantities of urine until the subject decides to release them. Contents and chemical characteristics of the urine can vary depending on diet, daily intake of fluids, particular diseases, and also climate factors.

Moreover, in the presence of a pH slightly acid (pH: 5.0-6.0), urine are filtered as hypertonic solution containing many solutes.

Some of these solutes are electrolytes: Na^+ , K^+ , Cl^- , Ca^{2+} . Others are phosphates and ammonium that block the hydrogen ions, and further components are urea, creatinine, urates, most of which are in the ionised status. The bladder mucosae (urothelium) is similar to a paling, composed from 6 to 8 layers of cells. The system connecting these cells among them, makes the urothelium almost completely impermeable to all of the solutes, both ionised and normal, water included.

So, in reference to the Nernst-Planck equation, D_i , the diffusion coefficient, is effectively zero.

Any bladder pathology may alter the above-described condition. Presence of bladder tumors may modify the integrity of the urothelium in the tumor's site, thus allowing the reabsorption of urinary solutes or the absorption of drugs introduced in the bladder. A similar situation occurs with an infected cystitis.

ELECTROMOTIVE DRUGS ADMINISTRATION: BASIC PRINCIPLES

If a solution containing a ionised drug (D^+) and its counter-ion (A^-) is introduced in the

bladder by means of a catheter, with the addition of an electric current, two events could happen: if a sample drug has positive polarity, a positive electrode will be positioned on the top of the urethral catheter and the electrode with negative polarity will be positioned on an area of the skin (the abdomen). Two phenomena are supposed to happen:

1. Probably, some molecules on the surface of urothelial cells line up, so that the electrical poles are opposite;
2. The repulsion among these two charges creates, obviously, a space between the cells, thus facilitating the passage of water and solute;
3. Commonly, the ions with positive charge (D^+) are rejected soon from the anode contained in the urethral catheter to the underneath layers of the urothelium.

To summarize, the use of electricity in a ion solution transforms the urothelium from impermeable to permeable to solutes and water.

The correct use of the polarity by the electrode positioned in the bladder will significantly increase the transport of ions across the bladder's walls, even ten or more times.

On the contrary, if the chosen ion has negative polarity, the use of the negative electrode will give the same result.

INTRAVESICAL INSTILLATION BY IONTOPHORESIS

The bigger the drug's volume solution, the larger the bladder's surface, and much thinner will be the urothelium: all these elements are positive for intravesical therapies by means of EMDA. When we perform an electromotive drug administration, we have to insert into the bladder a urethral catheter with a balloon containing 5-10 ml of water, whose diameter is about 1.4 cm. If half of the small balloon is positioned on the bladder neck, a long part equal to 1.4 cm projects into the bladder itself. Moreover, the distal part of the catheter, which is about 2.0 cm, has to be

considered. Thus, we obtain a long body equal to 3.4 cm projecting into the bladder.

If we put into the bladder a volume solution of 50 ml, we get a spheroid whose diameter is 4.6 cm. In this case, any part of the catheter is very close to the bladder walls and an electric interruption would occur, so the administration of drugs would take place only in that area.

On the contrary, a volume solution of 100 ml determines a bladder spheroid of 6 cm and a surface equal to 100-105 cm². This diameter would assure a uniform distribution of electricity and its use up to 30 mA.

DRUGS

Generally drugs selected for the EMDA must present the following characteristics: 1) they have to be ionised; 2) they must be kept in a water mean: water or hydrogel.

Drug concentration diluted in 50-100 ml solutions should respect two rules that are often in conflict one with the other: 1) the number of the molecules should be as sufficient as to properly conduct electricity; 2) the concentrations of drugs must not exceed the highest values allowed, otherwise useless side-effects should be considered.

TECHNOLOGY

The current generator (Figure 1) is equipped with rechargeable batteries; it produces con-

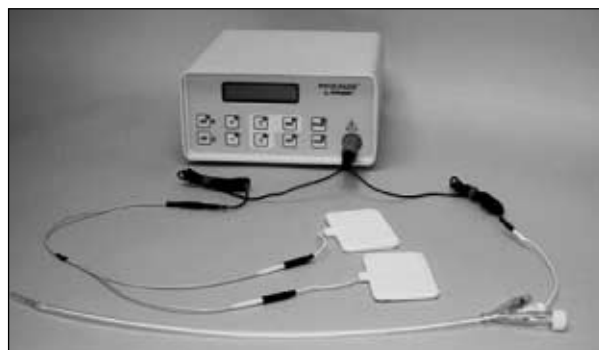


Figure 1 - The current generator.

tinuous current in a variable and easily-verifiable manner, up to a maximum of 30 mA and it also shows the user all the procedures as follows: a) choice of electric current (mA); b) choice of time (min); c) start of therapy; d) end and switching off.

The machine has also an alarm signal for not complete or interrupted circuits; a lightning signal shows when the battery is discharged, another signal shows when the battery is in charge, an automatic track of lights shows slowly the increasing amplitude of the applied current, and an automatic track of lights with an alarm system indicates the end of the treatment.

ACTIVE ELECTRODES

The active electrodes are placed on the top of the urethral catheter and perfectly fit for all sizes (14-22F). They are made of two conductive materials, silver and steel, to satisfy all therapeutic needs. The intravesical section of this electrode is spiral shaped in order to develop an area of contact as large as possible with the drug solution within the bladder.

THE DISPERSIVE ELECTRODE

The dispersive electrode (made of various materials) is positioned on the skin of the patient and fixed on a rubber conductive plate so as to allow a uniform distribution of electricity on all the surface involved.

CONCLUSIONS

Several laboratory and clinical studies have been performed with EMDA in urology, in different fields of application as uro-oncology, neuro-urology, andrology and infective urological diseases (7-26). All these studies confirmed that EMDA is superior in terms of subjective and objective results to intravesical drug passive diffusion, without producing any local or systemic side-effects. Further-

more, EMDA has been employed also for anesthetic purposes, as it can allow the transport of drugs to anesthetize the bladder before performing different intravesical treatments (27, 28). The basic premises of EMDA, as a greater knowledge of physical and chemical properties of the bladder wall and a more comprehensive knowledge of the employed drug solutions, allow us to perform a non-empiric intravesical treatment. Repeatability of the results is one of the major concerns, which makes this methodology a really scientific treatment modality.

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