CORNEAL IONTOPHORESIS APPLIED TO CXL PROCEDURE
IONTOPHORESIS (from iōntos=ion and phòresis = to move across, ions moving across) consists in the one way movement of charged molecules throughout the tissue that needs to be treated, thanks to a low intensity electrical field applied.

Several drugs can be transported within the tissue that needs to be treated.

Polarized drugs are applied onto the electrodes, based on their polarity: positively charged molecules are applied on the positive electrode, while negatively charged molecules are applied on the negative electrode. On either cases, the other electrode is applied nearby the area that will be treated.

It allows to reach concentrations superior than those obtained using passive permeation (up to 50-100 folds)
HOW IONTOPHORESESIS WORKS
In 1905, Leduc investigated the transdermal transport of strychnine (+) using iontophoresis.
Iontophoresis represents today the most commonly used technique for the introduction of a drug through the epidermis.

- It allows to directly treat the area affected by pain from rheumatic pathologies (arthritis, sciatic, low back pain, etc.) and also by other pathologies such as cellulites, fat deposits, etc, obtaining a rapid therapeutic effect.

- The intake of drugs orally is avoided, thus minimizing any systemic side effects.

- Acyclovir
APPLICATIONS IN DERMATOLOGY AND OPHTHALMOLOGY

Lidosite Lidocaine patch (Vyteris)

Iontopatch Dexamethasone (Teikoku Pharma)

Ionsys Fentanyl patch (Incline therapeutics)

Eyegate Trans-scleral device (Eyegate Pharma) Phase III
Iontophoresis in ophthalmology has been investigated for few years now, and several publications have been presented. For example, the work of Frucht-Pery et al. on the transcorneal administration of dexamethasone or the studies performed in the US by the Company Eye-Gate.
Results: 1 to 20 of 180

   PMID: 22517211 [PubMed - in process]
   Related citations

2. Gaudana RJ, Gokulgandhi MR, Boddu SH, Mitra AK.
   PMID: 22493694 [PubMed - in process]
   Related citations

3. Chopra P, Hao J, Li SK.
   PMID: 22366336 [PubMed - in process]
   Related citations

4. He L, Wendt M, Glasser A.
   PMID: 22125278 [PubMed - indexed for MEDLINE]
   Related citations
[Fundamental and experimental studies on iontophoresis of vitamin B2 (FMN & FA)].

KANAIZUKA D.
PMID: 13751115 [PubMed - indexed for MEDLINE]

[Behavior of hydrogen ion concentration in iontophoresis with unbuffered iodide solutions and with natural and synthetic spring-water products from Bad Hall iodine mineral springs (Upper Austria)].

POMMER H.
PMID: 13339652 [PubMed - indexed for MEDLINE]

Influence of iontophoresis on the permeability of the excised cornea.

DYSON C.
PMID: 15396659 [PubMed - indexed for MEDLINE]
- 17 patients undergoing PKP
- Administration of methylprednisolone (MP), 62.5 mg/ml using the Eyegate system, by applying 1.5 mA electrical current for 4 minutes
- 1 application/day for 3 days

- No significant side effects were observed
FACTORS AFFECTING IONTOPHORESIS

\[ J_{\text{TOT}} = \left[ \left( \frac{I}{AF} \right) \frac{u_{\text{drug}}}{\sum \zeta u_i A_i} + \frac{V_{A \rightarrow C}}{c_{\text{drug}}} \right] \]

Main factors are:

- Physico-chemical properties of molecules:
  - Molecular dimensions
  - Charge
  - Concentration \((C_{\text{drug}})\)

- Drug delivery system characteristics:
  - Diluents
  - Buffers (competitive ions, \(C_i\))

- Current intensity \((I)\)

- Treatment time
SPECIFICITY OF APPLICATIONS THROUGH THE CORNEA

Corneal epithelium is a natural barrier to the penetration of macromolecules
- Up to 150 kDa for the sclera vs 1 kDa for the cornea

Cornea is sensitive to electrical currents
- 5 mA/cm² for the sclera vs 1 mA/cm² for the cornea
- Cornea contains nervous fibres

3 ways to enhance stromal penetration

- Removal of the epithelium (RICROLIN®): long treatment time, painful and possible side effects
- Use of enhancers (RICROLIN® TE): long treatment time
- IONTOPHORESIS
RIBOFLAVIN: THE PERFECT CANDIDATE

✓ low molecular weight (376.36 Da + Ph⁻)
✓ Negatively charged at physiological pH
✓ Highly soluble in water
Treatment in ocular iontophoresis is done through the application of two electrodes connected to a power generator.

The main electrode (-) is contained in a rubber ring that is applied on top of the cornea that needs to be treated; the other electrode (+) is a patch that is positioned on the patient forehead.
CORNEAL IONTOPHORESIS
Current flux (low intensity) between the two electrodes allows a specific formulation of riboflavin (RICROLIN®+), specifically formulated for iontophoresis application, to rapidly penetrate the corneal stroma, through the intact epithelium (no removal of the epithelium).
Current intensity that originates from the iontophoresis generator is 1 A/min (5 min treatment).
The supplied current is continuous and battery powered.
Treatment duration is automatically monitored by a software within the generator.
When the 5 min treatment are reached, the iontophoresis is automatically stopped.
IONTOPHORESIS: TREATMENT OBJECTIVES

- Total corneal impregnation in 5’ with EPI-ON technique
- Safe, no side effects
- More reproducible stromal Riboflavin concentration
- Increased patient compliance
CORNEAL IONTOPHORESIS FOR CXL: STUDIES

✓ STRESS STRAIN EFFECT
Prof. Paolo VINCIGUERRA, PROF. Eberhard SPOERL
ARVO 2012, XXX ESCRS 2012

✓ RIBOFLAVIN PERMEATION
Prof. François MALECAZE
XXX ESCRS 2012

✓ IMMUNOHISTOLOGICAL ANALYSIS
Rita MENCUCCI, MD
XXX ESCRS 2012
Comparative Stress Strain Measurements Of Human Corneas After Transepithelial UV-A Induced Cross-linking: Impregnation With Iontophoresis, Different Riboflavin Solutions And Irradiance Power

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Purpose: To compare the change in biomechanical properties of human cadaver corneas after standard transepithelial cross-linking (CXL-TE) versus CXL-TE using iontophoresis, different solutions and UV-A power.

Methods: Twelve human cadaver corneas were divided in 4 different groups according to methods of impregnations and UV-A power used: Group A (three corneas, treated with CXL-TE using an irradiance power of 3 mW/cm² for 30 minutes and riboflavin solution with 15 % dextrane and Tromethamine); Group B (three corneas treated with CXL-TE using an irradiance power of 3 mW/cm² for 30 minutes and riboflavin solution with Tromethamine); Group C (three corneas treated with CXL-TE using an irradiance power of 10 mW/cm² for 10 minutes and riboflavin solution with Tromethamine); Group D (three corneas treated with an irradiance power of 10 mW/cm² for 10 minutes, the impregnation was obtained with the aid of iontophoresis and a riboflavin solution with Tromethamine). After cross-linking, static stress-strain measurements of the corneas were performed using a microcomputer-controlled biomaterial tester with a pre-stress of 5x10⁶ Pa. Stress strain curves were fitted with an exponential function and the Young’s modulus was calculated. Thickness of the corneas was measured with an ultrasound pachymeter.

Results: Stress strain measurement showed an increase in corneal rigidity after cross-linking compared to standard CXL-TE, indicated by a rise in strain and in Young’s modulus calculated at 10% strain. Considering group A as standard of comparison, group B showed an increase by a factor of 1.45, group C by a factor of 1.26, group D by a factor of 1.81. Mean corneal thickness was: 627 µm for group A, 628 µm for group B, 527 µm for group C, 665 µm for group D.

Conclusions: CXL-TE is able to increase mechanical rigidity in human corneas in selected groups. Stress strain results showed a maximal effect in the iontophoresis group, probably due to the increased riboflavin concentration in the stroma. Stress strain measurement in the other groups showed a better results using riboflavin solution without dextrane and 3 mW/cm² of irradiance power.