Current Practice in Ophthalmology

Eye drops
- Multiple drops a day
- Multiple bottles a time
Problems with Eye Drops

- Non-compliance
- Suboptimal drug absorption
- Side effects
Optimize Ocular Drug Delivery

- Non-invasive
- Sustained release
- Multiple drugs
First goal:

- No eye drops before or after cataract surgery
  - Dropless Cataract Surgery
Cataract Surgery

Number of cataract surgeries in NL
Post surgery:
- 4 drops a day
- 2 different drops
- Tempering schemes
- For 4 weeks
Why the Eye Drops?

To prevent:
- an inflammation
- an infection

Cystoid Macular Edema
~4% of the surgeries!
Which Drug is Best?

Combination treatment:
- NSAIDs (non-steroidal anti-inflammatory drugs)
- Corticosteroids is more effective compared to single drug treatment
Unique method to deliver drugs: the ocular coil

- Non-invasive
- Easy to insert
- Easy to remove

Does not affect vision

Slippery coating to increase comfort

Capacity to contain multiple drugs

Sustained drug delivery up to one month
The Ocular Coil
Preparations for the Animal Study - License

**1st study:**
Quantification of drugs by Raman spectroscopy

**2nd study:**
Pharmacokinetic study using Raman spectroscopy

**2nd study:**
Pharmacokinetic study using HPLC

**3rd study:**
Efficacy study

- Positive results
- Negative results

- Ethical committee Maastricht
  - Application (intern) >12 months
  - Application to government 2 months

- ~4 months for a working protocol
Hurdles during the preparation

- Laboratory was not suitable for animal experiments
  - Animal lab needed laser safety regulations
  - Lab needed a new coating
  - Relocate the equipment to the new lab
  - Transport regulations for the animals needed to be created

- Housing of the animals
  - Limited number of animals could be housed due to the large number of experiments performed in the UM
1st Animal study:

1st study: Quantification of drugs by Raman spectroscopy

Positive results

2nd study: Pharmacokinetic study using Raman spectroscopy

2nd study: Pharmacokinetic study using HPLC

Negative results

3rd study: Efficacy study

Positive results
Prof. dr. C.V. Raman
- 1930 Nobel prize physics

Energy in = energy out

Energy in > energy out (Stokes)

Energy in < energy out (anti-Stokes)

Only happens in $1 \times 10^9$ or $1 \times 10^{10}$ times
Quantification of Raman Spectroscopy

Invasive sampling, purification, and HPLC analysis

VS.

In vivo, non-invasive, and real-time Raman detection
Aqueous Humor

◆ Fluid in the anterior part of the eye:
  – regulates the IOP
  – provides nutrients to the cornea
  – removal of waste products
Confocal Raman spectroscopy: Evaluation of a non-invasive technique for the detection of topically applied ketorolac tromethamine in vitro and in vivo

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Animal Study - License

1st study: Quantification of drugs by Raman spectroscopy

2nd study: Pharmacokinetic study using Raman spectroscopy

Positive results

2nd study: Pharmacokinetic study using HPLC

Negative results

3rd study: Efficacy study

Positive results

Negative results
Drug Loading in the Ocular Coil

- Manual filling of the ocular coil
- Ketorolac tromethamine loaded microspheres
  - 3 mg microspheres
    - ~0.9 mg ketorolac
  - 1 eye drop (50µL) = ~2.5 mg ketorolac (0.5% solution)

From eye drops it is known that > 95% of one drop is spilled!
<0.125 mg of drug is used!
Development of an *in vitro* Lacrimal System

Flow in, 2µL/min

Flow out, 2µL/min

Reservoir
Results

- Cumulative final concentration = 0.94 mg ± 0.03 mg
- Release in 28 days: 69.9% ± 4.8%
- Ketorolac left in the ocular coil: 30.1% ± 4.8%

n=4 coils
Animal studies

- Pharmacokinetic study
- Efficacy study

Eye drops

9 rabbits:
3x a day eye drops

Ocular coil

9 rabbits:
1 ocular coil
Animal studies

◆ Pharmacokinetic study
  – Tears
  – Aqueous humour
  – Blood

Eye drops

9 rabbits:
3x a day eye drops

Ocular coil

9 rabbits:
1 ocular coil
Pharmacokinetics in Tears

<table>
<thead>
<tr>
<th>Duration</th>
<th>Tears Concentration (ng/μL)</th>
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<tbody>
<tr>
<td>4 hours</td>
<td>1</td>
</tr>
<tr>
<td>24 hours</td>
<td>10</td>
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<tr>
<td>4 days</td>
<td>100</td>
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<tr>
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<td>1,000</td>
</tr>
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<td>28 days</td>
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</table>

- **Eye drops**
- **Ocular coil**
Pharmacokinetics in Tears

- **Tea r s**
- **E y e d r o p s**
- **O c u l a r c o i l**

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Pharmacokinetics in Aqueous Humor

Aqueous humor

concentration (ng/mL)

4 hours
24 hours
4 days
7 days
28 days

Ocular coil
Eye drops
Pharmacokinetics in Aqueous Humor

Aqueous humor

Concentration (ng/mL)

4 hours
24 hours
4 days
7 days
28 days

10
100
1,000
10,000

Ocular coil
Eye drops
Pharmacokinetics in Blood

Plasma concentration (ng/mL)

- Ocular coil
- Eye drops

4 hours 24 hours 4 days 7 days 28 days

Concentration (ng/mL)
Pharmacokinetics in Blood

Plasma

- Ocular coil
- Eye drops

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- 4 hours: Low concentration
- 24 hours: Intermediate concentration
- 4 days: Stable concentration
- 7 days: Stable concentration
- 28 days: Stable concentration

Ocular coil shows a faster decline in concentration compared to eye drops.
Pharmacokinetics Summary

Pharmacokinetics
◆ Ketorolac is released for 28 days
  – *In vitro*
  – *In vivo* (tears)
◆ In the eye, the concentration is below detection levels
  – 7 days in aqueous humour
  – 4 days in blood

Question
◆ Is it effective?
Animal studies

- Pharmacokinetic study
- Efficacy study

8 rabbits:
No treatment

8 rabbits:
3x a day eye drops

8 rabbits:
1 ocular coil
Inflammation Mechanism

- Increased production of AH
- Blood vessel breakdown
- Cytokine recruitment:
  - IL-6
  - TNF-α

Intra Ocular Pressure (IOP)

Time

0 4h 8h 24h 4d 7d 14d 21d

Control
Eye drops
Ocular coil

NSAIDs

↑PGE₂
Total Protein Concentration

Protein concentration in AH

- Control
- Eye drops
- Ocular coil
We are sorry

- Not all samples have been analyzed.
In 4 years we were able to develop and test a new drug delivery device.

Release of ketorolac by the ocular coil is higher in aqueous humor 4h after insertion compared to eye drops.

Drug release rapidly decreases:
- Aqueous humor: 7 days too low for detection
- Plasma: 4 days too low for detection

Analysis of the samples from the animal study should show whether the ocular coil is more/equally/less effective compared to eye drops.
Thank you

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