EYES WIDE SHUT!

Time to review handling of autologous serum eyedrops in UZ Leuven

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Introduction

Since 1999, autologous serum eyedrops (ASE) are used in the treatment of persistent corneal epithelial defects, which are caused by a variety of diseases (such as Sjögren's syndrome, GvHD, Rheumatoid arthritis, drug toxicity, diabetes mellitus, …). Patients who suffer from CED do not have sufficient tears to support epithelialization. ASE is thought to act on corneal epithelium regeneration due to the fact that most epithelial-promoting growth factors (such as fibronectin, epidermal growth factor, transforming growth factor-β) next to vitamin A and albumin are present in serum. ASE is considered safe, as the risk for allergic reactions or infectious complications is decreased.

In UZ Leuven, ASEs are prepared by a protocol by the hospital pharmacy after centrifugation (3000 x g during 10 min) of patients' whole blood in the hospital lab. Serum is diluted with normal saline (typically in a 1:4 ratio) in a horizontal airflow. The diluted solution is aliquoted in 10 mL eyedrop bottles, and kept after opening for one week at 4°C. Unopenend bottles are stored for 1 month in the fridge or for 2 months when frozen at -20°C.

The aim of this study is to evaluate **the appropriateness of the current preparation protocol of ASEs** and **to evaluate the potential impact of chronic medication intake** by patients treated with ASE on corneal epithelialization.

All details associated with this study is provided in the abstract.

Methods

1) Optimalisation of current ASE protocol based on **literature search Pubmed** using 'autologous serum, autologous serum eyedrops, preparation, procedure and corneal defects' as search terms.
2) **Retrospective review of all patients treated with ASE** in UZ Leuven during 2013: demographic data, data on medical history, opthalmological history, details on ASE use.
3) Evaluation of potential corneal toxicity of chronic systemic medication based on **physicochemical characteristics**
4) **Measurement of pH** of serum and of prepared ASE

Results (1) – Optimization of ASE protocol

Necessary changes:

- optimal centrifugation parameters: 3000 g x 15 min
- protection from UV light
- dilution with BSS
- filtration using 0.22 µ filters
- storing during 3 months at -20 °C
- preparation in vertical air flow
- extend viral screening before preparation (HIV, HBV, HCV, syphilis)
- microbiological screening after preparation?

Results (2) – Details on patients and ASE use

(NM = not measured)

No.	M/F	Age	ASE use		pH	
			Duration of ASE treatment	Frequency	Un diluted serum	Diluted ASE
1	F	77	>3 yrs	6 x/day	7.682	7.508
2	F	78	>2 yrs	6x /day	NM	NM
3	M	35	>4yrs	Once per hour	7.548	7.484
4	F	75	>3 yrs	Once per hour	7.525	7.489
5	F	37	>4 yrs	Once per 2 hrs	NM	NM
6	M	80	>3 yrs	6x/day	7.512	7.447
7	F	69	>3 yrs	6x/day	7.482	7.422
8	F	44	>3yrs	6x/day	NM	NM
9	F	74	>2yrs	6x/day	7.644	7.522

Results (3) - Chronic medication intake and potential corneal damage

In total, 75 drugs were taken systemically by the 9 reviewed patients treated with ASE, which is more than 8 drugs per patient. **Drugs ranged from sedatives, antibiotics, corticosteroids, calciumsupplements, antihypertensives, vitamins, and NSAIDs to immunosuppresants such as cyclosporine and methotrexate,, anti-epileptics such as carbamazepine, and new agents such as rivaroxaban**. Nothing is known in literature on their potential corneal effects, when bringing them several times a day on the eye. The only advice that is given is that antihypertensives should be avoided in order to maintain eye pressure.
Based on an extensive physicochemical evaluation, drugs with a low molecular weight (< 500 Da) and a lipophilic character (positive octanol/water partition coefficient) were not considered as agents inducing potential corneal toxicity. These agents will also reach most parts of the eye while crossing easily the blood/opthalmological barrier. Also hydrophilic agents (negative octanol/water partition coefficient) were excluded as it is presumed that these agents will be rapidly removed via tear formation. The remaining agents with a very high octanol/water partition coefficient (Log P > 4) were considered as potentially dangerous, as these may accumulate in the first eye barrier, i.e. the corneal epithelium, without clearance or penetration to the deeper parts of the eye. **Accumulation of these drugs to higher than usual systemic concentrations may result in toxicity, or remaining keratoconjunctivitis sicca. Agents fulfilling this criterium were calcipotriol, cholecalciferol, cyclosporine, oestradiol, irbesartan and montelukast.** It is not clear from literature review if protein binding is an important parameter to consider, as at the level of the eye conformational changes in albumin may occur, changing expected protein binding.

Lessons learnt and Future Perspectives

- 9 patients are treated on a longterm basis with ASE, ASEs are used **very frequently**
- current ASE **preparation protocol should be adapted** in order to protect the preparing pharmacist and to increase quality of ASE
- **pH** is only slightly deviating from physiological pH. After dilution pH is approaching physiological pH.
- ASE patients are using **a lot of chronic systemic medication**
- To avoid corneal epithelium damage, very lipophilic drugs should be avoided. Another option is **to withdraw these agents few days before phlebotomy** (based on their halflives), this will not lead to significant side effects
- Nothing is known on the impact of **potential metabolites** formed by chemical degradation when stored for one week in the fridge
- Future projects measuring **vitreal concentrations** of chronic systemic medication in patients undergoing vitrectomy might add important information in the impact of this medication.