APPENDIX II: Corneal Penetration and Median Effective Dose of Antiviral Agents

Median Effective Dose (ED50)

The median effective dose is a statistically derived dose of drug expected to produce a certain effect in 50% of test organisms. Topical and oral antivirals are both capable of achieving adequate corneal tissue levels. These levels are measured indirectly by the aqueous humor concentration. Drugs in the aqueous humor equilibrate with drugs in the surrounding tissue, including the cornea. Below is a list of established ED50 levels in the published literature.

Topical Antiviral Agents: Corneal Tissue Penetration (Aqueous Concentration)

TRIFLURIDINE ED50: 0.75–1.81 µM[1] (plaque reduction method) 15–45 µM[1] (yield reduction method) or ED50: 0.2–1.7 µg/ml[2]			
Formulation	**Dosage**	**Therapeutic Level (aqueous humor)****	**Model**
1% Solution	1 drop Q 10 minutes in OR for 4 doses	"Unhealthy" epithelium* 6.4–43.9 µM "Healthy" epithelium 6.4–43.9 µM	Human[3]
1% Solution	1 drop Q 30 minutes preoperatively for 5 doses	No epithelial defect Not detected (sensitivity 2µM or 0.5 mg/ml)	Human[4]
1% Solution	1 drop Q 5 minutes for 4 doses	1. No epithelial defect Mean: 6 µg/ml 2. Dendrite Mean: 37 µg/ml	Rabbit[5]
ACYCLOVIR ED50: 0.1–1.6 µM[6-11] or ED50: 120–240 ng/ml[10]			
Formulation	**Dosage**	**Therapeutic Level (aqueous humor)****	**Model**
3% Ointment	4 times daily	Dendrite Mean: 308 ng/ml (s.d.: 146)	Rabbit[10]
3% Ointment	Q 4–6 hours for 4–6 doses prior to surgery	Normal cornea 1.7 µg/ml (7.5 µm) Range: (1.5–1.9 mg/ml)	Human[4]

GANCICLOVIR ED50: 0.2–0.5 μM[7] (plaque reduction method)			
Formulation	**Dosage**	**Therapeutic Level (aqueous humor)****	**Model**
0.2% Gel	4 times daily for 10 days	Dendrite 394 ng/ml (s.d.: 419)	Rabbit[10]
0.05% Gel	4 times daily for 10 days	Dendrite 18 ng/ml (s.d.: .25)	Rabbit[10]
3% Ganciclovir salt in ointment	Q 5 hours for 6 doses	Normal cornea Mean: 4.73 μM (2 hours post administration) to 1.84 μM (3 hours post administration)	Rabbit[12]

* The term "unhealthy epithelium" is quoted directly from the cited study, in which epithelial "health" was graded from poor to fair.
** Therapeutic levels are listed as in the original cited reports.

Systemic Antiviral Agents: Corneal Tissue Penetration (Aqueous Concentration)

ORAL ACYCLOVIR ED50: 0.1–1.6 μM[6-11]			
Dosage	**Frequency**	**Therapeutic Level (aqueous humor)****	**Model**
400 mg	Q 4–6 hours times 5 doses prior to surgery	3.26 μM (1.10–5.39)	Human[11]
800 mg	Q 4 hours times 6 doses prior to surgery	5.37 μM	Human[13]
ORAL VALACYCLOVIR ED50: 0.1–1.6 μM[6-11]			
Dosage	**Frequency**	**Therapeutic Level (aqueous humor)****	**Model**
100 mg	Q 8 hours times 3 doses prior to surgery	9.63 μM	Human[13]

ORAL FAMCICLOVIR ED50: 0.04–0.06 µg/ml[14]			
Dosage	**Frequency**	**Therapeutic Level (vitreous humor)**	**Model**
500 mg	Q 8 hours times 3 doses prior to surgery	1.21 µg/ml	Human[15]

Acyclovir ED50 References

Reference	**ED50**	**Type of Study**
Inoue 1989[6]	0.07 µg/ml (0.02–0.14)	In vitro (cell culture, plaque inhibition)
Smee 1983[7]	0.3–0.8 µM	In vitro
Smee 1985[8]	0.5–1.0 µM	In vitro
Castela 1994[10]	180 +/- 63 ng/ml (120–240) Mean=0.8 µM	In vitro
Crumpacker 1979[16]	0.15 µM	In vitro
De Clercq 1980[17]	0.18 µM 0.04 µM/ml	In vitro
Smolin and Thofts, The Cornea[18]	0.1–1.6 µM	Range of means from above references
Betz 2002[19]	22 mg/kg	Murine lethal challenge model

Trifluridine ED50 References

Reference	**ED50**	**Model**
Lin 1976[18]	0.2–1.7 µg/ml	In vitro

Ganciclovir ED50 References

Reference	**ED50**	**Model**
Inoue 1989[6]	0.23 µg/ml (0.062–0.50)	In vitro
Smee 1983[7]	0.2–0.5 µM	In vitro
Smee 1985[8]	0.2–0.5 µM	In vitro
Castela 1994[10]	260 +/- 60 µg/ml (200–320) Mean=1.05 µM	In vitro
Trousdale 1984[20]	Mean 0.23 µg/ml Range: (0.06–0.5)	Rabbit (GCV precursor)

Smith 1984[21]	Mean: 0.23 µg/ml Range: (0.06–0.5)	Rabbit (GCV precursor)
Inoue 1989[6]	Mean: 0.23 µg/ml Range: (0.06–0.5)	In vitro
Betz 2002[19]	2.5 mg/kg	Murine lethal challenge model

Valacyclovir ED50 References

Reference	ED50 (mg/kg)	Model
Betz 2002[19]	17 mg/kg	Murine lethal challenge model

Famciclovir ED50 References

Reference	ED50 (mg/kg)	Model
Betz 2002[19]	17 mg/kg	Murine lethal challenge model

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