

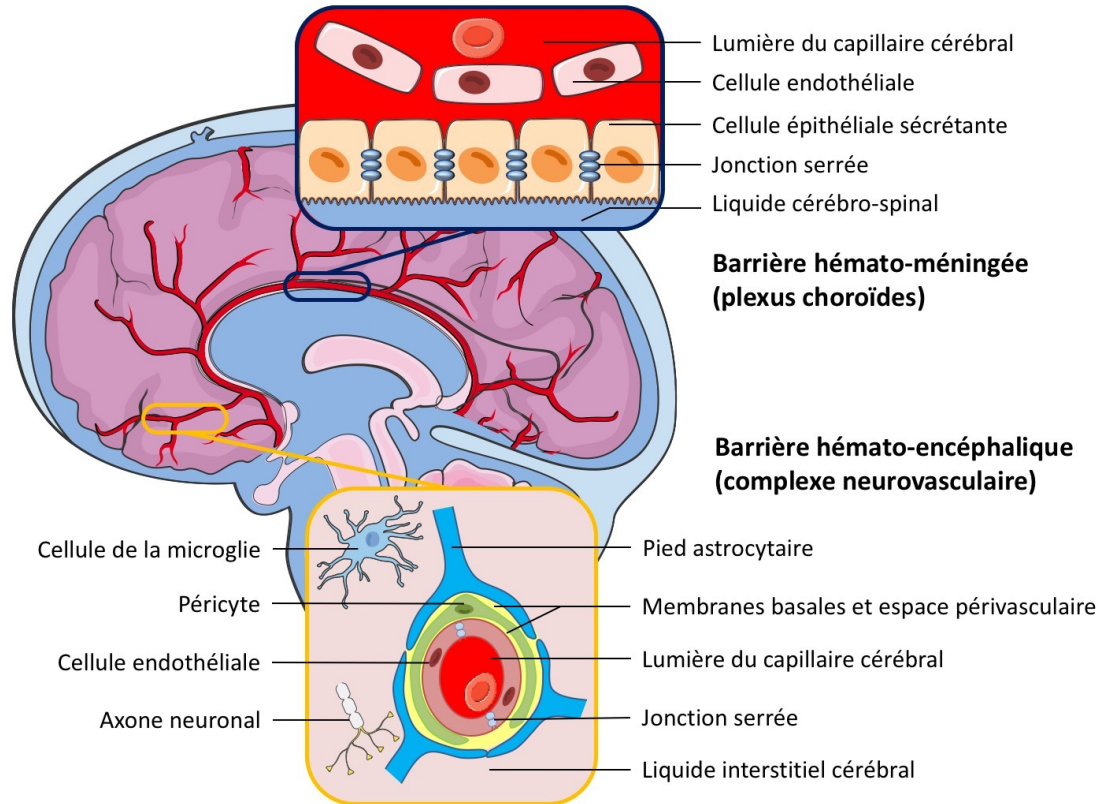
Pharmacocinétique et pharmacodynamie des antiviraux (hors ARV) dans le SNC

Matthieu GREGOIRE – CHU Nantes

Déclaration d'intérêts de 2014 à 2023

- Intérêts financiers : NA
- Liens durables ou permanents : NA
- Interventions ponctuelles : CORREVIO, GILEAD, JANSSEN, MERCK, MSD, PFIZER et Viiv HEALTHCARE
- Intérêts indirects : NA

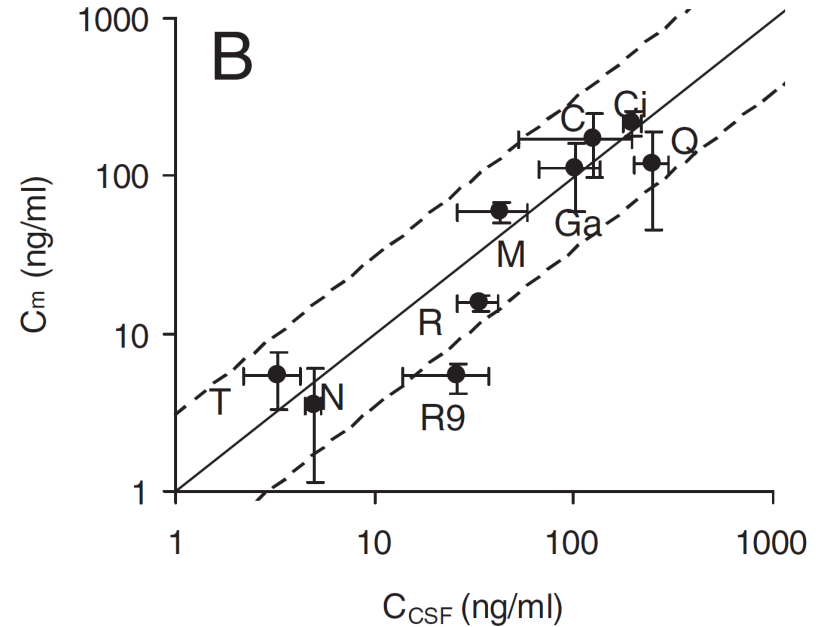
Principes de la diffusion neuroméningée



Principes de la diffusion neuroméningée

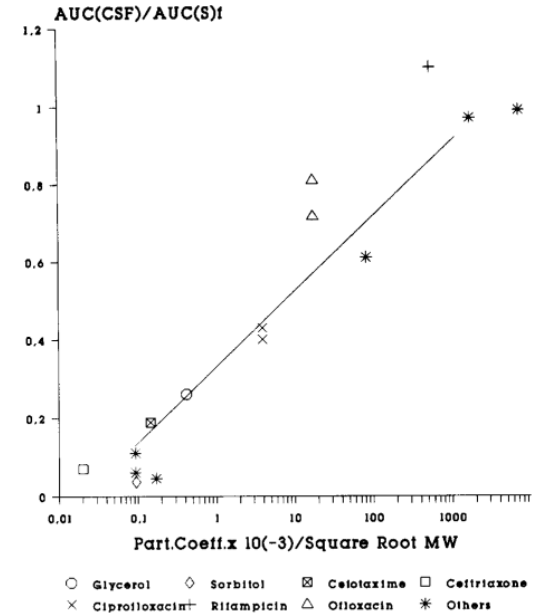
- $C_{LCS} \approx C_{LIC}$ (range acceptable de 3 fois)

- Rat
- Primate



Principes de la diffusion neuroméningée

- La masse moléculaire (<1000 Da)
- La lipophilie (LogP=octanol/eau)
- Le degré d'ionisation
- La liaison aux protéines plasmatiques
- L'arsenal métabolique de la barrière (pompe à efflux)
- L'intégrité des barrières (ex: inflammation et BHM)



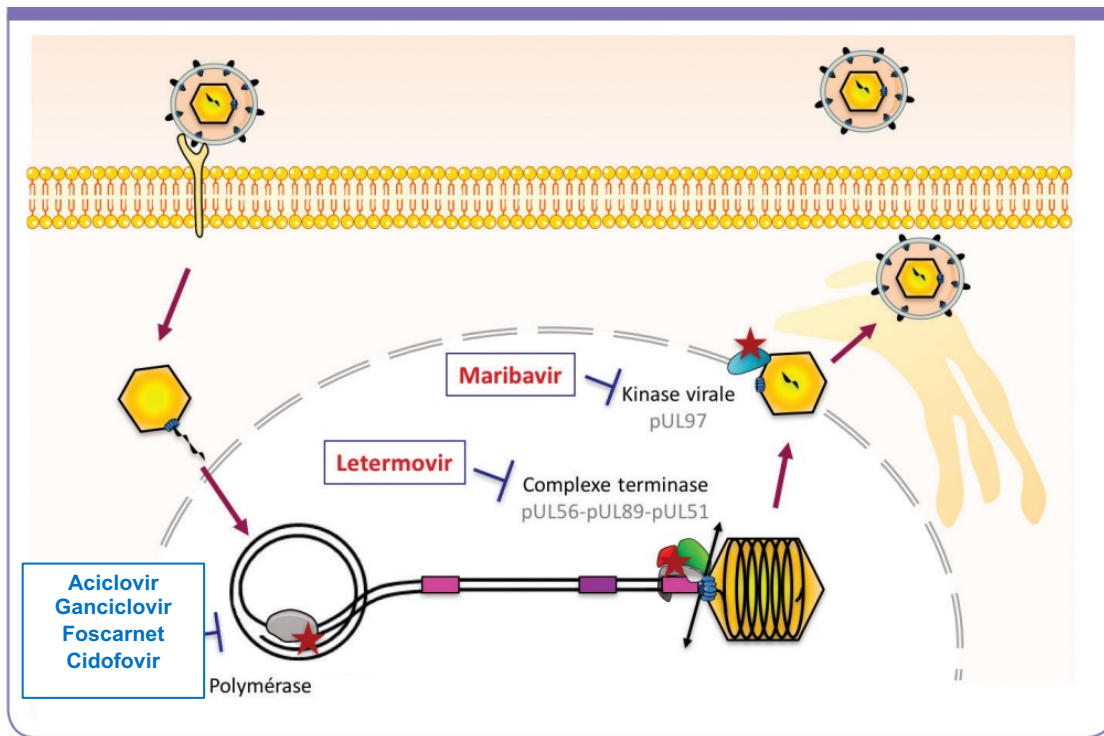
Quels virus?

Table 3. Identified Etiologic Causes of Encephalitis, France, 2007 (n = 131)

Etiologic diagnosis	No. (%) of patients	No. of patients with confirmed cases	No. of patients with probable cases	No. of patients with possible cases	Comments
HSV	55 (42)	55	0	0	All had an initial positive PCR result of a CSF specimen, although 27 of 55 had their initial HSV PCR performed during the first 2 days of neurologic signs
VZV	20 (15.2)	16	0	4	...
<i>Mycobacterium tuberculosis</i>	26 (19.2)	18	0	4	Patients with probable cases had an isolation of bacteria in urine, sputum, and gastric tube. Patients with possible cases of encephalitis were 63 to 72 years old. Two were born in France, 1 in China, and 1 in Algeria. All 4 experienced rapid loss of weight before onset of neurologic signs. All had high levels of protein in the CSF and high WBC counts in the CSF. One had lesions evocative of ancient tuberculosis on chest radiography examination.
<i>Listeria monocytogenes</i>	13 (10)	11	1	1	...
Cytomegalovirus	3 (2.3)	2	0	1	...
Epstein-Barr virus	3 (2.3)	1	2	0	...
Tick-borne encephalitis	3 (2.3)	0	1	2	...
Enterovirus	2 (1.5)	0	2	0	...
Toscana virus	2 (1.5)	1	1	0	1 Patient infected in Southeast France and 1 in Italy
Lyme disease	2 (1.5)	1	1	0	...
<i>Mycoplasma pneumoniae</i>	2 (1.5)	0	2	0	...
<i>Rickettsia conorii</i>	1 (0.8)	0	1	0	...
<i>Francisella tularensis</i>	1 (0.8)	0	1	0	...
<i>Legionella pneumophila</i>	1 (0.8)	0	1	0	...
Influenza A	1 (0.8)	0	1	0	...
West Nile virus	1 (0.8)	0	1	0	Patient infected in Egypt
<i>Cryptococcus neoformans</i>	1 (0.8)	1	0	0	...

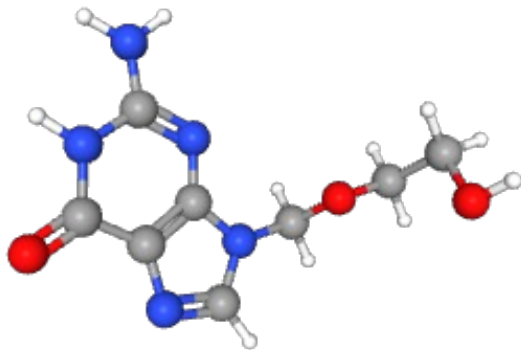
NOTE. CSF, cerebrospinal fluid; HSV, herpes simplex virus; PCR, polymerase chain reaction; WBC, white blood cell; VZV, varicella-zoster virus.

Quels antiviraux?

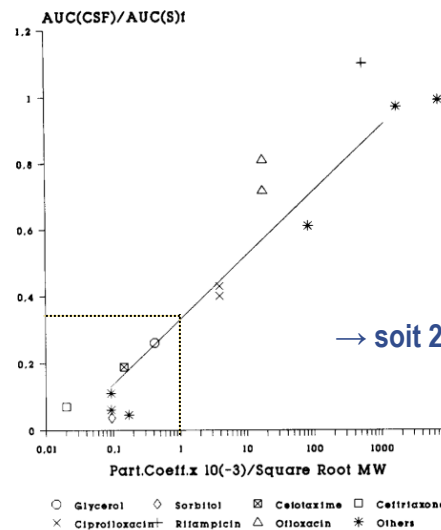


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Aciclovir

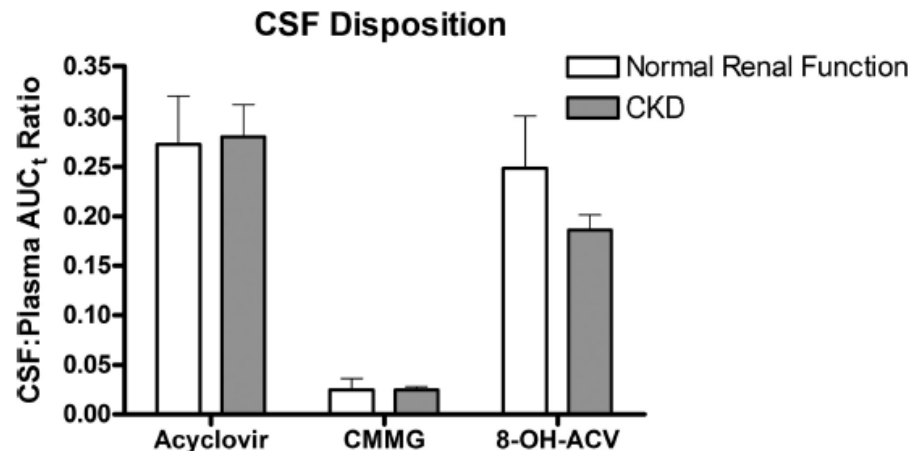


- MM: 225.20 g/mol
- LogP: -1.76
- LPP: 9 à 33%



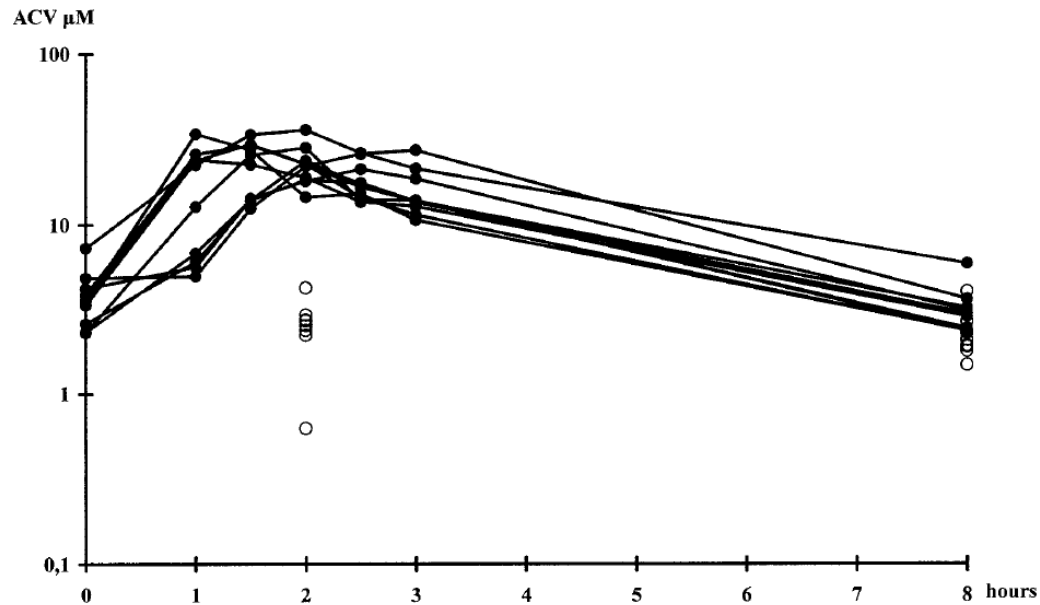
Aciclovir: diffusion dans le SNC

Analyte	Parameter ^a	Normal renal function (n = 6)	
		Systemic	CSF
Acyclovir	C_{max} (μM)	42 ± 6.8 (33–49)	7.8 ± 1.5 (4.9–8.7)
	t_{max} (h)	2.1 ± 0.49	2.3 ± 2.2
	AUC_{τ} ($\text{h} \cdot \mu\text{M}$)	137 ± 18 (118–161)	37 ± 7.5 (25–44)
	CL/F (ml/min)	759 ± 100 (638–873)	
CMMG	C_{max} (μM)	4.1 ± 1.1 (2.5–5.1)	0.095 ± 0.046 (0.034–0.16)
	t_{max} (h)	3.3 ± 0.52	1.8 ± 2.0
	AUC_{τ} ($\text{h} \cdot \mu\text{M}$)	17 ± 4.1 (11–22)	0.42 ± 0.21 (0.17–0.79)
8-OH-ACV	C_{max} (μM)	0.32 ± 0.10 (0.22–0.46)	0.062 ± 0.014 (0.050–0.089)
	t_{max} (h)	3.5 ± 0.55	2.4 ± 1.5
	AUC_{τ} ($\text{h} \cdot \mu\text{M}$)	1.4 ± 0.38 (0.96–1.9)	0.34 ± 0.070 (0.27–0.48)



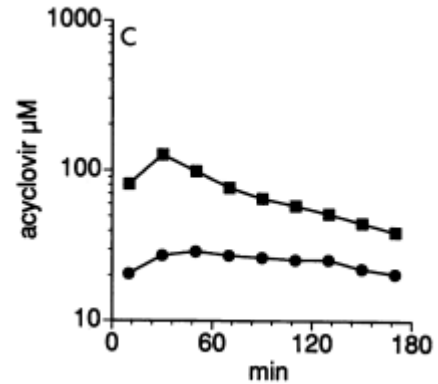
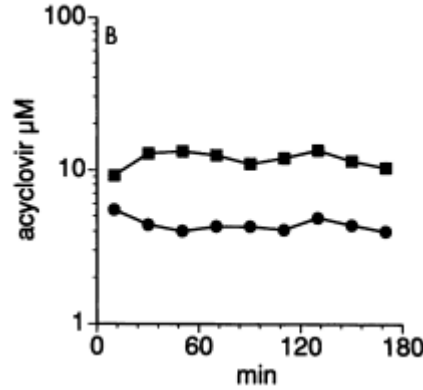
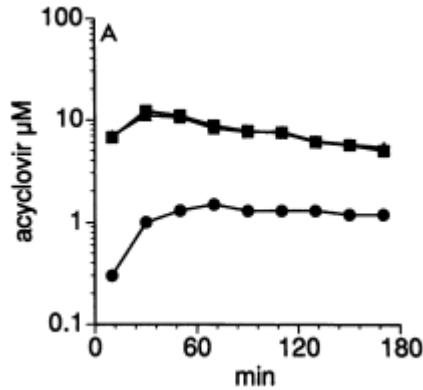
→ diffusion d'environ 20% dans le LCS

Aciclovir: diffusion dans le SNC



→ diffusion d'environ 20% dans le LCS

Aciclovir: diffusion dans le SNC



→ diffusion significative dans le cerveau

Aciclovir: PK-PD

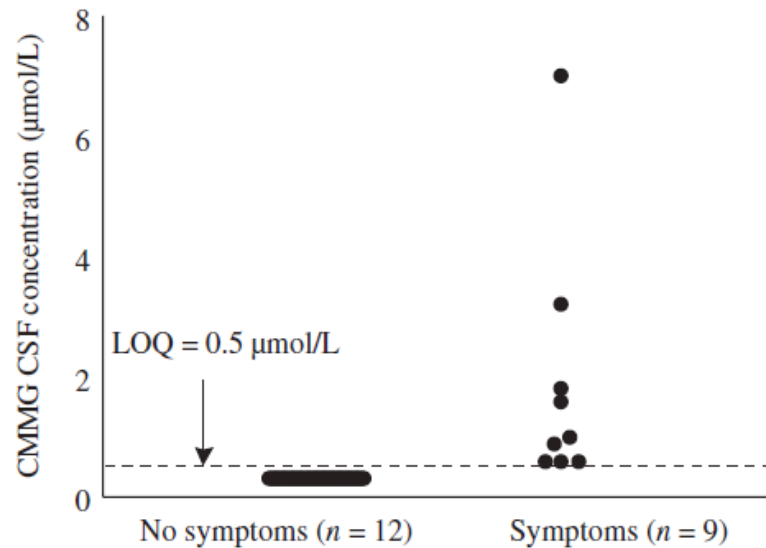
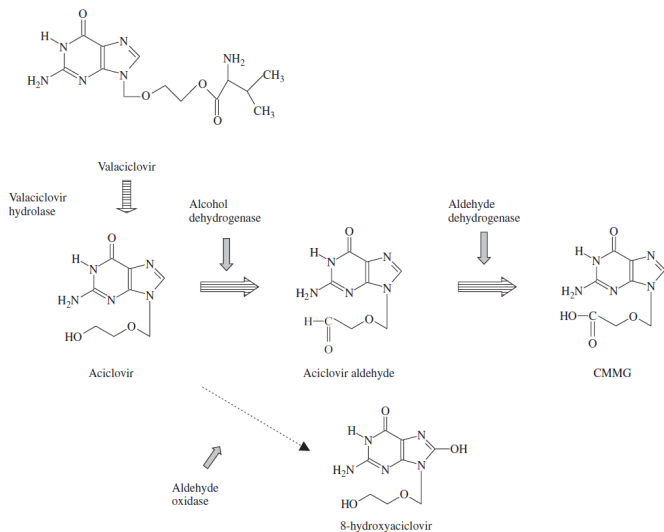
- CI_{50}
 - HSV-1: 0,02-0,9 mg/L → 10 mg/kg/8h
 - HSV-2: 0,03-2,2 mg/L
 - VZV: 0,8-4 mg/L → 15 mg/kg/8h
- Cible PK-PD: $50\%fT > CI_{50}$ ou $fC_{res} > CI_{50}$
- Concentrations plasmatiques cibles : $C_{res} = 2-3$ mg/L

Grit *et al.* Pharmaceutics 2022

Das *et al.* VP 2019

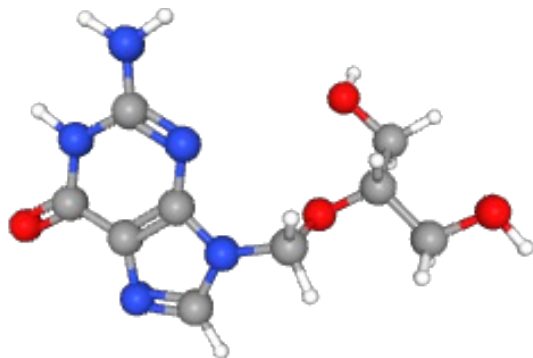
Bounaadja *et al.* JCM 2013

Aciclovir: neurotoxicité

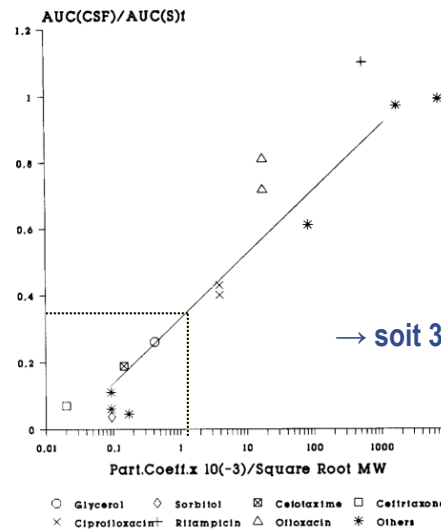


→ Toxicité neurologique potentiellement associée au métabolite

Ganciclovir



- MM: 255.23 g/mol
- LogP: -1.66
- LPP: 1 à 2%



Ganciclovir: diffusion dans le SNC

Table IV. CSF concentrations of DHPG

Patient No.	Dose (mg/kg)	Interval	CSF concentration ($\mu\text{g/ml}$)	Dosing day	Hr after dose	Model-predicted plasma concentration ($\mu\text{g/ml}$)	% penetration*
2	2.5	q.12h.	0.62	1	5.67†	0.92	67
	2.5	q.12h.	0.68	13	3.5	2.20	31
	2.5	q.8h.	0.51	13‡	2.75	1.96	26
4	2.5	q.8h.	0.50	9	0.25§	2.05	24

*Penetration = CSF/plasma \times 100%.

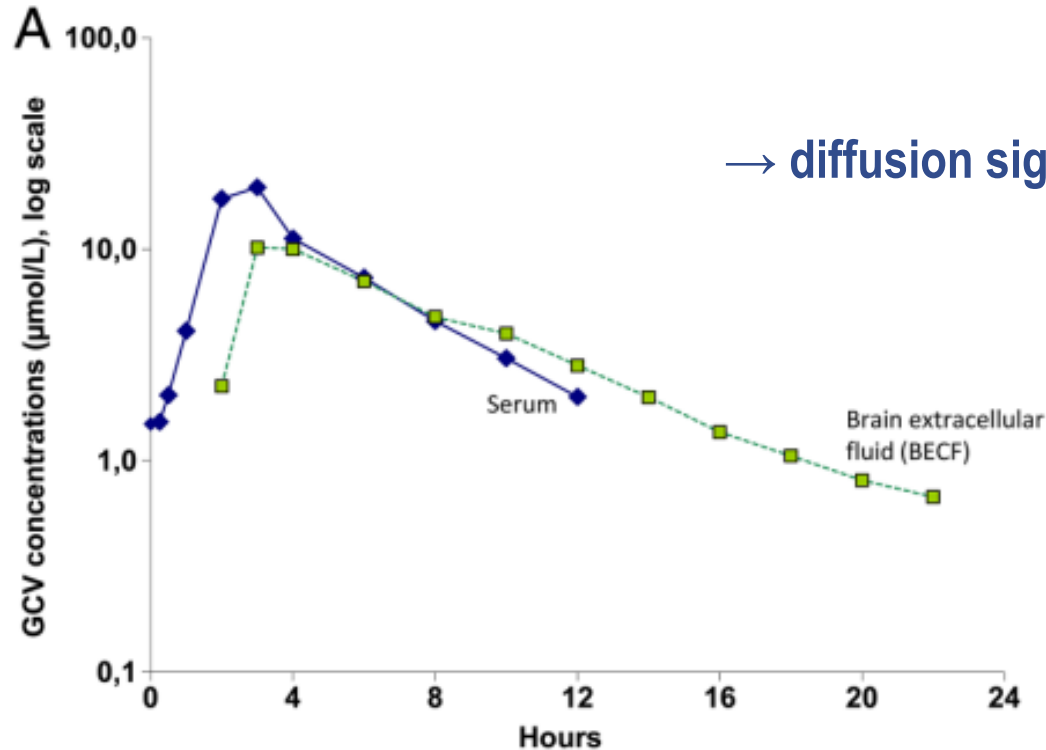
†After dose number 2.

‡Day 13 of second 20-day course.

§0.25 hr from start of infusion, all others after end of infusion.

→ diffusion entre 10 et 30% environ dans le LCS

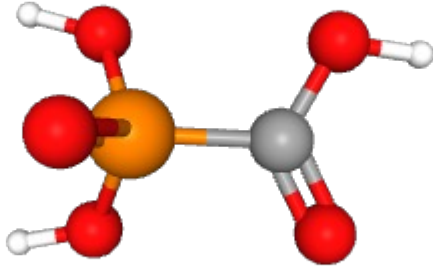
Ganciclovir: diffusion dans le SNC



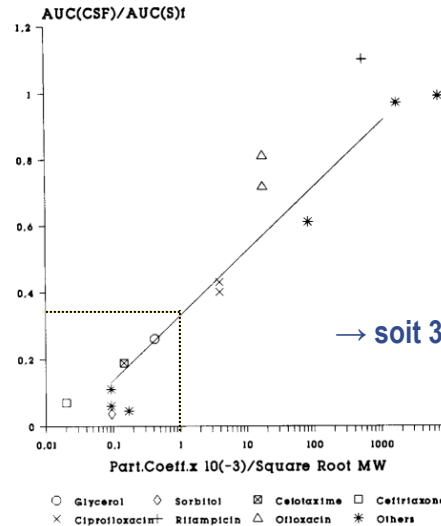
Ganciclovir: PK-PD

- **CI₅₀**
 - CMV: 0,5-1,5 mg/L
- **Cible PK-PD**
 - Prophylaxie: C_{res}: 1-2 mg/L dans le plasma ou ASC_{0-24h} > 50 mg.h/L
 - Curatif: C_{res}: 2-4 mg/L dans le plasma ou ASC_{0-24h}: 80-120 mg.h/L

Foscarnet



- MM: 126.01 g/mol
- LogP: -1.93
- LPP: < 20%



Foscarnet: diffusion dans le SNC

Sample	Foscarnet dosage (mg/kg) ^a	No. of samples	Concn (μmol/liter) in CSF	CSF/plasma ratio
All samples				
Cells in CSF				
Absent	126.04 ± 45.31	25	70 ^b	0.21 ^c
Present	125.33 ± 46.91	12	160 ^b	0.465 ^c
Sampling at end of intravenous infusion				
Cells in CSF				
Absent	107.8 ± 31	13	67 ^d	0.11 ^e
Present	120.8 ± 56.2	5	110 ^d	0.43 ^e

→ diffusion entre 20 et 70% environ

Foscarnet: diffusion dans le SNC

Patient no.	Foscarnet concn ^a (µg/ml) in:		Q _{fos} ^b
	Plasma	CSF	
22	634 ± 29	437 ± 17	0.69
23	219 ± 24	175 ± 19	0.80
24	567 ± 28	322 ± 14	0.56
25	183 ± 16	98 ± 8	0.54
26	715 ± 19	511 ± 14	0.71

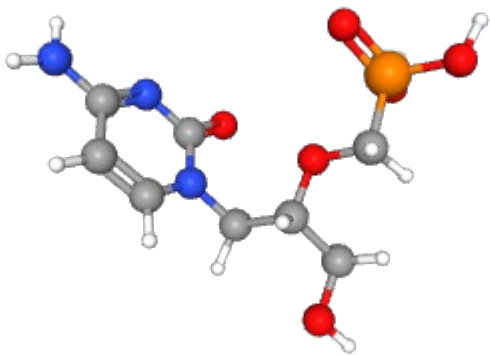
→ diffusion entre 20 et 70% environ

Foscarnet: PK-PD

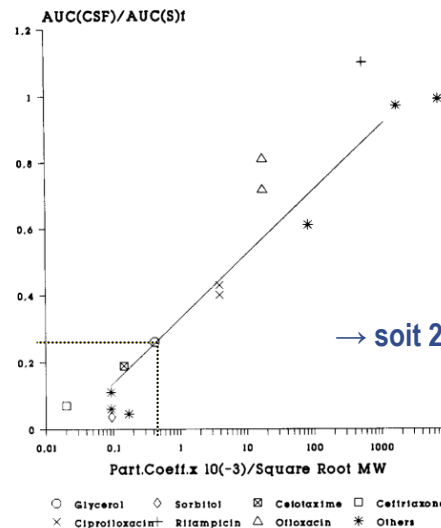
- **CI₅₀**
 - HSV: 1-20 mg/L
 - VZV: 6-12 mg/L
 - CMV: 5-100 mg/L

- **Cible PK-PD**
 - $fC_{res} > CI_{50}$

Cidofovir



- MM: 279.19 g/mol
- LogP: -3.9
- LPP: <10%



Cidofovir: diffusion dans le SNC

Peu de données...

« Aucun passage dans le SNC »

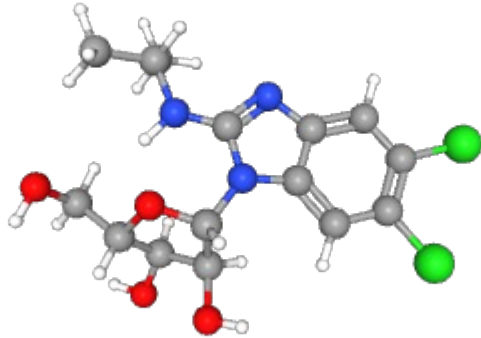
« Meilleur passage du brincidofovir »

Cidofovir: PK-PD

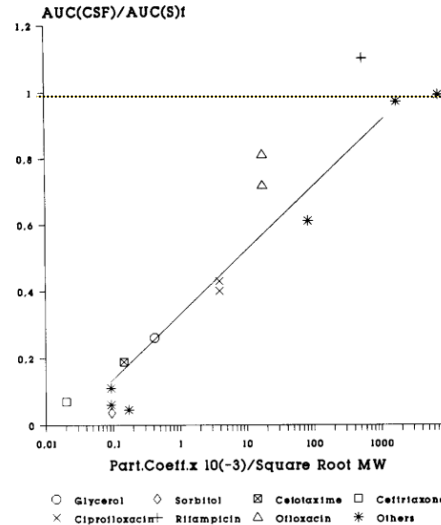
- **CI_{50}**
 - CMV sauvage ou foscarnet R: 0,17-0,19 mg/L
 - CMV ganciclovir R: 2 mg/L

- **Cible PK-PD**
 - $fC_{res} > CI_{50}$

Maribavir



- MM: 376.2 g/mol
- LogP: 2,15
- LPP: 98%



→ soit 2% de la concentration totale

Maribavir: diffusion dans le SNC

Uniquement des données précliniques...

- **Chez le singe:**

- Cerveau: 4-20% du plasma
- Liquide cérebrospinal: 1-2% du plasma

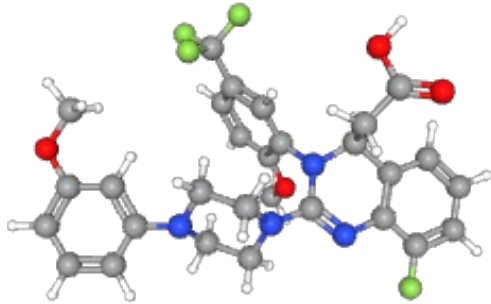
Maribavir: PK-PD

- CI_{50}
 - CMV: 0,045 à 0,2 mg/L

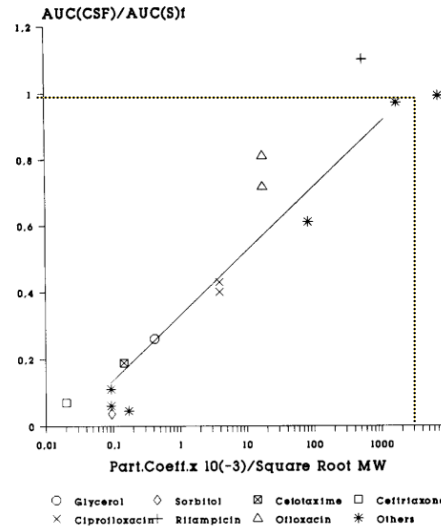
Tableau 6 : Propriétés pharmacocinétiques du maribavir chez les transplantés d'après une analyse pharmacocinétique de population

Paramètre MG (% de CV)	$ASC_{0-\tau}$ $\mu\text{g}^*\text{h/mL}$	C_{max} $\mu\text{g/mL}$	C_{min} $\mu\text{g/mL}$
Maribavir 400 mg deux fois par jour	128 (50,7 %)	17,2 (39,3 %)	4,90 (89,7 %)
MG : moyenne géométrique, % de CV : coefficient de variation géométrique			

Letermovir



- MM: 572.5 g/mol
- LogP: 4,58
- LPP: 98,2%



→ soit 2% de la concentration totale

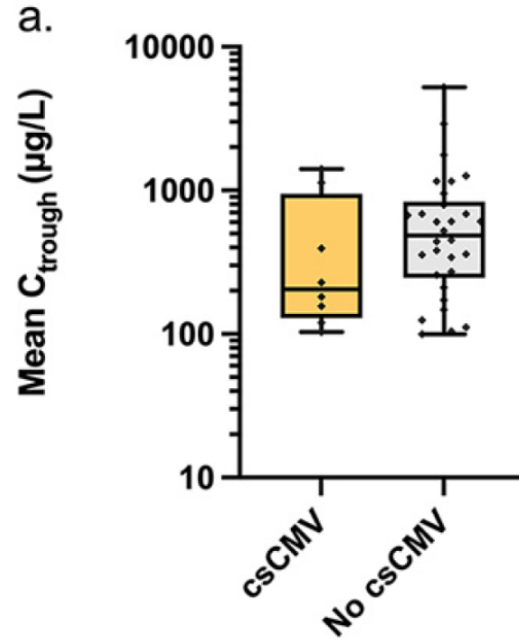
Letermovir: diffusion dans le SNC

Peu de données...

RCP « faibles concentrations dans le cerveau »

Letemovir: PK-PD

- CI_{50}
 - CMV: 0,0008 à 0,0016 mg/L



Place du Suivi Thérapeutique Pharmacologique

- **Niveau de preuve faible**
- **Intérêt**
 - En fonction de la gravité
 - En cas de mauvaise évolution
 - En cas de risque de surdosage (insuf. rénale)
- **Nécessité d'avoir plus de données de diffusion (mesures dans le LCS++)**

Conclusions

Molécules	Diffusion correcte	Diffusion incertaine	Diffusion insuffisante
Aciclovir			
Ganciclovir			
Foscarnet			
Cidofovir			
Maribavir			
Letermovir			