Overton's Rule Helps To Estimate the Penetration of Anti-Infectives into Patients' Cerebrospinal Fluid

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In 1900, Ernst Overton found that the entry of anilin dyes through the cell membranes of living cells depended on the lipophilicity of the dyes. The brain is surrounded by barriers consisting of lipid layers that possess several inward and outward active transport systems. In the absence of meningeal inflammation, the cerebrospinal fluid (CSF) penetration of anti-infectives in humans estimated by the ratio of the area under the concentration-time curve (AUC) in CSF (AUC_{CSF}) to that in serum (AUC_{CSF}/AUC_S) correlated positively with the lipid-water partition coefficient at pH 7.0 ($\log D$) (Spearman's rank correlation coefficient $r_s = 0.40$; $P = 0.01$) and negatively with the molecular mass (MM) ($r_s = -0.33$; $P = 0.04$). The ratio of AUC_{CSF} to the AUC of the fraction in serum that was not bound ($AUC_{CSF}/AUC_{S,free}$) strongly correlated with $\log D$ ($r_s = 0.67$; $P < 0.0001$). In the presence of meningeal inflammation, AUC_{CSF}/AUC_S also correlated positively with $\log D$ ($r_s = 0.46$; $P = 0.002$) and negatively with the MM ($r_s = -0.37$; $P = 0.01$). The correlation of $AUC_{CSF}/AUC_{S,free}$ with $\log D$ ($r_s = 0.66$; $P < 0.0001$) was as strong as in the absence of meningeal inflammation. Despite these clear correlations, Overton's rule was able to explain only part of the differences in CSF penetration of the individual compounds. The site of CSF withdrawal (lumbar versus ventricular CSF), age of the patients, underlying diseases, active transport, and alterations in the pharmacokinetics by comedications also appeared to strongly influence the CSF penetration of the drugs studied.

The entry of many endogenous and exogenous compounds into the central nervous system (CNS) is restricted by the blood-brain and blood-cerebrospinal fluid (CSF) barriers, which ensure proper neuronal function. Paul Ehrlich was the first to demonstrate the existence of these barriers by injecting dyes into the circulation systems of laboratory animals at the end of the 19th century: he noticed that all organs with the exception of the brain were stained (26). Twenty-five years later, Ehrlich's student Edwin Goldmann injected trypan blue systemically or into the CNS. After systemic injection, trypan blue stained the choroid plexus and the dura mater, but not the brain and CSF. In contrast, after direct injection of trypan blue into the CSF, the brain and spinal cord were stained (32, 33). These and subsequent morphological studies gave rise to the idea that the CNS was surrounded by a lipid layer comparable to a second cell membrane.

In 1900, Ernst Overton discovered that the entry of dyes into plant cells depends on the lipophilicity of the dyes (100). Later, this rule was refined by the acknowledgment of the importance of molecular size for the penetration through lipid membranes and was applied to the penetration of drugs through the blood-brain or blood-CSF barrier (for example, see references 12, 50, 96, and 99). Recently, the validity of Overton's rule has been questioned by membrane physiologists. In particular, violations of Overton's rule for small molecules, including carboxylic acids and gases were reported (for example, see reference 35). With some exceptions, however, Overton's rule is still considered a valid explanation of how molecules pass through lipid membranes (82).

The pharmacokinetic interactions between blood and the different compartments of the CNS are complex (Fig. 1). Unlike other deep compartments, the steady-state concentrations of many drugs, including most anti-infectives, do not reach CSF concentrations equal to the respective serum levels or concentrations of unbound drug in serum. For some drugs, this is caused by

strong outward transport systems. However, this phenomenon also occurs in the absence of active transport, where it is caused by CSF bulk flow (approximately 20 to 30 ml/h under physiological conditions). For this reason, in the absence of active transport, the intercompartmental outward clearance CL_{out} is greater than the inward clearance CL_{in} by approximately 20 to 30 ml/h (86, 95). Active outward transport and CSF bulk flow often represent obstacles for the achievement of intracranial concentrations of anti-infectives effective for the treatment of CNS infections.

The present study reanalyzes previously published pharmacokinetic data with the aim of assessing the influence of the drugs' physicochemical properties on the entry of anti-infectives into the CSF.

MATERIALS AND METHODS

Previously generated and compiled data (95) were analyzed. Relevant publications were identified by a PubMed search using the following algorithm: name of the antibiotic and location (cerebrospinal or brain) and the concentration or concentrations and human. We also contacted the manufacturers for information on the penetration of the respective drugs into the cerebrospinal fluid. Previously we outlined the importance of the ratios of the areas under the concentration-time curves in CSF and serum or plasma (AUC_{CSF}/AUC_S or AUC_{CSF}/AUC_{plasma}) for the description of drug entry into the CSF (96, 97). Only pharmacokinetic studies that either reported AUC_{CSF}/AUC_S ratios or that permitted calculation of these ra-

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FIG 1 Pharmacokinetic relationships between blood, brain, and cerebrospinal fluid (CSF) illustrated on a normal cranial computer tomogram (CCT). (Left) The different spaces and their average volumes are listed. The volumes of these spaces vary greatly and depend on age, skull volume, genetic factors, and underlying diseases. Tight diffusional barriers containing active inward and outward transport systems separate blood and brain tissue (blood-brain barrier) as well as blood and CSF (blood-CSF barrier). Conversely, no tight barrier separates CSF from the extracellular fluid of the brain. The arachnoid granulations, one-way valves for the return of CSF to the blood, even allow the passage of bacteria and red and white blood cells. The CSF space and the interstitial space of the central nervous system are not homogeneous compartments, e.g., at equal concentration-versus-time curves in serum (plasma), the pharmacokinetics of a drug in ventricular and lumbar CSF can strongly differ. (Right) The sites of CSF production and drainage are listed. CSF flow has a strong circadian rhythm. It also depends on underlying diseases, blood and intracranial pressure, and drugs influencing the activity of the choroid plexus or the permeability of the blood-brain barrier. In addition to physiological drainage sites, an external ventricular and lumbar catheter are also shown: in many studies analyzed, CSF was drawn from indwelling catheters. Regions where the CSF flow is often interrupted in clinical routine are also depicted. Blockade of the CSF flow can alter the volume of distribution of the CSF space. The average volumes and fluxes were taken from Davon et al. (20). Interindividual variation is great. The host-dependent variables influencing CSF kinetics of an anti-infective make it very difficult to predict the course of the concentration-time curves in the CSF of patients. The CCT was kindly provided by J. Gossner, Department of Radiology, Evangelisches Krankenhaus Göttingen-Weende, Germany, reproduced with permission.

tios or that clearly reported CSF-to-serum concentration ratios at steady state (C_{CSFss}/C_{Sss}) were analyzed. For subsequent calculations, we used the means or (in the absence of Gaussian distribution) medians of AUC_{CSF}/AUC_S (C_{CSFss}/C_{Sss}) ratios determined for individual patients. When several investigations were identified for an individual compound, the data from all studies meeting the criteria outlined above were used independently. No pharmacokinetic CSF data after intraventricular or intraspinal injection of antibiotics alone or in combination with systemic administration were included in this analysis.

First, we analyzed data derived from patients with uninflamed meninges (31 compounds; 40 independent sets of data derived from different studies). Then, data reporting the entry of antibiotics into the CSF in patients during meningitis in patients were studied (27 compounds; 47 independent sets of data).

We established a correlation matrix between the following parameters: AUC_{CSF}/AUC_S , ratio of the areas under the concentration-time curves in CSF and of the fraction that was not bound in serum ($AUC_{CSF}/AUC_{S,free}$), common or decadic logarithm of the octanol-water partition coefficient of the un-ionized drug ($\log P$), decadic logarithm of the octanol-water partition coefficient at pH 7.0 ($\log D$), molecular mass (MM), fraction unbound to serum proteins (FF), and the ratios of $\log P/\sqrt{MM}$ and $\log D/\sqrt{MM}$. Moreover, the polar surface area (PSA) and molecular volume

were correlated with AUC_{CSF}/AUC_S and $AUC_{CSF}/AUC_{S,free}$. To ensure a homogeneous set of data, we used $\log P$, $\log D$, PSA, and molecular volume calculated with Advanced Chemistry Development (ACD/Labs, Toronto, Canada) software (V8.14 and V11.02) published online by SciFinder 2007, unless indicated otherwise. Data on binding to serum (plasma) proteins were taken from the references indicated in Tables 1 and 2. Since the relation between individual variables was clearly nonlinear in many cases even after transformation, Spearman's nonparametric correlation coefficient r_s was used (112).

RESULTS

In the absence of meningeal inflammation ($n = 40$), the CSF penetration of anti-infectives in humans as estimated by AUC_{CSF}/AUC_S (C_{CSFss}/C_{Sss}) correlated positively with the lipid-water partition coefficient at pH 7.0 (D or $\log D$) (Spearman's rank correlation coefficient $r_s = 0.40$; $P = 0.01$) and negatively with the molecular mass (MM) ($r_s = -0.33$; $P = 0.04$). The correlation of AUC_{CSF}/AUC_S with $\log D/\sqrt{MM}$ was not stronger ($r_s = 0.40$; $P = 0.01$) than the correlation with $\log D$. AUC_{CSF}/AUC_S did not correlate with the fraction unbound in serum ($r_s = -0.06$; $P = 0.70$). The ratio of AUC_{CSF} to the unbound fraction of AUC_S ($AUC_{CSF}/AUC_{S,free}$) strongly correlated with $\log D$ ($r_s = 0.67$; $P < 0.0001$) and $\log D/\sqrt{MM}$ ($r_s = 0.69$; $P < 0.0001$) (Fig. 2). The correlation of AUC_{CSF}/AUC_S and $AUC_{CSF}/AUC_{S,free}$ with $\log P$ was substantially weaker than with $\log D$ (0.31 versus 0.40 and 0.56 versus 0.67).

In the presence of meningeal inflammation ($n = 47$), AUC_{CSF}/AUC_S also correlated positively with $\log D$ ($r_s = 0.46$; $P = 0.002$) and negatively with MM ($r_s = -0.37$; $P = 0.01$). Moreover, AUC_{CSF}/AUC_S correlated with the fraction unbound in serum ($r_s = 0.33$; $P = 0.025$). The correlation of $AUC_{CSF}/AUC_{S,free}$ with $\log D$ ($r_s = 0.66$; $P < 0.0001$) was as strong as in the absence of meningeal inflammation. The use of $\log D/\sqrt{MM}$ instead of $\log D$ did not increase the correlation with $AUC_{CSF}/AUC_{S,free}$ ($r_s = 0.66$ for both; $P < 0.0001$). Again, the correlation of AUC_{CSF}/AUC_S and $AUC_{CSF}/AUC_{S,free}$ with $\log P$ was substantially weaker than with $\log D$ (0.28 versus 0.46 and 0.60 versus 0.66).

The $AUC_{CSF}/AUC_{S,free}$ of a few highly protein-bound compounds both with uninflamed (lopinavir) and inflamed meninges (one of two reports on ceftriaxone) strongly exceeded 1.0.

In both patients with uninflamed meninges and patients with meningitis, the polar surface area (PSA) correlated with AUC_{CSF}/AUC_S ($r_s = -0.51$, $P = 0.001$, and $r_s = -0.64$, $P < 0.0001$) to a higher degree than $\log D$ correlated with AUC_{CSF}/AUC_S , but PSA correlated less strongly with $AUC_{CSF}/AUC_{S,free}$ ($r_s = -0.38$, $P = 0.02$, $n = 38$, and $r_s = -0.36$, $P = 0.02$, $n = 42$) than $\log D$ correlated with $AUC_{CSF}/AUC_{S,free}$. The molecular volume did not significantly correlate with either AUC_{CSF}/AUC_S or $AUC_{CSF}/AUC_{S,free}$.

DISCUSSION

We found a strong correlation between the octanol-water partition coefficient at pH 7.0 ($\log D$) and AUC_{CSF}/AUC_S both in the absence and presence of meningeal inflammation. The assumption of a Gaussian distribution of the data and use of Pearson correlation with or without logarithmic transformation of the scales instead of Spearman's rank correlation coefficient did not make the correlation between AUC_{CSF}/AUC_S and D stronger. In accordance with Overton's rule in its original form, which focuses on lipophilicity and neglects molecular mass and binding to serum protein, D ($\log D$) had a great explanatory value for the be-

TABLE 1 CSF penetration versus physicochemical properties of anti-infectives in patients with uninfamed meninges

Drug	Molecular mass (g/mol)	Partition coefficient ^a		Protein binding (%)	Protein binding reference	AUC _{CSF} /AUC _S	AUC _{CSF} /AUC _{S,free}	Pharmacokinetic reference(s)
		Log <i>P</i> _{O/W}	Log <i>D</i> _{O/W}					
Penicillins								
Cloxacillin	436	2.53 ± 0.34 ^b	−0.87 ^c	93	68	0.0087	0.12	114
Piperacillin	518	1.88 ± 0.37 ^b	−2.69 ^c	25	118	0.034	0.045	87
β-Lactamase inhibitors								
Clavulanate	199	−1.98 ± 0.78 ^b	−3.47 ^c	26	67	0.037	0.05	F. Sörgel et al., unpublished data
Tazobactam	300	−1.70 ± 0.84 ^b	−3.10 ^c	21.5	118	0.106	0.135	
Cephalosporins								
Cefotaxime	455	1.20 ± 0.89 ^b	−2.47 ^b	25.5	71	0.12	0.16	93
Ceftriaxone	555	−0.25 ± 1.12 ^b	−4.43 ^c	94.5	73	0.007	0.13	93
Ceftazidime	547	−1.21 ^d	−2.07 (135)	14.5	72	0.057	0.067	90
Carbapenem meropenem	383	−3.13 ± 0.75 ^b	−3.74 ^c	2	7	0.047, 0.21, 0.25	0.048, 0.21, 0.26	61, 89
Aminoglycoside netilmicin	476	−1.90 ± 0.84 ^b	−7.02 ^c	0	16	0.24	0.24	94
Fluoroquinolones								
Ciprofloxacin	331	1.31 ± 0.79 ^b	−0.33 ^c	30	52	0.24, 0.43	0.34, 0.61	91, 133
Ofloxacin	361	1.61 ± 0.81 ^b	−0.20 ^c	32.5	52	0.65	0.96	88
Levofloxacin	361	1.61 ± 0.81 ^b	−0.20 ^c	32.5	132	0.71	1.05	103
Moxifloxacin	401	1.90 ± 0.82 ^b	−0.63 ^b	37.5	132	0.46	0.74	43
Fosfomycin	138	−2.98 ± 0.60 ^b	−4.77 ^c	0	111	0.092, 0.128	0.092, 0.128	45
Chloramphenicol	323	1.02 ± 0.37 ^b	1.10 ^c	60	75	0.67	1.68	31
Colistin	1,155	−1.28 ^d		55	28	0.051	0.11	59
Rifamycin rifampin	823	1.09 ± 0.74 ^b	−0.38 ^c	87.5	78	0.22	1.76	92
Folate antagonists								
Trimethoprim	290	0.79 ± 0.38 ^b	0.27 ^c	44	77	0.18	0.32	24
Sulfamethoxazole	253	0.89 ± 0.42 ^b	−0.22 ^c	70	64	0.12	0.4	24
Glycopeptide vancomycin	1,449	−1.44 ± 1.02 ^b	−4.67 ^c	40	47	0.14, 0.18	0.30, 0.23	1
Antiherpesvirus nucleoside analogues								
Aciclovir	225	−1.76 ± 0.49 ^b	−1.48 ^c	21	63	0.31	0.39	56, 57
Foscarnet	126	−1.63 ^d	−6.78 ^c	15	53	0.27, 0.43	0.32, 0.51	108, 116
Antiretroviral drugs								
Abacavir	286	0.72 ± 0.82 ^b	0.58 ^b	48	11	0.35	0.67	62
Zidovudine	267	1.15 (31a)	−0.58 (127a)	27	11	0.75	1.03	110
Indinavir	614	2.88 ± 0.86 ^b	2.86 ^b	60	11	0.06, 0.147	0.15, 0.37	36, 49
Lopinavir	629	6.26 ± 0.84 ^b	6.26 ^b	98	11	0.285	14.3	13
Antiparasitic drugs								
Albendazole	265	3.07 ± 0.83 ^b	2.99 ^c	70	21	0.37, 0.38, 0.43	1.23, 1.27, 1.43	42, 123
Praziquantel	312	2.44 ± 0.69 ^b	2.66 ^c	80	21	0.24	1.2	42
Sulfadiazine	250	−0.12 ± 0.26 ^b	−0.68 ^c	44	69	0.27, 0.34	0.54	2
Tetroxoprim	335	0.46 ± 0.43 ^b	−0.03 ^c	15	135	0.23, 0.39	0.36	2

^a The logarithm of the octanol-water partition coefficient of the drug (log $P_{O/W}$) and the logarithm of the octanol-water partition coefficient (log $D_{O/W}$) are shown. The drug was tested at pH 7 unless specified otherwise.

^b Calculated using Advanced Chemistry Development (ACD/Labs) software V8.14 (1994 to 2011 ACD/Labs) published online by SciFinder 2007.

^c Calculated using Advanced Chemistry Development (ACD/Labs) software V11.02 (1994 to 2011 ACD/Labs) published online by SciFinder 2007.

^d Data from the DrugBank database (<http://drugbank.ca/>).

havior of anti-infective drugs at the human blood-CSF barrier. The correlation between log D and AUC_{CSF}/AUC_S (Fig. 2A and B) would have been even stronger if the highly hydrophilic foscarnet (log D -6.78), which readily enters the CSF because of its small

molecular size, and if the lipophilic compounds (log D of >1.5 corresponding to a partition coefficient of >30), which are usually highly bound to serum proteins (128), had been excluded from the analysis (for patients with uninfamed meninges, $r_s = 0.52$,

TABLE 2 CSF penetration versus physicochemical properties of anti-infectives in patients with inflamed meninges

Drug	Molecular mass (g/mol)	Partition coefficient ^a		Protein binding (%)	Protein binding reference	AUC _{CSF} /AUC _S	AUC _{CSF} /AUC _{S,free}	Pharmacokinetics reference(s)
		Log <i>P</i> _{O/W}	Log <i>D</i> _{O/W}					
Penicillins								
Amoxicillin	365	0.61 ± 0.33 ^b	−2.08 ^c	18.5	76	0.058	0.071	8
Piperacillin	518	1.88 ± 0.37 ^b	−2.69 ^c	25	118	0.32	0.43	22
β-Lactamase inhibitor								
clavulanate	199	−1.98 ± 0.78 ^b	−3.47 ^c	26	67	0.084	0.11	8
Cephalosporins								
Ceftriaxone	555	−0.25 ± 1.12 ^b	−4.43 ^c	94.5	73	0.17, 0.041	3.09, 0.75	60
Cefepime	481	−0.36 ^d	−1.07 ^e	20	70	0.103	0.13	113
Cefpirome	515	−1.70 (82a)	−1.5 ^e	10	83	0.145, 0.31	0.16, 0.34	30
Carbapenems								
Imipenem	299	−2.78 ± 0.76 ^b	−5.28 ^b	17	66	0.14	0.17	134
Cilastatin	358	2.42 ± 0.55 ^b	−2.77 ^c	40	66	0.1	0.17	134
Meropenem	383	−3.13 ± 0.75 ^b	−3.74 ^c	2	7	0.39	0.4	15
Fluoroquinolones								
Ciprofloxacin	331	1.31 ± 0.79 ^b	−0.33 ^c	30	52	0.92	1.31	133
Moxifloxacin	401	1.90 ± 0.82 ^b	−0.63 ^b	37.5	132	0.94, 0.74, 0.82, 0.71	1.50, 1.18, 1.31, 1.14	3, 4
Macrolide								
clarithromycin	748	3.16 ± 0.78 ^b	1.71 ^c	69.5	19	0.18	0.59	58
Fosfomycin	138	−2.98 ± 0.60 ^b	−4.77 ^c	0	111	0.23, 0.27	0.23, 0.27	106
Chloramphenicol	323	1.02 ± 0.37 ^b	1.10 ^c	60	75	0.60, 0.65, 0.67	1.50, 1.63, 1.68	31, 136
Colistin	1,155	−1.28 ^d		55	28	0.051, 0.16	0.11, 0.36	41, 59
Oxazolidinone linezolid	337	0.43 ± 0.73 ^b	0.41 ^b	31	117	0.8, 1.0	1.16, 1.45	9
Nitroimidazole metronidazole	171	−0.01 ± 0.30 ^b	−0.14 ^c	20	65	0.87	1.09	130
Rifamycin rifampin	823	1.09 ± 0.74 ^b	−0.38 ^c	87.5	78	0.05	0.4	27
Folate antagonists								
Trimethoprim	290	0.79 ± 0.38 ^b	0.27 ^c	44	77	0.47	0.84	51
Sulfamethoxazole	253	0.89 ± 0.42 ^b	−0.22 ^c	70	64	0.3	1	51
Glycopeptide vancomycin	1,449	−1.44 ± 1.02 ^b	−4.67 ^c	40	47	0.07, 0.30, 0.29, 0.48	0.12, 0.50, 0.48, 0.80	1, 105, 109
Antituberculosis drugs								
Isoniazid	137	−0.89 ± 0.24 ^b	−0.77 ^c	0	39	0.78, 0.86, 1.17	0.78, 0.86, 1.17	23, 27, 115
Streptomycin	582	−2.53 ± 0.85 ^b	−5.46 ^c	46.2	39	0.12	0.22	27
Foscarnet	126	−1.63 ^d	−6.78 ^c	15	53	0.23, 0.66, 0.27	0.27, 0.78, 0.32	38, 108
Antifungal drug fluconazole	306	0.50 ± 0.89 ^b	0.45 ^c	12	10	0.74, 0.86, 0.89	0.84, 0.98, 1.01	80, 126
Antiparasitic drugs								
Albendazole	265	3.07 ± 0.83 ^b	2.99 ^c	70	21	0.38, 0.43	1.27, 1.43	42, 123
Praziquantel	312	2.44 ± 0.69 ^b	2.66 ^c	80	21	0.24	1.2	42

^a The logarithm of the octanol-water partition coefficient of the drug at pH 7 (log $P_{O/W}$) and the logarithm of the octanol-water partition coefficient at pH 7.0 (log $D_{O/W}$) are shown. The drug was tested at pH 7 unless specified otherwise.

^b Calculated using Advanced Chemistry Development (ACD/Labs) software V8.14 (1994 to 2011 ACD/Labs) published online by SciFinder 2007.

^c Calculated using Advanced Chemistry Development (ACD/Labs) software V11.02 (1994 to 2011 ACD/Labs) published online by SciFinder 2007.

^d Data from the DrugBank database (<http://drugbank.ca/>).

^e Calculated for pH 7.4. Data were provided by LookChem (www.lookchem.com).

$P = 0.003$, and $n = 31$; for patients with meningeal inflammation, $r_s = 0.62$, $P < 0.0001$, and $n = 38$). The partition coefficient of the un-ionized drug (log P) explains less well the intercompound variations of drug entry into the CSF than does the partition co-

efficient at a fixed pH (log D), in this case pH 7. Since most of the substances discussed have acidic or basic properties and therefore are ionizable, this result is not astonishing.

In vitro and in murine animal models, penetration through the

FIG 2 Entry of anti-infectives into the CSF in the absence (A) and presence (B) of meningeal inflammation depends on the octanol-water partition coefficient at pH 7.0. The abscissa shows the log of the octanol-water partition coefficient at pH 7 ($\log D$). The ordinate shows the ratio of the concentration-time curves in cerebrospinal fluid and serum (AUC_{CSF}/AUC_S). $\log D$ correlated with AUC_{CSF}/AUC_S (Spearman's rank correlation coefficient r_s was 0.40 in the absence of meningeal inflammation [A], and r_s was 0.46 in the presence of meningeal inflammation [B]; $P = 0.01$ and $P = 0.002$, respectively). The correlation would have been even stronger if the highly hydrophilic foscarnet ($\log D$ of -6.78), which readily enters the CSF because of its small molecular size, and if lipophilic compounds ($\log D$ of >1.5 corresponding to a partition coefficient of >30), which were often highly bound to serum proteins, had been excluded from the analysis (for patients with uninflamed meninges, $r_s = 0.52$, $P = 0.003$, and $n = 31$; for patients with meningeal inflammation, $r_s = 0.62$, $P < 0.0001$, and $n = 38$).

blood-brain barrier was proportional to the product of the lipid-water partition coefficient and diffusion coefficient. Because the diffusion coefficient in aqueous solvents inversely correlates with the molecular size, it approximately correlates with $1/\sqrt{MM}$ (50). In the present study, the correlation between the MM and drug entry into the CSF was statistically significant, but comparatively low. Use of the molecular volume instead of the MM did not lead to a stronger correlation with CSF penetration. Similarly, use of $\log D/\sqrt{MM}$ instead of $\log D$ did not substantially increase the correlation with AUC_{CSF}/AUC_S or $AUC_{CSF}/AUC_{S,free}$ both with uninflamed and inflamed meninges. The probable reason for the comparatively low influence of MM is the small range of molecular size studied (126 to 1,449 Da). For large hydrophilic molecules, e.g., proteins, molecular size is a strong determinant of drug entry into the CSF (29). Both with uninflamed and inflamed meninges, the correlation of $AUC_{CSF}/AUC_{S,free}$ with $\log D$ was substantially stronger than the correlation of AUC_{CSF}/AUC_S with $\log D$, underlining the importance of drug binding to serum (plasma) proteins.

The polar surface area (PSA) correlated to a higher degree with AUC_{CSF}/AUC_S than $\log D$ did, but PSA correlated less strongly with $AUC_{CSF}/AUC_{S,free}$ than $\log D$ did. For this reason, its use did

not represent a substantial advantage compared to $\log D$ under these conditions. The molecular volume did not correlate significantly either with AUC_{CSF}/AUC_S or with $AUC_{CSF}/AUC_{S,free}$ in the absence or presence of meningeal inflammation.

Reasons for failure to establish nomograms. Our data do not allow us to establish nomograms to predict CSF penetration on the grounds of physicochemical drug properties and binding to serum proteins (e.g., Fig. 2A and B). There are several reasons for this failure, involving the great variability in CSF pharmacokinetics.

(i) Variation in serum pharmacokinetics. Particularly in critically ill patients, the pharmacokinetics of anti-infectives is very heterogeneous (104). A meta-analysis of 57 studies of 6 different β -lactam antibiotics showed a more than 2-fold variation both in the volume of distribution (V) and in total body clearance (CL) (34).

(ii) Influence of age of the subjects investigated on the permeability of the blood-CSF barrier and the volumes of the intracranial compartments. Many studies included patients of different ages, including newborns. Physiologically, the CSF-to-serum albumin ratio as a combined measure of the state of the blood-CSF barrier and the CSF flow, which both affect the AUC_{CSF}/AUC_S of a drug administered into the circulation system, depends on the subject's age. In newborns, the CSF-to-serum albumin ratio is high. It then decreases to its minimum at approximately 4 years and then slowly increases with age (138). As a consequence of the age-related physiological involution of the brain, the ratio of CSF space/brain tissue increases with age (137).

(iii) Different underlying diseases in patients without meningeal inflammation. The studies reporting CSF entry in the absence of meningeal inflammation did not investigate healthy persons in most cases, but patients with different degrees of abnormal blood-CSF barrier or CSF flow. In many studies, patients with external CSF drains were included. The additional clearance by external bulk flow in patients treated with either ventricular or lumbar CSF drainage is an important determinant of CSF pharmacokinetics of anti-infectives after intravenous (i.v.) administration. The clinical decision, whether the drain is open, and the amount of CSF drained or whether the drain is closed during the pharmacokinetic study can strongly influence the CSF kinetics of the drug studied. However, data on the flow through an external CSF drain are usually not reported in pharmacokinetic studies. Moreover, a blockade of the CSF circulation at the level of the aqueduct or of the basal cisterns decreases the volume of distribution of the CSF space, thereby influencing the pharmacokinetics of a drug in the CNS.

(iv) Intensity of meningeal inflammation. In patients with meningitis, capillary permeability is increased, and transport across the epithelium of the choroid plexus may be affected (107). The degree of meningeal inflammation in the patients studied was highly variable. In experimental animals, dexamethasone, which is recommended as adjunct therapy for community-acquired bacterial meningitis in industrialized countries, causes a reduction in the CSF concentrations of vancomycin by approximately 30%, resulting in a delay in CSF sterilization not observed in non-dexamethasone-treated animals (102). In children with bacterial meningitis receiving adjunct dexamethasone treatment, the CSF concentrations of cefuroxime were reduced on an average by one dilution step (i.e., approximately 50%) (48).

(v) Lumbar versus ventricular CSF. Some studies investigated

lumbar CSF, others used ventricular CSF, and several studies either investigated CSF from both sites or did not clearly state from which site CSF was obtained. Physiologically, the CSF-to-serum albumin ratio is approximately 2 times lower in the ventricular CSF than in the lumbar CSF (124, 131).

(vi) Binding to serum proteins. It is generally believed that only the free fraction in serum is available for penetration into the compartments of the central nervous system (98). For some highly protein-bound drugs (e.g., ceftriaxone) (122), the percentage of protein binding in serum depends on the total serum concentration. Binding to serum proteins is also influenced by the patient's protein concentration and composition in blood and on the co-medication (79, 121, 127). Moreover, the notion that only the free serum fraction equilibrates with the drug fraction unbound in CSF has been questioned: the amount of some highly protein-bound drugs available for transport into the CNS may be not restricted to the free (dialyzable) fraction but may include the much larger globulin-bound fraction (101). Because of the low protein concentrations in normal CSF, binding of anti-infectives to CSF proteins has usually been neglected (60). In the case of drugs with a high affinity to serum proteins, however, this is a simplification. In children with *Haemophilus influenzae* meningitis, $19\% \pm 6\%$ of the total CSF ceftriaxone concentration was bound to protein (40). Drug binding to CSF proteins is probably one explanation for the $AUC_{CSF}/AUC_{S,free}$ ratios far above 1 encountered with some compounds (lopinavir in patients with uninfamed meninges, ceftriaxone in patients with inflamed meninges) in the present study.

(vii) Possible limitation of the validity of Overton's rule to molecules with a molecular mass below 500 Da. In experimental animals, molecules with a molecular mass above 500 Da crossed the blood-brain barrier less readily than expected by Overton's rule (50). Equivalent data for the blood-CSF barrier in humans are not available.

(viii) Active transport. In recent decades, many anti-infectives have been identified as ligands of active transport systems that remove toxic compounds from the compartments of the central nervous system (81, 120). The influence of these systems on the drug concentrations in the intracranial compartments varies from strong to absent. Since these transport systems in most cases bind to several drugs (for a review, see reference 55), interactions between antibiotics and the comedication can occur. P-glycoprotein (P-gp) has a broad spectrum of ligands favoring lipophilic compounds. This pump can remove substrates of approximately 300 to 4,000 Da from the compartments of the central nervous system (81). It is difficult to predict whether a drug is a strong ligand of P-gp (5). Polymorphisms of the ABCB1 gene, which codes for P-gp, can influence the kinetics of several drugs (14). The organic anion transporter 3 (OAT3) and peptide transporter 2 (PEPT2) remove several penicillins and cephalosporins from the CNS (46, 84). OAT3 is an active outward transport system for weak organic acids. Cephalothin, a strong ligand of OAT3, appears to be unsuitable for treatment of bacterial meningitis, because it is rapidly removed from CSF (120). Among other compounds, OAT3 is involved in the uptake of histamine H_2 receptor antagonists used in intensive care medicine for the prophylaxis and therapy of gastric ulcers (cimetidine, ranitidine, and famotidine). It has been shown that drug-drug interactions cause an increase in the CSF concentrations of H_2 receptor antagonists without affecting their plasma concentrations (85). OAT3 decreases CSF concentrations

of ligands particularly in the absence of meningeal inflammation and is inhibited by probenecid. In experimental animals with uninfamed meninges, inhibition of OAT3 by probenecid increased the CSF concentrations of penicillin G after intracisternal injection by a factor of 1.5 to 3 (129) and the CSF-to-serum concentration ratio during continuous i.v. infusion by 2 to 3 times (18). This effect tended to be weaker in patients with meningitis (18). In 4 patients with late uncomplicated syphilis receiving 600,000 IU penicillin G procaine intramuscularly, CSF penicillin concentrations were $\leq 0.015 \mu\text{g/ml}$. Coadministration of probenecid 500 mg every 6 h orally caused an increase in the CSF penicillin concentration to 0.016 to $0.29 \mu\text{g/ml}$ (median of $0.033 \mu\text{g/ml}$) (25).

The influence of the transport system of weak organic acids on the exchange of many β -lactam antibiotics at the blood-CSF barrier appears to be moderate (for example, see reference 119). In children on the 10th day of treatment for bacterial meningitis (i.e., after the acute phase), coadministration of probenecid increased the AUC from 0 to 4 h (AUC_{0-4}) of amoxicillin in plasma by approximately 40% and in CSF by approximately 75%. The average $AUC_{CSF,0-4}/AUC_{S,0-4}$ of amoxicillin rose from 0.04 without probenecid coadministration to 0.05 with probenecid (estimated from Tables 2 and 3 in reference 17). Ceftriaxone, cefotaxime, and meropenem, belonging to the standard therapy of community- and hospital-acquired bacterial meningitis, have low affinity to OAT3 and PEPT2 (95).

In rats, the antivirals aciclovir and zidovudine had a high affinity to OAT3: probenecid increased the CSF-to-unbound plasma concentration ratio from 17 to 29% (zidovudine) and from 8 to 17% (aciclovir), whereas the concentration ratio of cytarabine (AraC) was unchanged (44). In laboratory rabbits, coadministration of probenecid increased AUC_{CSF}/AUC_{plasma} of zidovudine from 0.15 ± 0.02 to 0.57 ± 0.22 (37).

Detailed reviews on the affinity of anti-infectives and other drugs for the different transport systems located at the blood-CSF and blood-brain barriers have been published recently (54, 81, 95, 120).

(ix) pH gradient. In patients with uninfamed meninges, there is a small pH gradient between blood (pH approximately 7.4) and CSF (pH approximately 7.3) (20, 125). The pH gradient between blood and CNS is greater in patients with meningitis, where a brain interstitial pH as low as 6.9 has been encountered (6). The un-ionized more-lipophilic fraction of acids therefore is higher in the compartments of the central nervous system than in blood. For this reason, weak acids diffuse more readily from CSF to blood than from blood to CSF, and this effect is greater in patients with inflamed meninges than in patients with uninfamed meninges (125).

(x) Publication bias. In the present analysis, several studies reporting AUC ratios for vancomycin from 0.07 to as high as 0.48 were included (Tables 1 and 2). Conversely, after 1 g of vancomycin was administered i.v., we were unable to detect measurable vancomycin concentrations in CSF (detection limit of $0.05 \mu\text{g/ml}$) (R. Nau and J. Bircher, unpublished observation). Since negative results are often not published, the CSF penetration of some compounds, in particular vancomycin, colistin, and netilmicin, may have been overestimated by the analysis of published data.

In conclusion, the entry of an anti-infective into the compartments of the central nervous system is determined by the variable properties of the drug, host, or both. The most important host-independent physicochemical drug property is lipophilicity at pH

7. In other words, Overton's rule is still valid. At the molecular sizes studied, molecular mass accounted for less of the interdrug variation than did lipophilicity at a neutral pH. Active transport and drug binding to serum proteins both depend on the drug's properties, on comedications which either influence drug protein binding or the activity of transport systems, on polymorphisms of genes encoding the transport proteins, and on the protein content in the circulation system and CSF. Host variables independent of the drug's physicochemical properties are the subject's age, an underlying disease affecting the state of the barriers and CSF flow, and the site of CSF withdrawal. Physicochemical drug properties help to predict which anti-infective will readily enter the CNS, and from data generated in animals under uniform experimental conditions, nomograms for the estimation of penetration into the compartments of the central nervous system have been constructed. Because of the great heterogeneity of published human data, predicting exact CSF concentrations based on physicochemical drug properties and pharmacokinetic data in the circulation system, however, in clinical practice is very difficult.

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