CEREBROSPINAL FLUID CONCENTRATIONS OF PROPRANOLOL, PINDOLOL AND ATENOLOL IN MAN: EVIDENCE FOR CENTRAL ACTIONS OF β -ADRENOCEPTOR ANTAGONISTS

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1 Single and multiple oral dose studies of the penetration into CSF of three β -adrenoceptor antagonists were performed in groups of patients needing lumbar puncture as part of their neurological investigation. Propranolol, pindolol and atenolol were chosen because of their differing physico-chemical properties.

2 The CSF concentration of propranolol (lipid-soluble) and pindolol (moderately lipid-soluble) was proportional to the free plasma concentration and was similar to, although generally lower than, that theoretically predicted.

3 The CSF concentrations of the poorly lipid-soluble atenolol were similar in different patients and were independent of plasma concentration. This may be due to the slow rate of diffusion of atenolol into CSF preventing the predicted concentrations being achieved.

Introduction

To understand the mechanism of action of a drug it is important to know its site of action. β -adrenoceptor antagonists are used to treat many disorders as different as hypertension, angina pectoris, hyperthyroidism and schizophrenia (Conway, Greenwood & Middlemiss, 1978; Turner, 1979) although exactly how they act is not known. These drugs may act directly on the central nervous system. Animal studies have shown that highly lipid-soluble propranolol and alprenolol equilibrate rapidly between the brain and plasma (Hayes & Cooper, 1971; Bodin *et al.*, 1974). Hydrophilic β -adrenoceptor antagonists such as practolol have also been found in the brain of dogs after oral administration (Scales & Cosgrove, 1970) but the rate of transfer to the brain and the equilibrium ratio of brain:plasma drug concentration was lower than for the more lipid-soluble β -adrenoceptor blocking drugs mentioned.

In view of the obvious difficulty in obtaining tissue samples and measuring drug concentrations in the human brain, the present studies were undertaken to discover the extent of penetration of three β -adrenoceptor antagonists, propranolol, pindolol and atenolol, into cerebrospinal fluid (CSF), a more accessible compartment in the central nervous system (CNS). Furthermore, if, as has been suggested, there is free movement of molecules between CSF and brain extracellular water (Matsen & West, 1972; Matakas, Stechele & Keller, 1978), then knowledge of drug concentration in CSF rather than in brain

tissue may be more important when considering drug action. It is believed by some that β -adrenoceptors are situated on the surface of cells. If this is true then CSF drug concentration, which possibly reflects that in the extracellular fluid which is in contact with brain cell surfaces, may represent the drug concentration at the receptor.

These studies also assessed the influence of each drug's pK_a , lipid-solubility, and binding to plasma proteins on their respective concentrations in CSF. The three drugs were chosen because of their differing physicochemical characteristics: propranolol has a log octanol:water partition coefficient (log P) of 3.65* (*values taken from I.C.I. Ltd., internal data) and is highly bound to plasma proteins (approximately 90%); pindolol is moderately lipid-soluble (log P = 1.75*) and about 70% bound to plasma proteins; and atenolol is hydrophilic (log P = 0.23*) and only about 5% protein bound in plasma.

Methods

All the patients in the following studies received a β -adrenoceptor antagonist as an anxiolytic agent before routine diagnostic lumbar puncture. Most of the patients chosen for these studies underwent lumbar puncture as part of the investigation of headache, suspected multiple sclerosis, and abnormalities of the vertebral column. Patients who were thought

to have diffuse changes in the blood-brain barrier, as occur in meningitis, were excluded. No patient was receiving any other medication with the exception of one patient, subject 4 in Study 5, who was taking diazepam. CSF samples were not used in the studies if they were blood-stained, or xanthochromic which would indicate an impaired blood-brain barrier.

CSF composition was analysed in the routine hospital laboratory and was considered abnormal if the protein content was greater than 40 mg/100 ml and if the cell count was more than 10 ml⁻¹. CSF pressure was measured at the time of sampling.

Drug concentrations of propranolol, pindolol and atenolol were measured fluorimetrically by modifications of the methods of Shand, Nuckolls & Oates (1970), Pacha (1969) and Kaye (1974), respectively. The lower limit of detection for the assay of propranolol in CSF was 2 ng ml⁻¹. This low concentration was measurable because of the very low blank value of drug-free CSF in this assay. Blood samples were taken into lithium-heparin and plasma separated and stored at -20°C until assayed. CSF samples were similarly stored. Binding to plasma proteins was measured by equilibrium dialysis across a Cuprophane membrane (Enka, GmbH) for 5 h at 37°C and pH 7.4.

Propranolol

Study 1: Methods

Seventeen patients (eleven men and six women) aged 30 to 73 years received propranolol 80 mg orally one, two or three hours before lumbar puncture. In addition to the CSF required for diagnostic purposes, a 2–4 ml sample of CSF was taken and a 10 ml blood sample was then drawn from the antecubital vein, one immediately following the other. Drug concentrations were measured as described above.

Results

Table 1 shows the diagnosis for all the patients and the composition of the CSF samples. None of the diagnoses were known to be associated with abnormal drug concentrations in CSF. Fourteen patients had CSF of normal composition. In three cases protein was slightly raised and in two of these three subjects the CSF:plasma drug concentration ratio seemed unaffected by this. The third patient, subject 10, who had a higher than normal concentration of protein, also had a raised lymphocyte count and the CSF:plasma drug ratio was approximately twice the mean of all 33 patients who took propranolol in these studies.

The concentration of propranolol in plasma and CSF from the 17 patients in Study 1 is shown in Table 1 and graphically in Figure 1. Propranolol was

detected in the plasma of fifteen patients, but not in two patients where sampling was at 1 h. Of the group who took the drug 1 h before lumbar puncture, only one person had a measurable concentration of propranolol in CSF. A similar result was obtained at 2 h. Plasma concentrations were highest in the group who took propranolol 3 h before sampling and the drug was detectable in the CSF of all these patients. The mean $\pm$ s.d. of the five ratios at 3 h (0.051 ± 0.019) is in the region of the two ratios at 1 h (0.085) and 2 h (0.113). It appears that the time after dosage at which propranolol is detectable in the CSF is only important in so far as plasma drug concentration is time dependent; where there are high plasma levels at 1 and 2 h the drug is detectable in the CSF and where there are low plasma concentrations at 2 and 3 h there is little drug in the CSF. In these cases, when the plasma concentration exceeded 40 ng ml⁻¹ propranolol was detectable in the CSF.

Study 2: Methods

Eleven patients (seven men and four women) were given a single oral dose of propranolol 160 mg 3 h before lumbar puncture. Samples of CSF and plasma were taken as in Study 1, except that in five of the patients (subjects 29–33) an additional 30 ml of blood was taken to measure the amount of drug bound to plasma protein by the method described above.

Results

The biological data for each subject and the results of the study are shown in Table 1 for subjects 18–23 and in Table 2 for subjects 29–33. The plasma drug concentration of all 11 patients was greater than 40 ng ml⁻¹ and propranolol was measurable in the CSF of each patient. The CSF:plasma drug ratio varied from 0.02 to 0.24 with a mean of 0.064 ± 0.059 . The ratio of 0.24 was the highest obtained in any of the studies with propranolol and it is unfortunate that the amount of drug protein bound in the patient's plasma is not known. The CSF from this patient was of normal composition and the amount of protein present was not raised. The other ratio was similar to those in the patients in Study 1 who received propranolol 80 mg.

There was a significant correlation between the concentration of unbound drug in plasma and the concentration in CSF ($r = 0.91$; $P < 0.001$). The slope of this regression line was 0.495 which was significantly less than 1.0.

Study 3: Methods

Oral propranolol 40 mg was given 8 hourly to five patients (subjects 24 to 28) for 48 h before lumbar

Table 1 Individual concentrations of propranolol in plasma (P) and cerebrospinal fluid (CSF) of 28 patients after taking a single or multiple oral doses at various times before lumbar puncture. CSF:P ratio, diagnosis and CSF composition are also shown

Subject	Age (years)	Sex	Drug (mg)	Time after dosage (h)	Concentration (ng ml ⁻¹) Plasma	CSF	CSF:P ratio	Diagnosis	CSF cells	Composition Protein (g l ⁻¹)
1	61	F	80	1	22	ND	—	MS	0	0.32
2	55	F	80	1	ND	ND	—	Headache	0	0.40
3	35	F	80	1	82	7	0.085	Headache	0	normal
4	66	M	80	1	18	ND	—	Radiculopathy	0	normal
5	52	M	80	1	29	ND	—	—	—	—
6	64	M	80	1	13	ND	—	CS with cord compression	0	0.70
7	66	M	80	1	ND	ND	—	MND	0	normal
8	57	F	80	1	18	ND	—	Pre-senile dementia	0	normal
9	30	M	80	2	19	ND	—	?MS	0	normal
10	31	M	80	2	53	6	0.113	Relter's syndrome	18	0.72
11	48	M	80	2	31	ND	—	MND	0	normal
12	61	M	80	2	17	ND	—	CS	0	normal
13	33	M	80	3	39	2	0.051	NYD	0	normal
14	73	F	80	3	72	2	0.028	Peripheral neuritis	0	normal
15	58	M	80	3	102	6	0.059	Cerebellar degeneration	0	0.76
16	53	M	80	3	172	7	0.041	Dystrophica myotonica	0	—
17	61	F	80	3	90	7	0.078	MS	0	normal
18	65	M	160	3	51	12	0.235	CS with mild cord compression	0	0.30
19	52	F	160	3	309	10	0.032	?MS	0	normal
20	72	F	160	3	254	10	0.039	Polymyositis	0	normal
21	53	M	160	3	114	2	0.018	MS	0	0.45
22	52	M	160	3	96	6	0.062	?MS	0	normal
23	44	F	160	3	47	2	0.043	?CS	0	0.40
24	28	F	40/8hourly	3	12	ND	—	Root compression	0	normal
25	69	F	40/8hourly	3	35	ND	—	Cervical myelopathy	0	0.31
26	21	M	40/8hourly	3	58	3	0.052	NYD	0	normal
27	62	F	40/8hourly	3	63	4	0.061	—	—	—
28	48	F	40/8hourly	5	14	ND	—	—	—	—

MS = Multiple sclerosis

MND = Motor neurone disease

CS = Cervical spondylosis

NYD = Not yet diagnosed

Table 2 Individual and mean $\pm$ s.d. concentrations of propranolol in plasma [P] and cerebrospinal fluid [CSF] 3 h after taking a single dose or multiple oral doses. Percentage of drug protein bound in plasma, CSF:P, ratio, diagnosis and CSF composition are also shown.

Subject	29	30	31	32	33	34	35	36	37	Mean	$\pm$ s.d.
Age (years)	43	22	40	18	30	53	31	53	66	39.6	15.8
Sex	M	M	M	M	F	M	M	M	M		
Dose	160 mg	160 mg	160 mg	160 mg	160 mg	80 mg 12 hourly	80 mg 12 hourly	80 mg 12 hourly	80 mg 6 hourly		
Time after last dose (h)	3	3	3	3	3	3	3	4.5	3		
[P] ng ml ⁻¹	155	339	111	233	94	86	86	57	101	140.2	90.6
[CSF] ng ml ⁻¹	9.8	18.5	6.1	8.5	6.7	5.1	2.8	4.6	15.6	8.6	5.2
% drug bound	89.4	90.7	94.4	90.0	88.5	92.6	92.4	91.8	77.6	89.7	4.9
[Free P] ng ml ⁻¹	16.4	31.5	6.2	23.3	10.8	6.4	6.5	4.7	22.6	14.3	9.6
CSF:P	0.063	0.055	0.055	0.036	0.071	0.059	0.033	0.081	0.154	0.067	0.036
Theoretical CSF:P ratio	0.119	0.104	0.063	0.112	0.129	0.083	0.085	0.092	0.251	0.115	0.055
Diagnosis	MS	MS	CNS degeneration	MND	Retrobulbar neuritis	Benign intracranial hypertension	MND	Essential tremor	Dementia		
CSF composition											
Cells	—	—	—	—	0	0	0	2	0		
Protein (g l ⁻¹)	—	—	—	—	0.46	0.41	0.43	0.39	0.64		
Pressure	—	—	—	—	200	180	140	170	250		

MS = multiple sclerosis

MND = motor neurone disease

Figure 1 Plasma and cerebrospinal fluid (CSF) propranolol concentrations in 17 patients 1 (●), 2 (○) or 3 (■) h after taking one 80 mg tablet.

puncture with the last dose 3 h before the samples were taken. The procedure described in Study 1 was used for sampling.

Results

The results are shown in Table 1. Plasma levels were low and propranolol was detectable only in two CSF samples which corresponded with the highest plasma concentrations. These CSF:plasma drug concentration ratios, 0.05 and 0.06, were similar to those found after a single dose of drug.

Study 4: Methods

In view of the low concentrations of drug in the preceding study, three patients took propranolol 80 mg orally twice daily for 48 h with the last dose 3 h before lumbar puncture. A patient taking 80 mg four times daily for hypertension who required diagnostic lumbar puncture was included in this investigation, sampling was again 3 h after taking the drug. In all four patients sampling was as described in Study 1 except that an additional 30 ml of blood was taken to measure protein binding of propranolol in plasma.

Results

The results are shown in Table 2 (subjects 34 to 37). As expected, the concentration of propranolol in plasma was higher than after 40 mg twice daily and there was drug measurable in the CSF of all four subjects. The CSF:plasma drug ratios of subjects 34 to 36 were similar to earlier values whereas the CSF:plasma ratio of 0.154 in subject 37 was very high and this was associated with a large percentage of free drug in plasma.

The significance of the correlation coefficient of the concentration of unbound propranolol in plasma against CSF drug concentration is described in the results of Study 2.

Figure 2 shows a plot of CSF propranolol concentration against plasma concentration for all 37

Figure 2 Cerebrospinal fluid (CSF) v plasma propranolol concentrations in 37 patients after taking either a single (●) or multiple (○) oral doses.

patients investigated. Figures 3a and 3b show that the correlation of CSF propranolol with that free in plasma (for the nine subjects in which this was measured) is better than with total plasma drug.

Pindolol

Study 5: Methods

Five patients received a single oral dose of pindolol 10 mg 3 h after lumbar puncture. In addition to that required for diagnostic purposes, a 4 ml sample of CSF was taken followed by a 40 ml sample of venous blood. Plasma was separated and kept as described above until assayed for pindolol concentration and protein binding.

Results

Table 3 shows the biological data, diagnoses, and CSF composition for all subjects. None of the diagnoses were thought to be associated with an abnormal drug concentration in CSF and four of the five patients had CSF of normal composition; subject 3 had a raised protein concentration and a high cell count which indicates an abnormal blood-brain barrier. The concentration of pindolol in plasma and CSF is shown in Table 3. Pindolol was detected in the plasma of each patient. However, only subject 1 had a measurable CSF pindolol concentration, the CSF:plasma ratio being 0.25. The concentration of unbound drug in the plasma of this subject was 12.7 ng ml⁻¹ which was similar to the CSF concentration of 12.0 ng ml⁻¹ (Table 3.)

Figure 3 Cerebrospinal fluid (CSF) propranolol concentration *v* plasma concentration (a) and free plasma concentration (b).

Study 6: Methods

Seven patients were studied, three of whom received pindolol 5 mg orally twice daily and 4 received 10 mg orally twice daily. The last dose was given approximately 3 h before lumbar puncture in all except subject 8 from whom samples were taken 16 h after the last dose of drug. Sampling was as described in Study 5.

Results

Table 3 shows the biological data, diagnoses, and CSF composition. In six subjects the diagnoses did not appear to be associated with abnormalities of the blood-brain barrier and in only 1 of the 6 was the CSF composition abnormal, protein being slightly raised. In contrast, the protein concentration in the CSF sample from subject 8 was raised markedly which might be explained by the finding of cord compression, CSF being sampled below the occlusion. Due to the long time interval between the patient receiving the last dose of drug and the samples being taken, the plasma concentration of pindolol in this subject was at the limit of detection of the assay method however, there was still a high drug concentration in the CSF and the CSF:plasma drug ratio obtained (1.362) was the highest measured.

The concentration of pindolol in plasma and CSF is shown in Table 3. Pindolol was detectable in the CSF of all 7 subjects, the highest concentrations being associated with the higher dose. The mean $\pm$ s.d. CSF:plasma drug ratio was 0.292 ± 0.085 excluding subject 8 and was similar to that in subject 1, Study 5.

Due to a technical fault, it was only possible to measure the extent of plasma protein binding of pindolol in four patients from this group. The results are shown in Table 3. There was a significant correlation between the concentration of unbound drug in plasma and the concentration in CSF ($r =$

0.99 ; $P < 0.001$). The slope of the regression line of CSF pindolol concentration versus free plasma concentration was 0.837 which was significantly less than 1.0 and significantly greater than that for propranolol.

Atenolol

Study 7: Methods

Four patients (three men, one woman) aged 27 to 47 years took a single oral dose of atenolol 100 mg approximately 3 h before lumbar puncture. In addition to that required for diagnostic purposes, a 4 ml sample of CSF was taken followed by a 10 ml venous blood sample. Drug concentrations in plasma and CSF were measured as described above. The amount of atenolol bound to plasma proteins was not measured in this investigation because this is normally low (about 5%) and therefore was not considered to be an important factor in determining the CSF concentration.

Results

Table 4 shows the diagnoses and CSF composition. Two subjects had a slightly raised protein concentration and in subject 2 the CSF pressure was higher than normal. None of these values was grossly abnormal.

The concentration of atenolol in plasma and CSF is shown in Table 4. Atenolol was detected in the plasma and CSF of each patient. The mean $\pm$ s.d. plasma concentration was $0.328 \pm 0.220 \mu\text{g ml}^{-1}$ and the mean CSF concentration was $0.053 \pm 0.019 \mu\text{g ml}^{-1}$ resulting in CSF:plasma drug ratios that varied between 0.081 and 0.494 . The concentration of atenolol in CSF was remarkably constant between individuals.

Table 3 Individual concentrations of pindolol in plasma [P] and cerebrospinal fluid [CSF] at various times after a single or multiple oral doses. Percentage of drug protein bound in plasma, packed cell volume (PCV), CSF:P ratio, diagnosis and CSF composition are also shown.

Subject	1	2	3	4	5	6	7	8	9	10	11	12
Age (years)	38	52	30	65	24	32	47	54	50	42	24	43
Sex	F	M	M	M	F	M	F	M	M	M	M	M
Dose	10 mg	10 mg	10 mg	10 mg	10 mg	5 mg b.d.	5 mg b.d.	5 mg b.d.	10 mg b.d.	10 mg b.d.	10 mg b.d.	10 mg b.d. (6 days)
Time after last dose (h)	3	3.5	2.25	2.5	1	3	3	18	3	2.5	3.5	4.5
[P] ng ml ⁻¹	47.9	39.0	26.5	27.5	57.8	17.1	27.2	11.6*	66.7	47.5	48.5	27.6
[CSF] ng ml ⁻¹	12.0	ND	ND	ND	ND	5.1	6.2	15.8	24.5	17.3	16.5	5.3
% drug bound	73.5	79.8	81.5	64.7	61.7	—	—	—	56.3	61.7	63.5	76.8
[Free P] ng ml ⁻¹	12.7	7.9	4.9	9.7	35.7	—	—	—	29.2	18.2	17.7	6.4
CSF:P	0.250	—	—	—	—	0.298	0.228	1.362	0.367	0.364	0.340	0.192
Theoretical CSF:P ratio	0.297	—	—	—	—	—	—	—	0.489	0.429	0.409	0.260
Diagnosis	NYD	CS	MS	Dementia	NYD	MND	Anxiety	Cord compression	NYD	?Demyelination	L'hermittes tension headache	CS
CSF composition												
cells	0	2	124	0	0	0	3	1	4	0	0	0
Protein (g l ⁻¹)	0.27	0.28	0.69	0.46	0.22	0.41	0.26	1.03	0.35	0.58	0.42	0.34
Pressure	—	—	—	—	—	110	130	160	120	130	130	—

* at limit of detection of assay method

ND = not detectable

MS = multiple sclerosis

MND = motor neurone disease

CS = cervical spondylosis

NYD = not yet diagnosed

Table 4 Individual and mean $\pm$ s.d. concentrations of atenolol in plasma (P) and cerebrospinal fluid (CSF) in nine subjects after taking a single dose of 100 mg atenolol orally or 100 mg twice daily for 3 days. CSF:P ratios, diagnosis and CSF composition are also shown

Subject	Age (years)	Sex	Dose (mg)	Time after last dose (h)	Concentration ($\mu\text{g ml}^{-1}$)		CSF:P ratio	Diagnosis	CSF cells	Composition Protein (g l^{-1})	Pressure
					Plasma	CSF					
1	27	M	100	4.5	0.083	0.041	0.494	NYD	0	0.33	150
1	47	F	100	3	0.215	0.082	0.381	Brainstem demyelination	0	0.53	250
3	44	M	100	3	0.446	0.044	0.099	?Cord compression	0	0.52	160
4	38	M	100	3	0.569	0.046	0.081	?MS	9	0.38	190
5	31	M	100 12 hourly (2 doses)	3.5	0.582	0.225	0.387	Old cardiovascular accident	0	0.60	160
6	30		100 12 hourly	5	2.355	0.174	0.074	?MS	0	0.23	170
7	24		100 12 hourly	5	1.680	0.127	0.076	?MS	0	0.47	130
8	24		100 12 hourly	3	0.537	0.181	0.337	Tension headache	0	0.39	160
9	39		100 12 hourly	3	0.865	0.159	0.184	?MS	15	—	180

NYD = Not yet diagnosed
MS = Multiple sclerosis

Study 8: Methods

An oral dose of atenolol 100 mg was given twice daily for 3 days to five patients aged 24 to 39 years. The last dose was taken 3 or 5 h before lumbar puncture. Sampling was as described in Study 7.

Results

Subject 5 had a raised CSF protein concentration and subject 9 a slightly raised cell count; all other findings were normal and did not suggest any abnormality in the blood-brain barrier of these patients (Table 4).

The concentration of atenolol in plasma and CSF is also shown in Table 4. Atenolol was detectable in the plasma and CSF of all 5 patients in higher concentrations than those measured in Study 7. The plasma concentrations varied from $0.537 \mu\text{g ml}^{-1}$ to $2.355 \mu\text{g ml}^{-1}$ whereas the CSF concentrations were similar in all five patients (mean $\pm$ $0.173 \pm 0.036 \mu\text{g ml}^{-1}$). These findings were similar to those of Study 7 where a single dose of atenolol was given. The CSF:plasma drug concentration ratios varied substantially from 0.074 to 0.387.

Discussion

The results of the present work confirm that lipid-solubility, pK_a , and the extent of plasma protein binding govern the extent and rate of penetration of a drug into CSF. The lipophilic drug propranolol achieved equilibrium between CSF and plasma less than 1 h after oral administration and its concentration in CSF was related to the free concentration in plasma. Propranolol was 90% bound to plasma proteins which is between the values of 82.3% and 84.2% reported by Barber *et al.* (1978) and Mucklow *et al.* (1978) and that of 93.6% published by Evans & Shand (1973). The concentration of propranolol in CSF was always less than that free in plasma. Due to the pH of CSF being slightly lower than that of plasma, a CSF:free plasma drug ratio of a little greater than unity would be predicted from theoretical considerations. Equation 1 describes the theoretical equilibrium across a lipid membrane for weak bases such as the β -adrenoceptor antagonists:

$$R = \frac{1 + 10^{(\text{pK}_a - \text{pH}_{\text{CSF}})}}{1 + 10^{(\text{pK}_a - \text{pH}_p)}} \times \frac{f_p}{f_{\text{CSF}}} \quad \dots \text{Equation 1}$$

where: R = concentration ratio between CSF and plasma

pK_a = pK_a of drug (= 9.45 for propranolol; 9.26 for pindolol; 9.50 for atenolol)

pH_p = pH of plasma (assumed to be 7.40)

- pH_{CSF} = pH of CSF (7.32 to 7.37)
 f_p = fraction of drug unbound to plasma proteins
 f_{CSF} = fraction of drug unbound to CSF proteins (assumed to be 1.0)

The theoretical CSF:plasma ratios of propranolol concentrations are shown for individual patients and as a group mean in Table 2. It may be that because propranolol is so lipophilic its removal from the CSF via brain tissue and blood capillaries prevents the theoretical equilibrium being attained. A similar CSF:plasma ratio to that of 0.07 in the present work, 0.1, has been found by Cruickshank *et al.* (1981) in three patients; however, the free concentration of propranolol in the plasma of these patients is unknown.

The concentration of pindolol in CSF is governed by the same factors as for propranolol, however, in the case of this less lipid-soluble drug, the experimental CSF:plasma ratio of 0.29 is only a little lower than that of 0.34 which equation 1 predicts (Table 3). Further support for the theory of passive drug distribution across membranes was that the patient who took pindolol and who had spinal cord compression with raised CSF protein (subject 8) also had an elevated drug level in his lumbar CSF which was presumably sampled below the blockage. It is not known why four of the five patients who received a single dose of pindolol had no detectable pindolol in their CSF when the concentration in plasma was similar to that after multiple oral doses. A brain:blood pindolol concentration ratio of 4:1 has been measured in animals (Aellig, personal communication) and this fits in with the lower lipid-solubility of pindolol compared with propranolol.

The penetration of atenolol into CSF contrasts with that of propranolol and pindolol and agrees with the results of animal investigations. From equation 1, a theoretical CSF:plasma equilibrium ratio of 1.06 would be predicted for atenolol due to its low protein binding, however, the experimental ratio varied from 0.08 to 0.41. This variability was due to the fact that although plasma concentrations of atenolol differed between patients, the CSF concentrations in the small number of patients studied were relatively constant at about $0.05 \mu\text{g ml}^{-1}$ after a single oral dose and about $0.17 \mu\text{g ml}^{-1}$ after multiple oral doses. The findings suggest that the concentration of atenolol in CSF might be kept low by means of a continual 'washout' effect; the rate of penetration of atenolol into CSF is low and the renewal of CSF by bulk flow which occurs every 10 h is sufficiently rapid to prevent 'true' equilibrium being attained. Cruickshank *et al.* (1981) have similar results. In three patients they found the CSF concentration was $0.07 \mu\text{g ml}^{-1}$ after taking atenolol for one week and the mean brain:plasma concentration ratio (obtained during repair of an aneurysm)

was variable with a mean of 0.1 due to the brain concentration being fairly constant at about $0.15 \mu\text{g ml}^{-1}$. The brain:CSF concentration ratio in these patients was about 2:1 which contrasted with the reported values of 17:1 for propranolol and 16:1 for metoprolol. However, these ratios suffer from the limitations of not taking into account the blood trapped in each sample of brain tissue at assay; had this been done, the difference between the lipophilic and hydrophilic β -adrenoceptor antagonists might have been even greater. Also concentrations of drugs are only known in the small samples of brain tissue made available for drug assay in the process of surgically repairing an aneurysm and the particular brain areas of origin of these samples are not known. It would seem from these nevertheless interesting findings, that there is a separate equilibrium of drug concentration between brain and CSF which is again dependent on lipid-solubility. CSF concentration seems a poor predictor of β -adrenoceptor antagonist concentration in the brain and clearly, when one thinks of drug concentrations in the CNS this difference must be considered. It is, however, open to discussion whether drug concentration in CSF or brain tissue is best related to pharmacological action. If there is free passage of a drug between CSF and brain extracellular water, as mentioned earlier, drug in CSF might be equally important in determining a central action.

Propranolol has recently been shown to effectively treat florid symptomatology in some cases of both acute and chronic schizophrenia and in manic patients (Atsmon *et al.*, 1972; Yorkston *et al.*, 1977; Sheppard, 1979). Where beneficial effects have been observed doses have been high in relation to those normally required to effect peripheral β -adrenoceptor-blockade, suggesting that a metabolite or other actions of the drug such as antagonism of 5-hydroxytryptamine receptors (Conway *et al.*, 1978) might be involved. Typical plasma concentrations with these high doses of propranolol would be in the region of $1 \mu\text{g ml}^{-1}$. If the CSF:plasma drug ratio of 0.07 were maintained at these plasma levels, the concentration of propranolol in the CSF would be approximately 70 ng ml^{-1} which is within the range of plasma concentrations where peripheral β -adrenoceptor blockade is seen (although it is still high if one considers free plasma concentrations of drug).

The possibility that a central action of β -adrenoceptor antagonists may account for their anti-hypertensive effect had been discussed by Prichard (1978) and largely rejected. One of the reasons given for this was that a β -adrenoceptor blocking drug with low brain penetration such as atenolol is still an effective anti-hypertensive agent. It must be remembered that the CSF concentration of this and other hydrophilic drugs is likely to be adequate for β -adrenoceptor antagonism at the high doses often used to treat

hypertension and consequently, that a central action of β -adrenoceptor antagonists cannot be ruled out on the grounds that they do not penetrate the CNS as a whole.

Adverse reactions relating to the CNS, such as psychosis, depression, hallucinations, nightmares and insomnia are relatively rare with atenolol (Simpson, 1977; Fleminger, 1979; Henningsen & Mattiasson, 1979). Psychotic problems and other CNS side-effects appear to arise with lipid-soluble agents which enter the brain in high concentrations (Hinshelwood, 1969; Shaw & England, 1977; Fleminger, 1978). In view of this evidence it seems likely that it is the brain concentration and not that in the CSF which is important in determining whether a β -adrenoceptor antagonist will produce CNS-side-effects.

This series of experiments has shown that the rate of entry and the attainment of the theoretical equilibrium ratio between the concentration of a β -adrenoceptor antagonist in CSF and that free in

plasma depends on the lipid-solubility of the compound. This is in agreement with recent work by Feller *et al.* (1980) who showed that for eleven unrelated drugs the CSF:plasma water concentration ratio bore what appeared to be an approximate hyperbolic relationship to the lipid-solubility of the drug (represented by the log of the octanol:water partition coefficient (P)). For drugs with P values below 2, the CSF:plasma water concentration ratio < 1.0 and, for drugs with a P value from 2 to 900, the CSF:plasma water concentration ratio was 1.0. The data from the present work for atenolol and pindolol fit the plot obtained by Feller *et al.* (1980), however, we found that the CSF:plasma water ratio of propranolol concentrations was consistently less than 1.0 and it is possible that at very high octanol:water partition coefficients, such as that of propranolol (log P = 3.65), this ratio falls as seen across other lipid membranes (Penniston *et al.*, 1969) and drug penetration into CSF is thus more of a parabolic function of log P. This remains to be shown.

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(Received December 18, 1980)