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β-ADRENOCEPTOR BLOCKERS AND THE BLOOD-BRAIN BARRIER

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1 This study on 21 neurosurgical patients was set up to investigate the extent to which four chronically administered β-adrenoceptor blockers, propranolol, oxprenolol, metoprolol and atenolol, cross the blood-brain barrier and enter the cerebrospinal fluid (CSF) and brain tissue. The concentration in the CSF of the three lipophilic β-adrenoceptor blockers, propranolol, oxprenolol and metoprolol, approximated to the free drug concentration in the plasma, and was a poor predictor of brain concentration. These three lipophilic β-adrenoceptor blockers appeared in brain tissue at concentrations 10–20 times greater than that of hydrophilic atenolol. The approximate brain/plasma ratio for propranolol was 26, for oxprenolol 50, for metoprolol 12 and for atenolol 0.2.

2 The low concentration of atenolol in brain tissue is possibly responsible for the low incidence of central nervous system-related side effects in patients on this agent compared to lipophilic β-adrenoceptor blockers.

Introduction

β-adrenoceptor blockers are now well accepted agents for the treatment of hypertension and angina. They are, as a group of drugs, efficacious with relatively few accompanying side effects. However, there are marked pharmacodynamic and pharmacokinetic differences between the various β-adrenoceptor blockers which may have important clinical implications.

The present study is concerned with the central nervous system (CNS) and the ability of four β-adrenoceptor blockers to cross the blood-brain barrier. The two important properties which determine the extent of penetration of the blood-brain barrier are the lipid/water partition coefficient and plasma protein binding. Propranolol (Inderal®, ICI Ltd) is lipophilic (log octanol/water partition coefficient of 3.65 = log P) and highly plasma protein bound (approx. 90%); oxprenolol (Trasicor®, Ciba Laboratories) is also lipophilic (log P = 2.18) and highly plasma protein bound (approx. 70%); metoprolol (Lopresor®, Geigy Pharmaceuticals) is lipophilic (log P = 2.15) but lowly plasma protein bound (approx. 10%) and atenolol (Tenormin®, ICI Ltd) is hydrophilic (log P = 0.23) and lowly plasma protein bound (approx. 5%).

Methods

β-adrenoceptor blockers were not given to any patient with a history of airways obstruction, heart failure or heart block. The dose of β-adrenoceptor blocker was chosen in accordance with both makers' recommendations and commonly used dosage. It was also considered that the doses used would effect approximately the same amount of β-adrenoceptor blockade over 24 h. The study fell into two sections:

1. Nine patients (8 had sustained a subarachnoid haemorrhage (SAH) at least 1 week before, and one had back pain) received β-adrenoceptor blocker therapy for 5–11 days (Table 1) before lumbar puncture. Such patients have already been shown to benefit β-adrenoceptor blockade (Neil-Dwyer, Walter, Cruickshank, Doshi & O'Gorman, 1978; Neil-Dwyer, Walter & Parsons, 1979). β-adrenoceptor-blockers are also useful as anxiolytics before lumbar puncture. Lumbar puncture was performed for diagnostic purposes in the case of SAH and for myelography in the case of back-pain. Three of the patients, comprising three women of mean age 52 years, received atenolol 100 mg once daily; three, comprising two

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Table 1 Mean pulse rates and blood pressures before and on last day of β-adrenoceptor blocker treatment

	β-adrenoceptor blocker	Before treatment		Last day on β-adrenoceptor blocker	
		Pulse rate (beats/min)	BP (mmHg)	Pulse rate (beats/min)	BP (mmHg)
	Propranolol ($n = 3$)	77	142/80	63	113/73
Study 1	Metoprolol ($n = 3$)	82	162/90	61	137/73
	Atenolol ($n = 3$)	93	210/123	70	140/80
	Propranolol ($n = 3$)	73	140/83	60	117/70
	Oxprenolol ($n = 3$)	77	143/80	68	133/77
Study 2					
	Metoprolol ($n = 3$)	78	140/80	69	123/73
	Atenolol ($n = 3$)	83	133/83	66	120/73

women and one man of mean age 48 years, received propranolol 80 mg twice daily; and three, comprising two women and one man of mean age 56 years, received metoprolol 100 mg twice daily. Two hours after the last tablet, a blood (plasma for metoprolol) sample was taken and then a lumbar puncture performed for CFS collection. Propranolol concentration was estimated according to the GLC method (McAinsh, Baber, Smith & Young, 1978), and atenolol and metoprolol (Hazleton Laboratories) concentrations were estimated according to an amended method of Scales & Copsey (1975).

2. Twelve patients, ten with either anterior or middle cerebral arterial aneurysms and two with chronic depression/anxiety requiring stereotactic tractotomy, received the β-adrenoceptor blocker for 3–22 days before surgery (Table 1). Three patients, comprising two women and one man of mean age 44 years, received propranolol 80 mg twice daily; three, comprising two women and one man of mean age 42 years, received metoprolol 200 mg daily (one on 100 mg twice daily and two on the 200 mg slow release preparation); three, comprising three women of mean age 36 years, received oxprenolol 160 mg slow release; and three, comprising two men and one woman of mean age 58 years, received atenolol 100 mg once daily. Last tablets were given 1–10 h pre-operation (Table 1). At operation, in order to display the difficultly placed aneurysms, small portions of brain (from frontal or temporal cortex—this is a routine procedure) were removed. Prior to stereotactic tractotomy, a routine small portion of brain is removed. The samples were wiped with a dry gauze and immediately deep frozen. At the same time, a CSF and blood (plasma) sample were taken. These samples were put immediately into deep freeze. In the case of metoprolol, the blood was centrifuged. Propranolol concentration was estimated according to the GLC method (McAinsh *et al.*, 1978) and atenolol, metoprolol (Hazleton Laboratories) and oxprenolol (Hazleton Laboratories) concentrations were estimated according to an amended method of Scales & Copsey (1975).

Results

Study 1

The mean pulse rates and blood pressures before, and on the last day of β-adrenoceptor blocker treatment are shown in Table 1. Table 2 shows the mean blood (plasma) and CSF concentrations of propranolol, metoprolol and atenolol. Atenolol (being virtually non-metabolised) appeared at higher concentration in the blood than the other two β-adrenoceptor blockers. Propranolol was only just detectable in the CSF, whereas the other two β-adrenoceptor blockers occurred at concentrations more than 10 times greater than that of propranolol. The blood/CSF

Table 2 Mean concentration of β-adrenoceptor blockers (chronic oral administration) in blood (plasma), CSF and brain

β-adrenoceptor blocker (dose)	n	*Individual time on drug (days)*	*Individual pre-op dose time (h)*	*Plasma concentration (ng/ml)*	*Mean value*	*CSF concentration (ng/ml)*	*Mean value*	*Brain concentration (ng/g)*	*Mean value*	*Plasma/CSF ratios*	*Mean value*	*Brain/Plasma ratios*	*Mean value*	*Brain/CSF ratios*	*Mean value*
Propranolol		11	2	336		9*				37					
80 mg twice daily	3	7	2	204	207	16*	12	Not done		13	19				
		5	2	82		10				8					
Metoprolol		5	2	140		80*				2					
100 mg twice daily	3	8	2	90	150	150	163	Not done		0.6	1	—		—	
		8	2	220		260				1					
Atenolol		7	2	1800		110				16					
100 mg once daily	3	10	2	1330	1270	135	127	Not done		10	10	—		—	
		7	2	680		135				5					
Propranolol		9	5	17		3*		830		5.7		49		277	
80 mg twice daily	3	11	10	72	153	3*	15	1183	2561	24	13	16	26	394	273
		11	4	370		38		5669		10		15		149	
Oxprenolol		11	4	1580		50		1440		32		0.9		29	
160 mg daily	3	8	4	370	650	40	40	1250	1380	9.3	13	3.4	50	31	36
		13	4	10		30		1443		0.3		144		48	
Metoprolol		22	4	150		130		2108		1.2		14		16	
200 mg daily	3	14	4	40	240	90	100	685	1520	0.4	3	17	12	11	17
		3	4	350		70		1752		7.6		3.3		25	
Atenolol		10	10	500		72		100		8		0.2		1.4	
100 mg once daily	3	3	1	300	1000	40	66	140	133	7	14	0.5	0.2	0.5	1.3
		6	4	2000		85		160		26		0.1		1.9	

*Not significantly different from zero

ratio was approximately 19 for propranolol, 10 for atenolol and 1 for metoprolol.

Study 2

Table 1 shows the mean pulse rates and blood pressures before, and on the last day of, β-adrenoceptor blocker treatment. Table 2 shows blood (plasma), CSF and brain concentrations of propranolol, oxprenolol, metoprolol and atenolol. The blood and CSF concentrations of propranolol, metoprolol and atenolol are broadly in agreement with those in Study 1. Oxprenolol, being highly plasma protein bound like propranolol, appeared at low concentration in the CSF relative to plasma concentration, with a plasma/CSF ratio of approximately 13.

The brain concentration for the three lipophilic β-adrenoceptor blockers was high, particularly for propranolol. The concentration of propranolol in the brain was about 20 times greater, and of oxprenolol and metoprolol about 10 times greater, than the concentration of hydrophilic atenolol. The brain/plasma ratios were approx. 26 for propranolol, 50 for oxprenolol, 12 for metoprolol and 0.2 for atenolol. The brain/CSF ratios were approx. 273 for propranolol, 36 for oxprenolol, 17 for metoprolol and 1.3 for atenolol.

Discussion

Administration of β-adrenoceptor blockers was in no way detrimental to the patient or the surgical procedure. Indeed it has already been shown that propranolol prevents catecholamine-linked myocardial necrosis in SAH (Neil-Dwyer *et al.*, 1978) and that the quality of survival in cases of SAH is improved (Neil-Dwyer *et al.*, 1979).

Figure 1 illustrates how a β-adrenoceptor blocker might theoretically be expected to be distributed in the plasma and CNS. Unbound, or free, β-adrenoceptor blocker in the plasma should equilibrate with both the bound drug in the plasma and the free drug in the CSF and brain: the free drug in the CSF and brain will in turn equilibrate with bound drug in the CSF and brain. The blood-brain barrier, which is the tightly packed endothelial cells of the capillaries supplying brain tissue, will be no obstacle to lipophilic agents which pass freely through cell membranes. Thus equilibration has been shown to be rapid for lipophilic propranolol (Myers, Lewis, Reid & Dollery, 1975) and metoprolol (van Zwieten & Timmermans, 1979). Hydrophilic β-adrenoceptor blockers appear to equilibrate more slowly (van Zwieten & Timmermans, 1979; Scales & Cosgrove, 1972).

In the present study the CSF levels of the three lipophilic β-adrenoceptor blockers did indeed approximately reflect the concentration of unbound, free drug in the plasma. Likewise, the high brain concentration of these three β-adrenoceptor blockers closely reflected their octanol/water partition coefficients and thus the high affinity of brain tissue

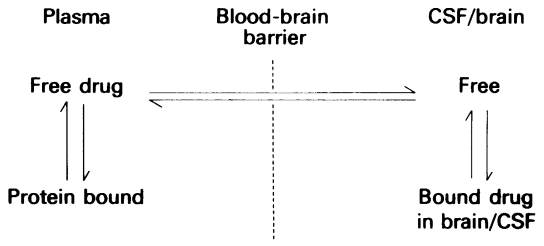

Figure 1 CNS/β-adrenoceptor blocker study: β-adrenoceptor blocker distribution—blood/CSF/brain

for these lipophilic agents. Atenolol like metoprolol is lowly bound to plasma proteins but, being hydrophilic, appears to have difficulty in crossing the blood-brain barrier into the CSF resulting in a high plasma/CSF ratio. Similarly relatively small amounts of atenolol enter the brain tissue, irrespective of the time of exposure to the agent or its plasma concentration. Thus effectively the CNS appears to be buffered against peak plasma levels of atenolol. It seems unlikely that had the patients been exposed to a longer period of atenolol administration (mean approximately 1 week in the present sudy), higher brain concentrations would have arisen. Street, Hemsworth, Roach & Day (1979) showed that in the rat brain the concentration of atenolol after 3 weeks' dosing was no higher than that observed at one week.

It might be questioned as to whether or not the blood-brain barrier is intact in patients who have had a SAH, thus throwing doubt on the validity of the data in this study. In fact it seems unlikely that the blood-brain barrier is impaired as the brain concentrations of propranolol, oxprenolol, metoprolol and atenolol in this study are almost identical to those obtained by Street *et al.* (1979) in the rat. Likewise, our results are consistent with those of Taylor, Carroll & Jefferson (1979) who studied CSF/plasma ratios for atenolol, propranolol and pindolol in patients receiving routine lumbar punctures.

The marked differences in brain concentration of the hydrophilic and lipophilic β-adrenoceptor blockers shown in this study might be clinically relevant. Two patients suffering from troublesome hallucinations on propranolol became well on switching to atenolol (Fraser & Carr, 1976). In another report all seven patients experiencing hallucinations on propranolol benefited from the switch to atenolol (Fleminger, 1979). In a group of

720 patients receiving a variety of lipophilic β-adrenoceptor blockers, 167 were experiencing unacceptable side effects: all were switched to a hydrophilic β-adrenoceptor blocker (atenolol) (Mattiasson & Henningsen, 1978). Of the 62 cases who were experiencing CNS-related side effects (hallucinations, nightmares and insomnia), 58 either lost their symptoms completely or were markedly improved.

Finally it should be said that an antihypertensive action mediated via the CNS by the various β-adrenoceptor blockers is neither proven nor disproved by the present data.

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