THE EFFECT OF ACEBUTOLOL ON THE CEREBRAL CIRCULATION OF MAN

Although it is now well established *in vitro* that cerebral blood vessels have β as well as α adrenoceptors (Edvinsson & Owman, 1975) the effects of β-adrenoceptor agonist and antagonist drugs upon man's cerebral circulation have as yet not been fully studied.

Intravenously-administered isoprenaline in animals precipitates anaerobic glycolysis despite a substantial increase in brain blood flow and oxygen utilization (Xanalatos & James, 1972). Associated with these changes in brain metabolism hyperventilation occurs. The flow, metabolic and respiratory alteration are prevented by the prior administration of propranolol (James & MacDonell, 1975). Propranolol itself, in anaesthetized dogs, causes a fall in cerebral blood flow which does not appear to be secondary to a fall in arterial blood pressure (James & MacDonell, 1975). The fall in brain blood flow is accompanied by a greater fall, in percentage terms, of cerebral oxygen and particularly of cerebral glucose utilization. Similar results were found by McCulloch, O'Keane, Harper & MacKenzie (1975) in the baboon. These workers also noted that the responsiveness of cerebral blood vessels to CO_2 was diminished following β-adrenoceptor blockade. The mechanism by which these changes occur is obscure.

Acebutolol hydrochloride (M & B 17803A) is a β-adrenoceptor antagonist which has been shown in dogs to cause a fall in brain blood flow at the same time as decreasing metabolic requirements (Hares & James, 1976 unpublished observations). It also attenuates the effect of isoprenaline on brain metabolism. The purpose of the present work was to determine the effect of intravenous acebutolol on the cerebral circulation of man. However, it should be noted that whilst in the dog acebutolol has a greater affinity for β_1-adrenoceptors than for β_2-receptors, in man there is no evidence of significant cardioselectivity (Briant, Dollery, Fenyvesi & George, 1971).

The significance of this in relation to the cerebral circulation is unclear at present, but certainly in its absence of cardioselectivity acebutolol is representative of most of the β-adrenoceptor blocking agents currently available commercially. The drug also has moderate intrinsic sympathomimetic activity and membrane stabilizing activity.

Seven healthy volunteers mean age 34 years (range 30–38) and three hypertensive patients (age range 50–70 years) were studied. None of the patients had overt cardiac, renal or cerebrovascular disease. Informed consent was obtained from both volunteers and patients. The study was approved by the ethical committee of the hospital.

Cerebral blood flow was measured by the new ^{133}Xenon inhalation method of Wyper, Lennox & Rowan (1976) and their technique was very closely followed, with no significant differences in procedure. This technique combines the inhalation method pioneered by Obrist, Thompson, King & Wang (1967) and Mallett & Veall (1965) with the initial slope method of Paulson, Cronqvist & Risberg (1969). Corrections for arterial recirculation of the gas were made by monitoring the radio-activity of the end tidal air. Subsequent deconvolutional analysis of the cerebral decay curves was performed in the manner suggested by Wyper *et al.* (1976). The important point about this technique is that the inhalation period is very short. The radio-active gas is carried principally to the highly perfused organs such as the brain and only little is carried to the poorly-perfused structures in so short a period of time. Error due to extracranial contamination by isotope is thus minimized. This technique has been shown to give good agreement with the more direct but unacceptably traumatic internal carotid artery injection method (Wyper *et al.*, 1976).

End tidal CO_2 measurements were performed in the conventional way with a Beckman Infra red CO_2 analyser. The plasma acebutolol concentration was determined spectrophotometrically by the method of Cuthbert & Collins (1975).

The subjects were rested in the supine position for 15 min before recordings were commenced. The resting values of pulse, blood pressure and end tidal pCO_2 given represent the mean of three consecutive readings. Cerebral blood flow was then measured by the method given above. As soon as all control readings had been obtained acebutolol was infused in a total dosage of 0.2 mg/kg over a 10 min period. Ten minutes after the termination of infusion a blood sample for plasma acebutolol concentration was taken from the contralateral arm. Further measurements of heart rate, blood pressure, end tidal pCO_2 and cerebral blood flow were then recorded.

The effect of acebutolol on cerebral blood flow, end tidal pCO_2, blood pressure and heart rate are shown in Table 1. Following the infusion there was a significant increase in end tidal pCO_2, decrease in heart rate and fall in cerebral blood flow. Systolic and diastolic blood pressure were not significantly changed.

Fluctuations of pCO_2 have been shown by this and other methods to exert an appreciable influence on cerebral blood flow (Lennox, Wyper & Jawad, 1975). Following acebutolol, end tidal pCO_2 is increased. In the past several authors have made 'corrections' for fluctuations in CO_2 but such an adjustment does not

Table 1 The effect of acebutolol on cerebral blood flow (CBF), end tidal pCO_2, blood pressure (BP) and heart rate (HR)

	Before acebutolol				*After acebutolol*				
Volunteer	*HR (beats min^{-1})*	*BP (mmHg)*	*CBF (ml 100 g^{-1} min^{-1})*	*pCO_2 (mmHg)*	*HR (beats min^{-1})*	*BP (mmHg)*	*CBF (ml 100 g^{-1} min^{-1})*	*pCO_2 (mmHg)*	*Plasma level (mg ml^{-1})*
1	84	100/70	56	31	72	90/68	54	33	1.23
2	60	130/90	38	33	52	130/100	32	40	1.06
3	72	120/78	36	37	66	120/80	36	41	0.93
4	77	118/80	51	40	69	120/85	45	43	0.86
5	72	105/70	51	41	66	105/80	41	47	0.67
6	62	125/78	43	38	54	118/75	36	40	1.10
7	78	130/80	55	34	66	130/70	42	37	1.68
Mean	72.1	118/78	47.1	36	63.6**	116/80	40.9**	40**	1.08

** Significantly different from control at 1% level (paired *t*-test)
Fall in heart rate correlated with plasma acebutolol level ($P<0.01$) ($r=0.91$)
Fall in CBF did not correlate with plasma acebutolol level ($r=0.34$)

Patient									
1	84	200/115	52	36	84	180/100	34	40	0.34
2	108	160/95	31	30	80	174/98	27	36	0.11
3	94	190/110	37	41	80	190/115	30	43	0.87
Mean	95	183/107	40	36	81	181/104	30.3	40*	0.44

* Significantly different from control at 5% level (paired *t*-test)
Other parameters showed similar trend to volunteer results but with small numbers did not attain significance.

appear justifiable since it has been shown that following β-adrenoceptor blockade the reactivity to CO_2 is altered. Nevertheless in this study the decrease in brain blood flow cannot be explained by pCO_2 changes as the pCO_2 changes observed might have been expected to produce brain blood flow changes in the opposite direction; neither can the changes be ascribed to variation in blood pressure. There furthermore seems to be little relationship between the plasma concentration of acebutolol and the effect on cerebral blood flow. This study in man seems to confirm our finding in dogs (Hares & James, 1976 unpublished observations) that acebutolol causes a fall in cerebral blood flow. In that species the fall was associated with an even greater fall in oxygen and glucose demands.

Although no direct measurements of metabolism were made in this study, in situations where flow falls more than oxygen requirements or indeed where oxygen requirements increase more than flow, hyperventilation usually results (James, 1968). It thus seems likely that the effect of acebutolol on brain blood flow and metabolism is similar in both man and dog.

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