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COMPARISON OF EFFECTS ON CEREBRAL BLOOD FLOW OF RAPID REDUCTION IN SYSTEMIC ARTERIAL PRESSURE BY DIAZOXIDE AND LABETALOL IN HYPERTENSIVE PATIENTS: PRELIMINARY FINDINGS

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1 Diazoxide 300 mg and labetalol 150 mg were each injected intravenously on separate occasions into five patients with essential hypertension. The reduction in BP caused by labetalol was slightly greater than that produced by diazoxide.

2 In contrast the reduction in cerebral blood flow (CBF) by labetalol was not statistically significant, whereas diazoxide gave a greater and statistically significant reduction in CBF.

3 These observations suggest that labetalol may have an advantage over diazoxide for the rapid reduction in BP.

Introduction

THERE are various drugs available for intravenous injection to achieve rapid reduction in BP. These include diazoxide and labetalol. In order to obtain a consistent effect diazoxide must be injected rapidly; the maximum hypotensive effect is seen within 2 min after completion of the injection (Sellers & Koch Weser, 1969).

Whenever the systemic BP rises too high or falls too low, the cerebral arteries constrict or dilate, respectively, to ensure a constant CBF. This phenomenon of autoregulation occurs primarily in the small 'resistance' cerebral arteries. In a normotensive young person, the lower limit at which autoregulation can hold CBF constant is at a mean arterial BP of about 60 mmHg. When the BP falls below this, even maximal dilatation of the vascular bed of the brain cannot compensate for the decreased perfusion BP and CBF declines.

In chronically hypertensive patients, the lower limit of BP for autoregulation is higher than the limit for normotensive individuals. It has been shown (Strandgaard *et al.*, 1973) that CBF begins to decline when the mean arterial pressure (MAP) is lowered to about 120 mmHg. Rapid reduction in BP by bolus injections of diazoxide may reduce CBF below the limit of autoregulation (Goldberg *et al.*, 1977). The rapid reduction in BP and consequent reduction in CBF cause cerebral ischaemia which may progress to a completed stroke (Kumar *et al.*, 1976; Heinrich *et al.*, 1977). It therefore seemed appropriate to compare the effects on CBF of a rapid reduction in systemic BP by diazoxide and a newer drug, labetalol.

Methods

Five patients, all men, were selected for study. All were investigated to exclude curable causes of hypertension and were suffering from uncomplicated essential hypertension. Plasma urea concentration was in all cases less than 10 mmol/litre. None had received any regular treatment for hypertension, nor any other medication for 1 month before the study. Details of the patients' ages, weights and time since diagnosis are shown on Table 1.

BP was measured in the right arm with an automatic recording sphygmomanometer (Roche Arteriosonde) the accuracy of which had been checked against a Random-zero (Hawksley) sphygmomanometer.

Cerebral blood flow was measured using a 2-min slope[133] Xenon inhalation technique (Wyper *et al.*, 1976). The results were calculated using a nomogram (Wyper & Rowan, 1976). Changes in thoracic impedance were used to calculate stroke value, two tape electrodes being placed around the neck and two around the thorax (Kubicek *et al.*, 1970). From the

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Table 1 Details of patients

	Mean	*(Range)*
Age (yr)	54.8	(51–58)
Weight (kg)	74.2	(54–97)
Years since diagnosis	1.8	(0.5–4)

stroke volume thus derived and the pulse rate measured from the ECG, cardiac output was derived. The impedance method for cardiac output measurement correlates well with the standard dye dilution (Gabriel *et al.*, 1976) and thermodilution techniques (Handt *et al.*, 1977). Patients attended on two occasions 7 d apart, having taken only water after 2200 on the preceding evening. BP and pulse rate were measured 3 min and 30 min after lying down. In previous studies (Pearson & Havard, 1976) there was no further fall in BP after more prolonged rest. At the end of this period CBF and cardiac output were measured. The patients then received either an injection of diazoxide (300 mg/20ml) or labetalol (150 mg/30 ml), irrespective of body weight, into an antecubital vein. Injection was completed within 10 s for diazoxide and within 60 s for labetalol. The order of diazoxide and labetalol injection was randomized between patients.

After injection, BP and stroke volume measured at 1, 3, 5, 10, 30 and 60 min. CBF measurement was repeated 1 min and 60 min after injection was completed. Patients were asked to describe any symptoms that they experienced. In order to prevent symptoms due to postural hypotension, patients remained supine for 6 h after injection apart from sitting up 2 h after injection to eat breakfast and a light meal after a further 2 hours.

Informed written consent was obtained from all patients for their studies. Statistical significance was tested using Student's *t* test for paired observations.

Results

Blood pressure

BP after lying for 30 min was identical on each occasion (Table 2). One minute after injection of diazoxide, average ($\pm$ s.e. mean) BP fell from $196/116 \pm 13/6$ mmHg, to $168/87 \pm 6/3$ mmHg. This fall was statistically significant ($P < 0.01$) for systolic and diastolic BPs. Following injection of labetalol, BP fell from $200/113 \pm 9/6$ to $150/95 \pm$ mmHg after 1 min. The fall was again statistically significant ($P < 0.01$) for both systolic and diastolic BPs. Systolic BP fell further after injection of labetalol and at 5 min was significantly lower ($P < 0.05$) than that recorded after injection of diazoxide. Thereafter the BP recorded after injection of labetalol was slightly lower than that recorded after injection of diazoxide but there was no statistically significant difference on all occasions up to and including 1 h after injection.

There was no correlation between the weight of the patient and the maximum reduction in MAP despite a 150% variation in the doses of diazoxide and labetalol expressed as mg/kg. The maximum reduction in MAP was also independent of the pretreatment BP. In no case was excessive hypotension encountered. The minimum BP achieved was 115/91 mmHg.

Pulse rate

Injection of diazoxide produced a highly significant ($P < 0.01$) elevation in average pulse rate from 74 to 91 beats/min at 1 min after injection. This rose further to 97 beats/min after 5 min and there was still a significant tachycardia 1 h after injection. In contrast, labetalol caused a small reduction in pulse rate which was not statistically significant.

Cerebral blood flow (CBF)

The average CBF before injection was identical on both occasions. No reduction was detectable 1 min after injection. However, at 1 h after injection of diazoxide, CBF had fallen from 48 to 40 ml/100 g/min and this fall was statistically significant ($P < 0.02$). In contrast, 1 h after injection of labetalol, CBF had fallen from 48 to 43 ml/100 g/min but this was not statistically significant.

Cardiac output, stroke volume and ECG

Before injection, cardiac output was the same on both occasions. After diazoxide there was an increase of 27% in cardiac output by 3 min after injection, and this contrasted with a reduction of 18% at the same time after injection of labetalol. However, these changes were not statistically significant. Stroke volume was unaltered by either drug. All the patients had normal resting ECGs and there was no change in ST segments with either drug.

Side-effects

One patient felt hot and nauseated within 1 min of injection of labetalol and another patient developed scalp tingling within 5 min after labetalol. Both side-effects had disappeared within 20 min after injection.

Discussion

In the doses used in this study, both drugs caused large significant reductions in BP but labetalol was

Table 2 Mean values of BP, pulse rates, CBF and cardiac output of patients before and after intravenous injections of diazoxide and labetalol.

		Time after injection (min)									
		Pre 3	*Pre 30*	*1*	*2*	*3*	*4*	*5*	*10*	*30*	*60*
Blood pressure (mm Hg)		198	196	168‡	164‡	163‡	176‡	178‡	172‡	169‡	167‡
		109	116	87‡	90‡	91‡	92‡	90‡	93‡	99‡	101‡
Diazoxide	MAP	138	143	115‡	115‡	116‡	119‡	119‡	119‡	121‡	124‡
		205	200	150‡	154‡	154‡	151‡	148‡	143‡	151‡	155‡
Labetalol		112	113	95	103‡	99‡	92‡	100‡	96‡	95‡	98‡
	MAP	143	141	114†	120‡	118‡	116‡	116‡	114‡	114‡	117‡
Pulse rate											
	Diazoxide	80	74	91*	92*	96‡	97‡	97‡	94‡	86‡	80*
	Labetalol	87	70	71	72	72	72	68	69	68	65
CBF	Diazoxide		48	46							40†
(ml/100g/min)	Labetalol		48	48							43
Cardiac output	Diazoxide	4.7	4.3	5.4		5.5		5.4	4.9	4	6.0
(l/min)	Labetalol	4.6	4.5	4.5		4		4.9	4	6.8	6.0
Stroke volume (ml)											
	Diazoxide	64.8	57.3	63		57		60	57	68	60
	Labetalol	59.2	52	51		54		56	57	60	60

†P <0.05 compared with value pre-injection; †P <0.02 compared with value pre-injection; ‡P <0.01 compared with value pre-injection.

slightly more effective. In contrast, labetalol caused a smaller, statistically insignificant reduction in CBF, whereas diazoxide caused a larger, significant fall in CBF. As reduction in CBF caused by diazoxide may be related to the occasional cerebral ischaemia described after injection it may be important to consider this when choosing a drug for the rapid reduction in BP in chronically hypertensive patients.

The extent of the fall in BP after injection of diazoxide is difficult to control by adjusting either the rate of injection or the dose. In contrast, the rate and magnitude of reduction in BP achieved with injection of labetalol are easily controlled (Trust *et al.*, 1976; Pearson & Havard, 1978).

The increases in heart rate and cardiac output and lack of effect in stroke volume are in agreement with those observed in an earlier study (Prichard *et al.*, 1975). Clearly further studies are indicated to confirm these observations which have implications for the choice of drug for the rapid reduction in BP.

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