increased in a dose dependent fashion by betahistine hydrochloride (Seipel & Floam, 1975). It is unusual to find a drug that is taken orally that increases cerebral blood flow and we therefore designed a small trial to examine the effects of betahistine on cerebral blood flow in healthy volunteers.

The form of betahistine used was betahistine methanesulphonate contained in dialysing microgranules (The Laboratoires Gallier), the rate of betahistine release being dependent upon the pH of the digestive juices.

The trial was designed as a randomized, placebo controlled, double-blind, crossover study. Ten male subjects (mean age 37 years, range 23–51) were selected and medically examined for their suitability for inclusion in the trial. Written informed consent was obtained from each subject.

The dose of betahistine given was 30 mg/day taken in three doses after a meal for a week. A washout period of 1 week was allowed between the two treatments. Cerebral blood flow was measured by the 2 min slope $^{133}\text{Xenon}$ inhalation method of Wyper, Lennox & Rowan (1976) and analysed using the nomograms synthesized by Wyper & Rowan (1976).

End expiratory PCO_2 was continuously monitored by an infra-red capnograph. Blood pressure was measured using a standard mercury sphygmomanometer and simple reaction time using the reaction timer manufactured by Southern Techniques (Electronics) Ltd, Maidenhead, Berks.

The only side-effect was reported by subject 3 who complained of slight upper abdominal pain when taking the drug.

The results (Table 1) were analysed using Student's *t*-test.

No significant differences between the treatment groups for blood pressure, pulse rate, simple reaction time, the maximum end-tidal PCO_2 during the desaturation phase of flow measurement were found.

Cerebral blood flow however increased by 15% if this group is compared to the placebo group ($t=2.06$, $P<0.1$).

We consider the results of this small study worth reporting as we believe it to be the first time betahistine had been shown to increase cerebral blood flow in normal individuals by a reliable and well documented method.

It is interesting that the 15% increase seems attributable to three subjects. This suggests that there are certain predisposing factors that influence the response of the cerebral vessels to betahistine, one possibility being that these subjects suffer from some degree of cerebral arteriosclerosis. The nature of such factors is at present under investigation.

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Received August 4, 1980

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THE EFFECTS OF INTRAVENOUS DISOPYRAMIDE ON CEREBRAL BLOOD FLOW IN VOLUNTEERS

Disopyramide is widely used both orally and intravenously in the management of cardiac arrhythmias especially after myocardial infarction. It is generally a well tolerated drug with a low incidence of side effects. However, there have been a number of docu-

mented cases of collapse after intravenous (Mazgala & Huvelle, 1976) and oral administration (Manolas, Hunt, Dowling, Luxton, Vohra & Sloman, 1979). Dizziness and mental confusion have also been noted (Ward & Kinghorn, 1976) and convulsions have

occurred (Johnson, Martin & Strathdee, 1978). The mechanism for these episodes has not been clearly established although hypotension has been noted during collapse and ascribed to myocardial depression caused by the drug (Hayler, Holt & Volanis, 1978). Anticholinergic properties of the drug have been suggested as a cause for mental symptoms and convulsions (Johnson *et al.*, 1978). A fall in cerebral blood flow could account for these findings, and it therefore seemed appropriate to measure the effect of intravenous disopyramide on cerebral blood flow (CBF) and to document changes in stroke volume, pulse rate and blood pressure.

Seven subjects were studied. The mean age of the subjects was 37 years (range 25–56 years) and the mean weight 75.7 kg. Blood pressure was measured in right arm using a standard mercury sphygmomanometer. CBF was measured using a 2 min slope ¹³³Xenon inhalation technique (Wyper, Lennox & Rowan, 1976). The results were calculated using a nomogram (Wyper & Rowan, 1976). Two mylar tape electrodes placed around the neck and two around the thorax were used to record changes in thoracic impedance (Kubicek, Patterson & Witsof, 1970). The impedance method of cardiac output measurement correlates well with the standard dye dilution (Gabriel, Atterhog, Oro & Etelund, 1976) and thermodilution techniques (Handt, 1977). From the stroke volume thus derived and the pulse rate, measured simultaneously on the electrocardiogram, and cardiac output was calculated.

Baseline readings of pulse, BP, stroke volume and CBF were taken after the patient had been at rest for at least 15 min. Each subject then received an infusion in the left arm of disopyramide 2 mg/kg body weight (maximum dose 150 mg) over exactly 5 min. In the first 5 min and again between 15 and 20 min after the end of the infusion, the pulse rate, BP and stroke volume were recorded. Between 5 and 10 min after the end of the infusion, CBF was again measured.

Informed written consent was obtained from all subjects for the study. Statistical significance was tested using Student's *t*-test for paired observations.

The results are shown in Table 1.

Cerebral blood flow

No statistically significant change in CBF was noted after the disopyramide infusion.

Stroke volume and cardiac output

In every subject there was a reduction in both stroke volume and cardiac output after disopyramide. These were most marked immediately after the infusion of disopyramide when the mean falls 28% and 21% respectively. Both the changes were statistically highly significant ($P < 0.01$). Later measurement, between 15 and 20 min after the infusion, of stroke volume and cardiac output showed that they had increased again but had not yet reached baseline levels. These rises were also statistically significant ($P < 0.05$).

Pulse rate and blood pressure

The mean resting pulse rate rose significantly ($P < 0.05$) from 66 beats/min to 72 beats/min immediately after disopyramide infusion. Between 15 and 20 min after the infusion, the mean pulse rate had fallen to 70 beats/min, which was not statistically significantly different from the baseline value.

Side effects

All subjects complained of a dry mouth after disopyramide but no other symptoms were noted.

The dosage and infusion rate of disopyramide was the maximum recommended by the manufacturer, but no significant changes in CBF were noted. The

Table 1 The mean values of pulse rate, stroke volume, cardiac output, blood pressure and cerebral blood flow before and after infusion of disopyramide.

	Mean values			Blood pressure (mmHg)		CBF (ml 100 g ⁻¹ min ⁻¹)
	Pulse rate (beats/min)	Stroke volume (ml)	Cardiac output (l/min)	Systolic	Diastolic	
Baseline	66 (±10)	61 (±17)	3.9 (±0.8)	121 (±7)	82 (±7)	42 (±7)
Time after end of disopyramide infusion (min)						
0–5	72 (±11)*	44 (±10)†	3.1 (±0.5)‡	114 (±5)	85 (±8)	42 (±5)
5–10						
15–20	69 (±7)	50 (±10)†	3.4 (±0.6)‡	118 (±8)	88 (±4)	

* $P < 0.05$, † $P < 0.02$, ‡ $P < 0.01$

decrease in cardiac output noted was a reflection of the fall in stroke volume. The increase in pulse rate only partially compensated for the reduced stroke volume. As the blood pressure did not significantly change during the study, this suggests that the peripheral resistance increased to compensate for the reduction in cardiac output.

The decrease in cardiac output noted was consistent with previous observations in patients with heart failure (Jensen, Sigurd & Uhrenholt, 1976) and in patients with arrhythmias (Hulting & Rosenbamer, 1976) although another study (Sutton, 1976) using a smaller dose of disopyramide showed no significant change in cardiac index in subjects with normal left ventricular function. The observation of a reduction in cardiac output in this study, supports the suggestion that myocardial depression was responsible for

or contributed to some cases of collapse that have occurred with disopyramide (O'Keefe, Holt, Hayler & Medd, 1978; Manoles *et al.*, 1979) and that caution should be exercised in patients with impaired left ventricular function.

We thank Roussel Laboratories for financial support.

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Received August 4, 1980

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QUINIDINE DETERMINATION IN SERUM: ENZYME IMMUNOASSAY (EIA) V HPLC

Quinidine (Q) is an effective and widely used drug for the treatment of supraventricular and ventricular arrhythmias. The therapeutic-toxic ratio of Q is, however, quite narrow and its rate of elimination from the organism may considerably vary with age (Ochs, Greenblatt, Woo & Smith, 1978), cardiac (Ueda & Dzindzio, 1978) and liver (Kessler, Humphries, Black & Spann, 1978) function.

Measurement of serum levels is therefore often necessary to optimize the dosing regimen for individual patients. For this purpose HPLC techniques appear to be the most reliable, since they also allow a quantification of active Q-metabolites (Guentert & Riegelman, 1978). Yet, the utilisation of HPLC methods in the clinical laboratory is limited by the availability of instrumentation and time