METHODS FOR ASSESSMENT OF THE EFFECT OF DRUGS ON CEREBRAL BLOOD FLOW IN MAN

I.M. JAMES
Section of Clinical Pharmacology, Academic Department of Medicine, Royal Free Hospital, Pond Street, London NW3 2QG

Introduction

The importance of separately considering the effect of any drug on the cerebral as opposed to the rest of the circulation should really need no emphasis. Although the brain represents only 2% of the body mass it has a blood supply of 15% of the resting cardiac output, and utilises nearly a quarter of the body's total oxygen requirements at rest (Folkow & Neil, 1971). Even small regional changes in flow can result in catastrophic clinical sequelae.

Techniques and methods which are so often useful when studying other circulatory beds are frequently inappropriate or impossible to apply. The problems are not only methodological but in part physiological as well. Purves (1971) writes in his 'Physiology of the Cerebral Circulation', 'A review of the literature reveals that confusion has arisen most commonly not because faulty methods have been used but because important variables have not been adequately controlled. This applies most particularly to pharmacological studies of the cerebral circulation'.

Changes in the calibre of cerebral vessels occur over a large range of perfusion pressure in such a way as to hold cerebral blood flow constant. This is achieved by neurogenic and metabolic factors which are ill understood; (James, 1975). It may well be possible to miss a significant effect of a drug on the brain's circulation because of these inbuilt compensating factors.

Changes in blood gas tensions cause large changes in flow in such a way as to protect the metabolic environment of cerebral tissue. Thus hypoxia and hypercapnia increase flow whilst hypocapnia decreases it. It has to be decided in any study whether to allow ventilation to change freely or whether it should be controlled. Measurements of cerebral blood flow without any CO$_2$ tension measurements are useless. Moreover the so called correction for CO$_2$ tension changes are obviously spurious since cerebral blood flow—CO$_2$ curves are known to be affected by drugs. The effect of a drug may only be seen when the study is carried out at the extremes of the physiological range (MacDonnell & James, 1975). There has been a welcome tendency recently to evaluate the effect of drugs on the cerebral circulation not only at normal CO$_2$ tensions but over a range of tensions. Such an approach can give a great deal of further information but unfortunately increases the number of measurements necessary.

Technical problems

Only very few methods give quantitative information about blood flow in the human brain. This is due to the inaccessibility of the brain within the skull and to the anatomical complexity of the cerebral arterial and venous systems.

Although great efforts have been made since the last war to develop atraumatic methods many of these have yielded results of questionable value. It is only in the last few years that the problem has come near to solution. Even now there is no method which is satisfactory in all respects. In this review it will be necessary to describe some methods which although unsuitable for normal volunteer studies facilitate the understanding of recent trends and developments in methodology. By and large indicator methods constitute the only useful group currently available.

Indicator methods

In all these methods the indicator is delivered to the brain tissue and subsequently removed by the blood stream. There are two main groups of indicator methods. Firstly there are those methods which utilise indicators that are freely diffusible across the blood brain barrier and secondly those that utilise non diffusible indicators that remain within the cerebral vasculature.

The freely diffusible indicator methods are by far the most important and will be considered first.

Total cerebral blood flow: Measurement with diffusible indicators

This method which really is a variation of the Fick principle was described by Kety & Schmidt (1945, 1948). Although the brain does not clear substances from the blood in the same way as the kidney or the liver, it does absorb by physical solution an inert gas
such as nitrous oxide which reaches it by way of the arterial blood. The subject inhales a constant low concentration of nitrous oxide over a period of 10 min. During this 10 min inhalation period a series of blood samples are taken from either a brachial or femoral artery and from the internal jugular vein. At 10 min the arterial blood, cerebral venous blood and brain tissues are assumed to be in equilibrium. The quantity of a substance taken up by an organ in a given time equals the blood flow times the arterio-venous difference.

Flow in time t = \( \frac{Q_t}{C_a - C_v} \)

where \( Q_t \) = quantity of substance taken up in time t.

\( C_a \) = concentration of substance in the arterial blood.

\( C_v \) = concentration of substance in the venous blood.

In this instance the arteriovenous difference is of course continuously changing but nevertheless can be averaged over the period of inhalation if the sum of all the arteriovenous differences are taken

\( C_a - C_v = \int_0^t (C_a - C_v) \, dt \)

One can thus substitute in the initial equation for arterio-venous difference the area between the arterial and venous concentration curves drawn with respect to time. Furthermore so long as equilibrium is assumed, the total quantity of a substance taken up is a product of the venous concentration, blood brain partition coefficient \( \lambda \), and brain weight. Cerebral blood flow expressed per unit weight of brain can thus be shown to be equivalent to the height (i.e. cerebral venous concentration) times the blood brain partition coefficient over the area of the curve.

Flow per unit weight = \( \frac{C_v t}{\int_0^t (C_a - C_v) \, dt} \)

\[ = \frac{\text{Height of curve} \times \lambda}{\text{Area between arterial and venous curves}} \]

Unfortunately whilst ten minute inhalation is sufficiently long for a normal cerebral blood flow, where flows are low, 15 min or longer may be necessary (Lassen & Munck, 1955).

** Modifications **

The substitution of the radioactive gas \(^{85}\)Krypton for nitrous oxide was first suggested by Lassen & Munck (1955). Counting the beta radiation from Krypton is much easier than the long and tedious nitrous oxide analysis. The amount of blood required is also much less. Another advance came in 1964 when McHenry suggested looking at the desaturation curves as opposed to the saturation curves. In the classical Kety Schmidt method it is often difficult to ensure that the subject is breathing a constant concentration of gas. A temporary small leak of air around the mask whilst blood samples are being obtained can ruin a curve. In the McHenry method small leaks during the saturation phase do not have the same devastating effect on the desaturation phase so long as saturation has been achieved. The curves obtained therefore are much smoother Lassen & Klee (1965).

Concern has been expressed over the question whether samples taken from the jugular bulb are truly representative of cerebral venous drainage. However usually less than three percent of internal jugular vein blood at the level of the jugular bulb in man is derived from extracerebral sources (Shenkin, Harmel & Kety, 1948). Gross contamination is very unusual indeed (Lassen & Lane, 1961).

Whilst bilateral sampling of internal jugular blood has been recommended (Munck & Lassen, 1957), the complexity of such a procedure more than offsets any advantages for most investigations. One major advantage of the Kety Schmidt and similar methods is that cerebral metabolism can be calculated by multiplying the flow by the appropriate arteriovenous difference.

The disadvantages of these methods are obvious. Although with practice puncture of the jugular bulb and femoral artery should present no problems to the operator and although by using special needles and special local anaesthetic techniques the discomfort to the subject is minor (Brant, James & Pitcher, 1974), it nevertheless is often difficult to persuade normal subjects to volunteer for studies. The thought of a needle in the neck would seem to be very disconcerting to many people. Whilst retrograde catheterisation via the femoral or brachial vein is a possible alternative this introduces an appreciable radiation dosage due to the necessary screening.

** Measurement of regional cerebral blood flow:**

** Determination by intra-arterial injection of radioactive inert gas **

The passage through brain of an inert gas can be followed also by external scintillation detectors. The tracer, a gamma radiation emitter such as \(^{133}\)Xenon, dissolved in saline is given as a bolus injection onto the internal carotid or vertebral artery. An almost instantaneous peak of radioactivity is recorded by the head counter as equilibration takes place between blood and brain tissue. The ensuing clearance curve is dependent on the tracer being washed away by fresh uncontaminated arterial blood. The faster the blood flow, the faster the rate of clearance. Since the solubility of Xenon is much higher in air than in blood or tissues for practical purposes no recirculation of gas occurs.

Ideally in all the intraarterial methods in order to