Effect on intracranial pressure of meglumine iothalamate ventriculography

M. D. M. SHAW, J. D. MILLER, AND J. L. STEVEN

From the Institute of Neurological Sciences, Glasgow

SYNOPSIS Intraventricular pressure was studied in 12 patients undergoing ventriculography with a water soluble positive contrast medium. Isovolumetric instillation of meglumine iothalamate into the lateral ventricles and the anterior part of the third ventricle caused only a small increase in ventricular fluid pressure (1.3 ± 0.3 mmHg), but the pressure increased markedly (46.3 ± 3.7 mmHg; $P < 0.001$) when the contrast medium entered the posterior end of the third ventricle, aqueduct of Sylvius, and fourth ventricle. This sharp increase in intracranial pressure could not be attributed solely to postural changes or to alterations in arterial blood pressure. Possible mechanisms are discussed.

Pneumoventriculography and encephalography have been shown to produce pronounced increases in the intracranial pressure, particularly in those patients with intracranial space occupying lesions (Cronqvist *et al.*, 1963; Chawla, 1969; Philippon *et al.*, 1974). Dilatation of the ventricular system occurs, which increases with successive air injections (Lim *et al.*, 1972) and with passage of time (Schatzi *et al.*, 1947; Le May, 1967). These effects appear to be due to the large volume of air involved and the tendency of this volume to increase with the change from room to body temperature.

Since late 1969 it has been the practice in the Institute of Neurological Sciences, Glasgow, to use the water soluble contrast medium meglumine iothalamate for ventriculography on the grounds that clearer definition of the ventricular system is obtained, that the volumes of contrast medium used are small, and that there will be no tendency for the volume to change with the increase in temperature. Over 770 meglumine iothalamate contrast ventriculograms have been undertaken at this Institute without any clinical evidence of intracranial hypertension during, or after, the procedure. It was considered important to test the validity of this impression by monitoring intracranial pressure during positive con-

trast ventriculography in a limited number of patients.

METHODS

Studies were carried out in 12 patients in whom positive contrast ventriculography was undertaken as part of their normal management. Informed consent was obtained in all cases. The male/female ratio was 7/5, and the age range 3 months to 71 years. The diagnoses are shown in Table 1. Five of the patients had significant hydrocephalus.

A soft Jacques catheter (FG 8) was inserted into the right lateral ventricle through a right frontal burr hole, either immediately or some hours before ventriculography. In the interim period, intraventricular pressure monitoring was carried out using a small pressure transducer (Statham P 37B), which was taped to the vertex and which was connected to a two-channel amplifier chart recording system (Devices M2). This location of the transducer was to minimize hydrostatic pressure changes due to change in the position of the transducer relative to the ventricle during postural changes required for ventriculography. The transducer could not be placed on the head at the level of the foramen of Monro, because at this site it would have obscured part of the ventricular system on the radiographs.

Baseline intraventricular pressure in the recumbent position in bed was recorded, followed by a baseline recording in the sitting position in the x-ray unit (Elema Schönander Mimer III). The volume/

TABLE 1

DIAGNOSES OF 12 PATIENTS UNDERGOING POSITIVE CONTRAST VENTRICULOGRAPHY

Diagnosis	Level of response		Total
	Alert	Drowsy	
Thalamic neoplasm*	2	1	3
Brain-stem glioma	—	2	2
Head injury	1	1	2
Aqueductal stenosis*	1	—	1
Acoustic neurinoma*	1	—	1
Posterior fossa metastasis*	1	—	1
Pinealoma	1	—	1
Occipital lobe cysts*	1	—	1

* Patient with significant hydrocephalus.

pressure response was then determined by alternately removing and adding 1.0 ml cerebrospinal fluid (CSF), repeating the complete manoeuvre twice, and taking the mean value of the change in pressure occurring during the last four observations. This pressure change provides an index of brain compliance (Miller *et al.*, 1973). With the patient in the sitting position and the head slightly flexed forwards 5.0 ml CSF were removed and 4.0 ml meglumine iothalamate 35% w/v (Retro-Conray; May and Baker) introduced slowly into the frontal horn of the lateral ventricle and the catheter was flushed with 1.0 ml CSF so that no net volumetric change resulted. In two cases it was possible to remove only 1.0 ml CSF initially, and in a third case the meglumine iothalamate was introduced by barbotage before a second aliquot was introduced in the usual way. Ventriculography was then undertaken using fluoroscopy. Intraventricular pressure was monitored continuously during the positional change from the vertical to the horizontal (supine) sitting position. In the seven patients who did not immediately require a further procedure, intraventricular pressure monitoring was continued overnight. The volume pressure response was redetermined at the end of ventriculography and again in the seven patients at the completion of the overnight monitoring. In four patients intraventricular pressure was first recorded during the positional changes without injection of contrast medium. Significances were determined using Student's *t* test for paired and unpaired data.

RESULTS (Table 2)

Several patients were suffering from raised intracranial pressure (> 15 mmHg) so that the mean

TABLE 2

EFFECT OF POSITION AND OF VENTRICULAR INJECTION OF MEGLOMINE IOTHALAMATE ON VENTRICULAR FLUID PRESSURE AND ARTERIAL PRESSURE IN 12 PATIENTS

Position	Ventricular fluid pressure (mmHg)	Arterial blood pressure (mmHg)
Supine at rest	14.4 ± 1.83	98.4 ± 5.3
Sitting upright	-0.7 ± 2.6	101 ± 5.8
Sitting horizontal (4 patients only)	16.2 ± 2.51	—
Sitting upright + meglumine iothalamate	3.9 ± 3.5	—
Sitting horizontal + meglumine iothalamate	50.2 ± 4.3	98.2 ± 6.0

Values shown are the mean and the standard error of the mean.

value for ventricular fluid pressure in the recumbent patients was above normal at 14.4 ± 1.8 mmHg. When patients were moved from the horizontal lying to the upright sitting position, there was a fall in ventricular pressure of 15.2 ± 2.4 mmHg ($P < 0.001$).

On instilling meglumine iothalamate into the lateral ventricle there was a very small but constant increase in the intraventricular fluid pressure averaging 1.3 ± 0.3 mmHg ($P < 0.01$) (Table 3). A much larger increase (Fig. 1) occurred when the patient was tilted from the vertical to the horizontal, 46.3 ± 3.7 mmHg ($P < 0.001$), the larger proportion of which occurred after 40° of backwards tilt (Fig. 2), when the contrast medium could be seen flowing into the posterior part of the third ventricle, the aqueduct, and the fourth ventricle. The increase reached a maximum 15 ± 4.2 seconds after completion of the manoeuvre, although in the patient with aqueductal stenosis it did not occur

TABLE 3

EFFECT OF MEGLOMINE IOTHALAMATE IN NINE SITTING PATIENTS IN WHOM THERE WAS NO VOLUME CHANGE INDUCED

	Ventricular fluid pressure (mmHg)	
	Mean	SEM
Before	-0.7 ± 2.6	
After	0.6 ± 3.2	
Difference	1.3 ± 0.3	

Paired *t* test, 4.4; $P < 0.01$.

FIG. 1 Change in ventricular fluid pressure (VFP) after addition of meglumine iothalamate on change from vertical to horizontal position.

FIG. 2 Change in ventricular fluid pressure (VFP) with increasing degree of tilt.

until 55 seconds had elapsed. This increase in ventricular fluid pressure was significantly higher than the baseline ventricular pressure in the horizontal position ($P < 0.001$); it was transient (46.7 ± 1.96 min) and fell exponentially to resting levels with no evidence of neurological dysfunction during the period of raised pressure. There was no change in the volume/pressure response. There was no significant correlation between the baseline pressure, or the volume/pressure response, and the degree of change in the ventricular fluid pressure produced by meglumine iothalamate on tilting. The failure to

find a correlation between the volume/pressure response and the change in the intraventricular fluid pressure may be explicable on the basis that almost half the patients had significant hydrocephalus and that large ventricles interfere with the volume/pressure response (Miller and Leech, 1975). There was no change in the blood pressure during the change in ventricular fluid pressure. Tilting without meglumine iothalamate in four patients produced a significantly smaller rise in ventricular fluid pressure ($P < 0.001$), from -0.75 ± 3.2 to 16.2 ± 2.5 mmHg.

In one patient, in whom the whole ventricular system required outlining, the contrast medium was introduced by barbotage and he was then rotated forwards to 90° . This resulted in a small increase in pressure (from 9 to 17 mmHg). At this point fluoroscopy showed that, although there was contrast medium in the third ventricle, the aqueduct, and the fourth ventricle, it was very dilute; on adding further contrast medium in the usual way and tilting the patient backwards a considerable increase in ventricular fluid pressure (32 mmHg) was obtained.

In one patient iophendylate (Myodil; Glaxo) ventriculography was also undertaken. Replacement of 3.0 ml cerebrospinal fluid with 3.0 ml iophendylate in the sitting position produced no change in the intraventricular pressure, which remained at 19 mmHg, while tilting backwards through 90° produced a small increase of 6 mmHg to 25 mmHg.

DISCUSSION

Meglumine iothalamate is not liable to rapid expansion in volume and is, in this respect, theoretically safer than air. This is confirmed by the small change in ventricular fluid pressure which occurred when the contrast medium was added in the sitting position. Before the investigation, we thought that there could be a later slow increase in the intracranial pressure due to a possible osmotic effect of the meglumine iothalamate in augmenting CSF volume, but the sudden and dramatic rise in ventricular fluid pressure on tilting the patients to the horizontal position was a surprise finding which could not be accounted for by variations in the position of the transducer relative to the ventricular system

or to changes in the arterial blood pressure. Nearly all the patients were conscious and co-operative (Table 1), and no obvious respiratory changes were noted.

Some increase in the cerebrospinal fluid pressure is known to occur on tilting patients from the vertical to the horizontal position (Bradley, 1970). We have confirmed in a small number of patients that, while they are sitting in the ventriculography chair, an increase occurs in cerebrospinal fluid pressure on changing from the vertical to the horizontal position. This change is, however, much smaller than that produced by meglumine iothalamate on tilting in this study.

This change in ventricular fluid pressure might be due either to an increase in CSF volume, or to an increase in blood volume resulting from cerebrovascular dilatation and a consequent change in cerebrovascular resistance.

The increase in ventricular fluid pressure was almost immediate, except in the patient with aqueductal stenosis in whom the contrast medium was seen to pass very slowly through the aqueduct into the fourth ventricle. It seems unlikely that the response is due to an osmotic effect drawing extra fluid into the ventricular system. The patient who demonstrated the response to meglumine iothalamate but not to iophendylate suggests that water solubility may be of importance in determining the production of the response, which may be due to the chemical structure, the pH, or the molar concentration of the meglumine iothalamate.

Meglumine iothalamate can produce microscopical changes in the ipsilateral cerebral hemisphere when administered into the carotid artery of rabbits in high doses (Murphy, 1973). The changes seen are swelling of both the astrocytic foot processes and mitochondria, together with disruption and separation of myelinated fibres. In addition, breakdown of the blood-brain barrier was observed, consisting of: opening of the tight interendothelial junctions; increased pinocytotic transport across the endothelial cells; and, finally, as the injury progressed, opening of the interastrocytic junctions, thus opening up the extracellular space. The blood-brain barrier can also be opened by hypertonic sodium chloride and other water soluble contrast media—for example, 50% sodium diatrizoate (Hypaque) (Harrington *et al.*,

1966; Jeppsson and Olin, 1970; Waldron *et al.*, 1973)—which suggests that the damage may be the result of the molar concentration. Comparison of the effects of different water soluble media reveals that the extent of the damage to the blood-brain barrier is not proportional to the molar concentration, but correlates well with the protein binding ability of the contrast medium—for example, sodium acetrizate (Urokon 70%) is more toxic and a better protein binder than sodium diatrizoate (Harrington *et al.*, 1966).

The rapidity of the increase in intracranial pressure in this study strongly suggests cerebrovascular dilatation as the source. Since meglumine iothalamate can open the blood-brain barrier, it seems likely that it will penetrate relatively freely through the less tight junctions of the ventricular ependyma (Brightman, 1968; Rall, 1968). The contrast medium might also be taken up by the choroid plexus of the fourth ventricle (Brightman, 1968). It is tempting to speculate that meglumine iothalamate, having reached the extracellular space of the brain-stem, produces cerebrovascular dilatation by direct action on some structure in the brain-stem.

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