Positive contrast cerebral ventriculography using water-soluble media

Clinical evaluation of 102 procedures using methylglucamine iothalamate 60%

R. F. HEIMBURGER, J. E. KALSBECK, R. L. CAMPBELL,
AND J. MEALEY, JR.

From the Neurological Surgery Section, Surgery Department, Indiana University Medical Center, Indianapolis, Indiana, U.S.A.

Stereotactic surgery has created a need for more accurate radiographic visualization of the cerebral ventricles. Ideally, projections of both the anterior and the posterior commissure into the third ventricle on a single lateral film, and of both lateral walls of the third ventricle, in a single anterior-posterior or posterior-anterior (axial) film, are needed to guide precise placement of lesions in the basal ganglia. Injections of air and other gases do not often provide ventriculograms of this quality. Recognizing this deficiency of air studies, many neurological surgeons use positive contrast ventriculography for stereotactic procedures, and for more reliable visualization of mass lesions in the third and fourth ventricles. A review of the literature by Jefferson and Occleshaw in 1960 and by the authors revealed that ethyliodophenylundecylate was used in all the reports of positive contrast ventriculography after 1940, except by Gonsette, Dereymaeker, Hou, and Cornelis (1958) who used Lipiodol. Ethyliodophenylundecylate did not completely satisfy our criteria, so a number of other positive contrast media were tested in animals (Heimbürger, Campbell, Kalsbeck, Mealey, Goodell, in press).

Reproductions of human ventriculograms made with thorium dioxide 25% in 1932 by Radovici and Meller indicated that water-miscible, and possibly water-soluble media, were capable of producing the complete visualization of the third ventricle desired. Use of this medium was ruled out by reactions reported by Alexander, Jung, and Lyman (1934) and Stuck and Reeves (1938). Late sequelae were reported more recently by Hughes (1953) and Kyle, Oler, Lasser, and Rosomoff (1963).

Methylglucamine iothalamate 60% (NMG Ioth) was reported to produce less reaction when used for angiography (Dotter, Straube, Bilboa, and Hinck,

1962; Foster, Winfrey, Killen, and Sessions, 1962; and Hinck and Dotter (1962) than previously available media. It was also found to be well tolerated when injected in small doses into the cerebral ventricles and cisterna magna of dogs and rabbits (Back, 1963; and Kodoma, Butler, Tusing, and Hallett, 1962). We injected three water-soluble positive contrast media, frequently used for angiography, and emulsified iodized oils into the cisterna magna or ventricles of 150 animals. The water-soluble positive contrast media provided considerably better visualization of the ventricular system than did the emulsified iodized oils. Excessive doses of water-soluble positive contrast media, injected either into the cisterna magna or ventricle, were lethal. Less than one-third of the lethal dose was needed to produce good visualization of the ventricular system. Cisterna magna injections of large amounts of water-soluble medium produced convulsions. Convulsions were less likely to result from injections into the ventricular system. Autoradiographs made after injection of sodium iothalamate 60% containing radioactive iodine demonstrated that the material was absorbed through the pia mater over the cerebral cortex much more readily than through the ventricular ependyma. Convulsions were produced by placing 0.5 to 1.0 ml. of an isotonic solution of methylglucamine iothalamate on exposed cortex. Radioactive iodide injected into the cisterna magna as a part of sodium iothalamate appeared in the blood stream in less than five minutes. Virtually 100% of the radioactivity was excreted in the urine in 24 hours. Our figures agree that NMG Ioth is the least toxic of the water-soluble positive contrast media tested. Details of these toxicity studies will be reported in other papers (Heimbürger, Campbell, Kalsbeck, Mealey, and

Goodell, Campbell, Campbell, Heimburger, Kalsbeck, and Mealey, 1964).

Provided with these data NMG Ioth was first used for human ventriculography on 4 April 1962. A total of 102 ventriculograms were carried out in 90 patients between that date and 1 January 1964. Each of the patients has been followed for at least two years to detect evidence of later reactions or sequelae.

METHOD USED FOR WATER-SOLUBLE POSITIVE CONTRAST VENTRICULOGRAPHY

Methylglycamine iothalamate 60% was used first for ventriculography in preparation for stereotactic surgery. The stereotactic apparatus at Indiana University Medical Center holds the patient's head rigidly, with skeletal fixation, in a lateral position. The vertex of the head is slightly above the base, at an angle of 10°. For these studies a 14-gauge ventricular needle was introduced stereotactically into the uppermost lateral ventricle. The needle tip was directed toward the foramen of Munro, and stopped approximately 1 cm. cephalad to it. The slightly elevated position of the head resulted in low intraventricular pressure, and fluid did not usually flow spontaneously from the needle, to indicate that the ventricle had been cannulated. Following the first few cases measurement of electrical impedance at the needle tip was used to determine when the ventricle was entered (Fry, Fry, Leichner, and Heimburger, 1962). A small amount of air (1 to 3 ml.) was introduced through the needle and radiographs were taken to make sure the needle was in the ventricle, and not in an enlarged subarachnoid space. One to 3.5 ml. of NMG Ioth was diluted to 10 ml. with ventricular fluid. At first the entire 10 ml. of solution was injected rapidly into the ventricle. Lateral, straight axial and Chamberlain-Towne (half axial) radiographs were taken in rapid succession. Visualization of the anterior and posterior commissure on a single lateral view was excellent, but demonstration of both lateral walls of the third ventricle in the other two views was not up to expectations. To remedy this 6 ml. of the 10 ml. of NMG Ioth ventricular fluid mixture was injected and the lateral film taken immediately. The remaining 4 ml. was injected after the film cassettes were changed, and preparation completed for immediate exposure of the straight axial view. The third, half axial, view was exposed last within 30 seconds after the last 4 ml. of contrast material had been injected. This change in technique permitted clear visualization of both lateral walls of the third ventricle.

Reactions were minimal, and the films so good (Fig. 1) that NMG Ioth was also used for general purpose ventriculography. To fill the midline ventricles (third, aqueduct of Sylvius, and fourth) the patient was placed supine. The ventricular needle was introduced through a burr or twist drill hole near the coronal suture, 2.5 to 3.0 cm. lateral to the midline. The tip of the needle was directed toward the foramen of Munro, and the undiluted contrast material injected into the lateral ventricles in a single bolus. Equally good visualization has been achieved by injecting the medium in the same way with the patient in

the prone position ready for posterior fossa surgery. Occipital burr holes have not been used for ventriculography with NMG Ioth as it was thought that the contrast would not flow or diffuse into the third ventricle as readily if it were introduced from that direction.

Methylglucamine iothalamate 60% was injected into 10 dilated ventricular systems to demonstrate posterior fossa masses. This was done in the operating room. Lateral and axial radiographs were taken immediately after the material was injected. Surgery was usually started on these patients 10 to 15 minutes after the contrast material had been injected into the ventricle. Films of excellent quality were available to provide the information needed to continue with definitive surgery (Fig. 3). This procedure permitted introduction of ventriculojugular shunts in some of the patients without having to wait for air to leave the ventricular system.

Methylglucamine iothalamate 60% has been introduced into the ventricular confluence when supratentorial masses were suspected. Our limited experience suggested that the contrast medium should be diluted with several times its volume of ventricular fluid. The diluted solution was injected rapidly but without force. Films were exposed immediately after injection, as the radio-opacity started to disappear, within seconds or minutes.

RESULTS OF INTRAVENTRICULAR INJECTION

One hundred and two ventriculograms using NMG Ioth were performed on 90 patients. Sixty-nine were done in preparation for stereotactic surgery and 33 as general neurological surgery procedures. Seven of the patients had ventriculography with this material twice in preparation for separate stereotactic and surgical procedures, and two have undergone it three times.

VISUALIZATION OF THE VENTRICULAR SYSTEM All the ventriculograms made in preparation for stereotactic surgery produced the desired third ventricular visualization. The first four studies done for general neurosurgical purposes showed markedly enlarged ventricular systems. Visualization of the midline ventricles was not adequate in these four, because it was not realized how rapidly the radio-opacity disappears. When films were exposed immediately after injection of the material, more satisfactory ventriculograms resulted. The contrast started to disappear from the midline ventricles in seconds or minutes and was completely out of the lateral ventricle in 60 to 90 minutes (Figs. 1 and 2).

In a few instances a combination of pneumoencephalography and positive contrast ventriculography provided information which neither did separately. Figure 4 reproduces films made on a 3½-month-old child suspected of having a diencephalic neoplasm. Several attempts at ventriculography and pneumoencephalography failed to

FIG. 1

FIG. 1. Methylglucamine iothalamate 60% ventriculogram, performed under local anaesthesia for stereotactic surgery on a 69-year-old woman with Parkinsonian tremor. Note calcific deposits in the falx cerebri in the axial views.

FIG. 2

FIG. 2. Same patient as Figure 1. Film exposed one and a half hours after injection of methylglucamine iothalamate 60%. The contrast material disappeared from the third ventricle in about two minutes. It seems to disappear even more quickly from the ventricles of younger patients.

FIG. 3. Methylglucamine iothalamate 60% ventriculogram performed through the separated coronal suture of a 4-year-old child. The aqueduct of Sylvius is obstructed and kinked. Surgery for removal of a cerebellar astrocytoma was started 15 minutes after contrast material was injected.

FIG. 4. Comparison of pneumoencephalogram and methylglucamine iothalamate 60% ventriculogram in an emaciated 6-month-old boy suspected of having a tumour in the third ventricle. Pneumoencephalography and attempted air ventriculography failed to demonstrate the normal third ventricle. The positive contrast ventriculogram did not hint at the enlarged sulci. Note positive contrast material in the foramina of Lushka and Magendie. Escape of this small amount of material into the subarachnoid space had no adverse effect.

TABLE I

RADIOGRAPHIC VISUALIZATION OF HUMAN CEREBRAL VENTRICLES WITH METHYLGLUCAMINE IOTHALAMATE 60%

Purpose of Ventriculography	No.	Lateral Ventricles Visualized						Midline Ventricles Visualized								
		Ipsilateral			Contralateral			Third Ventricle			Aqueduct of Sylvius			Fourth Ventricle		
		Com- plete	Par- tial	None	Com- plete	Par- tial	None	Com- plete	Par- tial	None	Com- plete	Par- tial	None	Com- plete	Par- tial	None
Stereotactic surgery	69	8	61		68	1	32	37 ¹			28	34	7	14	38	17
Hydrocephalus with ventriculo-atrial shunt	10 (3)	2	6	2	2	6	2	2	2	6	2	1	7	1	3	6
Infratentorial mass	10	1	9		7	3	6	3	1	5	2	3	4	1	5	
Supratentorial mass	13	5	8		2	9	2	5	6	2	3	7	3	3	6	4
Totals	102	16	84	2	4	90	8	45	48	9	38	44	20	22	48	32
Percentages	100	15.7	82.3	1.9	3.9	88.2	7.9	44.1	47.1	8.8	37.2	43.1	19.6	21.6	47.1	31.3

¹The portion of the third ventricle cephalad to the massa intermedia was not filled in these studies.

The floor and the anterior and posterior recesses were well visualized.

TABLE II

COMPARISON OF RADIOGRAPHIC VISUALIZATION OF CEREBRAL VENTRICLES TO VOLUME OF METHYLGLUCAMINE IOTHALAMATE 60% INJECTED

Body Weight (mg./kg.)	Average Conray (ml.)	No. Procedures	Lateral Ventricles Visualized						Midline Ventricles Visualized								
			Ipsilateral			Contralateral			Third Ventricle			Aqueduct of Sylvius			Fourth Ventricle		
			Com- plete	Par- tial	None	Com- plete	Par- tial	None	Com- plete	Par- tial	None	Com- plete	Par- tial	None	Com- plete	Par- tial	None
10-19	1.43	17		17			17		6	11		5	9	3	1	7	9
20-29	2.40	29	3	25	1		28	1	12	16	1	10	15	4	6	18	5
30-39	2.96	13	2	11			12	1	6	6	1	4	7	2	2	8	3
40-49	4.17	6		6			6		4	2		3	3		3	2	1
50-59	3.81	8	2	6		1	7		4	4		3	5		2	4	2
60-99	5.00	7	2	5		1	5	1	4	2	1	3		4	2	2	3
100-499	8.38	11	3	8		1	7	3	7	3	1	6	4	1	3	5	3
500-999	6.50	9	1	7	1	1	5	3	2	3	4	3	2	4	2	3	4
1,000-1,099	7.50	2		2			2		1	1				2			2
Totals		102	13	87	2	4	89	9	45	38	9	37	45	20	21	49	32
Percentages		100	12.7	86.4	1.9	4.0	87.2	8.8	44.1	37.2	8.8	36.2	44.1	19.6	20.6	48.0	31.4

demonstrate the third ventricle. Two ml. of NMG Ioth produced clear visualization of the midline ventricles. The positive contrast material did not demonstrate the marked enlargement of sulci. The normal third ventricle was never adequately visualized with air.

Table I outlines visualization of the ventricular system in studies carried out for a variety of reasons. Filling of normal sized ventricles, with normal cerebrospinal fluid circulation, can be standardized into a routine quite quickly. Accurate and clear visualization of the anterior and posterior commissures and both lateral walls of the third ventricle was produced without fail in patients being prepared for stereotactic surgery. Ventricular systems larger than twice normal size were difficult to visualize completely, when water-soluble positive contrast media were used. Large amounts of NMG Ioth were used to visualize adequately the dilated ventricular systems of hydrocephalic infants. The enlarged lateral ventricles

sometimes obscured the third ventricle in lateral films. It was not possible to pour water-soluble positive contrast material from one ventricle to another to eliminate confusing shadows, as it is with air or iodized oil. When the ventricles are moderately dilated, as with posterior fossa tumours, the water-soluble positive contrast material outlined the midline ventricles so well that only lateral and axial films were needed for an accurate diagnosis. It was not necessary to move the head and take multiple films to visualize the essential portions of the ventricular system, as it was when air or ethyl iodophenylundecylate was used.

Three studies using NMG Ioth have been carried out in children with ventriculo-atrial shunts (Table I) in the hope that patency of the shunt could be demonstrated. These were not informative studies, even though 10 ml. of the contrast material was used (and well tolerated).

The lateral ventricles have been more difficult to

demonstrate completely than the midline ventricles (Table I). The one case that we have studied with a ventricular shift had adequate visualization. Table I indicates that the lateral ventricle into which the contrast medium is injected fills more completely than does the contralateral ventricle.

Not only does NMG Ioth diffuse because of its solubility in cerebrospinal fluid, it also flows with gravity, because of its viscosity. This can be demonstrated by comparing in Fig. 1 the axial view (upper right film) with the half axial view (lower film), remembering that the head was in the lateral position and the needle had been introduced into the upper lateral ventricle. The half axial view was exposed 30 to 40 seconds after the axial film.

Ventriculograms made with water-soluble positive contrast media showed a gradation of opacity corresponding to the depth of the portion of the ventricle visualized. Ventricular visualization seems to be enhanced by this gradation. Similar gradation is present in air encephalograms, but not when iodized oils are used as the contrast medium.

Toxic reactions occurred when too much NMG Ioth was injected into the ventricular system. It was important, therefore, to compare the completeness of ventricular visualization with the volume of positive contrast medium injected. Table II demonstrates that adequate ventricular visualization was achieved with considerably less than toxic doses of contrast medium. No complications, and few reactions appeared in the last 68 cases of the 102 studied by ventriculography, once the technique for avoiding toxicity was learned.

REACTIONS TO INTRAVENTRICULAR INJECTION OF METHYLGLUCAMINE IOTHALAMATE 60%

Reactions to NMG Ioth ventriculography have been few and mild in a large majority of patients. Table III indicates that there are fewer reactions, characterized by nausea and vomiting, headache, fever, or meningismus, than would be expected from introduction of air into the ventricular system of a similar group of patients. Many of the patients had general anaesthetics, and stereotactic or other definitive surgery immediately after the positive contrast ventriculogram. Some of the reactions can be attributed to the anaesthetic and subsequent surgical procedure.

Vomiting was severe in only one patient in the series of 102 ventriculograms. This study was made using local anaesthesia. The patient started to vomit vigorously three minutes after 3.5 ml. NMG Ioth diluted to 10 ml. with ventricular fluid was injected. Severe vomiting persisted for 15 minutes and necessitated postponement of his stereotactic procedure. He had not received any preoperative medication.

Less severe vomiting, lasting two to three hours, occurred two to five hours after 38 of the 102 ventriculograms using methylglucamine iothalamate 60%. Some of these were performed under general anaesthesia, and most of the patients had definitive surgery immediately after ventriculography.

Premedication with small amounts of barbiturate and atropine diminishes nausea and vomiting. Premedication also inhibits the Parkinsonian tremor

TABLE III

REACTIONS AND COMPLICATIONS OF METHYLGLUCAMINE IOTHALAMATE 60% VENTRICULOGRAPHY

Body Weight (mg./kg.)	Average Conray (ml.)	No. of Procedures	Reactions			Complications			
			Nausea and Vomiting	Headache	Fever	Meningismus	Confusion ^a	Convulsions	Death
10-19	1.43	17	5	8	11		1		
20-29	2.40	29	14	11	12		2		
30-39	2.96	13	9	5	6		1		
40-49	4.17	6	2	4	4			1 ^a	
50-59	3.81	8	3	2	5				
60-99	5.00	7	1	1	1				
100-499	8.38	11	2	1	4	2		2 ^a	
500-999	6.50	9	2		3			1 ^a	2
1,000-1,099	7.50	2			1				
Totals		102 ¹	38 ^a	32	47	2	4	4	2
Percentages		100	37.2	31.4	46.1	1.9	3.9	3.9	1.9

¹One hundred and two procedures performed on 90 patients. Seven had two separate ventriculograms and two had three separate ventriculograms, 10 days to six months apart.

^aTwenty of the 38 had definitive surgery immediately after ventriculography.

^aConfusion was intermittent for two to five days after ventriculography followed immediately by stereotactic surgery in these four Parkinsonian patients over 60 years of age.

^aSubarachnoid and intraventricular injection. (Described in section on complications.)

^aOne of these patients had severe convulsions before ventriculography, they were unchanged by the procedure, the other had a single focal seizure one week after having 21 ml. methylglucamine iothalamate 60% injected into the lateral ventricle.

^aSevere convulsions before as well as after ventriculography.

and other dyskinetic movements, which must be present for adequate evaluation while stereotactic lesions are being made. Rectal suppositories containing homatropin, pyrilomine, and pentobarbital have been used for premedication in recent cases. This combination controlled nausea and vomiting without abolishing tremor or producing excessive drowsiness.

Headache was an infrequent reaction to ventriculography using methylglucamine iothalamate 60%. The headaches that occurred were easily controlled with salicylates. Three patients' headaches were classified as severe and 29 patients admitted headache when asked but did not complain of it spontaneously. No headache was experienced after 70 of the 102 procedures.

Fever was mild, rising to less than 102°F., eight to 10 hours after 46 of the ventriculograms. The fever lasted one to two hours. Much of the fever was thought to be due to the surgery which followed immediately after ventriculography. Fever of 103.5°F. was recorded for 24 hours after ventriculography in one patient who will be discussed under complications.

Meningismus was mild and present in only two patients for a few hours after ventriculography using methylglucamine iothalamate 60%.

COMPLICATIONS

Complications of ventriculography using NMG Ioth are listed in Table III.

The most severe complication occurred in an 18-year-old girl being investigated for recurrence of a fourth ventricle ependymoma operated and treated with radiotherapy 10 years previously. At the time of her positive contrast ventriculogram the very rapid absorption of NMG Ioth was not realized and 21 ml. of the material was injected into the right lateral ventricle in 3 ml. increments during a 90-minute period. The enlarged fourth ventricle with faint evidence of the tumour mass was inadequately demonstrated. A ventriculo-atrial shunt was performed immediately after ventriculography and radiotherapy started in five days. The girl became confused and incontinent after injection of the last increment of contrast material. Confusion continued for two weeks and the ventricular fluid remained bloody. She had a single generalized convulsion one week after the ventriculogram. The confusion, incontinence, and possibly the fever were complications of ventriculography. The bleeding, convulsion, and perhaps the prolongation of confusion could possibly have resulted from the intraventricular ependymoma. This patient died 29 months after the ventriculogram, due to failure of the ventriculo-

atrial shunt and pneumonia. Granular ependymitis of the lateral ventricles was seen on microscopic section. Similar ependymal changes are frequently seen in patients with intracranial inflammation or gliomas (Courville, 1945). It was not thought that the ependymal changes were of any clinical significance. They were probably not due to the positive contrast ventriculography.

Two deaths are listed as complications in Table III. One was a desperately ill 2-year-old child suspected of having a posterior fossa neoplasm. He stopped breathing a few minutes after being brought to the admitting room and developed a cardiac arrest. The positive contrast ventriculogram was an heroic measure carried out when he had been placed on a mechanical respirator and a faint apical pulse obtained. It was felt that his precarious intracranial dynamics would not be disturbed as much by positive contrast as by air ventriculography. The contrast material did not diffuse, or flow out of the lateral ventricle into which it was injected. Necropsy was refused.

The second death occurred 98 hours after a 10 ml. ventriculogram using NMG Ioth in a 17-month-old child with rapidly increasing hydrocephalus. The initially high intracranial pressure was not changed by the ventriculogram. It was reduced for only short periods by repeated ventricular taps. Episodes of apnoea occurred, and the ventricular fluid became increasingly bloody. Necropsy revealed a few petechial haemorrhages in the ventricular lining attributed to the periods of apnoea. The ventricular walls were glistening and smooth without evidence of reaction either grossly (Fig. 5) or microscopically (Fig. 6). The brain showed microgyria and an anomalous septum pellucidum. Although the coincidence of death with the ventriculogram using NMG Ioth cannot be disregarded, the evidence did not suggest that the drug was the cause of death.

Six other patients have died 23 days to 21 months after ventriculography with NMG Ioth as a result of their original illness. No evidence of adverse effect from the ventriculography was observed while these patients were alive. Necropsy was performed on four. The other two died at home. No gross or microscopic evidence of damage from the ventriculograms was detected.

The other 81 patients are alive and show no ill effects from water-soluble positive contrast ventriculography 18 to 34 months after the procedure.

Convulsions occurred after four of the 102 ventriculograms. Two of the patients were being investigated for severe epilepsy. Their convulsions were neither increased nor diminished by water-soluble positive contrast ventriculography. The girl who received 21 ml. NMG Ioth had a single focal

FIG. 5. Brain of 1½-year-old male with rapidly enlarging head and increasing lethargy, who died 98 hours after 10 ml. methylglucamine iothalamate 60% was introduced into the right lateral ventricle. No irritation of the ependyma could be seen grossly or microscopically (Fig. 6). The petechial haemorrhages seen probably arose during several prolonged periods of apnoea. The ventriculogram was not considered to be the cause of death.

FIG. 6. Microscopic section of ependyma from brain shown in Figure 5. $\times 200$.

convulsion one week after her ventriculogram, but had none subsequently.

One 63-year-old Parkinsonian patient started to convulse 50 minutes after 3 ml. of the medium was inadvertently injected into the enlarged interhemispheric space. He had no immediate reaction. Prophylactic anticonvulsant medication was given. The needle was replaced in the ventricle and an additional 4.5 ml. NMG Ioth injected. Fifty minutes after the original subarachnoid injection he developed focal convulsions on the side contralateral to the injection. These became generalized before they were controlled four hours after onset. He has had no convulsions since. The convulsive pattern was identical to those seen after injection of 3 ml. or more of the material into the cisterna magna of experimental animals. The patient was weak and confused for three weeks following this procedure. Intracranial injection of 7.5 ml. NMG Ioth was learned to be excessive, particularly if some of it gets into the subarachnoid space. Subsequent to this experience 1 to 3 ml. of air was injected and radiographs made, before injecting the positive contrast material, to be sure that the needle tip was in the lateral ventricle and not in a dilated subarachnoid space.

One ml. NMG Ioth injected in the same way into the interhemispheric sulcus of a 66-year-old man with Parkinsonism produced no reaction, even though the needle was replaced into the ventricle and 3 ml. more of contrast medium injected. No undesirable reactions to this procedure, or the subsequent stereotactic surgery was observed.

CEREBROSPINAL FLUID STUDIES FOLLOWING VENTRICULOGRAPHY

Fourteen of the 90 patients had cerebrospinal fluid determinations two hours to 18 days following ventriculography using methylglucamine iothalamate 60%. The remainder had no symptoms to suggest the need for lumbar or ventricular puncture. Seven had red blood cells in the cerebrospinal fluid. In five of these definitive surgery was carried out immediately after ventriculography, to account for the red blood cells. The other two had 17 and 35 R.B.C.s/c.mm. respectively. These two had no white cells. White cell counts were compatible with the red cell counts in the other five.

Eleven and eight polymorphonuclear leucocytes per c.mm. were found in two patients who had no red cells. The remaining five of the 14 patients had no cells in their cerebrospinal fluid.

Cerebrospinal fluid total protein was elevated in two of the 14 patients. It was 77 mg. per 100 ml. three days after uncomplicated ventriculography and

stereotactic surgery, in the patient who had 8 W.B.C.s per c.mm. of fluid. Total protein reached a peak of 121 mg. in the girl who received 21 ml. of methylglucamine iothalamate 60%.

OTHER CONSIDERATIONS

The patient's age, young or old, did not seem to increase or decrease reactions or complications to ventriculography using methylglucamine iothalamate 60%.

There was no evidence to indicate that the water-soluble positive contrast medium diffused along the tract of the ventricular needle in any of the 102 procedures.

The second or third ventriculogram performed with NMG Ioth on the same patient did not appear to increase the risk of reactions or complications.

No evidence of iodine sensitivity was observed in any of the patients in this study.

DISCUSSION

The unparalleled radiographic visualization and the minimal reactions and complications of ventriculography with NMG Ioth are gratifying. The advantages provided by this technique of more complete visualization of the ventricles with less alteration of intracranial dynamics are partially offset by the toxicity which appears if the material reaches the cerebral cortex. If the head is immobilized during ventriculography the contrast medium diffuses throughout the ventricular system and is absorbed through the ependyma before it reaches the cortex in dangerous concentration. Moving the head to shift the contrast medium and visualize inadequately filled ventricular areas forces the cerebrospinal fluid to flow out of the ventricles and over cortical surfaces to increase the chance of complications. When the material was allowed to diffuse into unfilled ventricular areas, rather than trying to pour it into them as neurosurgeons have learned to do with air and insoluble hyperbaric oils, fewer and less severe reactions and complications occurred. Multiple rapid exposures made as the x-ray tube was rotated around the immobilized head provided excellent visualization of the desired ventricular areas.

The experience of Mullan (1965), with approximately 40 injections of 4 ml. of NMG Ioth into the upper cervical subarachnoid space to guide his percutaneous chordotomies, also suggests that the head and spine be immobilized when water-soluble positive contrast media are used near cortical surfaces. In his procedure the head and neck were kept immobile for about one and a half hours after

injection of the medium. He reported that there were no complications and minimal reactions. He recently stopped using this medium because of occasional vomiting which disrupts the procedure unduly.

An index for estimating the amount of water-soluble positive contrast material needed to visualize ventricles dilated to various degrees has not been worked out as yet. Patients with hydrocephalic ventricles seem able to tolerate large volumes of NMG Ioth. This may be due to dilution of the medium by the larger volumes of cerebrospinal fluid. It also appears to be absorbed more slowly from hydrocephalic ventricles.

Repeated injections of NMG Ioth during short periods of time have proven dangerous, so the optimal dose has been chosen and injected in one bolus. If inadequate visualization is achieved at least 24 hours have been allowed to elapse before more of the medium is administered. Our animal studies (Heimbürger *et al.*, in press) have indicated that almost 100% of the material is excreted in the urine within 24 hours after injection. It is probably unwise to subject a patient to angiography or pyelography using iodinated media within 24 hours before or after ventriculography using iodinated media. Repeated ventriculography after intervals of one week to nine months did not appear to increase the reactions or complications in this series.

Methods will undoubtedly be devised to decrease further the incidence of reactions and complications resulting from positive contrast ventriculography using water-soluble media. Premedication with barbiturates diminishes nausea and vomiting. Dilution of NMG Ioth before injection into the ventricles also appears to decrease reactions and aids diffusion within the ventricular system. Further investigation of the amount of dilution and of different diluting solutions is needed. Possibly NMG Ioth will remain radiopaque in the ventricles for a longer time if it is diluted with solutions other than cerebrospinal fluid or normal saline. A slower rate of absorption may decrease reactions and complications, as well as simplifying the radiographic procedure.

No direct correlation is apparent between reactions, complications, or cerebrospinal fluid changes and the quantity of NMG Ioth per kilogram of body weight or per cubic centimetre of estimated cerebrospinal fluid volume. The total volume of NMG Ioth injected into the ventricular system does relate directly to reactions and complications in our small series. We have expressed the results in milligrams per kilogram of body weight as well as total volume injected, so they can be compared with data in other reports of positive contrast media.

PRECAUTIONS FOR METHYLGLUCAMINE IOTHALAMATE 60% VENTRICULOGRAPHY

Several precautions are necessary for the safe performance of ventriculography with methylglucamine iothalamate 60%. Small amounts of barbiturate and atropine should be used as premedication. One to 3 ml. of air should be injected into the lateral ventricle and radiographs taken to make sure that the needle tip is in the ventricle before the positive contrast material is injected. A larger volume of air may block flow of the contrast material into the third ventricle or aqueduct of Sylvius. One and one half to 3 ml. of contrast medium diluted to 10 ml. with ventricular fluid is ample to fill a normal ventricular system. No more than 6 ml. of undiluted contrast medium should be injected into a dilated ventricular system. This amount has not been helpful in evaluating infantile hydrocephalus. Tumour masses involving the third and fourth ventricles and aqueduct of Sylvius can be best visualized if NMG Ioth is injected with the needle tip near the foramen of Munro. The medium has not been injected directly into the third ventricle.

Methylglucamine iothalamate 60%, diluted two to six times with cerebrospinal fluid, should be injected rapidly, but without undue force. Radiographs should be exposed immediately and in rapid succession, so that all the desired views are obtained within a minute after injection. The patient's head and neck should be immobilized during injection and kept immobile for at least one hour. Nausea and vomiting are decreased if the patient is not allowed to sit up for 12 hours after ventriculography. At least 24 hours should elapse between intraventricular injections of this material. Angiography and pyelography should not be performed for 24 hours before and 24 hours after ventriculography using water-soluble iodinated solutions. Sodium glucamine iothalamate 90% should not be used for ventriculography.

Adherence to these precautions eliminated all complications and most reactions in the last 68 of the 102 ventriculograms reported.

The rare patient with iodine sensitivity must be considered when iodinated positive contrast media are used for ventriculography. No evidence of sensitivity has been observed in this series.

SUMMARY

Water-soluble positive contrast cerebral ventriculography using methylglucamine iothalamate 60% (NMG Ioth) for 102 studies in 90 patients is reported. Excellent radiological visualization of the ventricular system was obtained. These water-soluble positive-

contrast ventriculograms are superior in detail to those obtained with air or with ethyl iodophenylundecylate.

Intraventricular injection of excessive quantities of this material produces toxicity. The most severe toxic reaction observed was convulsions, when the material reached cortical surfaces in sufficient concentration. Precautions for avoiding reactions and complications are suggested. By using these precautions ventriculography with NMG Ioth can be carried out with less disturbance of intracranial dynamics than can be achieved with air or other gases. Almost complete and immediate filling of the entire ventricular system without moving the head makes the technique ideal for stereotactic surgery. This feature plus the gradation of the intensity of shadows may prove it to be preferable to ethyl iodophenylundecylate ventriculography for stereotactic surgery and possibly for demonstrating abnormalities of the third and fourth ventricles and aqueduct of Sylvius.

We are grateful to Professor W. Zeman and Dr. J. Muller for their opinions on the neuropathological material; to Dr. William McKinney, Fort Worth, Texas, who suggested homatropine, pyrilamine, and pentobarbital for premedication. Some of the clinical studies were carried out by Dr. R. E. Kreps, Dr. R. C. Jones, Dr. C. L. Goodell, and Dr. C. C. Whitlock.

REFERENCES

- Alexander, L., Jung, T. S., and Lyman, R. S. (1934). Colloidal thorium dioxide: Its use in intracranial diagnosis and its fate on direct injection into the brain and the ventricles. *Arch. Neurol. Psychiat.* (Chic.), **32**, 1143-1158.
- Back, N. (1963). Effects of subacute intraventricular administration of meglumine iothalamate (Conray). In *Adult purebred Beagle Dogs, Roswell Park Memorial Institute*. (Unpublished data.)
- Campbell, R. L., Campbell, J. A., Heimbürger, R. F., Kalsbeck, J. E., and Mealey, J. Jr. (1964). Ventriculography and myelography with absorbable radiopaque medium. *Radiology*, **82**, 286-289.
- Courville, C. B. (1945). *Pathology of the Central Nervous System*, pp. 40-42. Pacific Press Publishing Ass., Mountain View, California.
- Dotter, C. T., Straube, K. R., Bilbao, M. K., and Hinck, V. C. (1962). A new contrast medium for intravascular use. *Northw. Med. (Seattle)*, **61**, 41-46.
- Foster, J. H., Winfrey, E. W., III, Killen, D. A., and Sessions, R. T. (1962). A new angiographic contrast medium, sodium iothalamate 80%. *J. Amer. med. Ass.*, **182**, 1009-1013.
- Fry, W. J., Fry, F. J., Lechner, G. H., and Heimbürger, R. F. (1962). Tissue interface detector for ventriculography and other applications. *J. Neurosurg.*, **19**, 793-798.
- Gonsette, R., Dereymaeker, A., Hou, H., and Cornelis, G. (1958). L'iodoventriculographie. I. Technique, indications, images normales. II. Le diagnostic radiologique. *Acta neurol. belg.*, **58**, 778-796 and 797-809.
- Heimbürger, R. F., Campbell, R. L., Kalsbeck, J. E., Mealey, J. Jr., and Goodell, C. L. (1966). Positive contrast ventriculography using water-soluble media. 1. Animal toxicity studies. (In press.)
- Hinck, V. C., and Dotter, C. T. (1962). Cerebral angiography with 60% Conray. Preliminary report. *J. Neurosurg.*, **19**, 312-313.
- Hughes, R. (1953). Chronic changes in the central nervous system following thorotrast ventriculography. *Proc. roy. Soc. Med.*, **46**, 191-195.

- Jefferson, A., and Occleshaw, J. (1960). The identification of pathological processes in the posterior cranial fossa by Myodil ventriculography. *Acta neurochir. (Wien)*, 8, 468-494.
- Kyle, R. H., Oler, A., Lasser, E. C., and Rosomoff, H. L. (1963). Meningioma induced by thorium dioxide. *New Engl. J. Med.*, 268, 80-82.
- Kodama, J. K., Butler, W. M., Tusing, T. W., and Hallett, F. P. (1962). Iothalamate: A new intravascular radiopaque medium with unusual pharmacotoxic inertness. *Exp. molec. Path.*, suppl. 2, 65-80.
- Mullan, S. (1965). Subarachnoid injection of methylglucamine iothalamate (Conray 60%) to visualize cervical spinal cord. (Personal communication.)
- Radovici, A., and Meller, O. (1932). Essai de liquidographie céphalo-rachidienne. Encéphalo-myélographie par le thorotrast sous-arachnoïdien. *Bull. Acad. Méd. (Paris)*, 107, 314-317.

- Stuck, R. M., and Reeves, D. L. (1938). Dangerous effects of thorotrast used intracranially, with special reference to experimental production of hydrocephalus. *Arch. Neurol. Psychiat. (Chic.)*, 40, 86-115.

GENERIC AND TRADE NAMES FOR DRUGS MENTIONED

- ¹Mallinckrodt Pharmaceuticals, Mallinckrodt Chemical Works, St. Louis 7, Missouri, U.S.A.
- Ethyl iodophenylundecylate (Myodil, Pantopaque)
- Thorium dioxide 25% (Thorotrast)
- Methylglucamine iothalamate 60% (Conray 60%)
- Sodium glucamine iothalamate 90% (Angioconray)
- Homatropine methylbromide .. 10 mg.
- Pyrimidine maleate 8 mg. } (Matropinol suppository)
- Pentobarbital 15 mg. }