

Evaluation of Radioactivity in the Bladder after Injection of ^{131}I Hippurate into Lateral Ventricles of Hydrocephalic Patients

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Introduction

This paper is a report on a computer simulation based on Bladder-scans which were recorded from hydrocephalic patients between 1965 and 1970 at the University Hospital, Rotterdam. From these scans, which show the accumulation of radioactive ^{131}I hippurate molecules in the bladder, values were derived for the rates at which the molecules left the cerebral ventricles and reached the bladder. The state of both systems could then be assessed, as could the state of renal function.

A correlation study was also set up in which the data were compared with clinical data in an attempt to find out whether the bladder-scans gave any indication of CSF resorption (physiological or pathological) and, consequently, any indications for the prognosis for patients with hydrocephalus.

Material and Method

A total of 103 bladder scans were available for examination from 97 non-surgically treated hydrocephalic patients. In obtaining the original scans, the procedure had been to inject $5\mu\text{Ci}$ of ^{131}I hippurate intraventricularly, usually through the anterior fontanelle. The collimator was then positioned over the bladder and the level of radioactivity in the bladder was recorded continuously for one hour. The procedure ended by establishing a standard to represent the total radioactivity of the dose administered, fixed at 100 per cent and expressed as radioactivity per cm. The bladder activity could then be expressed at successive stages as a percentage of the original amount of ^{131}I hippurate injected. The moment at which the radioactivity commenced in the bladder had also been recorded as accurately as possible.

Mathematical Model

In order to extract more information from the bladder scans, a mathematical model was set up to determine the processes of disappearance of the tracer element from the ventricles and its appearance in the bladder. This three-compartment model (the CSF system, the blood, and the bladder) formulates two processes which are independent of each other: (a) the disappearance of the tracer from the CSF into the blood, and (b) its renal excretion. Premises on which our model was based are: (1) the ventricular disappearance fraction per unit of time is constant; (2) the renal excretion rate per unit of time is constant; and (3) the amount of tracer disappearing from the blood into the extracellular spaces can be ignored since the tracer is not involved in any metabolic process.

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CSF to Blood

Per unit of time, a constant amount of tracer disappears from the CSF, which can be expressed in the formula:

$$x = a(1 - e^{-k_1 t}) \quad (1)$$

in which a = amount of tracer injected, x = amount of tracer excreted into the blood as a percentage of a , and k_1 = disappearance constant.

Blood to Bladder

Per unit of time, a constant fraction of the tracer in the blood disappears into the bladder. The amount excreted into the bladder (y) depends upon two processes which can be formulated as:

$$y = x - a \frac{k_1}{k_2 - k_1} (e^{-k_1 t} - e^{-k_2 t}) \quad (2)$$

in which k_2 = excretion constant of the kidneys.

The blood level of ^{131}I hippuran will increase, with decreasing velocity, until the renal excretion exceeds the ventricular disappearance. At the moment when the maximum concentration is reached, the formula

$$k_1(a - x) = k_2(x - y) \quad (3)$$

is valid. The net amount of tracer added to the tracer in the blood per unit of time is then zero. This point is represented in the bladder-scans as a turning-point, while the whole excretion pattern is sigmoid, following the increase and decrease in the blood levels.

Computer Simulation

At first, we calculated the values of k_1 and k_2 arithmetically, and the graphs using formula (2) showed remarkable similarity to the original bladder-scans. We found that k_2 was many times greater than k_1 and that while k_1 varied widely, k_2 remained fairly constant, varying only between 0.04 and 0.16 per minute.

As this method of calculation was found to be unsatisfactory, we decided to do a computer simulation. The computer was instructed to compute a large number of theoretical bladder scans, using formula (2), for ten different values of k_2 and 22 different values of k_1 for each k_2 value, the total renal excretion being computed at five-minute intervals for one hour.

From the data so acquired, graphs were plotted on 10 cards, one card for each value of k_2 , and it became obvious that the k_2 value had a marked influence on the bladder-scans. Of the original bladder-scans, 28 showed a satisfactory resemblance to one of the theoretical graphs, which indicated that while the rate of disappearance of tracer molecules differs from one patient to another, the manner of disappearance is the same. In another 24 of the original scans there was, at first, an equally satisfactory resemblance to another theoretical graph; at a later point, however, the k_1 value changed suddenly while the k_2 value remained constant, after which the scan followed the new theoretical graph again almost exactly. It was also seen that k_1 sometimes changed twice or more, and in varying directions. Nevertheless, the ratio between two succeeding k_1 values averaged 2 (Fig. 1). In fact there must be some processes which influence k_1 , for example the processes of resorption or secretion must stop and start; what is noteworthy is that after each sudden change in k_1 the scans follow another part of a theoretical graph almost exactly.

The disappearance of ^{131}I hippurate is a first-order process, whether dependent on the

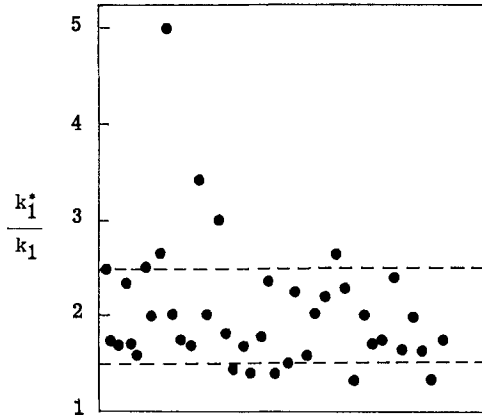


Fig. 1. Scatter diagram of the ratio between two succeeding disappearance constant (k_1) values. The ratio k_1^*/k_1 is plotted on the ordinate, k_1^* always being the larger. The plotting on the abscissa is arbitrary.

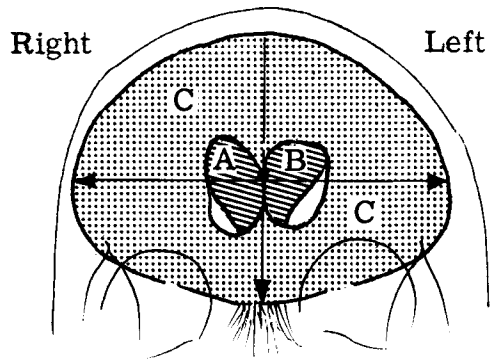


Fig. 2. Drawing from an AP ventriculograph to show how the ventricular index (VI) is calculated. $(VI) = \frac{A+B}{C}$. A=area of right cella media; B=area of left cella media; C=area of cortical coronal section.

amount of CSF resorption or on the concentration of tracer in the CSF. The renal excretion is also a first-order process. The value of k_2 is such that, of an amount of tracer injected intravenously, 71.2 to 99.6 per cent will be excreted within 30 minutes. This corresponds to the values mentioned in the literature. Meade and Shy (1961) report that more than 65 per cent appears in the urine within 30 minutes of intravenous injection, and Nordyke *et al.* (1962) give values varying between 60 and 85 per cent.

Because some processes must be responsible for the transfer of the tracer material from the CSF to the blood, correlation tables were constructed between the disappearance constant (k_1) and onset times, and the clinical data which were thought to influence or be connected with CSF resorption (such as speed of development of hydrocephalus, the type of ventriculograph, CSF pressure, and the planimetric surface measurements of the cross-section of the cella media as shown on AP ventriculographs and expressed in a ventricular index). The influence of protein concentration and aetiology on secretion was also surveyed.

Ventricular Index (VI)

This is expressed as the ratio between the combined areas of both ventricular cross-sections of the cella media and the surface of the cortical coronal section as seen in the AP ventriculograph, which has an elliptical shape. The longest axis is formed by the greatest horizontal diameter, the shortest axis by a perpendicular line from the longest axis to a point midway between both wings of the sphenoid bone (Fig. 2).

Speed of Development of Hydrocephalus

If the ratio between the largest surface of the cella media cross-section and the highest pressure measures (O/P) exceeds a factor of 0.4, we speak of a chronic process; if equal to or smaller than 0.4 we speak of an acute process.

Type of Ventriculogram

Clinically, three types are distinguishable: type I, in which air does not reach the

TABLE I
Summary of correlations

	Clinical data†	Disappearance constant (k_1)	Onset time (t_b) in mins.
Type of ventriculograph	I + II (69)	> 0.001*	> 15
	III (20)	≤ 0.001*	≤ 15
Speed of development of hydrocephalus ..	> 0.4 (40)	≠ 0.0025*	> 15
	≤ 0.4 (24)	< 0.0025*	≤ 15
Ventricular index	≠ 0.2 (52)	≠ 0.0025*	> 15*
	< 0.2 (26)	< 0.0025*	≤ 15*
CSF pressure	> 12 (60)	> 0.001	> 15
	≤ 12 (19)	≤ 0.001	≤ 15
Aetiology	meningocele (41)	> 0.001	> 15
	congenital (34)	≤ 0.001	≤ 15
	post-meningitic (14)	> 0.001	> 15
	other causes (13)	≤ 0.001	≤ 15
Protein concentration	lowered/normal (50)	> 0.001	> 15
	raised (22)	≤ 0.001	≤ 15

* statistically significant.

† numbers in brackets represent number of graphs which could be linked up with clinical data.

cisterna magna; type II, in which air reaches the cisterna magna but not the convexity; and type III, in which air reaches the convexity.

Results

The results of the correlation study are shown in Table I. A few have a high degree of significance, but the majority are negative. The disappearance constant (k_1) is inversely proportional to both the speed of development of hydrocephalus and the ventricular index (Figs. 3 and 4). Furthermore, patients with a vi lower than 0.2 more often have an onset time for renal excretion between 0 and 15 minutes than do those with a higher vi (Table II), which indicates that some of the tracer molecules must cross the ependyma

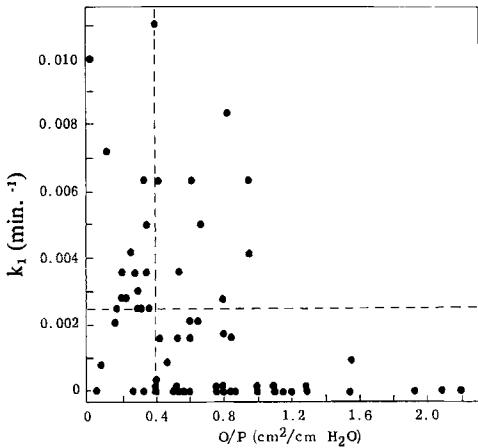


Fig. 3. Scatter diagram showing the relationship between disappearance constant (k_1) and the speed of development of hydrocephalus (O/P). The dotted lines indicate the distribution in groups. ($0.0005 < p < 0.001$, χ^2).

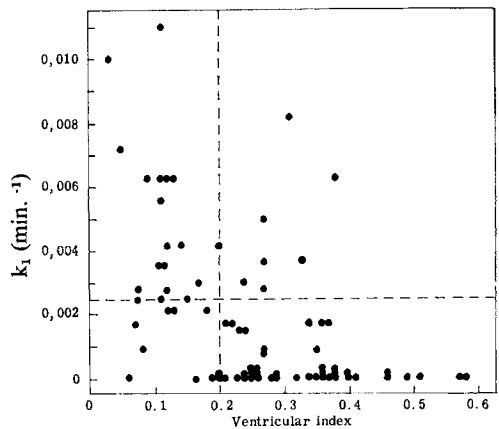


Fig. 4. Scatter diagram showing the relationship between disappearance constant (k_1) and ventricular index (vi). The dotted lines indicate the distribution in groups. ($p < 0.0005$, χ^2).

TABLE II
Correlation between ventricular index (VI) and onset time (t_b)*

	VI < 0.2	VI ≥ 0.2	Total
t _b ≤ 15 ..	21	12	33
t _b > 15 ..	6	39	45
Totals ..	27	51	78

* This table shows the relationship between the relative ventricular size and onset of excretion. A relatively small ventricle is coupled with an increase in bladder radioactivity within 0-15 minutes. $p < 0.0005 (\chi^2)$.

TABLE III
Correlation between type of ventriculographs and disappearance constant (k₁)

	Types I + II	Type III	Total
k ₁ > 0.001 ..	24	16	40
k ₁ ≤ 0.001 ..	45	4	49
Total ..	69	20	89

* In communicative hydrocephalus (type III) excretion is seen more often with k₁ > 0.001 than in obstructive hydrocephalus. (0.0005 < p < 0.001.)

to the effluent circulation of the cortex rather than drain through the subarachnoid villi.

Table III, in which the type of ventriculogram is related to k₁, shows that children with type III ventriculograms more often have high excretion rates than those with types I or II, which indicates the presence of some normal physiological CSF resorption at the convexity in the former cases.

Neither protein concentration nor aetiology had any influence on the rate of disappearance of tracer from the ventricles, nor on onset time.

A somewhat surprising finding was that CSF pressure appears to have no important influence. This finding, taking into account the ventricular enlargement in long-standing hydrocephalus, argues for a diminished production of CSF when CSF pressure is raised.

Discussion

The findings from this study confirm previous findings in animal experiments about the mechanisms of ventricular enlargement (Bering 1962), and ventricular escape mechanisms for such small water-soluble molecules as ¹³¹I (Coben *et al.* 1965). In his experiments with dogs with kaolin-induced hydrocephalus, Bering observed that CSF pressure was not dramatically raised in most cases. From this, and his findings in plexectomised dogs, he argues that ventricular enlargement is caused by arterial pulsations in the choroid plexus which generate compression waves. These waves should be absorbed by the venous channels and the outflow of CSF to the convexity and spinal canal, but if obstructions are present CSF expulsion does not occur through the normal pathways and part of the damping effect is lost. Consequently, pressure pulsations will be greater.

We found that CSF pressure was only slightly raised in the patients in this study. The greater part of our population with chronic hydrocephalus (see definition above) had enlarged ventricles, but their pressure values were moderate. In most of these cases no

radioactive excretion was found. Taking all these factors into account, it can be assumed that the mechanism which Bering described is responsible for ventricular enlargement and cortical compression, which could be translated in terms of density changes in the cortical layer. It is possible then that the extracellular spaces are the first to be lost, with the consequence that there would be a reduction in transependymal fluid transfer.

High excretion rates were found more frequently in patients with an acute process, which could be primarily because of severe damage to the ependyma. Perhaps some forms of hydrocephalus go through an acute phase during which the elasticity of the ependyma is insufficient to follow rapid ventricular enlargement. As a consequence, ruptures could appear through which tracer material could escape by diffusion or CSF resorption.

In addition to this pathological transfer, the correlation between v_1 and k_1 (Fig. 4) provides an argument for the existence of an over-all transependymal diffusion. Considering that a volume increases to the third power if the corresponding surface increases to the second power, the molecular supply to the ependyma will diminish. The smaller the size of the ventricle, the more rapidly will the trace element spread through the CSF and be excreted. This mechanism may explain the rapid onset times in association with relatively small ventricles.

It is also possible that some active process is involved in the excretion of the trace element from the ventricles. Coben *et al.* (1965) observed that the rate of disappearance of ^{131}I from the lateral, third and fourth ventricles in dogs diminished after injections of perchlorate, which acts on a number of carrier mechanisms as a competitive inhibitor. Welch (1962) observed a similar process in rabbits, and Davson (1967) mentions a choroid plexus-bound transport of ^{131}I and p-amino-hippurate in the cat and the rabbit. It is of interest, in this connection, that there is a striking similarity between choroid plexus cells and the tubular cells of the kidney. Bering and Sato (1963) measured the degree of drainage over the surface of the ventricular lining, and it is possible that this method of drainage could also account for the disappearance of some of the trace element by intraventricular CSF resorption.

Because excretion rates may have prognostic value in the treatment of hydrocephalus, we shall be making further follow-up studies on our patient population.

Acknowledgements: The authors are grateful to Prof. Dr. B. Leijnse and Mr. R. Schwank for their assistance with the computer simulation.

SUMMARY

This correlative study sought an explanation for the appearance in the bladder of ^{131}I hippurate injected into the lateral ventricle. Part of the excretion seemed to depend upon a ventricular process. High disappearance constants and early onset times were related to small ventricles, and it is possible that this ventricular disappearance is promoted by ruptures in the ependyma in acute hydrocephalus. CSF pressure has no direct bearing on the disappearance of the tracer from the CSF compartment. Children with communicating hydrocephalus have higher excretion rates than those with obstructive hydrocephalus, which suggests a connection between the degree of radio-activity in the bladder and subarachnoid CSF resorption.

RÉSUMÉ

Appréciation de la radio-activité dans la vessie après injection d'hippurate marqué à l'iode 131 dans les ventricules latéraux d'hydrocéphales

Cette étude corrélatrice recherche une explication de l'apparition dans la vessie d'hippurate

injecté dans le ventricule latéral. Une partie de l'excrétion semble dépendre d'un processus ventriculaire. Dans les petits ventricules, on observe constamment une disparition importante et rapide; il est possible que cette disparition ventriculaire soit provoquée par des ruptures dans l'épendyme au cours de l'hydrocéphalie aiguë. La pression dans le LCR n'a pas d'influence directe sur la disparition des traceurs à partir des compartiments LCR. Les enfants présentant une hydrocéphalie communicante ont un taux d'expression plus élevé qu'en cas d'hydrocéphalie non communicante; ce qui suggère un lien entre le degré de radioactivité de la vessie et la résorption sous-arachnoïdienne du LCR.

ZUSAMMENFASSUNG

Die Messung der Radioaktivität in der Blase nach Injektion von ¹³¹I-Hippursäuresalz in die Seitenventrikel von Patienten mit Hydrocephalus

Durch die vorliegende korrelative Studie wurde versucht, für das Auftreten des in die Seitenventrikel injizierten Hippursäuresalzes in der Blase eine Erklärung zu finden. Ein Teil der Exkretion schien auf einem Vorgang im Ventrikel zu beruhen. Höhe Ausscheidungsraten mit frühzeitigem Beginn fand man bei kleinen Ventrikeln, und es ist möglich, daß diese ventrikuläre Ausscheidung durch Rupturen des Ependyms bei akutem Hydrocephalus gefördert wird. Der Liquordruck hat keinen direkten Einfluß auf die Ausscheidung der Tracersubstanz aus dem Liquorraum. Kinder mit einem Hydrocephalus communicans haben höhere Ausscheidungsraten, als die mit einem Hydrocephalus occlusivus, was an eine Beziehung zwischen der Menge der radioaktiven Substanz in der Blase und der subarachnoidalen Resorption denken läßt.

RESUMEN

Evaluación de la radioactividad en la vejiga urinaria después de la inyección de I-131 hipurato, en los ventrículos laterales de pacientes hidrocefálicos

Este estudio correlativo buscó una explicación a la aparición en la vejiga de hipurato inyectado en un ventrículo lateral. Parece que parte de la excreción depende del proceso ventricular. Constantes altas de desaparición y tiempos iniciales precoces estaban en relación con ventrículos pequeños y es posible que esta desaparición ventricular sea promovida por rupturas epndimarias en hidrocefalos agudos. La presión del LCR no tiene relación directa con la desaparición de la substancia radioactiva del compartimiento del LCR. Los niños con hidrocefalia comunicante tienen una velocidad de excreción más alta que aquellos con hidrocefalia obstructiva, lo cual sugiere una conexión entre el grado de radioactividad en la vejiga y la reabsorción de LCR subaracnoideo.

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