Perfusion mapping with Tc-HMPAO in cerebral haematomas

Marc Rousseaux, Marc Steinling, Damien Huglo, Andre Mazingue, Pascal Barbaste

Abstract

The cerebral distribution of HMPAO was mapped tomographically by SPECT in 20 patients with an intra cerebral haematoma. The images were assessed visually and by an analysis of an asymmetry index (AI) for various cerebral areas. Visual inspection identified the lesion in each of the 20 cases. Reduced tracer activity and abnormal AI were consistent findings. Remote effects (diaschisis) were also observed in the adjacent (19 cases) and frontal (14 cases) cortex, and in the contralateral cerebellum (16 cases). Sequential studies at 60, 150 and 300 minutes in 10 patients showed remarkably stable patterns. HMPAO maps were compared with cerebral blood flow (CBF) measured with ^{133}Xe in eight cases. The two methods showed similar results in the region of a lesion, but remote effects were more obvious with the ^{133}Xe in two patients.

Measurement of cerebral blood flow (CBF) by Xenon techniques and mapping of the cerebral distribution of radioactive tracers, such as ^{123}I Iodo-Amphetamine, by single photon emission tomography (SPECT) have proved useful in the evaluation of intracerebral haematomas.¹⁻⁴ These studies showed low rates of flow or low uptake of tracer in the lesion and its immediate vicinity, but also showed remote effects at other cortical sites and/or in the cerebellum. These may contribute to the neurological and neuropsychological deficits.^{3,5}

In addition, sequential studies with IAMP in patients with a stroke have shown late redistribution of the tracer. This has been proposed to provide an index of a cellular viability⁶ but this concept is controversial.^{7,8}

The aim of this study was to evaluate the use of technetium-99m hexamethylpropyleneamine-oxime (99m-Tc-HMPAO) in cerebral haematomas. We wanted to discover: 1) The value of HMPAO in demonstrating the lesion and any remote cortical or cerebellar effects; 2) The relationship between remote diaschisis and neurological or neuropsychological deficits; 3) The evolution of the tracer distribution with time; and 4) How HMPAO maps compared with conventional CBF evaluation with ^{133}Xe .

Patients and methods

1) Study of the HMPAO distribution

We studied twenty patients who were shown by CT to have a supratentorial intracerebral haematoma (11 on the left and nine on the right side) (table). There were nine females and 11 males, and the mean age was 62 years (range 43-82). Each patient had a stroke, considered to be "spontaneous" or secondary to arterial hypertension. The sites involved were: centrum semi ovalum and lenticular nucleus (eight cases); lenticular nucleus and internal capsule (five cases); thalamus and internal capsule (four cases); thalamus (three cases). The size of each haematoma was assessed by calculating the volume (in cm^3) of an ellipsoid whose diameter was measured in the three spatial axes.

The distribution of HMPAO was studied from one to 95 days after the onset of the stroke, using the Tomomatic 64 systems (Medimatic, Copenhagen). The examination was performed after a 15 minute adaptation period, with the subject lying in the apparatus, in the dark and in silence. The HMPAO was injected IV in a dose of 7.4 MBq/Kg. The tomograms were analysed on three slices, 15 mm thick, parallel to the orbito-meatal plane (OM +1, +5, +9). The recordings were realised five minutes after the injection in 10 patients and 60 minutes after in 10 others.

Two different analyses were performed: 1) A qualitative visual analysis was made by two independent observers to identify the lesion and estimate the "remote" effects ("diaschisis") in the ipsilateral non contiguous cortex, frontal ipsilateral cortex and contralateral cerebellum. Localised hypoactivities were labelled "certain", "questionable" or "absent". 2) A quantitative analysis, making use of a normalised calculation of the activity and asymmetry index (AI).

$$(\text{AI}) = \frac{\text{"normal side" activity} - \text{"lesion side" activity}}{\text{"normal side" activity} + \text{"lesion side" activity}} \times 200$$

This was done in the lesion area, in the ipsilateral (non contiguous) cortex, in the frontal cortex and in the cerebellum. The AI values were afterwards compared with the reference values obtained in six normal subjects.⁹

2) Comparison of the results of the clinical and CT and HMPAO study

For each patient, we assessed motor and sensory deficits (0: absent, 1: moderate, 2: major),

Service des
Convalescents, the
Service Central de
Médecine Nucléaire,
CHU, Lille, France
M Rousseaux
M Steinling
D Huglo
A Mazingue
P Barbaste

Correspondence to:
Dr Rousseaux, Service des
Convalescents, CHU, F
59037, Lille Cedex, France

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Table Presentation of the 20 patients. Abbreviations for the site of the lesions: CSO = centrum semi ovalum; LN = lenticular nucleus; IC = internal capsule; TH = thalamus. The autonomy in daily living (ADL) was assessed with the Barthel's index.

Sex	Age	Lesion site	Side	Volume (cm ³)	Days	ADL	Motor deficit	Sensory deficit	Psychological deficit
M	57	TH	L	2.7	21	20	1	0	2
M	73	TH + IC	L	3.5	34	5	2	2	2
M	51	LN + IC	R	6.5	10	5	2	2	2
M	62	TH + IC	R	10.0	29	35	1	2	2
M	55	LN + IC	R	10.7	12	80	1	0	2
M	73	CSO	L	13.5	16	25	2	1	2
F	43	LN + IC	R	14.0	26	0	2	1	2
M	53	TH + IC	L	15.5	95	75	1	2	1
M	75	TH + IC	L	15.9	53	0	2	2	2
F	65	CSO + LN	R	16.7	90	25	2	2	2
F	66	CSO + LN	R	17.4	45	55	2	2	1
M	79	TH	R	17.5	35	35	1	2	2
F	59	LN + IC	L	19.0	1	15	2	2	2
F	54	LN + IC	L	24.0	26	80	1	1	1
F	82	TH	L	24.2	35	45	1	1	1
F	50	CSO + LN	L	32.4	18	10	2	2	1
M	48	CSO + LN	L	45.7	28	30	2	2	1
F	61	CSO + LN	L	77.0	20	5	2	2	2
M	72	CSO + LN	R	79.2	32	10	2	2	2
F	66	CSP + LN	R	174.8	37	25	2	2	2

the severity of neuropsychological problems, such as, aphasia or neglect (0: absent, 1: moderate, 2: major), the severity of aphasia (from 0–6 with the “severity” subtest of the Boston Diagnostic Aphasia Examination in 11 patients). We used the Barthel index¹⁰ to assess independence in daily living, on a score ranging from 0–100.

Correlations were sought between the clinical data, the age of the patient, motor, sensory and neuropsychological deficits, Barthel's index, and the AI in three areas: haematoma, ipsilateral cortex, and frontal cortex. The Spearman test was used, with the Bonferroni correction¹¹ to assess significance (0.017 = 0.050/3 for each clinical variable).

3) Analysis of the time course of HMPAO activity

This was performed in 10 consecutive patients (cases 11–20), six men and four women (mean age: 66 years). We measured the initial activity for 10 minutes after injection with a classic gamma camera (Gamma Tome 1, CGR, Paris). We then used the Tomomatic 64 measured activity at 60, 150 and 300 minutes after injection. For each examination, the patient's head was carefully placed in the apparatus in the same position. The change over time was estimated by calculating the ratio of activities (second measure/first measure) for each area of interest. Data were corrected for the physical decay of activity of the 99 Technetium, taking into account its half life (six hours).

4) Comparison with CBF measured with ¹³³Xe
Cerebral bloodflow was measured in eight patients, with the Tomomatic 64, by continuous inhalation of ¹³³Xe (on the same tomographical slices).¹² We analysed the CBF maps qualitatively (visually) and quantitatively as in the HMPAO study.

Results

1) Qualitative analysis of the tracer distribution
A lesion was discovered in every patient at 10

(10 cases) or 60 minutes (10 cases). It was “certain” in 19 cases and “questionable” in one. In this case the haematoma was located in the periventricular area; the HMPAO hypoactivity was contiguous with the anterior horn of the lateral ventricle. This could explain the inconspicuous nature of the lesion.

Hypoactivity of the ipsilateral cortex was found in 19 cases (“questionable” in three). Frontal hypoactivity was principally observed with large lesions of the centrum semi ovalum (7/7 cases), but also with lesions that were judged to be capsulo-lenticular (3/5 cases), capsulo-thalamic (4/4 cases) and thalamic (1/3 cases). Contralateral cerebellar hypoactivity (crossed diaschisis) was noted in 16/19 patients (questionable: one case). When this cerebellar hypoactivity was absent, the lesions were in the centrum semi ovalum (one case), in the lenticular nucleus (one case) or in the thalamus and internal capsule (one case).

2) Quantitative analysis of the tracer distribution
Significant hypoactivity (AI > 0.04) was noted 20 times in the area of the haematoma, 18 times in the ipsilateral cortex, and 11 times in the homolateral frontal cortex. Contralateral cerebellar hypoactivity was found in 15/19 cases.

The comparison between qualitative and quantitative analysis showed the results were very similar for all the areas of interest. Usually, the “questionable” hypoactivities revealed by visual examination were not associated with significant AI.

Furthermore, significant correlations were observed between the cortical and cerebellar AI (0.012), and strong interrelationships between the haematoma and cerebellar AI (0.036) and between the cortical and frontal AI (0.037).

3) Correlations between clinical data, the results of CT and AI (HMPAO).

A significant correlation was observed between sensory deficit and the cortical AI (0.017), and a strong connection between motor deficit and the cortical AI (0.029). No correlation could be found between neuropsychological deficits and the AI.

Figure 1 Evolution of the HMPAO distribution in a left capsulo lenticular haematoma. The tracer activity was stable over time.

4) Analysis of the time course of HMPAO activity

HMPAO activity was remarkably stable over time (60, 150 and 300 minutes). No significant change could be noted, by quantitative analysis, at the level of the lesion, in the ipsilateral and frontal cortex, or in the cerebellum.

5) Comparison with the CBF studies (^{133}Xe).

In 8/8 patients, the lesion was discovered by visual examination (questionable in one case). A decrease of the CBF was noted in six cases in the ipsilateral cortex, in six cases in the frontal cortex (questionable in three) and in eight in the cerebellum. The AI were less frequently significant ($>8\%$). Consequently, the relation between the "visual" and the "quantitative" analyses was better in the HMPAO study.

All the lesions displayed on the HMPAO maps were also seen with the ^{133}Xe . Hypoactivity of the ipsilateral cortex was observed with both techniques. In one case, frontal hypoactivity was shown only by the ^{133}Xe study. Similar findings were present in two other cases with cerebellar hypoactivity.

Discussion

In each case, the lesion was identified by visual analysis. In most patients (19/20), the cortex was not anatomically affected. The main area of hypoactivity shown by HMPAO was in good accord with the site of the haematoma visualised on the CT scan. Quantitative analysis

always confirmed the presence of a significant AI in the area of the lesion. This validated the visual analysis. The AI was less important in the thalamic and capsulo-thalamic haematomas: the small size of the lesions may account for this result.

A remote hypoactivity (diaschisis) was observed frequently, mainly in the ipsilateral non contiguous cortex, but also in the anterior frontal cortex and the contralateral cerebellum. We did not observe a paradoxal area of hyperaemia in the periphery of the lesion. Such a phenomenon has only been observed in cerebral infarctions at a very early stage after stroke; but in our series, only one patient was examined on the first day. The large haematomas of the centrum semi ovalum and nucleus lenticularis resulted most often in a frontal hypoactivity. This might be related to extension of the haematoma into the deep structures associated with the frontal lobe.

We believe that the result of an HMPAO study is useful in the identification of intracerebral haematomas and their remote effects. In this respect the data were comparable to the results of previous studies with ^{133}Xe and IAMP.^{1 3 5 13 14}

Statistical analysis showed a significant correlation between the cortical and the cerebellar AI (HMPAO). This may indicate that hypoactivity of the contralateral cerebellum is the result of functional changes in the cerebral cortex, as seen with other techniques.¹⁵

Significant correlations were observed between the severity of the clinical neurological deficits and the cortical AI, but the Barthel's index was not correlated with the AI. We found similar results in a previous study with ^{133}Xe in patients with thalamic, capsulo-thalamic and lenticular haematomas.³ This is an interesting finding, because the cortical AI may be a good index of primary motor and sensory deficits. Other authors¹⁴ have suggested that remote hypoactivity was also related to the neuropsychological problems of the patients, but did not use a correlation procedure for their evaluations. Using ^{133}Xe to study CBF in patients with thalamic aphasia,^{16 17} we also observed that

Figure 2 Evolution of the relative uptake (second measure/first measure) in 10 patients in the adjacent cortex, contralateral cerebellum, haematoma area and frontal ipsilateral cortex.

the "severity" subtest of the Boston Diagnostic Aphasia Examination was not correlated with the AI of limited cortical areas. Caution is necessary in applying concepts such as cortical "deafferentation" or "diaschisis" to the mechanisms of the neuropsychological deficits associated with lesions of the basal ganglia and internal capsule.

Another interesting finding was the remarkable stability of the tracer over time in the lesion area, the perilesional area and the normal brain, when the primary values were corrected for the physical decrease of the activity of the 99 technetium. This stability or a very slow decline has already been described in the normal brain^{18,19} and in subacute stroke.²⁰

With IAMP, a late redistribution has been observed in cerebral haemorrhages and infarctions,^{6,21,22} which has been considered to be an index of cellular viability.^{6,21} In a previous study of cerebral haemorrhages with IAMP²² our results contradicted this interpretation. Furthermore, Oba *et al.*,⁸ showed that the late IAMP redistribution is the result of a marked reduction in protein synthesis (80%) and glucose metabolism (20%). Our data with HMPAO and the previous findings of Andersen *et al.*,²⁰ provide complementary arguments to support the absence of cellular viability in the area of the lesion. The results obtained with IAMP may reflect complex mechanisms. If the original distribution of IAMP is dependent on CBF, a redistribution may occur from passive diffusion across the altered blood-brain barrier, but also by a late capture of lipophilic IAMP metabolites of pulmonary origin.^{8,22}

The stability of HMPAO is another argument for its simplicity of use as a tracer. About 5% of its total administered activity is fixed in the brain, and it reaches a stable level about three minutes after injection. From that time the cerebral output is less than 1% per hour.^{18,23-25} This should allow delayed studies and cerebral tomography with the use of non specialised cameras which usually need long exposure times.

The HMPAO and the ¹³³Xe CBF studies showed similar results in the haematoma area. The remote effects were sometimes discordant, more anomalies being revealed in the frontal lobe and cerebellum with ¹³³Xe. The small number of patients, however, do not give a firm conclusion that the ¹³³Xe technique is superior.

In conclusion, this study demonstrated the usefulness of tomography with HMPAO in patients with an intracerebral hematoma, as already described in subarachnoid haemorrhages,²⁶ cerebral tumours²⁷ and focal epilepsy.

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