Dynamic SPECT of the Brain Using a Lipophilic Technetium-99m Complex, PnAO

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The lipophilic 99mTc-labeled oxime propylene amine oxime (PnAO) should, according to recent reports, behave like 133Xe in the human brain. This study compares SPECT images of the two tracers in six subjects: four stroke cases, one transitory ischemic attack case, and one normal subject. Technetium-99m PnAO was injected i.v. as a bolus of 15 to 25 mCi. The distribution was followed over 10-sec intervals using a highly sensitive, rapidly rotating SPECT (Tomomatic 64) and compared to 133Xe flow maps. Upon arrival of the PnAO bolus to the brain, a high uptake was found in brain tissue with high cerebral blood flow followed by rapid washout. In the stroke cases, low flow areas were equally well visualized by both tracers. Two dissimilarities were seen in the initial pictures: PnAO visualized the cerebral veins and showed a lesser contrast of gray-white matter uptake. The results suggest that PnAO has a high yet incomplete brain extraction yielding a flow dominated initial distribution with limitations mentioned.


Nuclear medicine studies of the brain would be greatly facilitated by technetium-99m (99mTc) tracers, having comparable avid uptake and prolonged retention in the brain as the iodine-123 (123I) labeled amines, isopropylamphetamine (IMP) and hydroxybenzyl-propanediamine (HIPDM). Such molecules would facilitate cerebral blood flow (CBF) tomography by conventional single photon emission computed tomography (SPECT). Technetium-99m is inexpensive, readily available, and well-suited for tomography because a high dose can be administered and because the energy of emission is optimal for the instruments. A lipophilic technetium chelate of propylene amine oxime (PnAO), passing the blood-brain barrier (BBB), has recently been described (1,2). The first-pass extraction efficiency of PnAO in baboons was estimated to be 80% at normal blood flow (2). Propylene amine oxime is not retained in the brain but diffuses rapidly back from the brain tissue when the blood concentration drops. In consequence, the initial distribution, dominated by blood flow, is very soon lost because of back-diffusion. Based on theoretical considerations it was suggested that PnAO should behave like xenon-133 (133Xe) in the human brain. This study deals with a direct comparison by SPECT between the initial distribution of [99mTc]PnAO and 133Xe flow maps in man.

MATERIALS AND METHODS

Propylene amine oxime forms a stable, neutral lipophilic complex with technetium (1,2). Preparations of the 99mTc complex were performed using a freeze-dried formulation.*† Free pertechnetate did not exceed 5% at the time of injection. Potassium perchlorate (500 mg) was given 30 min before administration of PnAO.

The studies were carried out with a rapid rotating, highly sensitive, single photon emission tomographic instrument, the Tomomatic 64, which has previously been described (3–5). It consists of four detector arrays with a total of 64 closely packed NaI-crystals continuously rotating around the patient’s head. One rotation takes 10 sec. Using the standard interlacing scheme, a
complete set of logical projections is obtained within 5 sec. Any point in the object is partially imaged from four directions at any time. Hence, this dynamic SPECT-system is well-suited to meet the requirements of the expected time course producing fairly true, time-averaged pictures in only 10 sec.

With the standard collimator used throughout this study, three slices of brain tissue are studied simultaneously. Each slice is ~2 cm thick (full width half maximum (FWHM) with 4 cm between slices, which are routinely placed 1, 5, and 9 cm over the orbitomeatal plane (OM). The resolution in the image plane is 17 mm, FWHM.

The sensitivity for $^{133}$Xe is 12,000 cps/(µCi/ml)/slice with a 40% window as measured from a 20-cm-diam, water-filled perspex phantom meter. For $^{99m}$Tc, the corresponding value is 27,000 cps/(µCi/ml)/slice with a 30% symmetrical window. Images are reconstructed using a filtered back projection algorithm with a parametrized filter function, adjustable to the obtained number of counts. Acceptable brain pictures with less than 10% statistical noise can be obtained from $\sim 10^5$ counts. Distribution images may be considered directly or further processed, e.g., by a flow calculation algorithm.

A single CBF study by the $^{133}$Xe inhalation method takes 4.5 min, during which period CBF is assumed to be constant. The calculation of flow is here based on a sequence of four xenon distribution images (4). The arterial input curve is estimated from a single, narrowly collimated, NaI-detector placed over the upper part of the right lung. In one case in the present study, an arterio-venous shunt was introduced, connecting the femoral artery to the cubital vein, in order to estimate the arterial input curve of the intravenously administered $[^{99m}$Tc]PnAO. A loop from this shunt was placed in a well counter, replacing the lung probe input to the computer for immediate visualization, storing, and outprint of the input function.

Six adult subjects have been investigated, four stroke patients, one with transitory ischemic attacks (TIA), and a normal volunteer. The duration of the sampling periods was shortened during the study, as it appeared that sufficient counts could be obtained within a 10-sec period. The administered dosage of $[^{99m}$Tc]PnAO ranged from 11–25 mCi dependent on the available activity. Data collection was started from the moment of the bolus injection.

PATIENTS AND RESULTS

Case 1 (53 yr, TIA)
Propylene amine oxime (15 mCi) was injected. Images were obtained in 6 × 30 sec followed by 6 × 60 sec with an interval of 120 sec. Peak count rate (267,000/30 sec) was observed in slice 2 during the period 30–60 sec. The $^{133}$Xe flow map and the $[^{99m}$Tc]PnAO distribution (0–30 sec) are seen on top of Fig. 1, both taken from the slice 2 (OM + 5 cm) level. The patient is recumbent with eyes open. On the $^{133}$Xe map the gray matter exhibits highest flow in the occipital lobe, the Sylvian fissure and the basal ganglia. By simple visual evaluation, the isotope distribution pattern in the PnAO map looks grossly like the $^{133}$Xe flow map, but the contrast is somewhat poorer in the PnAO image and the value is higher in the occipital region. The arterial curve peak starts at 20 sec and terminates after 40 sec. The FWHM is 12 sec. After 40 sec the level is about 10%, slowly decreasing. The initial delay in the arterial curve (0–20 sec) reflects bolus:heart:lung:heart:femoral artery shunt transit time. The shunt delay itself was found to be 14 sec.

Case 2 (38 yr, normal)
Pictures were obtained after i.v. administration of 24 mCi $[^{99m}$Tc]PnAO. The collection periods were 3 × 10, 2 × 20, 1 × 60, followed by 6 × 60 sec after a 150-sec intermission and 1 × 600 sec after 3.15 hr. Figures 2 and 3 demonstrate the sequential distribution of the PnAO in slice 1 and slice 2 during the first 4 × 10 sec. On Fig. 2 the lowermost slice (slice 1) is seen. At first (0–10 sec), the carotids are filling, then the upper cerebellum is seen with the lower parts of the temporal lobes. During the 20–30 sec period the carotids are fading, while the cerebellum is slightly asymmetric and at peak level.

The asymmetric appearance is probably due to a vessel cut lengthwise in the image plane in the right cerebellar hemisphere, i.e., part of the tracer is immediately seen in the veins. On the last (30–40 sec) map, the image is overall paler as the washout of the isotope became dominant and the vascular component is already less visible. In Fig. 3 the same sequence is seen in slice 2. The tracer can be followed from the arrival in two or three large arteries (probably the middle cerebral arteries, MCA) (0–10 sec) to the further distribution (10–20 sec) in the whole MCA-supplied area and in the occipital lobes. The count rate was highest in the third period (20–30 sec) in both slices (153,000/10 sec in slice 2). Again the highest count rate was in the area supplied by the posterior cerebral artery (occipital lobe) with predilection to the saggital sinus. After 3.5 hr, the highest count rate was obtained from areas dominated by the large veins with very little activity in the brain tissue. Slight bony uptake was seen in these late images [consistent with the presence of a small amount of free pertechnetate in the injectate (2)].

Case 3 (59 yr, stroke in chronic phase)
This patient was investigated by bolus injection of 17 mCi $[^{99m}$Tc]PnAO and data collection during 6 × 10 sec followed by 6 × 60 sec after 70-sec intermission.
FIGURE 1
Case 1: Patient with transitory ischemic attacks. PnAO distribution map (0–30 sec) (top, right) and $^{133}\text{Xe}$ flow map (top, left) are seen. Arterial input curve is seen at bottom.

FIGURE 2
FIGURE 3
Case 2: Normal volunteer. Sequential distribution of PnAO in middle slice during first 4 X 10 sec after injection

FIGURE 4
Case 3: Stroke patient with right-sided hemiplegia. 20-30 sec PnAO distribution map (top, left) is compared to 133Xe flow map
The patient had no shunt but a lung probe was positioned to evaluate the passage of the activity through the lung. In Fig. 4, the $^{133}$Xe map of slice 2 is juxtaposed besides the 20–30 sec PnAO distribution map. The normal high flow areas on the $^{133}$Xe map (occipital and parietal lobe, basal ganglia) can be seen on this early PnAO distribution map. The demarcation line between normal, high flow and the abnormal, low flow (the chronic infarct) is equally well seen by both tracers.

In reconstructions of the first 1–5 sec and 6–10 sec images of PnAO (not shown) the initial arrival of isotope is seen in the right MCA region and the demarcation line is already evident. The maximal count rate was in slice 1 during period 10–20 sec (141,000/10 sec). The lung curve rose after 2 sec and reached its maximum value after 7 sec. After 15 sec it remained almost constant at a level of 15–20% of the peak value.

**Cases 4, 5, 6 (stroke patients)**

All were investigated with longer counting periods than the previous three cases. Their PnAO distribution maps resembled the $^{133}$Xe maps in shape and overall distribution and both tracers allowed to visualize low-flow areas in the affected hemisphere. These patients did not demonstrate any significant PnAO uptake in bone.

In Cases 1–4, the number and duration of the data collections made it reasonable to perform semilogarithmic plots of the total counts. The washout appeared to be clearly biexponential with an initial $T'_1/2$ of 15, 26, 36, 38 sec, and a late $T'_1/2$ of 18, 12, 14, 14 min. The slow compartment corresponded to about 60% of the initial maximum.

**DISCUSSION**

The aim of the present study was to compare $^{133}$Xe flow maps with PnAO distribution images. The main result was that the initial PnAO images showed interesting similarities with the flow maps. Upon arrival of the PnAO bolus to the brain a high uptake was found in brain tissue with high CBF followed by a rapid washout. In the stroke cases low-flow areas were equally well visualized by both tracers. The distribution of a freely diffusible compound in the brain is expected to reflect cerebral blood flow immediately following i.v. administration of the compound; then the differences among partition coefficients, outwash, and eventually metabolic changes of the compound may distort the flow dominated distribution. The resemblance of the initial PnAO distribution to flow maps, suggests a high diffusibility across the blood-brain barrier, as seen in animal studies (1,2).

However, some dissimilarities were observed in the initial PnAO images when compared to the flow maps: PnAO was visualized in cerebral veins and showed a lesser contrast of gray:white matter uptake.

In baboons, a first-pass extraction of 80% was reported (2). A similar, or even lower value in man due to the i.v. injection used may explain the presence of PnAO in the veins in the initial pictures. Concerning the contrast, a higher value would be anticipated using $^{99m}$Tc compounds instead of $^{133}$Xe as the higher energy of $^{99m}$Tc implies less scattered radiation and better scatter rejection. This has consistently been found in (unpublished) phantom-studies from our laboratory. Simulation of rapid activity changes during data collection revealed no significant effect on the phantom contrast. Although the contrast might be slightly reduced due to the limited number of counts and “soft” filter used in reconstruction the further explanation of the observed distribution of the tracer must be sought in the kinetics of the compound.

The kinetics of PnAO is only partially known (1,2), in particular, partition coefficients between blood and brain tissue have not been reported. From our SPECT studies we have tried to derive aspects of the kinetics.

The arterial input curve has a very long tail at a level of 5–10% of the bolus maximum after 40 sec. This might be due to entrapment in the lungs or incomplete extraction with subsequent recirculation partly due to association of PnAO with RBCs or plasma proteins (2). To get some impression of the possible lung entrapment, the lung probe was used. The washout from the lung had an initial $T'_1/2$ of 4 sec. The counting rate after the bolus peak was, however, higher than that expected if no entrapment occurred. Volkert et al. accordingly found a high lung uptake with rapid washout after i.v. injection of PnAO in rats (2).

The washout of PnAO from the brain was evaluated from the total counts for each slice during sampling periods. The initial $T'_1/2$ ranged from 15 to 38 sec and the late $T'_1/2$ from 12 to 18 min, the curves being clearly biexponential. These values do not represent the ordinary two-compartment system of gray and white matter as seen in xenon studies. The variation among patients is unexpectedly high. The fast compartment probably contains a significant vascular component while the slow compartment is governed by the recirculation noticed in the input function above, thus representing clearance from the blood by other organs rather than clearance from the brain. Biexponential curves have also been observed in the rat (2). Half-times were here reported to be 75 and 180 sec, respectively. We have no explanation for these discrepancies.

In Case 1 (GS) we have tried to estimate the “fractional uptake” of PnAO in the brain, i.e., the maximum activity in the brain as a fraction of the bolus dose by comparing the observed count rate to the known sensitivity. If complete first-pass extraction and retention took place (no diffusion limits of the tracer) the mean
activity concentration in the brain should be 1.7 $\mu$Ci/g (i.e., 15 mCi diluted evenly in the blood, of which 15% is delivered to the 1,300 g brain). From this, a count rate of 37,000 cps would be expected, when corrected for actual brain size. The measured maximal count rate (slice 2) was, however, only 8,900 cps, indicating a fractional uptake of 3.6%. For the normal subject LH, the corresponding value was 3.8%. This is consistent with the data from Volkert et al. (2) in rats.

From the analysis of the limited kinetic data above an explanation of the bad contrast in the PnAO images can be suggested. Due to the possible association to blood constituents a significant vascular component superimposes the expected initially flow dominated distribution. Secondly the extraction might be flow dependent (6) thus decreasing the gray/white matter ratio. Finally, a low brain-to-blood partition coefficient consistent with the rapid washout might distort even the initial recordings. Before a quantification of the CBF can be obtained using PnAO further evaluation of a more detailed model of the kinetics, and measurement of e.g., partition-coefficients are necessary. Nevertheless PnAO is interesting being the first $^{99m}$Tc compound passing normal BBB allowing SPECT of the brain. The initial images show similarity to flowmaps, but the lack of retention and rapid outwash make the compound unsuitable for conventional rotating gamma cameras. However, with a dedicated brain scanner PnAO images based on 10-sec data sampling may be used to investigate patients unable to cooperate for longer studies, e.g., $^{133}$Xe of 4.5 min duration.

If full retention in the brain can be achieved by modifications of the ligand structure, it may be possible to obtain flow maps on rotating gamma cameras and to get a significant improvement of the resolution in the dedicated brain scanners within acceptable data collection periods. A new compound with better brain retention is currently under evaluation (7).

FOOTNOTES

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