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Technetium-99m HM-PAO SPECT in Patients with Delayed Neurologic Sequelae after Carbon Monoxide Poisoning

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We used single photon emission computed tomography (SPECT) with technetium-99m hexamethylpropylene amine oxime (^{99m}Tc-HM-PAO) in 14 studies on 6 patients with delayed neurologic sequelae from carbon monoxide (CO) poisoning to determine whether any changes in cerebral blood flow could be correlated with clinical or computed tomographic evidence of delayed deficits.

Among the six initial CT brain scans, two showed low density of both basal ganglia and two showed decreased density of the cerebral white matter. There was no correlation between the clinical outcome and the findings of the follow-up CT brain scans. Of the two SPECTS with ^{99m}Tc-HM-PAO performed during acute anoxic insult, one showed focal hypoperfusion which appeared 20 days prior to the onset of delayed neurologic sequelae after CO poisoning. Seven SPECTs in the six patients performing the delayed phase showed diffuse patched patterns of hypoperfusion which improved on follow-up images. There was good correlation between the clinical outcome and the findings of the ^{99m}Tc-HM-PAO SPECT. In preliminary conclusion, ^{9}Tc-HM-PAO brain SPECT can be used for predicting or evaluating the outcome of delayed neurologic sequelae after CO poisoning. Cerebral vascular changes may be the possible cause of hypoperfusion in patients with CO poisoning.

Key Words: *^{99m}Tc-HM-PAO SPECT, Hypoperfusion, Delayed neurologic sequelae, Carbon monoxide poisoning.*

INTRODUCTION

In Korea, carbon monoxide (CO) poisoning is still one of the most important conditions causing brain damage as a result of cellular oxygen lack: however, the incidence of CO poisoning is decreasing annualy (Whang and Choi, 1990).

It is well known that CO has the toxic effects of tissue hypoxia and produces acute neurologic deficits, but severe neurologic reaction may be delayed for days or weeks after anoxic exposure (Shillito et al., 1936; Meigs and Huges, 1952; Choi, 1983; Ginsberg, 1985). The prediction of outcome during the acute stage or the latent period is difficult in most cases because of variations in age, duration and severity of exposure, and individual susceptibility.

The initial laboratory findings do not provide any prognostic clues, and attempts at further predicting the clinical outcome of delayed neurologic sequelae by means of brain CT scans or other tests have remained unsuccessful (Nardizzi, 1979; Swada et al., 1980; Choi, 1985; Miura et al., 1985; Vieregge et al., 1989; Chang and Han, 1990).

Recently single photon emission computed tomography (SPECT) using technetium-99m (^{99m}Tc) hexamethylpropylene amine oxime (HM-PAO) provides tomographic images of cerebral perfusion (Neirinckx et al., 1987; Sharp et al., 1988; Davis et al., 1990). This

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chelated compound is lipophilic, readily crosses the blood-brain barrier, and has a high-first-pass cerebral extraction with long-term retention. Using the intravenous ^{99m}Tc-HM-PAO SPECT technique, cerebral blood flow (CBF) maps are obtained that compare with those derived using other tomographic methods. To our knowledge, there have only been two reported studies using tomographic CBF techniques in patients with delayed neurologic sequelae after CO poisoning in Korea (Ahn et al., 1988; Lee et al., 1988).

Using SPECT with ^{99m}Tc-HM-PAO, we aimed to determine whether changes in cerebral tissue perfusion in patients with CO poisoning predicted the onset of delayed deficits or correlated with the outcome of delayed deficits.

PATIENTS AND METHODS

Between March 1988 and October 1990 six patients with delayed neurologic sequelae were seen with a diagnosis of CO poisoning proved circumstantially or by CO-Hb determination. The patients were evaluated by two neurologist and the results were summarized in table 1.

All were women, and their ages ranged from 37 to

Table 1. Clinical summary of 6 patients with carbon monoxide poisoning

No	Age	Sex	Duration of unconsciousness (hours)	Lucid interval (days)	HBO therapy	Duration until recovery (months)	Outcome
1	70	F	8	20	+	8	Good
2	55	F	24	33	+	4	Excellent
3	63	F	12	21	+	6	Excellent
4	37	F	0	13	−	3	Excellent
5	65	F	20	21	−	3	Excellent
6	52	F	0	30	−	1	Follow up

HBO: Hyperbaric oxygen, +: performed, −: not performed

Table 2. Findings of CT brain scans and ^{99m}Tc-HM-PAO brain SPECTs in patients with delayed neurologic sequelae of CO poisoning

No	C-T brain scan		^{99m}Tc-HM-PAO brain SPECT		
	Initial	Follow-up	Acute phase	Delayed phase	Recovery phase
1	Hypodensity of cerebral white matter	Hypodensity of cerebral white matter with cortical atrophy	Normal	Diffuse patched hypoperfusion	Normal
2	Low density of globus pallidus	No interval change	Hypoperfusion on left frontal lobe	Diffuse patched hypoperfusion	Normal
3	Hypodensity of cerebral white matter	No interval change	—	Diffuse patched hypoperfusion	Normal
4	Normal	Normal	—	Diffuse patched hypoperfusion	Normal
5	Normal	—	—	Diffuse patched hypoperfusion	Normal
6	Low density of globus pallidus	—	—	Diffuse patched hypoperfusion	—

— : not performed

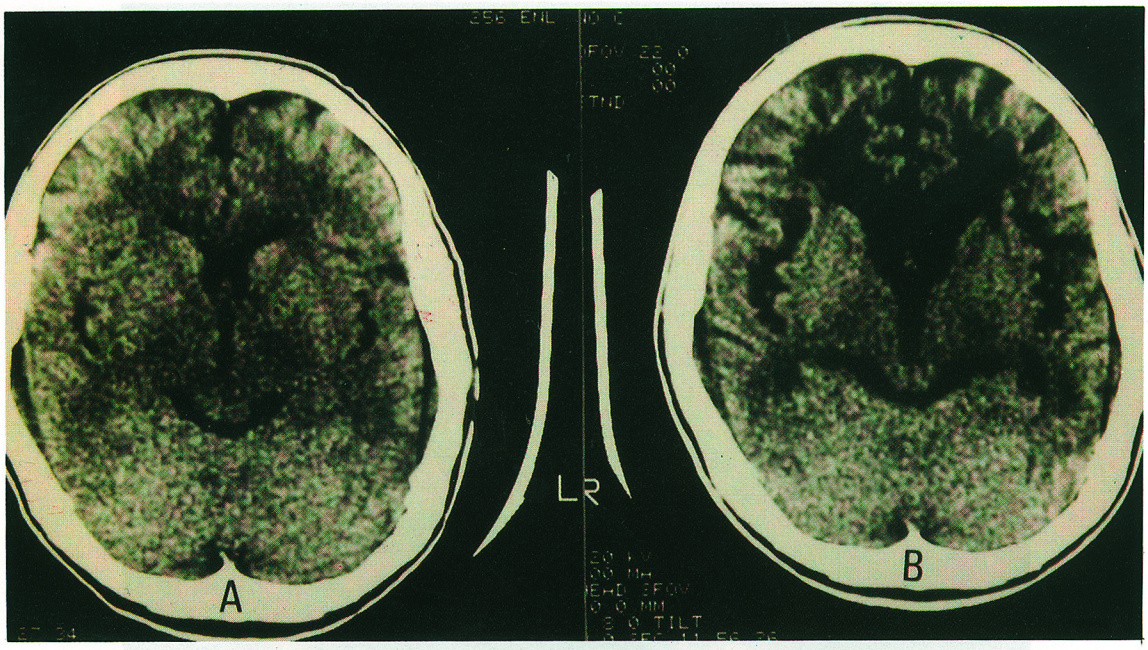

Fig. 1. A. CT brain scan 4 days after acute CO poisoning showed decreased density in cerebral white matter. B. CT brain scan 7 months after CO poisoning showed more aggravating pattern with cortical atrophy (patient 1).

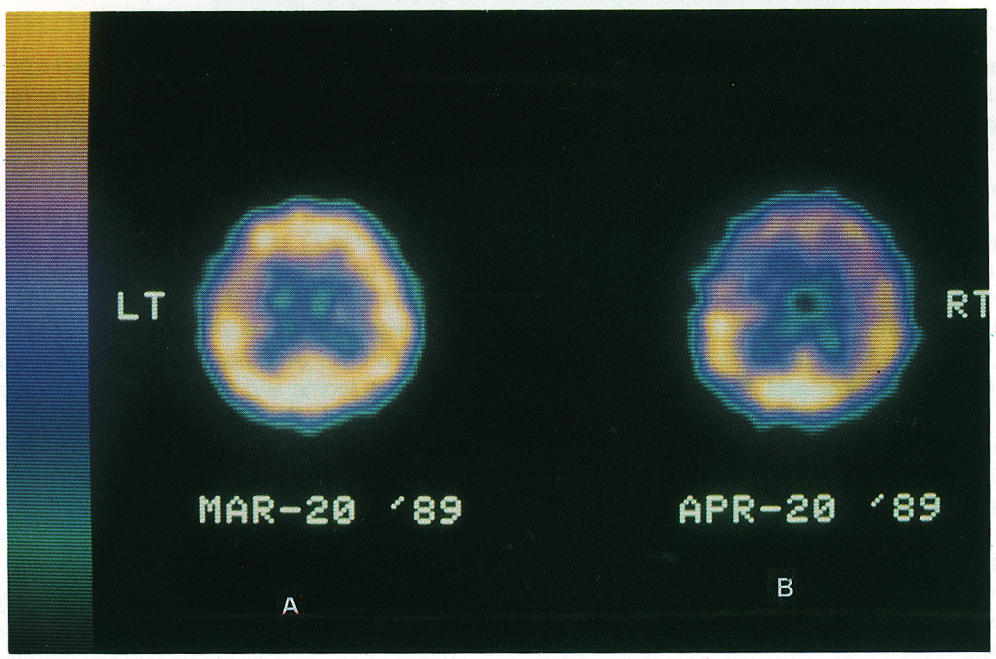

Fig. 2. A. SPECT with ^{99m}Tc-HM-PAO 10 days after acute CO poisoning showed decreased perfusion on left frontal lobe. B. SPECT with ^{99m}Tc-HM-PAO 10 days after delayed neurologic sequelae of CO poisoning showed decreased perfusion throughout the cerebral cortex, more prominently on left side (patient 2).

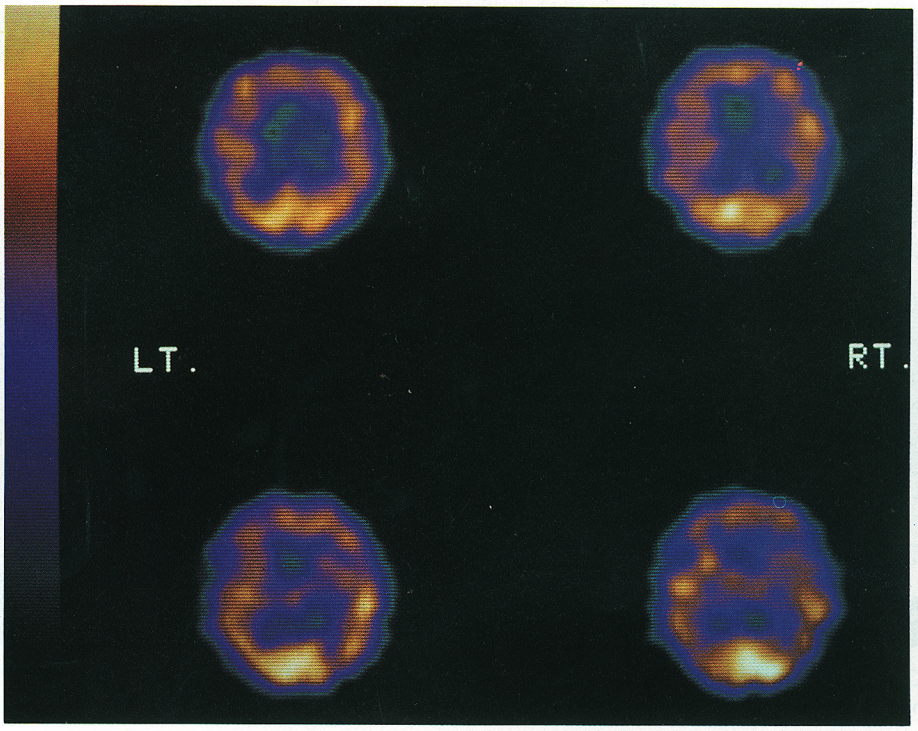

Fig. 3 SPECT with ^{99m}Tc-HM-PAO 8 days after delayed neurologic sequelae after CO poisoning showed patched decreased perfusion throughout the cerebral cortex (patient 3).

70 years (mean, 57 years).

The lucid interval before the appearance of neurologic sequelae varied from 13 to 33 days (mean, 23 days). Three patients received hyperbaric oxygen therapy during acute anoxic insult, and the two whose mental state was clear during the acute episode had no treatment. Of those 6 patients, 5 recovered within 3 to 8 months, but one (patient 1) had parkinsonism and one is still under study at the time of writing.

Initial and follow-up examinations included a detailed history, clinical examination, routine blood screens, EEG, CT brain scans, and ^{99m}Tc-HM-PAO brain SPECT. Follow-up CT brain scans were obtained a few days before or after performing ^{99m}Tc-HM-PAO brain SPECT.

We performed SPECT by the following method. Eluting with 0.5ml normal saline, (Eluent for du Pont Technetium^{99m} Generator), a maximum of 30 mCi ^{99m}Tc was prepared from NEN Medical Products Technetium^{99m} Generator, du Pont Co, and the vials containing freeze-dried HM-PAO (Ceretec^{R}) were reconstituted.

Within 10 minutes after preparation, intravenous administration of this radioactive pharmaceutical was conducted in a quiet room with dimmed light. Twenty minutes after injection, SPECT was performed with a rotating scinticamera (Maxicamera Autotune ZS, General Electric Co. 20 seconds 64 single scans per full rotation). Axial and coronal image reconstruction was achieved using a Star computer, General Electric Co. ^{99m}Tc-HM-PAO brain SPECTs were obtained in 2 studies on 2 patients at the acute phase, in 7 studies on 6 at the delayed phase, and in 5 studies on 5 at the recovery phase of CO poisoning. After SPECT imagination, we evaluated the correlation between the clinical outcome and the findings of CT brain scans and ^{99m}Tc-HM-PAO brain SPECT.

RESULTS

The results are summarized in table 2. Among 6 patients, 2 initial CT brain scans (patients 2 and 5) showed low density of both basal ganglia, two (patients 1 and 3) showed decreased density of the white matter of the cerebral cortex and two (patients 4 and 5) were normal.

Of the six patients, follow-up CT bain scans were obtained on 4. Two showed no interval change, and

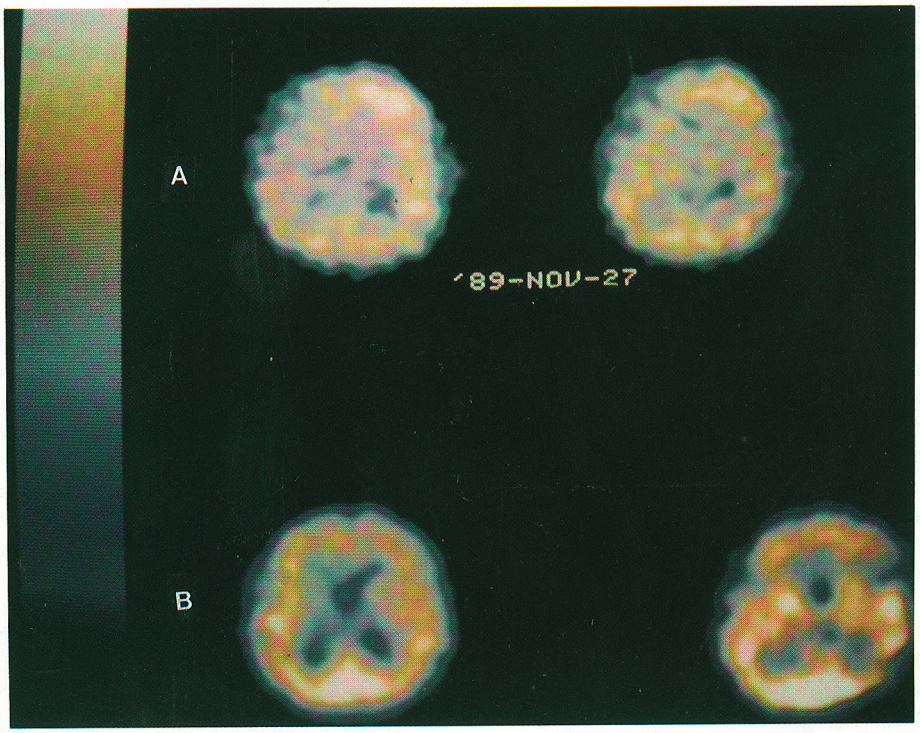

Fig. 4. A. SPECT with ^{99m}Tc-HM-PAO 7 days after delayed neurologic sequelae of CO poisoning showed decreased perfusion throughout the cerebral cortex, more prominently on the left side. B. SPECT with ^{99m}Tc-HM-PAO six and a half months after A showed markedly increased perfusion with the concomitant clinical improvement (patient 1).

one (patient 1) revealed aggravated findings, in spite of clinical improvement (Fig 1). There was no correlation between the clinical outcome and the findings of the follow-up CT brain scans.

Two ^{99m}Tc-HM-PAO brain SPECTs were obtained on 2 patients 5 days (patient 1) and 13 days (patient 2) after acute CO poisoning. One was normal, and the other (patient 2) revealed hypoperfusion on the left frontal area (Fig 2). The latter developed delayed neurologic sequelae 20 days after this finding.

Seven ^{99m}Tc-HM-PAO SPECTs were obtained on 6 patients during the delayed phase of CO poisoning. All showed diffuse patched hypoperfusion (Fig 3). Of the six patients, follow-up SPECT studies were done in 5 patients 3 to 8 months after anoxia, when the patients had recovered clinically. All were nearly normal (Fig 4). The outcome of delayed neurologic sequelae after CO poisoning correlated with the findings of ^{99m}Tc-HM-PAO brain SPECT.

DISCUSSION

The neurological manifestations of CO poisoning are exceedingly varied. Of considerable clinical interest, the development of delayed neurologic sequelae is more characteristic of anoxic encephalopathy after CO poisoning than of other types of anoxia (Sillito et al., 1936; Meigs and Huges, 1952; Choi, 1983; Ginsberg, 1985).

During the acute anoxic insult or the latent period, no clinical signs distinguish patients destined to suffer relapses from those who will have an uncomplicated recovery, although the possibility of delayed neurologic sequelae tends to increase in accordance with the duration of unconsciousness during the acute CO poisoning (Choi, 1983).

The initial laboratory findings also do not provide any prognostic clues. Attempts at further predicting the clinical outcome of delayed neurologic sequelae by means of CT brain scans have been tried in recent years (Nardizzi, 1979; Choi, 1983; Miura et al., 1985).

Nardizzi (1979), Swada et al. (1980), and Miura et al. (1985) reported that the CT finding in CO poisoning was low density bilaterally in the globus pallidus and correlated with the long-term outcome after acute CO poisoning. But the initial CT brain scan may fail to detect low density lesions on the globus pallidus or on the cerebral white matter (Choi, 1983; Vieregge et al., 1989). If present, these lesion may either have disappeared, diminished or remained unchanged at follow-up, without the correlation of the clinical outcome (Vieregge et al., 1989). So the prediction of the clinical outcome of CO poisoning by using CT brain scan has remained unsuccessful until now.

In 1985 one of our colleagues reported that brainstem auditory evoked potential (BAEP) has been used for providing prognostic values in acute CO poisoning (choi, 1985). We confirmed that BAEP was somewhat useful in evaluating the functional integrity of the auditory pathways and the lesions of the brainstem; however, these lessions are extremely rare in CO poisoning.

There have been a few reported studies using magnetic resonance imaging (MRI) in CO poisoning, but these were case reports concerned only with findings of MRI (Vieregge et al., 1989; Chang and Han, 1990).

Although SPECT with ^{99m}Tc-HM-PAO is the indirect and less accurate method for measuring cerebral blood flow, compared with positron emission tomography (PET), it has been used in clinical practice recently (Sharp et al., 1986; Neirinckx et al., 1987; Davis et al., 1990). Of our two SPECTs with ^{99m}Tc-HM-PAO performing during the acute episode, one showed focal hypoperfusion which appeared 20 days prior to the onset of delayed neurologic sequelae after CO poisoning. This may suggest that the ^{99m}Tc-HM-PAO brain SPECT, if used early, can be a predictor to distinguish patients destined to suffer relapses from those who will have an uncomplicated recovery. We will study this further.

All SPECTs with ^{99m}Tc-HM-PAO performing during the delayed phase showed diffuse patched hypoperfusion which improved on follow-up images taken during the recovery phase. The findings of SPECT were correlated with the clinical outcome of delayed neurologic sequelae after CO poisoning.

Thus, we think that ^{99m}Tc-HM-PAO brain SPECT is the most useful test for evaluating the outcome of CO poisoning.

The cause of delayed neurologic sequelae after CO poisoning is unknown, but there are several hypotheses based on pathologic studies (Ferraro, 1933; Yant et al., 1934; Hurst, 1952; Courville, 1957; Schwedenberg, 1959; Miura et al., 1980). We will discuss the possibility of vascular theory based on our's and others' studies. In 1928 Meyer postulated that the vascular smooth muscle might be altered by CO, and that distorted regional cerebral circulation is responsible for the lesions in the pallidum and the cerebral white matter (Courville, 1957). Data in several experimental models has suggested that the white matter was preferentially vulnerable to incomplete ischemia (Welsh et al., 1978; Ginsberg and Myer, 1989).

In 1957 Courville reported that the occurence of vascular changes, suggestively functional at first (vasopasm), is followed by secondary degenerative changes in the arteries of the white matter with consequent disappearance of the capillaries in the necrotic foci in CO poisoning. Also, when multiple small vascular lesions do occur in the brain, the result is perivascular infarction with loss of myelin, not simply diffuse demyelination as in the postanoxic state.

In clinical practice, one finds that there are some similarities between the delayed neurologic sequelae after CO poisoning and those of subarachnoid hemorrhage.

These are that they have a free interval after acute insult, and improve gradually for several months in case of survival. But the involvement of small arteries in delayed neurologic sequelae of CO poisoning is different from the involvement of large arteries in those of subarachnoid hemorrhage (Shillito et al., 1936; Meigs and Huges, 1952; Kassell et al., 1985; Miura et al., 1985; Davis et al., 1990).

The study herein showed diffuse patched hypoperfusion of SPECT; which was comparable to those of Ahn et al. (1988) and Lee et al. (1988), and correlated with the clinical outcome.

As the above mentioned findings are integrated, we can suggest that cerebral vascular changes such as vasospasm may be the possible cause of hypoperfusion in patients with delayed neurologic sequelae after CO poisoning.

Some have refuted this notion, because it was thought that the pathologic changes in the vessels were not sufficient to account for the diffuse, conspicuous softening of the white matter (Ginsberg and Myer, 1974; Jefferson, 1976). Of course, there are some questions to be solved in future. First, if functional vascular changes (vasospasm) initially cause decreased cerebral perfusion in patients with delayed deficits of CO poisoning, what is the possible factor causing vasospasm? Is it the CO itself (Plum et al., 1962), brain edema (Schwedenberg, 1959), acidosis

and hypotension (Siesjo, 1985), toxic oxygen reduction product such as free oxygen radicals or lipid peroxidation (Werner, 1985), or the rheological factor (Grogaard et al., 1989)?

Secondly, if hypoperfusion plays a role, why is the cerebral white matter, which needs only one fifth as much oxygen as the gray matter, predominantly damaged (Brucher, 1967; Ginsberg and Myer, 1974; Ginsberg 1979)? Further studies are needed to determine the mechanism of decreased cerebral perfusion in delayed neurologic sequelae after CO poisoning.

As a preliminary conclusion, SPECT with ^{99m}Tc-HM-PAO can be used for predicting or evaluating the clinical outcome of delayed neurologic sequelae after poisoning. The cerebral vascular changes may be the possible cause of decreased cerebral perfusion in patients with CO poisoning.

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