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N-isopropyl-*p*[^{123}I]iodoamphetamine, a new agent for lung imaging studies

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ABSTRACT *N*-isopropyl-*p*[^{123}I]iodoamphetamine, originally designed for brain scintigraphy, has been found to be retained by the normal lung and to produce excellent camera images. Ten patients with gross abnormalities on their chest radiographs due to lung cancer have been studied with this drug. The diseased parts of the lung consistently showed less uptake and these defects matched those obtained with microspheres labelled with technetium-99m, indicating that ^{123}I-iodoamphetamine has the characteristics of a perfusion tracer. In five out of the 10 patients studied sequential studies showed that improved iodoamphetamine uptake was encountered shortly after a favourable response to radiotherapy and reduced uptake was seen in congruence with the radiation field at a later stage. This first clinical demonstration indicates that the retention of ^{123}I-iodoamphetamine could be a sensitive marker for pulmonary vascular integrity and a useful new tool to identify the extent of disease where the pulmonary circulation is the initial site of the disorder.

During the last 10 years the lung has been recognised as an important metabolic organ. It has been shown to produce, inactivate, and modulate a variety of hormones, drugs, and amines, endothelial cells having a central role in these processes.[1–3] Recently a new radiopharmaceutical, *N*-isopropyl-*p*[^{123}I]iodoamphetamine, which was originally designed for brain scintigraphy, has received attention because of its high—possibly metabolic—retention by the lung.[4 5] In this study of patients with gross abnormalities on the chest radiographs due to lung cancer we examined the imaging properties of ^{123}I-iodoamphetamine to assess its use as a possible marker for pulmonary vascular (endothelial) integrity. In five of the patients sequential images were used to try to gain insight into the effects of radiation treatment on pulmonary uptake of ^{123}I-iodoamphetamine.

Methods

We studied 10 men, aged 34–67 years, with inoperable, histologically proved limited stage non-small cell lung cancer and a Karnofsky index greater than 70, and without overt cardiovascular, hepatic, thyroid, or neuropsychiatric disease. After giving informed consent the patients, while supine, received a bolus injection 2·5 mCi ^{123}I-iodoamphetamine (2·5 mCi or 92·5 MBq/ml, 50 Ci/g iodoamphetamine) via a cubital vein. Heart and respiration rates were monitored for 60 minutes after injection. The temporal behaviour of the ^{123}I-iodoamphetamine was determined from a sequence of images acquired over a period of 40–50 minutes after the injection. Data were recorded on a Siemens ZLC 75 gamma camera interfaced with a MDS A^2 data system. ^{123}I-iodoamphetamine images were compared with conventional perfusion studies obtained with human albumin microspheres labelled with technetium-^{99m} (^{99m}Tc). In five patients sequential ^{123}I-iodoamphetamine, ^{99m}Tc, and krypton-81m (^{81m}Kr) ventilation images were made just before and 8–24 weeks after the start of the radiotherapy. This consisted in all cases of 5500 rads (cGy) given in two (split) courses to the primary tumour and mediastinal nodes.

Results

In all 10 patients distinct areas of reduced ^{123}I-iodoamphetamine uptake were found, while other parts of the lungs were excellently delineated by appreciable retention of the iodoamphetamine. About 90% of the injected dose was found in the lung

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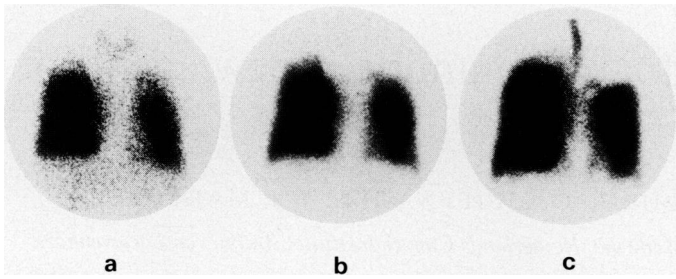

Fig 1 *(a) ^{123}I-iodoamphetamine uptake: (b) ^{99m}Tc perfusion; (c) ^{81m}Kr ventilation image in a patient with cancer of the left upper lobe.*

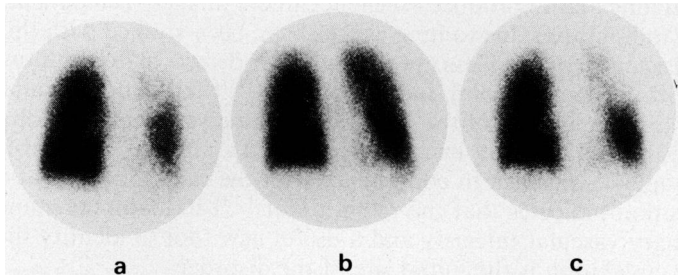

Fig 2 *Examples of ^{123}I-iodoamphetamine uptake in a patient (No 5 in the table) with non-small cell lung cancer of the left upper lobe, showing (a) a defect of uptake before treatment; (b) amelioration 11 weeks after initiation of radiotherapy; and (c) decrease of uptake congruent with the radiation field 15 weeks after the start of radiotherapy.*

within five minutes of administration. After 50 minutes 41% of the activity was left.

In the preradiation studies the areas with reduced uptake corresponded in each case to the abnormalities on the chest radiograph. The images with ^{99m}Tc, used as a perfusion reference tracer, mimicked the pattern of ^{123}I-iodoamphetamine uptake. In contrast to the slight uptake of the latter ^{99m}Tc was not retained at all by the affected parts of the lungs (fig 1).

All five patients who had repeat scans had a response to radiotherapy according to UICC criteria. In four of them the second ^{123}I-iodoamphetamine study was carried out 8–13 weeks after initiation of treatment and showed improved uptake in the diseased parts of the lung. Shortly afterwards (4–11 weeks), however, without any sign of recurrence, four of the five patients again showed an area of diminished retention (table). This time the defects seen were grossly congruent with the radiation field (fig 2). In contrast to the reduction of ^{123}I-iodoamphetamine and ^{99m}Tc concentrations in the irradiated parts, the ventilation image of those regions with ^{81m}Kr remained unaltered (four patients) or slightly improved (one patient) (table). Amphetamine like side effects were not seen in any patient.

Discussion

The potential for using ^{123}I-iodoamphetamine for quantitative pulmonary imaging studies was recognised by Rahimian *et al*, who produced experimental evidence for the suggestion that pulmonary retention of ^{123}I-iodoamphetamine was an active process, possibly due to an endothelial receptor binding.[6 7] This is an attractive hypothesis in view of the rapidly increasing reports on the metabolic properties of

Sequential pulmonary ^{123}I-iodoamphetamine scintigraphy before and after radiotherapy† in men with non-small cell lung cancer*

Patient No	Age (y)	Site of tumour	Before treatment		After start of radiotherapy					
			Scintigram appearance	Reg %	Week	Scintigram appearance	Reg %	Week	Scintigram appearance	Reg %
1	56	RUL	Defect RUL (~ Q/V̇)	56	13	↑	63	24	↓	53 (V̇ unchanged)
2	54	RUL	Defect RUL (~ Q/V̇)	78	8	↑	90	18	↓	67 (V̇ unchanged)
3	53	RUL	Defect RUL (~ Q/V̇)	80	(Q and V̇ at 10 w ↑)			15	↓	58 (V̇ unchanged)
4	59	Central left	Defect LUL and LLL (~ Q > V̇)	38	9	↑	58	19	↑	74 (V̇ improved)
5	51	LUL	Defect LUL	36	11	↑	73	15	↓	50 (V̇ unchanged)

*^{123}I-iodoamphetamine uptake is expressed as a regional percentage (Reg %) by dividing counts of the diseased part or parts of the lung by those of the contralateral (normal) lung. Arrows ↑ and ↓ indicate improvement or decrease of uptake by comparison with the previous image.
RUL—Right upper lobe; LUL—left upper lobe; LLL—left lower lobe; Q—perfusion as estimated by ^{99m}Tc-microspheres; V̇—ventilation as estimated by ^{81m}Kr.
†5500 rad (cGy) in split course fashion.

endothelial cells, which are more abundantly present in the lung than in any other organ. The capacity of the monoamine oxidase system of endothelial cells to metabolise endogenous and exogenous circulating amines has been proved in several studies (for review see ref 8).

Consequently changes in lung morphology or pulmonary vascular integrity can be expected to affect uptake and retention of radiopharmaceuticals that are actively handled by endothelium. Although the present study does not reveal the exact site of retention of ^{123}I-iodoamphetamine, this is the first clinical demonstration that it has the characteristics of a perfusion tracer. The uptake in areas where the ^{99m}Tc image is completely absent may be explained either by (1) the inability of the microspheres to penetrate into a considerably diminished pulmonary vascular bed with proportionally reduced perfusion or by (2) the vascularisation of the pathological part of the lung by the bronchial arterial system. There could be a combination of both processes. The amelioration of the defect shortly after a positive response to radiation treatment, seen in all of the patients studied, supports both explanations. We think that the reduction of the ^{99m}Tc image that accompanied the reduced ^{123}I-iodoamphetamine uptake within the margins of the radiation field without alteration of the ^{81m}Kr ventilation image is due to loss of pulmonary artery circulation induced by radiotherapy.[9] Since the endothelial cell has been identified as the initial site involved in the pathogenesis of radiation induced damage,[10] ^{123}I-iodoamphetamine may serve as a sensitive marker for early (vascular) damage. We believe that it might prove to be a useful marker for assessing the extent of disease in other disorders where the endothelial cell is affected early in the disease process. Moreover ^{123}I-iodoamphetamine might be used as an alternative in cases of severe pulmonary hypertension, where an embolising tracer is contraindicated.

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