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A N I N T E R N A T I O N A L J O U R N A L

Is Nuclear Medicine Really Safe?

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ABSTRACT

In nuclear medicine, radiation absorbed dose estimates calculated by standard models at the whole body or organ are very low. At cellular level, however, the heterogeneity of radionuclide distributions of radiation dose patterns may be significant. We present here absorbed doses at cellular level and evaluate their possible impact on the usually assumed risk/benefit relationships in nuclear medicine studies. The absorbed dose values calculated are surprisingly high, and are difficult to interpret. In the present study, we show calculated doses at the cellular level and discuss possible biological consequences, for two radiopharmaceuticals labelled with technetium-99m: human serum albumin microspheres used for pulmonary scintigrapies and HMPAO used to labelled leukocytes.

Key words: Technetium-99m, absorbed doses, biological effects

INTRODUCTION

Nuclear medicine (NM) practices have increased continually in recent decades. This modality is chosen for its diagnostic qualities and appears to be advantageous in delivering low radiation doses to patients. The distribution of the radiopharmaceuticals (RPs) and of the calculated absorbed doses are usually assumed to be uniform. Numerous studies, however, have shown that RP distribution can be very heterogeneous at the cellular level (Robinson et al., 1996). Thus, absorbed doses may be also be nonuniform in particular cells, with possible radiobiological consequences. It is known that the decay scheme of technetium-99m (99mTc) has 10% of cases involving emission of electrons of low energy, with short ranges in the tissue. For example, the Auger electrons of 99mTc (energy = 0.03 to 15.3 keV, abundance of ~4%, or 15% of the total electron emissions) have a range varying from 0.02 to 5.3 micrometers. In a previous study (Hindie et al., 1988) we showed that the dose absorbed by radiolabelled Kupffer cells after 99mTc-sulfur colloid injection was approximately 15,000 times the mean electron dose to the same cells as estimated using the conventional MIRD Schema; to this point this result has not raised significant concerns about routine NM practices. In another study, Makrigiorgos et al. (1990) used a computer program based on a theoretical model that accounted for the nonuniform distribution of 99mTc-labeled microspheres to calculate the doses delivered to lung cells from 99mTc electrons and photons. The dose to 8% of the cell population was very high (3 to 7500 times the standard MIRD estimate). The obvious question in these 2 results is: what are the possible radiobiological consequences of its high radiation doses? (Kassis et al., 1992).

We present here the results of 2 studies at our laboratory concerning the potential biological

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consequences of irradiation from two 99mTc-RPs currently used in NM:

1 Human Serum Albumin (HSA) microspheres (Robinson et al., 1996); and
2 HMPAO-99mTc (C. de Labriolle-Vaylet et al., 1998).

The relationship between calculated doses and biological effects and the possible inadequacy of standard models is discussed.

MATERIALS AND METHODS

1) Biological studies of lung cells irradiated by 99mTc

The principal results of our published study were presented:

1. The heterogeneity of the distribution of 99mTc-labelled microspheres (μs) in rat lung tissue was visualized and quantified using a microradioautographic "track" method (MRA) (Barbu et al., 1984);
2. A very heterogeneous tridimensional distribution of the microspheres within the lung was demonstrated with interparticle distances ranging from 57 to 4400 microns;
3. Thus only delivered doses closer to the microspheres were calculated;
4. These doses reached approximately 6 Gy for the closest endothelial cells and 2 Gy for epithelial cells.

Biological studies were performed using electronic microscope technique and biochemical technique (Surexpression of p53 protein, bioindicator of a DNA stress) (Jacquet et al., 1999).

a) Ultrastructural study

The aim of this study was to evaluate the histological damage to the pulmonary cells in the neighborhood of labelled microspheres compared with control cells. Three groups were compared, a control group (without μs), and two other groups with labelled and unlabelled μs.

b) Nuclear expression of p53 protein was assessed using immunohisstochemistry.

The intensity of the nuclear staining was graded by coloration. Two observers interpreted the nuclear staining.

2) HMPAO-labelled lymphocytes

At present, 99mTc-HMPAO labelling is routinely performed on mixed leukocyte preparations which include lymphocytes. HMPAO is not a specific tracer for polymorphonuclear cells. Global leukocyte labelling efficiency was 37.9%(+ or - 13.5%). After selective sedimentation, radioactivity was distributed as follows: 11.23% in mononuclear cells, 70.5% in PNMs, 13% in red blood cells and > 5% in plasma.(C. de Labriolle-Vaylet et al., 1998). MRA studies showed that the labelling was very heterogeneous (4% intensely labelled cells).

a) Effects of 99mTc-HMPAO labelling on lymphocyte function

PHA stimulation was used to evaluate the ability of labelled lymphocytes to the synthesis of DNA

b) Viability of HMPAO-labelled lymphocytes.

The plating efficiency of the labelled lymphocytes was compared with that of control lymphocytes. The experimental procedure was described previously (Sala-Trepat et al., 1990).

c) Chromosomal aberrations

Labelled and unlabelled lymphocytes were cultured with a classical technique (AIEA, 1986). The metaphases are identified after fluorescence with Giemsa staining. The dicentrics and rings were counted and the frequency of unstable chromosomal aberrations was calculated in the 2 groups.

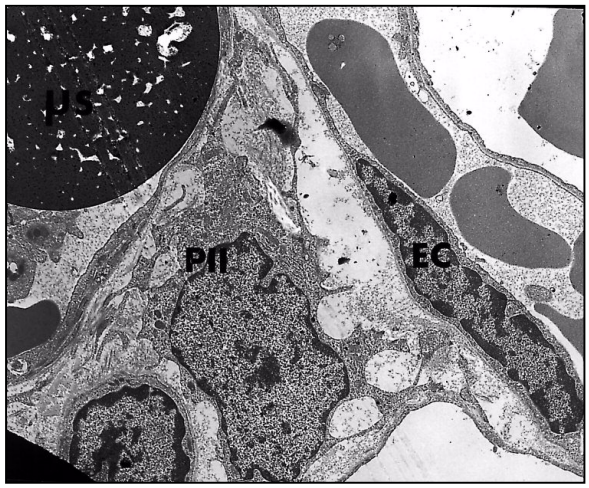
RESULTS

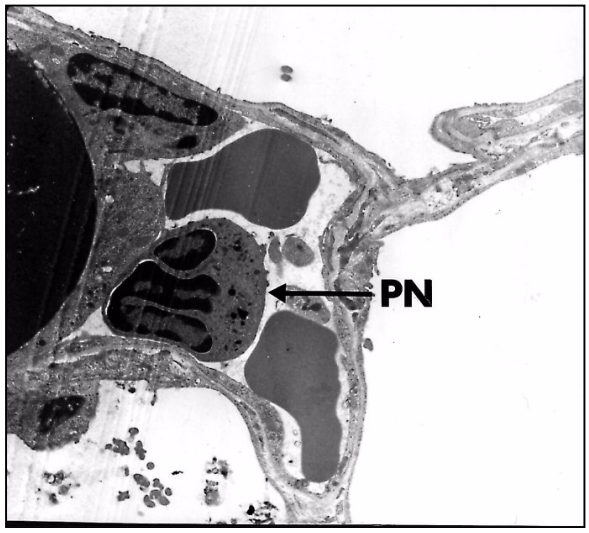
1) Irradiated lung cells

a) Morphological studies

Lung electron micrographs, obtained 6 hours after administration of labelled and unlabelled microspheres are shown. Cells in close contact to the labelled microspheres showed no lesions. No

signs of apoptosis were seen. Only an inflammatory response, corresponding to the presence of several polymorphonuclear cell (PNs), was found in the 2 groups in the capillary lumina. (Fig. 1).





On left, 6 hrs. After administration of unlabelled microspheres. Only a leukocyte infiltration (PN) is noted. On right, after administration of labelled microspheres, pneumocytes (PII) and endothelial cell (EC) are normal.

a) Nuclear expression of p53 in pulmonary cells

Statistical analysis showed no difference between the groups (control, with unlabelled and labelled microspheres).

2) HMPAO-labelled lymphocytes

a) Plating efficiency

The plating efficiency of 99m-Tc-HMPAO-labelled lymphocytes was found to be lower than for control lymphocytes. Some of the labelled lymphocytes were still viable, therefore, and able to form clones under routine conditions.

b) Chromosomal aberration

No abnormality was noted in the unlabelled lymphocytes. Aberration frequencies in labelled lymphocytes were found to be higher than in control cells (C. de Labriolle Vaylet et al., 1998)

DISCUSSION

1) Lung studies

The reference technique of electron microscopy was used to evaluate morphological cellular lesions (cell alterations, apoptosis, necrosis). In our study, numerous electron micrographs were analysed (about 400 for irradiated lungs). Despite the very high calculated mean doses delivered, no morphological damages or signs of cell death were observed. Only the introduction of microspheres induced inflammatory responses. No significant increase of nuclear expression of p53 was noted in the labelled cells. No correlation between the physical parameter (absorbed dose in Gy) was found with the biological fate of irradiated cells. Our laboratory has performed a further study tool using biological dosimetry (Jacquet et al., 1999). A specific curve for 99mTc was established to evaluate the dose-effect relationship between radiation dose and unstable radioinduced chromosomal aberrations.

2) HMPAO-labelled lymphocytes

99mTc-HPMAO is not a specific tracer for PMNs, it also labelled lymphocytes. After MRA studies, the degree of heterogeneity could not be visualized. Thus, it was clear that the mean absorbed dose (about 8 Gy) could not be used for evaluating the biological consequences of cell labelling. Did some of the cells die, as one might suppose? If others did not die, what lesions or other functional changes may have resulted, and

what were the cells' repair capacity? (Colas-Linhart, 2001). The most important result was the reduced plating efficiency of labelled lymphocytes as compared to control cells: some lymphocytes were able to form clones and were still "alive" by radiobiological definition. It was therefore suggested that lymphocytes should be removed from 99mTc-HMPAO cell preparation before administration to patients.

CONCLUSION

Biological studies are very important for evaluation of patient risk in NM studies. As Kassis wrote (Kassis et al., 1992) : "Nonetheless, the results would enhance our knowledge about radiation carcinogenesis and following Pascal'gamble (Pascal, 1878) : "**It is better to know than to be sorry.**"

RESUMO

Como avaliar a relação risco-beneficio de cintigrafias? Em medicina nuclear, a dose devida à radiação absorvida no corpo inteiro ou nos órgãos tem sido subestimada apesar de sua baixa intensidade. Os métodos de avaliação tem assumido uma distribuição uniforme do produto radioativo. Entretanto, em nível celular, existe uma distribuição heterogênea do produto radioativo e conseqüentemente uma heterogeneidade da emissão radioativa. Atualmente, as doses absorvidas em nível celular são calculadas considerando uma distribuição não uniforme. Os valores da dose absorvida estimados através dessa hipótese são geralmente relevantes mesmo nos casos mais complexos. No presente estudo, nós avaliamos as conseqüências biológicas, em nível celular, induzidas por dois produtos radioativos marcados com o tecnécio-99m: microesferas de albumina de soro humano usado para cintigrafias pulmonares e HMPAO utilizado em leucócitos marcados.

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