CYCLOTRON PRODUCED ISOTOPES FOR MEDICAL APPLICATIONS

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ABSTRACT

Cyclotron produced isotopes for medical use are classifiable as single photon emitters (^{201}Tl, ^{123}J, ^{67}Ga), used for planar and tomographic imaging (=**SPECT**), and as positron emitters (^{18}F, ^{15}O, ^{13}N, ^{11}C) as applied for tomographic organ imaging (=**PET**). There is a number of generator produced positron emitters. This paper reviews the application in clinical nuclear medicine for cardiology (myocardial scintigraphy), oncology (tumor scintigraphy), endocrinology (parathyroid scintigraphy), dermatology (malignant melanoma), neurology (brain tumors), AIDS, nephro-urology. Attention is also devoted to PET-imaging in neuropsychiatric diseases, oncology, and cardiology with instructive clinical examples underscoring the unique capabilities in detecting (patho)-physiologic basis of diagnosis and approaching a more adequate therapy and monitoring therapy response.

It is concluded that at least in F.R.G. the number of PET facilities (and cyclotrons) is disproportionally limited as compared to other countries.

1. INTRODUCTION

Present success and future survival of clinical nuclear medicine critically depends on the availability of cyclotron produced isotopes such as single photon emitters and positron emitters. Single photon emitters since many years play a reliable role in nuclear medicine decision making of most medical centers. Positron emitters, however, are available only in a few places whole over the world - about 76 - and in Federal Republic of Germany 5 centers contribute research and clinical work signalizing the underdeveloped stage of medical health care of our country in this particular field. Setting up a clinical positron emission tomography center has been described for instance by Hubner and Smith (1). Table 1 lists clinically important single photon- and positron emitters.

Table 1 : Cyclotron Produced Clinically Important Short Lived Single Photon- and Positron Emitters

SINGLE PHOTON -	POSITRON - EMITTERS
^{67}Ga	^{11}C
^{111}In	$^{13}NH_3$
^{123}I	^{15}O
^{201}Tl	^{18}F

2. PRINCIPLES OF SPECT AND PET

Radionuclide imaging with single photon emitters is achieved by means of a rotating gamma camera, a so called emission tomograph, which rotates around the patient 180 or 360 degrees. The procedure is named single photon emission computed tomography, abbreviated as SPECT.

Positron emitters however afford a more cost expensive device: A positron emission tomograph with multicristal ring detectors. Ideally the shortlived positron emitters are produced by a cyclotron at the hospital site which again in our country is available only in singular centers.

The aim of this review is to highlight some diagnostic possibilities of both categories of radionuclides out of the view of clinical nuclear medicine.

3. SINGLE PHOTON EMITTERS

As mentioned the equipment of choice is a single or double head detector gamma camera interfaced to a computer to produce single photon emission computed tomograms in a 3 dimensional display with the intention to visualize an organ and to quantify volumes in normal and diseased organs, for instance brain lesions. The computer reconstructs 64 or 128 section images out of which 16 are elected for documentation (2,3).

SPECT of the brain using ^{99m}Tc-HMPAO, a perfusion marker shows the extended regional perfusion deficit in the perfusion area supplied by the middle cerebral artery in patients with left or right sided carotic stenosis.

SPECT procedure is now the nuclear medicine examination broadly accepted in clinical practice.

3.1 ^{201}Tl

3.1.1 Cardiology

The easy production, the physical properties and the general availability keep ^{201}Tl - although not ideal - still in a prominent position in clinical cardiology as well as in cardiac surgery. ^{201}Tl- myocardial scintigraphy is an integrative part in diagnostic cardiology for selecting patients at risk of developing myocardial infarction, detecting myocardial ischemia, improving the estimation of the prognosis after infarction, especially in young and professionally active patients and lastly in the control of therapy, such as aorto-coronary bypass surgery or percutaneous transluminal coronary angioplasty (to dilate critical coronary artery stenoses by means of a balloon catheter) (4).

3.1.2 Endocrinology, oncology and infectiology

^{201}Tl turned out to be also helpful outside cardiology: In clinical oncology and endocrinology as an adjuvant diagnostic procedure to detect borderline cases of thyroid malignancy, where the malignant nature may be derived noninvasively by ^{201}Tl-scintigraphy of the thyroid nodule with quantification of the thyroidal ^{201}Tl-washout, which is delayed in malignant tissue as compared to benign thyroid diseases.

Non-Hodgkin lymphoma, malignant melanoma and its metastases are further indications as well as inflammatory processes and abscess, for which however immunoscintigraphy with ^{99m}Tc-labeled monoclonal antibodies became an attractive alternative.

Brain tumor recurrences are separable from other conditions (scar, gliosis, radiation necrosis after radiotherapy).

Parathyroid adenoma is successfully detectable by ^{201}Tl-/ ^{99m}Tc-subtraction scintigraphy in case conventional diagnostic procedures (X-ray digital subtraction angiography, ultrasound) are inconclusive.

The "Acquired Immunodeficiency Syndrom" - AIDS-emerged as a new serious and actual indication for ^{67}Ga-scintigraphy performed as whole body scanning, especially to rule out or to confirm non conclusive X-ray examinations in case the AIDS-pneumonia - the so called Pneumocystis carinii-pneumonia - is suspected (5).

It is hardly to explain by the way, why in U.S.A. ^{67}Gallium is used 250 times more frequently than in F.R.G.. AIDS is expected to increase the use of this cyclotron product in our country, too, supposed the facilities of nuclear medicine services will be approximated to the standard of other countries.

3.2 ^{123}I

The clinical demand for ^{123}I had its climax in the 70ties with declining indications in the 80ties and probably even more in the 90ties. This is due to the fact that some of the originally proposed indications have been replaced by ^{99m}Tc-complexes.

Today thyroidal clearance determinations belong to the limited scope of application where ^{123}Iodine is still used, for instance to find out patients in whom the suppresion of thyroid function should be quantified (so called autonomous thyreoid diseaes).

In neurology ^{123}I-Amphetamin offers considerable advantages for mapping of normal cerebral blood flow and for detecting cerebral ischemia in cerebrovascular diseases such as transient ischemic attacks as prerunner of stroke, also in preoperative decision making of and in therapy control after cerebrovascular bypass-surgery, especially, when conventional X-ray procedures are inconclusive, like in negative stages of x-ray computed tomography (6,7). First successful attempts at ^{123}I-labeled neuro-receptor imaging have been published (8).

In nephro-urology ^{123}I-Hippuran has been popularized over years in any kind of kidney diseases, both in adults and in children. Today ^{99m}Tc-complexes, such as ^{99m}Tc-MAG-3 are more and more prefered supplying us with comprehensive informations on total and on divided renal clearance function, including functional respectively dynamic morphology of perfusion, kidney (tubular) extraction and excretion (see in 2,3).

In gastroenterology hepatobiliary agents serve for functional scintigraphy of gallbladder function as well as to find out reflux (gastroephageal, duodenogastral) and to follow up and differentiate different forms of intestinal blockades (tumors, infection). Previously ^{123}I-labeled contrast material has been used, whereas since

1975 ^{99m}Tc-labeled compounds ("-ida", "hida") proved to be superior and easier available, hence cheaper (see in 2, 3).

In cardiology metabolic imaging of ^{123}I-labeled free fatty acids aid in studying metabolic disorders in cardiomyopathies, but also in coronary artery diseases (angina pectoris, myocardial ischemia, after myocardial infarction, before and after therapy, for instance to monitor the efficacy of percutaneous transluminal coronary angioplasty). ^{123}I-metaiodobenzylguanidin (MIBG) enables the in vivo mapping of neurotransmitter loss after myocardial infarction and in chronic myocardial failure. Therapeutic regimens could be possibly altered, in case more representative clinical data will be available (see 4).

In pediatrics as well as in adults ^{123}I-MIBG is increasingly used for diagnostic and therapeutic purposes in neuroblastoma (malignant tumor of childhood) and in pheocromocytoma (a malignant tumor of adrenomedullary tissue (see 2).

3.3 ^{111}In

Among single photon emitters finally ^{111}In has preferable and partly irreplaceable indications: Neurologists and neurosurgeons ask us for detection of dynamic disturbances of liquor circulation in case X-ray procedures (computed tomography) and nuclear magnetic resonance tomography are inconclusive.

Liquor sintigraphy visualizes the normal and impaired flow in the spinal cord and especially in the cysterns, through ventricular chambers, which are dilated in case hydrocephalus is the underlying cause. The procedure is also indicative of imaging fistulas of the liquor system subsequent to brain accidents prior to or after neurosurgical interventions (see in 2,3).

In oncology a further field arose: to perform immunoscintigraphy (9) with ^{111}In-labeled monoclonal antibodies when tumor recurrences after previous tumor operation are suspected. ^{111}In-antihuman-thyroidglobulin is applicable to find out metastases of malignant thyroid diseases or liver metastases of colorectal tumors. Different monoclonal antibodies labeled with ^{111}In are also diagnostically efficient in gynecology to indicate recurrences of ovarian cancer and again for monitoring the efficacy of chemotherapy, radiation therapy or surgery.

^{111}In-labeled leucocytes have been extensively explored in infectious instinal processes such as colitis and in abscesses. However we must be aware of future trends to replace ^{111}In by ^{99m}Tc-Anti-Granulocytes.

In cardiology and cardiac surgery a revolutionary development took place by the systematic exploration of the role of cardiac immunoscintigraphy to exclude myocardial infarction (vs nonstable angina pectoris), in confirming, localizing and sizing of infarcts as well as in establishing moderate rejections after cardiac allograft transplantation the aim being to reduce the number of invasive heart muscle biopsies (10). The future importance and the necessity of ^{111}In-Antimyosin-scintigraphy might be derived from the tremendous increase of the number of cardiac transplantations - 14ooo worldwide - . In F.R.G. more than 700 transplantations in this field have been done betweeen 1981 and 1989.

4. POSITRON EMITTERS

The impact of using positron emitters on clinical nuclear medicine has been underestimated for a long time. Table 1 lists these types of radionuclides to study perfusion, metabolism, receptor and neurotransmitter function as an universal spectrum of clinically outstanding questions, for which PET (positron emission tomography) offers unique answers. "PET enters clinical practice" (Dr. Henry Wagner jr, Baltimore, USA). It delivers "slices of life" unobtainable by any other medical examination. Thus physiology, pathophysiology and metabolism may be diagnozed and visualized as a reasonable prerequisite of adequate diagnosis, therapy planing and therapy monitoring. Nevertheless positron scanners and clinical cyclotron units are extremely limited in our country, even in major universities.

Pathbreaking results have been achieved with PET in following areas: Neurophysiology, neurology and psychiatry, but also in oncology, cardiology and other clinical fields. The following positron emitters are mentionable, as markers for physiological functions of the human body.

4.1 ^{18}F-Deoxyglucose

The stimulation of physiologic functions such as auditory center, frontal center, visual center are unique examples for the potentialities of PET, but also for detecting pathologic pattern (11,12,13,14,15,16).

^{18}F-fluorine-deoxyglucose metabolism may be portrayed and regional rate constants are quantifiable via metabolic models in cerebrovascular and tumorous diseases of the brain. Glucoseuptake is lost in infarcted brain lesions to be differentiated from non-infarcted ischemic tissue, which is salvageable by revascularization.

In degenerative brain disease, like Morbus Alzheimer typical metabolic pattern was demonstrated: symmetrical decrease of metabolism in distinct areas of brain (parieto-occipitally).

In cardiology PET belongs to the effective modalities, where vital myocardium may be visually separated from scarred tissue and also from so called hibernating myocardium (decreased perfusion, but still viable, hence suitable for revascularization) (14).

In gynecology metastases from mammary carcinoma are metabolically identifiable by means of ^{18}F-Oestradiol-PET-scintigraphy. Other metabolites and non- metabolites have been labeled by ^{18}F, for instance galactose, uracil to be used in oncology for tumor detection.

4.2 ^{15}O

Oxygen extraction mapping and determination of local metabolic oxygen rate are of clinical interest in brain tumors as well as in cerebrovascular diseases for the study of microcirculation which is not achievable by other techniques. The indication for surgically successful improvement is not only dependent on pathology of larger extracranial vessels, but is critically influenced by the functional status of cerebral microperfusion to be precisely imaged by flow-volume ratio mapping. Because of the short physical half life time of ^{15}O (1,5 min) a cyclotron must be installed close to the nuclear medicine department (1,11,12).

In occlusive cerebral artery disease single photon emitters and SPECT-method only show regional cerebral blood flow mapping and by some flow markers - as ^{123}I-amphetamine - cerebrovascular ischemia is also recognizable , whereas glucose uptake and oxygen extraction are only visible by PET. In brain tumors local cerebral oxygen extraction may be reduced, but cerbral blood flow around the tumor may be preserved or even increased, possible consequences for the neurosurgeon.

4.3 ^{11}C

This cyclotron-produced positron emitter covers a broad scope of application in clinical nuclear medicine and allied medical disciplines, again in neurology, psychiatry, oncology and cardiology (14,15).

^{11}C-methionine has been shown to be helpful in the differential diagnosis of brain tumor recurrences and gliosis or radiation necrosis by applying the physiological principle of occupancy. Nonlabeled aminoacid blockade is used to saturate binding of receptors and the biokinetic behavior of tumor tissue and non-tumorous tissue is quite different.

^{11}C-neurotransmitter (dopamin, serotonin, opiate) deserve special attention for cause - related therapy (15,16,17). By outweighing the antagonist-agonist principle medical therapy should succeed in adequate choice of radiopharmaceuticals, also in analgetics. Again it seems hardly understandable why pharmaceutical companies did not realize the inherent possibilities of PET for the practical outcome of their research. Far more than 5oo substances have been labeled so far, but only a minute quantity is explored in clinical medicine. Metabolic/antimetabolic therapy would benefit considerably from PET-guided diagnosis - instead of continuing to apply the pseudo-therapeutic principle of trial and error.

^{11}C-fatty acids (such as palmitate) assist in clinical analysis of metabolic disorders of different cardiomyopathies (hypertrophic, ischemic, dilative, immunogenic etc) (14).

^{11}C-thymidin has been tested in non-Hodgkin-Lypmphoma and it seems to be of general interest as a metabolic marker of malignant tumors resp monitoring tumor therapy.

4.4 $^{13}NH_4$

Perfusion and aminoacid metabolism was studied in heart diseases and in tumors. The investigations in this field seem to be rather preliminary (14).

5. CONCLUSIONS, OUTLOOK, DEMAND

The establishment of cyclotron centers should be promoted as intensively as financially possible. Several countries - even outside USA and Japan - have recognized the necessity of proportionate increase of PET centers complementary to other imaging equippment. Belgium and Italy seem to belong to the more progressive countries in Europe. Undoubtedly countries overlooking the expansive development in PET/Cyclotron research will decline irreparably in the standard of their health care. Politicians ommitting or postponing one of the most urgent problems of diagnostic medicine are well advised considering the repeated messages of far-advanced nuclear medicine experts "PET enters clinical practice", and "The future is now ..But do not expect comfort to come cheap" (WAGNER).

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