Clinical applications of Positron emission tomography

Essay

Submitted in partial fulfilment of the
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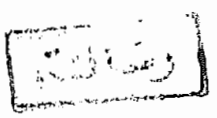

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LIST OF ABBREVIATIONS

*PET : positron emission tomography .

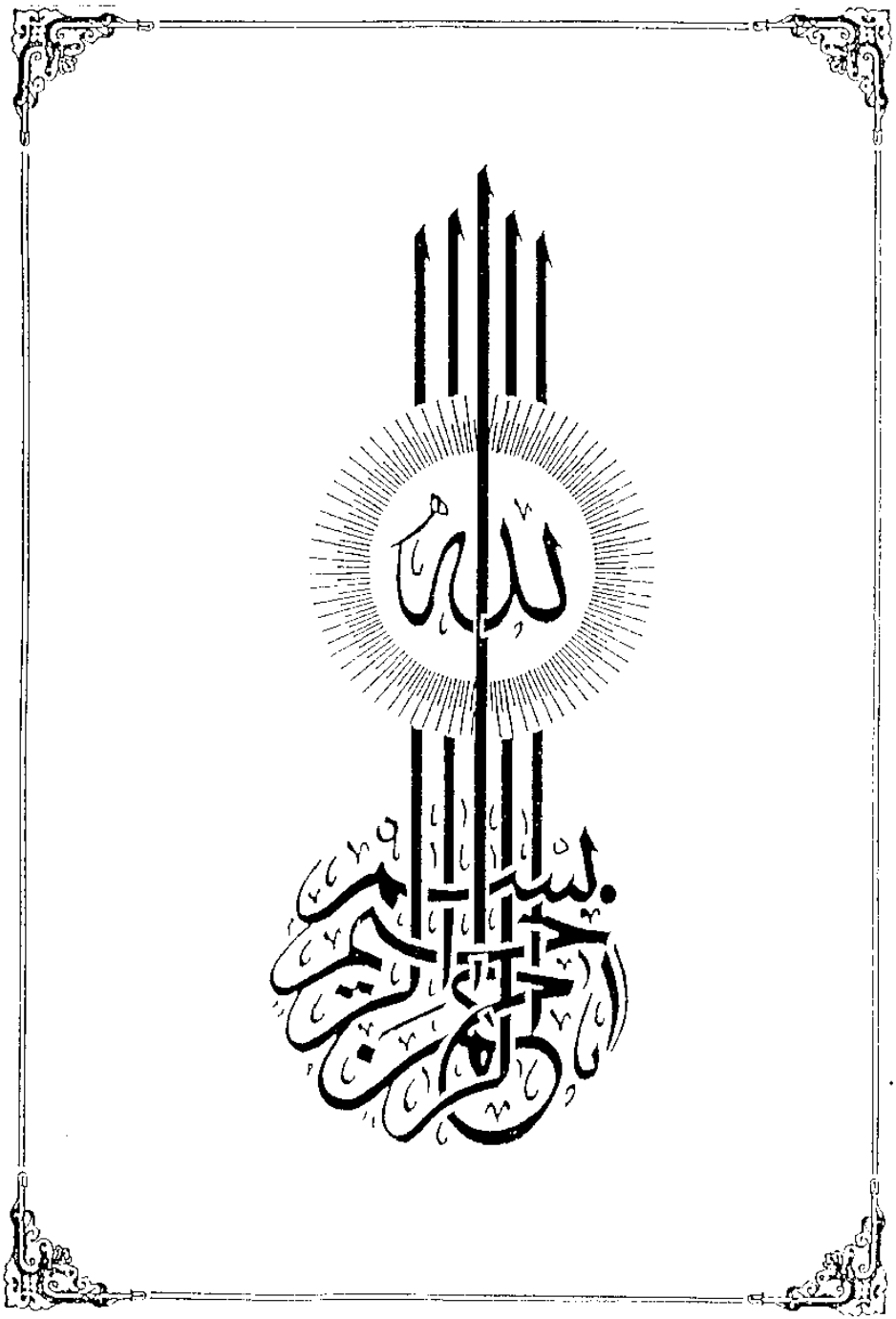
*FDG : fluorodeoxyglucose .

*SPECT : single photon emission computed tomography .

*CMRglc : cerebral metabolic rate of glucose .

*$CMRO_2$: cerebral metabolic rate of oxygen .

*CBF : cerebral blood flow .



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CONTENTS

1. Introduction and aim of work . 1

2. Cyclotron and Radiopharmaceuticals used in PET. 2

3. Clinical applications of PET in the brain . 11

4. Clinical applications of PET in cardiology. 32

5. Clinical applications of PET in oncology. 48

6. Illustration of cases . 61

7. Concluding discussion . 71

8. References . 76

9. Arabic summary.

CHAPTER 1:

INTRODUCTION AND AIM OF WORK

Introduction and aim of work

* Positron emission tomography is an emerging clinical imaging technique that gives important physiological and biological information beside its clinical relevance.

* Although positron emission tomography began showing utility in clinical medicine, its rate of proliferation has not matched that of new imaging technologies such as M.R. imaging and that is because positron emission tomography is an expensive technology that requires highly trained personnel.

* Positron emission tomography can be used to examine the functional anatomy of human brain and also it can measure the regional cerebral blood flow, oxygen consumption and glucose consumption.

* It provides a non-invasive assessment of myocardial metabolic processes and perfusion and is very helpful in assessing myocardial viability in patients with coronary artery disease.

* Positron emission tomography is growing as a very useful clinical tool in the field of oncology, receptor imaging and neurotransmission studies.

* Accordingly, the aim of this work is to discuss the clinical relevance of positron emission tomography and to highlight its potential benefits in clinical practice.

CHAPTER 2:

CYCLOTRON AND ITS RADIOPHARMACEUTICALS USED IN PET

CYCLOTRON AND ITS RADIOPHARMACEUTICALS USED IN PET

Cyclotrons have been used for isotope production. Most cyclotrons are capable of accelerating protons, deutrons, often He-3 nuclei and α particles, and rarely H-3 nuclei. A standard cyclotron delivers at least 50 microampere(μA), thus permitting saturation yields of 1Ci or more of the standard isotopes, which are usually more than sufficient for radiopharmaceutical production *(Mandelkern and Phelps, 1988).*

Cyclotrons have multiple advantages for isotopes production. The technology is well known and reliable. The beam current is continuous, causing minimum destructive effects on target windows and keeping target heating and unwanted chemical reactions at a minimum. However , at present a cyclotron installation is expensive. The machine is intrinsically sophisticated, including a high-quality magnet, vacuum system, radiofrequency (RF) power system, and so on. New self-shielded minicyclotrons designed specifically for production of O-15, N-13, C-11, and F-18 are under development with features designed for a hospital environment, including small size, low cost , minimal maintenance requirements , and technician-oriented operation. The cyclotron is excellent for isotope production,

however, it provides much better beam quality than is essential *(Mandelkern and Phelps , 1988).*

The light positron-emitting nuclides are made using high-pressure gas target and liquid target technologies. Gas targets can be employed for production of O-15, N-13, and C-11. Frequently some or all of the subsequent synthetic chemistry can also be carried out in the gas phase; for example, in the syntheses of O-15 water or of carbon monoxide or carbon dioxide labelled with C-11 or O-15. Fluorine-18- labelled fluorine gas requires the bombardment of the gaseous neon by deutrons. The F-18 fluoride ion (F^-) is obtained by bombardment of O-18 water by protons *(Mandelkern and Phelps , 1988).*

Further steps in the synthesis of labelled compounds are performed in conventional liquid phase chemistry. An important feature of all systems must be the ease and speed with which the final product is made and transported to the clinical setting , via gas transfer or pneumatic lines. This is absolutely essential for O-15 compounds with their 2-min decay half-life. Remote semiautomatic systems have been developed for routine production of nongaseous materials such as F-18 fluoro-deoxyglucose (FDG) *(Barrio et al, 1981).*

It is frequently necessary to add a quantity of the non-radioactive counterpart of the desired positron-emitting atom in order to improve yields from cyclotron targets. Examples are gaseous O-15 and F-18 production, in which the individual atoms are so reactive that they rapidly attach to the target container or react inappropriately with atoms of the target gas. If a quantity of O-16 oxygen (or F-19 fluorine) carrier gas were present, most of the radioactive atoms would displace stable ones in the diatomic molecule and be available in a chemically stable form. The result is that a very small fraction of the extracted oxygen or fluorine gas is radioactive, (ie, low specific activity), leading to labelled compounds with the same low specific activity. Some reactions are easily carried out without carrier gases, leading to high specific activities, particularly with N-13 and C-11 compounds. Even so, there is enough spontaneous dilution with natural nitrogen and carbon to lead to dilution of N-13 and C-11 by a factor of several thousand. Fluorine-18-labelled hydrogen fluoride has been made relatively carrier free by rapidly sweeping the reagents from the target to avoid trapping activity on the target walls. Aqueous fluoride ion can similarly be made relatively carrier free *(Mandelkern and Phelps, 1988).*

Low specific activity becomes a problem where the biologic system that is being investigated has saturable kinetics and

the quantity of pharmaceutical introduced significantly perturbs the system . The extreme case exists for pharmaceuticals intended to image specific receptor sites where high specific activity is desirable, since most receptors are present in very low concentration, typically in the range of picomoles per gram of tissue. Rapid synthesis and purification are essential to maintain high specific activity. Since the duration of such steps must be limited to about three decay half-lives in practice, automated synthesis and liquid chromatography purification are increasingly being used *(Wolf and Fowler , 1979).*

The synthesis of positron-emitting labelled compounds is a very active area of research and is necessary to extend research using PET. The pharmaceuticals successfully synthesized and used include carbohydrates (F-18 FDG,C-11 glucose , etc.) , amino acids (C-11 aspartic acid, C-11 leucine, N-13 glutamine, etc.) , fatty acids (C-11 palmitic acid , etc.), steroids (C-11 methyltestosterone, etc.) , precursors for neuroreceptor synthesis such as F-18 DOPA, ligands for receptor studies (F-18 spiperone, etc.), and others including labelled anticancer drugs. The labelled gases C-11 CO, O-15 CO_2, and O-15 oxygen play a central role in physiologic studies with PET , permitting quantification of blood volume, blood flow, and oxygen metabolism,respectively , when administered by inhalation.

Intravenous O-15 labelled water is an alternative technique for blood flow*(Mandelkern and Phelps, 1988).*

Carbon-11, N-13, and O-15 are extremely important since their stable counterparts are the building blocks of the chemical constituents of the body and can be replaced by these radioactive nuclei without changing the relevant biochemistry. The decay half-lives of C-11(20.3 min) and N-13 (10.0 min) are sufficiently long to permit chemical synthesis and administration to subjects of the labelled compound, yet short enough to avoid excessive patient exposure and permit serial studies. Oxygen-15 (124 sec)-labelled tracers are simple gases, including O-15- labelled oxygen gas, carbon monoxide, carbon dioxide, and also liquid water. They are rapidly synthesized , usually on line. Fluorine-18 (110 min) can substitute for hydrogen in a molecule in many cases without destroying the significance of the biologic response and is the label in F-18 FDG, a glucose analogue. Rubidium-82 is a generator-produced isotope that is useful as a myocardial flow tracer. Gallium-68 is another generator-produced isotope that is valuable in the laboratory for transmission scanning for attenuation correction, calibration, and other utility functions. Gallium-68- labelled compounds have been employed clinically to detect molecular diffusion resulting from disruption of the blood-brain barrier *(Mandelkern and Phelps, 1988).*

Local blood volume is measured by labelling red blood cells with a single breath of C-11 carbon monoxide or O-15 carbon monoxide. After equilibration the ratio of local tissue activity to blood activity gives the local blood volume after correction for the difference between systemic and local hematocrit *(Phelps et al, 1979).*

Glucose is the principle substrate utilized by the brain and is a significant substrate for all other organs. Methods for the measurement of local cerebral metabolic rate for glucose (LCMRgl) have been developed with C-11 glucose and with F-18 FDG, which is an analogue of glucose *(Mandelkern and Phelps, 1988).*

* Carbon -11 Glucose :-

A method for brain glucose transport and metabolism has been developed by using carbon-11 glucose. Because the measurement of regional activity must be made shortly after injection of the tracer, several important corrections must be modeled and made:

1. The unmetabolized tracer in the blood must be subtracted by performing a local blood volume measurement with C-11 carbon monoxide.

2. One must account for the egress of labelled metabolites from the regions of interest ; fortunately this is small during the first several minutes.
3. One must correct for unmetabolized tracer in tissues.

Carbon-11 glucose can be synthesized using plants that take up C-11 carbon dioxide. The great advantage of C-11 glucose is that it is transported and metabolized in the same manner as glucose. Repeated measurements are possible within the course of an experiment because of the short half-life of C-11.

(Straatman and Welch, 1973).

* Fluorine - 18 fluorodeoxyglucose (F-18 FDG):-

Fluorine-18 FDG is a glucose analogue that competes with glucose for transport and phosphorylation , and also it is not further metabolized but is trapped with high efficiency within cells since dephosphorylation of fluorodeoxyglucose 6-phosphate (FDG-6-P) is slow and only FDG may be transported across membranes. The long decay half-life of F-18 permits waiting until the tracer plasma activity reaches a low and nearly constant level before scanning the subject, at least 30 minutes after injection. Delayed scanning has the additional advantage that the model is least sensitive to assumed values of rate constants when data are obtained at times late after injection *(Huang et al, 1981).*