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FIRST CLINICAL RESULTS USING SHORT-LIVED RADIOISOTOPES PRODUCED BY A MEDICAL CYCLOTRON.

C.CROUZEL, D.COMAR, G.BERGER, M.MAZIERE, F.SOUSSALINE, A.TODD POKROPEK, J.C.BARON, H.GUENARD, M.VERHAS

C.E.A. - Département de Biologie - Service Hospitalier Frédéric Joliot - 91406 Orsay - France

Abstract

The advantages of short-lived radioisotopes produced by a medical cyclotron are discussed. The clinical results obtained with ^{13}N, ^{15}O, ^{11}C-methionine and ^{11}C-chlorpromazine are given.

1. Introduction

One of the main advantages of a cyclotron installed in a hospital is the possibility of using short-lived radioisotopes : ^{11}C (T=20.4 min), ^{13}N (T=10 min), ^{15}O (T=2.05 min).

The advantage of these isotopes /1/ lies in their high specific activity and favourable dosimetry, and as β^+ emitters they can be detected by coincidence methods. The SHFJ makes large quantities of these isotopes routinely by irradiation of gaseous targets with proton or deuteron beams. They are used either as simple compounds of nitrogen or oxygen or in the form of more complex ^{11}C-labelled molecules for medical purposes.

2. Advantages of the short-lived isotopes $^{11}C, ^{13}N, ^{15}O$

These isotopes are obtained by nuclear transmutation [$N(p,\alpha)^{11}C$, $C(d,n)^{13}N$, $N(d,n)^{15}O$] and hence with a high specific activity. For instance ^{11}C in $^{11}CO_2$ form is produced with a specific activity of 1 Ci/μM, which is still very far from the theoretical value of 10^4Ci/μM. Actually, ^{11}C, ^{15}O and ^{13}N are isotopes of the commonest elements in the biosphere, source of contamination by the stable elements are such that it is impossible to obtain the theoretical activity per unit mass.

One advantage of this very large amount of radioactivity they possess per unit mass is that short-lived radioisotopes can be used to label molecules otherwise banned because of their high toxicity or very low natural concentration in living organisms.

Another feature common to these 3 radioisotopes is their mode of disintegration. All being positron emitters, their decay scheme includes two 510 KeV γ rays emitted at 180° which can be measured in coincidence with a positron camera, showing exactly where the emission occurs. Since moreover a positron is given off per disintegration the γ radiation emitted amounts at equal radioactivity, to twice that of a radioelement decaying by β^- and γ emission. For a given number of photons emitted the ^{15}O, ^{13}N and ^{11}C radioactivity necessary will be at most half that of a non-positron emitter, a potential advantage from the dosimetric viewpoint.

3. Problems raised by the use of $^{11}C, ^{13}N, ^{15}O$

Being too short-lived to travel these isotopes must be used on the production site itself, which implies the presence of a cyclotron and chemical laboratories close to the examination rooms.

In addition, the use of ^{15}O and ^{13}N gases on a patient requires a few dozen metres of lead-shielded piping connecting the target outlet directly to the examination room so that the radioactive gas is delivered continuously.

Working with short half-lives, especially in the ^{11}C labelling of molecules, involves handling large amounts of radioactivity (several hundrer mCi) which means that entirely automatic synthesis systems are necessary

Clearly therefore the problems raised by the employment of these short-lived radioisotopes, whether from the viewpoint of manufacture (cyclotron), chemical preparation (automatic equipment) or detection (positron camera), call for the use of quite sophisticated and above all very expensive apparatus. The SHFJ acquired a compact cyclotron 3 years ago and for the last year has owned an ECAT-ORTEC positron camera. ^{11}C, ^{13}N and ^{15}O are now in current use.

4. Applications of ^{11}C

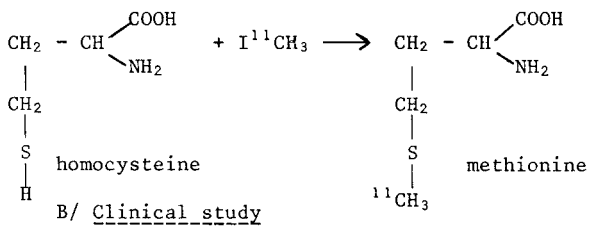
Carbon-11 has been used to label organic molecules, of which a dozen /2/ have been synthesized. Two examples concerning the use of methionine and chlorpromazine are given below.

I - Methionine

A/ Synthesis of the molecule /3/

L-homocysteine is methylated with $I^{11}CH_3$ in alkaline solution at 95°C for 7 minutes. After evaporation of the solvent (acetone) the solution is neutralised, taken up in physiological serum and sterilised by filtration over 0.22 mμ millipore. The specific activity obtained is around 500 mCi/μM.

$$N(p,\alpha)^{11}C \longrightarrow {}^{11}CO_2 \xrightarrow{H\ LiAl_4} {}^{11}CH_3OH \xrightarrow{IH} I^{11}CH_3$$



B/ Clinical study

^{11}C-methionine is used to study the cerebral metabolism of this molecule in phenylketonuric children /4/. Phenylketonuria is characterised by a rise in the plasma phenylalanine concentration to above 20 mg/100 ml at the end of the first week of life and the permanent presence of urinary phenylalanine metabolites, chiefly phenylpyruvic acid. The build-up of phenylalanine in the organism leads to irreversible damage to the brain of the developing child. Excess phenylalanine causes a general disturbance in the mechanism of amino acid transport across the blood-brain barrier and is certainly responsible therefore for total or partial blocking of the penetration of other amino acids (including methionine) into the brain.

The only treatment consists of a fairly strict diet (exactly known daily intake of phenylalanine)which must be established as soon as possible after birth and apparently followed until the child is 5 years old.

In order to define optimum conditions for the treat ment of these children we studied the influence of the blood phenylalanine concentration on the penetration and metabolism of another indispensable amico acid, methionine.

The examination takes place in 2 stages :

- a first examination carried out by ^{11}C-methionine injection during the diet, when the child's plasma phenylalanine concentration is practically normal (3 to

5 mg/100 ml) ;

- a second, several days later, after withdrawal of the diet to reach pathological concentrations (natural in untreated phenylketonuric children) of 30 to 40 mg/100 ml.

The γ camera images obtained show that in the latter case methionine fails to enter the brain, but does so when the diet is followed. (fig.1)

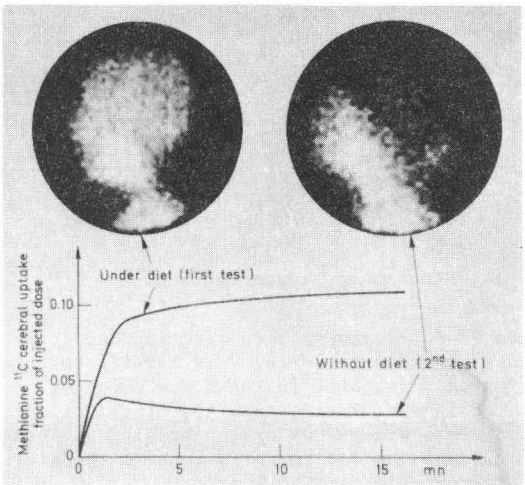


Fig.1 : Penetration of the ^{11}C-methionine into the child brain.

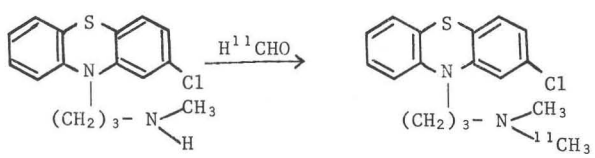
In addition the cerebral kinetics revealed by the two examinations are quite different. Analysis of the curves shows up a lesser quantity of free methionine in the brain of untreated phenylketonuric children.

II - Chlorpromazine

A/ Synthesis of the molecule /5/

Chlorpromazine is labelled with ^{11}C by a method derived from that described by ESCHWEILER-CLARKE for the methylation of amines, adapted to the special case of chlorpromazine and to the concentration range used.

$$N_2+O_2 \xrightarrow{p,\alpha} {}^{11}CO_2 \xrightarrow{H_4LiAl} {}^{11}CH_3OH \xrightarrow[500°]{Ag} H^{11}CHO$$



B/ Clinical use

Chlorpromazine, a major drug in the treatment of schizophrenia, penetrates strongly into the brain where it seems to block the dopaminergic receptor sites. In order to find out more about the relation between the therapeutic effect and the dose administered, the cerebral distribution of this drug was studied as a function of pathological state and the amount of drug entering the brain as a function of treatment.

After injection of the labelled molecule the cerebral radioactivity is measured with a positron camera to obtain tomographic transverse sections of the brain, i.e. a 3-dimensional image of the intracerebral drug distribution.

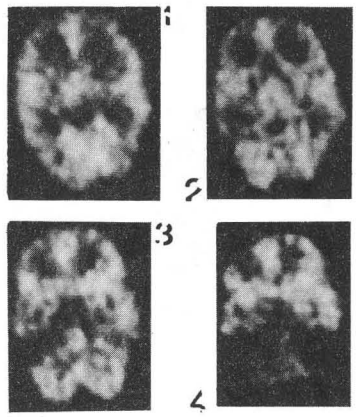


Fig.2 : repartition of ^{11}C-chlorpromazine into brain.

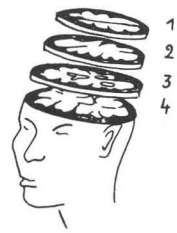


Fig.3 : cross sections of the brain obtained with the positron camera.

On figure 2, showing 4 cross-sections taken 2,4, 6 and 8 cm (figure 3) respectively above the plane passing through the orbits and the auditory meatus, the grey matter which fixes the drug is clearly distinguishable from the white matter which contains very little.

5. Applications of oxygen-15

A/ ^{15}O production

Oxygen-15 is produced continuously by 7 MeV deuteron irradiation of nitrogen gas containing 2 % oxygen. It is then carried out by the target nitrogen into soda lime and activated charcoal filters for purification, or into an activated charcoal filter heated to 400°C for conversion to $C^{15}O_2$; the radiochemical purity of these gases when inhaled is over 99 %. They are delivered continuously to the patient at constant output and radioactive concentration (4 mCi/min for $C^{15}O_2$, 11 mCi/min for $^{15}O_2$) through an ordinary oxygen mask where the radioactive gas is mixed with atmospheric air and its excess taken up by outside suction.

$$N_2+(O_2) \xrightarrow{d,n} {}^{15}O_2 \xrightarrow[400°C]{\text{charbon actif}} C^{15}O_2$$

B/ Clinical applications

The study undertaken at the SHFJ is based on the principle described by JONES /6/, who proposed a theoretical model for measuring the oxygen consumption and regional cerebral blood flow (RCBF) by continuous inhalation of $^{15}O_2$ and $C^{15}O_2$.

When $C^{15}O_2$ and $^{15}O_2$ are breathed in continuously a state of equilibrium, where the radioactive concentrations of the blood and tissues are stable, is reached after 6 to 8 minutes owing to the very short half-life of the tracer (2 min). When the gas in question is $C^{15}O_2$ the blood radioactivity is in $H_2{}^{15}O$ form, as shown by WEST and DOLLERY /7/ (1962), and at equilibrium the $H_2{}^{15}O$ concentration in the brain is proportional to the RCBF. When $^{15}O_2$ is breathed in the hemoglobin is labelled as $Hb^{15}O_2$ and the $^{15}O_2$, supplied to the tissues according to their oxygen extraction rate, immediately combines in situ with aerobic glycolyse hydrogen to form $H_2{}^{15}O$ which then diffuses secondarily into the aqueous volume of the blood and tissues. Thus at equilibrium the brain radioactivity concentration is in equilibrium with both the $Hb^{15}O_2$ concentration of the blood and the $H_2{}^{15}O$ in circulation and therefore simultaneously reflects the oxygen extraction rate and the RCBF.

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Simple division of the $^{15}O_2$ by that of $C^{15}O_2$ however eliminates from the former the CBF parameter and gives an image linearly proportional to the regional oxygen extraction rate.

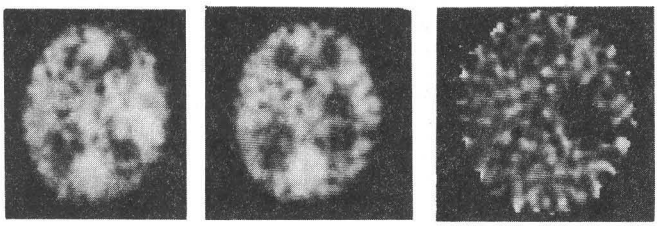

Fig.4 : $C^{15}O_2$ image, ^{15}O image , $\frac{^{15}O \text{ image}}{C^{15}O_2 \text{ image}}$

Figure 4 shows the positron camera images obtained on a subject suffering from a right side cerebral thrombosis, from successive counts taken at 3 adjacent levels (4,6 and 8 cm) above the orbit-meatus line.

The left-hand image was obtained with $C^{15}O_2$ and reflects the CBF . On the left a CRBF slightly higher than on the right is observed. The right-hand image is obtained with $^{15}O_2$. A "radioactivity hole" appears clearly on the right.

Division of these 2 images gives an image proportional to the regional oxygen extraction rate, with an extraction defect at the thrombosis point (on the right side of the image)

6. Applications of ^{13}N

A/ ^{13}N Production

^{13}N is produced by irradiation of CO_2 with 12 MeV deuteron

$$C\ (d,n))\ ^{13}N$$

After separation from CO_2 , ^{13}N is dissolved in physiological serum.

B/ Clinical applications

^{13}N is used to study the distribution of ventilation ($\dot{V}$) and perfusion ($\dot{Q}$) during oxygen breathing in hypoxemic patients. 24 patients were studied. 12 of them suffered from chronic bronchitis, the 12 others having a PaO_2 lower than 60 Torr.

7 mCi of ^{13}N were injected during a breath-holder period lasting 10 seconds. Then the patient breathed in closed circuit spirometer during 10 min. This was followed by a final washout period lasting 8 min.

A large field γ camera interfaced with an Informatek System was used for data stokage and off-line calculations. The function of each lung was analysed in three zones (lower, mid and upper zones)(Fig. 5). Relative perfusion of each zone was calculated from regional activity during breath-holding. Relative lung volume was calculated taking into account the lack of true equilibrium activity during the 'equilibrium period'. Ventilation was calculated from the regional washout curves using either a two or one compartment model. The patients performed the same procedure breathing air and breathing pure oxygen after a wash-in period of 10 minutes.

No significant change in perfusion has been observed in the two groups of patients. Thus there is no

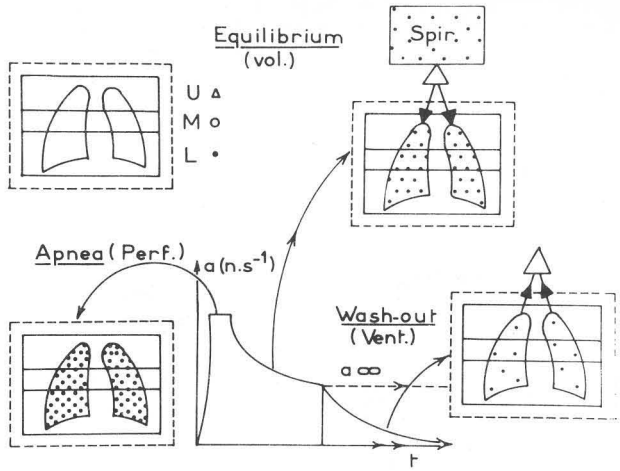

Fig.5 : ^{13}N pulmonary investigation.

evidence of pulmonary vasoconstriction due to arterial hypoxemia in these patients. $\dot{V}$ is significantly decreased by oxygen breathing in the zones which are poorly ventilated in air. Furthermore the distribution of ventilation is widened by oxygen breathing. These modifications could be due to variations in the static mechanical properties of the lungs.

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