Proceedings of the 9th International Conference on Cyclotrons and their Applications
September 1981, Caen, France

THE PRODUCTION AND IMAGING OF ^{55}CO LABELLED BLEOMYCIN

A.M.J. Paans, T. Wiegman, E.J. de Graaf, T. Kuilman, O.E. Nieweg, W. Vaalburg and M.G. Woldring.

Dept. Nuclear Medicine, University Hospital, Oostersingel 59, 9713 EZ Groningen, The Netherlands.

Abstract.-The production of ^{55}Co was embarked for the labelling of bleomycin. This radiopharmaceutical in combination with a high resolution, high sensitive positron camera is a valuable tool in the detection and staging of lung cancer. The production method and the positron camera are described.

1. Introduction.- Tumor detection with ^{55}Co-bleomycin was introduced in 1972 simultaneously by Nouel and Maeda[1,2]. It proved to be especially useful in the detection of lung cancer and malignant lymphoma[3]. Because of the long half-life of ^{57}Co, 270 d, and the short biological half-life of Co-bleomycin , which is excreted by the kidneys, the urine of the patients has to be collected for 24 hours after injection. During this 24 hours more than 30% of the injected dose is excreted. This disadvantage has inhibited its widespread acceptance. Many other radionuclides have been studied as potential labels for bleomycin. These compounds proved to be unstable in vivo[4-7] or showed a significant lower tumor-to-non-tumor ratio than could be obtained with ^{57}Co-bleomycin. To avoid the problem of the long half-life of ^{57}Co, ^{55}Co was suggested as a label for bleomycin[8,9]. The cobalt isotopes decaying by β- emission are not suited for imaging due to their half-life and their radiation characteristics. Of the cobalt isotopes decaying by positron emission cobalt-55, with a half-life of 18 hours, is the best suited. In this contribution the production of ^{55}Co and the positron imaging system will be described.

2. The production of ^{55}Co. Cobalt-55 is produced via the ^{56}Fe(p,2n)^{55}Co reaction with an external beam of the cyclotron at the Kernfysisch Versneller Instituut of the University of Groningen. The target thickness and the beam energy have been optimized to have a simultaneous production of ^{55}Co and ^{11}C. With an entrance energy of 35 MeV and a target of natural iron with a thickness of 1.25 mm the beam energy is degraded with 15 MeV. The resulting 20 MeV beam is optimal, with our target conditions, for the production of carbon-11 via the ^{14}N(p,α)^{11}C reaction. The production rate of ^{55}Co, with these beam conditions, is 3.5 mCi/μAh. This production rate is in accordance with the one calculated from the excitation function as given by Lagunas-Solar[10].

After the irradiation the target is placed in a hot cell and the cobalt is separated from the target material under remote control. First the target is dissolved in concentrated HCl and H_2O_2. After evaporation the residue is redissolved in HCl and H_2O_2. The iron is extracted with the addition of di-isopropylether (DIPE). Next the cobalt is obtained by column chromatography (Dowex 1x8, 100-200 mesh). The diameter of the column is 1.5 cm and its length is 6 cm. First the contaminants are eluated with 8N HCl and the cobalt is obtained by eluating the column with 4N HCl. The radioactivity washed from the column is monitored by a 2*2*2 mm^3 CdTe detector. This type of detector is easily incorporated in a hot cell due to its small outer dimensions. Another advantage is the fact that a low bias voltage of approximately 50 V is needed. After evaporation of the solution the cobalt is redissolved in 1 ml 0.1 N HCl. This solution is used for the labeling of the bleomycin. The whole radiochemical separation takes about 4 hours and is a modification of the description given by Lagunas-Solar[10].

For the labeling a quantity of 7.5 mg bleomycin-A2, dissolved in 1.8% aqueous NaCl, is added to 1.0 ml ^{55}Co-chloride in 0.1 N HCl. The pH is adjusted with Na- acetate. After ultra membrane filtration (0.22 μm pore size) under aseptic conditions the radiopharmaceutical quality is checked by thin layer chromatography. The amount of free ^{55}Co^{2+} should be less than 3%.

The radionuclidic purity of the ^{55}Co is checked before injection with a Ge(Li) detector. No ^{52}Fe, ^{52}Mn or ^{49}Cr should be present and the amount of ^{56}Co should be less than 2%. In the final product always some ^{56}Co and ^{57}Co will be present. The amount of ^{56}Co and ^{57}Co is respectively 1% and 0.01% at the end of the bombardment. A typical gamma ray spectrum of the end product is shown in fig. 1.

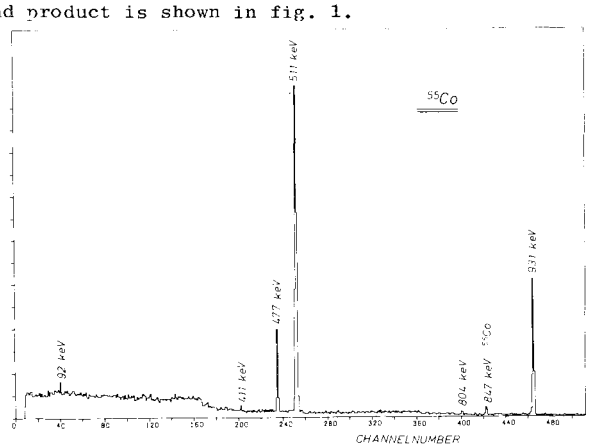

Fig. 1 *Ge(Li) spectrum of ^{55}Co. The only contaminant is ^{56}Co with a gamma ray energy at 847 keV.*

3. Positron camera. The positron camera consists of two uncollimated Large Field of View scintillation cameras (Searle). The scintillation cameras have a NaI(Tl) crystal (diameter 39 cm, thickness 1.27 cm) with 37 photomultiplier tubes each. The two uncollimated cameras are positioned colinear. This is achieved by using one camera in a conventional set-up while the other camera is mounted on a trolley which can be positioned nicely beneath the first, see fig. 2.

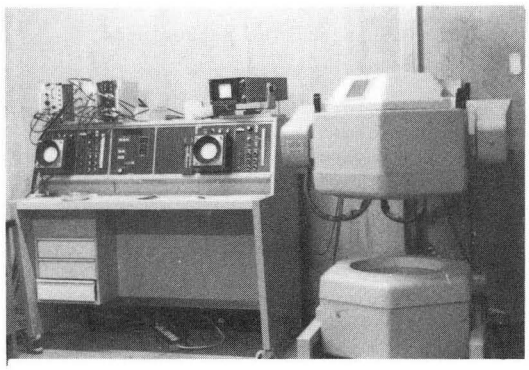

Fig. 2 *Positron camera with console and associated electronics.*

Both cameras can be operated individually from a single console. The crystals are shielded by lead rings from radiation originating from outside the sensitive volume. The maximum single count rate for each detector is 200 kHz. From the coincident 511 keV signals an image is reconstructed by back-projection. A block diagram of the system is shown in fig. 3. The

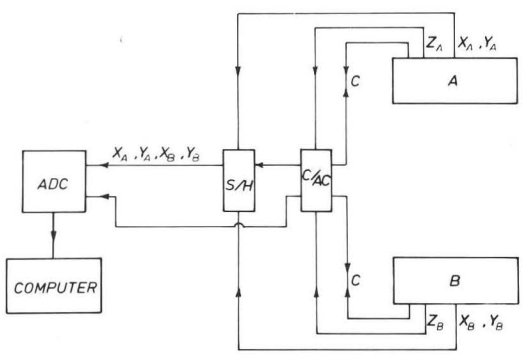

Fig. 3 *Block diagram of the positron camera. The energy signals (Z) of both cameras (A and B) are applied to a coincidence/anti-coincidence (C/AC) unit. The position signals (X,Y) of the coincidenct events are applied to a sample and hold (S/H) circuit before they are digitized by ADC system.*

coincident photo-peak events are detected by a coincidence/anti-coincidence (C/AC) unit. Input for this C/AC unit are energy signals (Z) of both cameras. If a coincident event is detected a sample and hold circuit (S/H) is activated and a separate ADC system is started. This sample and hold circuit is adapted to the characteristics of the ADC system, an AR-11 in a PDP-11/34. The digitized position signals are then stored on disk. After the data acquisition multiple focal planes, parallel to the cameras, are generated by a back-projection program. Then the images are stored on disk together with the patient administrative data as standard nuclear medicine patient studies. In this way the data analysis part of the nuclear medicine software package can be used for a further analysis. Before this analysis the images have to be corrected for the non-uniform response of the positron camera. This correction can be performed by measuring the systems response in the planes of interest.

Performance parameters

In table 1 the performance parameters of the positron camera are given.

Table 1: Performance parameters of the positron camera.

Crystal diameter	39 cm
Crystal thickness	1.27 cm
Maximum singles count rate per detector	200 kHz
Spatial resolution	5.5 mm FWHM
Temporal resolution	6.5 - 12 ns FWHM
Point source sensitivity +	200 Hz/μCi
Sensitivity for extended sources +	50 Hz/μCi
Maximum coincident count rate	7.5 kHz

+ at a detector separation of 50 cm.

The spatial resolution of the positron imaging system[11] is determined by a) the intrinsic resolution of the individual cameras; b) the range of the positrons; c) the spread of 0.5° around the mean angle of 180° of the two annihilation quanta; d) the angle at which the radiation can reach the crystals of the cameras. Of these factors the first and the last are the dominant ones. Especially the last factor, because the cameras do not discriminate for the depth in the crystal at which the interaction takes place, is of importance when a smaller detector separation is used.

At a detector separation of 50 cm the expected spatial resolution is 5 mm FWHM. The measured spatial resolution, with 22Na point sources, is 5.5 mm FWHM.

The temporal resolution of the system is 6.5 ns FWHM. When more radioactive material is used this number increases to 10 ns FWHM. The temporal resolution is of importance because the accidental coincident count rate is proportional to the time window used. Based on these measurements a time window of 30 ns is mostly used.

Due to the removal of the collimators the maximum single count rate of 200 kHz per detector is reached for a point source of 200 μCi in the geometrical center at a detector separation of 50 cm. The maximum coincident count rate of 7.5 kHz is reached for a point source of 100 μCi in the same geometrical conditions.

The sensitivity of the system is 200 Hz/μCi for a point source in the geometrical center at a detector separation of 50 cm. Due to the non-uniform sensitivity this number drops to 50 Hz/μCi for an extended source (diameter 45 cm, thickness 1 cm) in the mid-

plane.

A positron camera of this type can be assembled in every hospital with two scintillation cameras. Return to single photon scintigraphy is possible by replacing the collimators.

4. Imaging of ^{55}Co-bleomycin. The indications for ^{55}Co-bleomycin imaging in patients with (possible) bronchial carcinoma are:

a. Detection of the primary tumor
b. Detection of lymph node metastases
c. Detection of brain metastases

The imaging is performed 24 h after intravenous injection of 1 mCi of ^{55}Co-bleomycin. At this moment the amount of ^{55}Co still present in the body is 100 µCi at most. The region of interest, indicated by the chest X-ray, is imaged for ten minutes with a maximum of 150k counts. Other regions are imaged during five minutes with a maximum of 75k counts. After the imaging 31 focal planes, 1 cm apart, are generated by a back-projection program. After the correction for the non-uniform response of the system the images can be evaluated.

In fig. 4 the chest X-ray of a man of 60 years is shown, demonstrating a lesion in the left upper lobe.

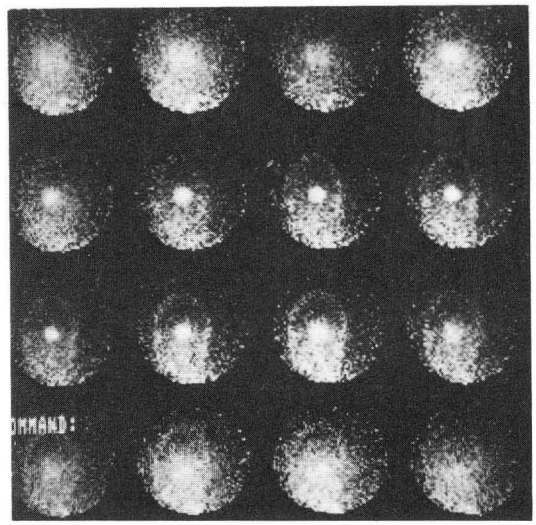

Fig. 5 *Frontal tomograms of a patient with brain metastasis of squamous cell bronchial carcinoma.*

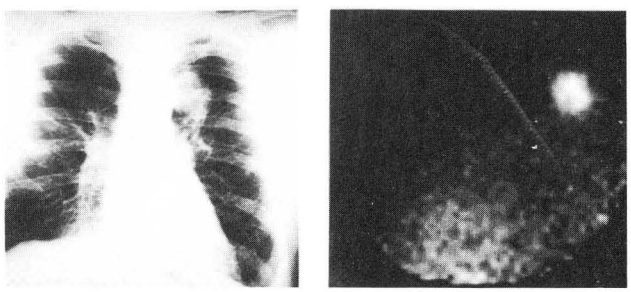

Fig. 4 *^{55}Co-bleomycin image and X-ray of a patient with small cell anaplastic carcinoma in the left upper lobe.*

The ^{55}Co-bleomycin scan clearly shows uptake in the lesion, which proved to be small cell anaplastic carcinoma. Activity in the lower part of the scan is caused by uptake in the liver, this is normal. In fig. 5 frontal images of the head of a 46 years old patient with a brain metastasis of squamous cell bronchial carcinoma are shown. The 16 equidistant planes are 1 cm apart. These tomograms demonstrate the lesion clearly. Images of the same patient are shown in fig. 6. The ^{99m}Tc-pertechnetate scintigram, on the right, shows a minimal abnormality in the left posterior fossa. Both, the ^{55}Co-bleomycin tomogram and the CT image, clearly depict the lesion.

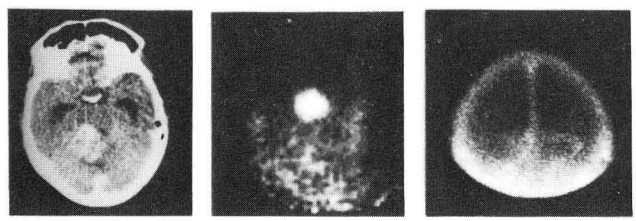

Fig. 6 *CT scan, ^{55}Co-bleomycin image and the ^{99m}Tc-pertechnetate scintigram (posterior view) of the same patient as in fig. 5.*

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