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Production, Automatic Delivery and Bolus Injection of [^{15}O]Water for Positron Emission Tomography Studies

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ABSTRACT.

An automatic system allowing repetitive bolus injection of oxygen-15-labeled water for PET studies is described in this report. The production of this radiopharmaceutical by the $^{16}O(p,pn)^{15}O$ nuclear reaction on $H_2{}^{16}O$, its purification and delivery nearby the PET camera, the injection system, and the quality controls are presented.

KEYWORDS: Oxygen-15-labeled water, Radiopharmaceutical production, Positron emission tomography, Blood flow, Brain activation

INTRODUCTION

Despite its very short half-life (2.05 min), oxygen-15 has proven to be of major importance for the *in vivo* study of numerous physiological processes with positron emission tomography (PET). Indeed, this radioisotope is extensively used in simple chemical forms such as [^{15}O]oxygen, [^{15}O]carbon monoxide, [^{15}O]carbon dioxide, [^{15}O]butanol, or [^{15}O]water to investigate oxygen metabolism, blood volume, or blood flow in man.
Among these radiopharmaceuticals, [^{15}O]-labeled water has found applications in various medical fields such as neurology (4, 6, 8], cardiology [1, 8], or oncology [16]. The availability of large amounts of labeled compound is therefore of great importance.
Various systems have already been developed for the production and delivery of [^{15}O]water for PET. Many of them use the $^{14}N(d,n)^{15}O$ nuclear reaction on a gaseous target filled with a mixture of N_2 and O_2 (0.2-4% vol) and bombarded with 6-8.4 MeV deuterons. Hydrogen is then added to the [^{15}O]O_2 obtained, and the mixture is passed on Pd (heating) [3 and references therein] or Pt [2]. Gaseous [^{15}O]water is then bubbled through sterile isotonic saline and used for bolus injection [12] or constant infusion [10].
To avoid further chemical reaction, some authors propose to produce labeled water in target by reaction of the recoiling oxygen-15 atoms with the 5% of molecular hydrogen contained in the irradiation target [17]. The [^{15}O]water is also prepared by the fast exchange reaction between labeled [^{15}O]CO_2 (obtained by reaction of [^{15}O]O_2 with activated charcoal at 400°C) and water [18].
All these methods require accelerated deuterons not available from single particule cyclotron and generally use hazardous chemical reduction. This first constraint has been bypassed by using the $^{16}O(p,pn)^{15}O$ nuclear reaction [14]. Production of [^{15}O]O_2 was described by Krohn *et al.* [5] and Ruth [13] using $^{16}O_2$ as gas target.
The last improvement was published by Mulholland et *al.* [11] who proposed an in-target production of [^{15}O]water by bombardment of low-cost natural water ($H_2{}^{16}O$) with 26 MeV protons.
This last method was chosen in our center for the routine production of labeled water. A simple, rapid, and efficient system allowing the production of [^{15}O]H_2O from the $^{16}O(p,pn)^{15}O$ nuclear reaction, its delivery nearby the tomograph, and the bolus injection to the patient are described in this paper.

MATERIALS AND METHODS

General

Injectable-grade water from B. Braun was used as target material ($H_2{}^{16}O$). The transfer of activity from the target to the tomograph was achieved using an HPLC pump model 307 from Gilson (Villiers-le-Bel, France). Between each PET study, a constant flow of 0.1 µL/min of sterile water was maintained to avoid precipitation of NaCl in the PEEK tubing. All valves and tubing installed in the PET room were sterile, pyrogen-free, and single-use. Both valves Vl-8 (Fig. 1) and the HPLC pump were controlled by a Simatic 135U (Siemens).

Production of [^{15}O]-Labeled Water

Oxygen-15 was produced via the $^{I5}O(p,pn)^{15}O$ nuclear reaction [14]. The [^{15}O]labeled water was directly obtained by bombardment of 280 µL of water ($H_2{}^{16}O$) [11] contained in a silver target holder (diameter = 10 mm; thickness = 3 mm) with 30-MeV protons. The target holder was automatically filled using the system

described in Fig. 1. The mean current during the irradiation was 25 μA, and the integrated current was 1 μAh (irradiation time = 2-3 min).

Purification and Delivery to the Tomograph

After irradiation, the radioactive material was passed through an anionic (AG 1-X8, carbonate form) and a cationic ion exchange membrane (AG 50W-X8, hydrogen form, Bio-Rex ion exchange membrane, BioRad, Richmond, CA) previously rinsed with 15 mL of ethanol and 20 mL of water. The [^{15}O]H_2O was collected in a buffer volume (Fig. 1).

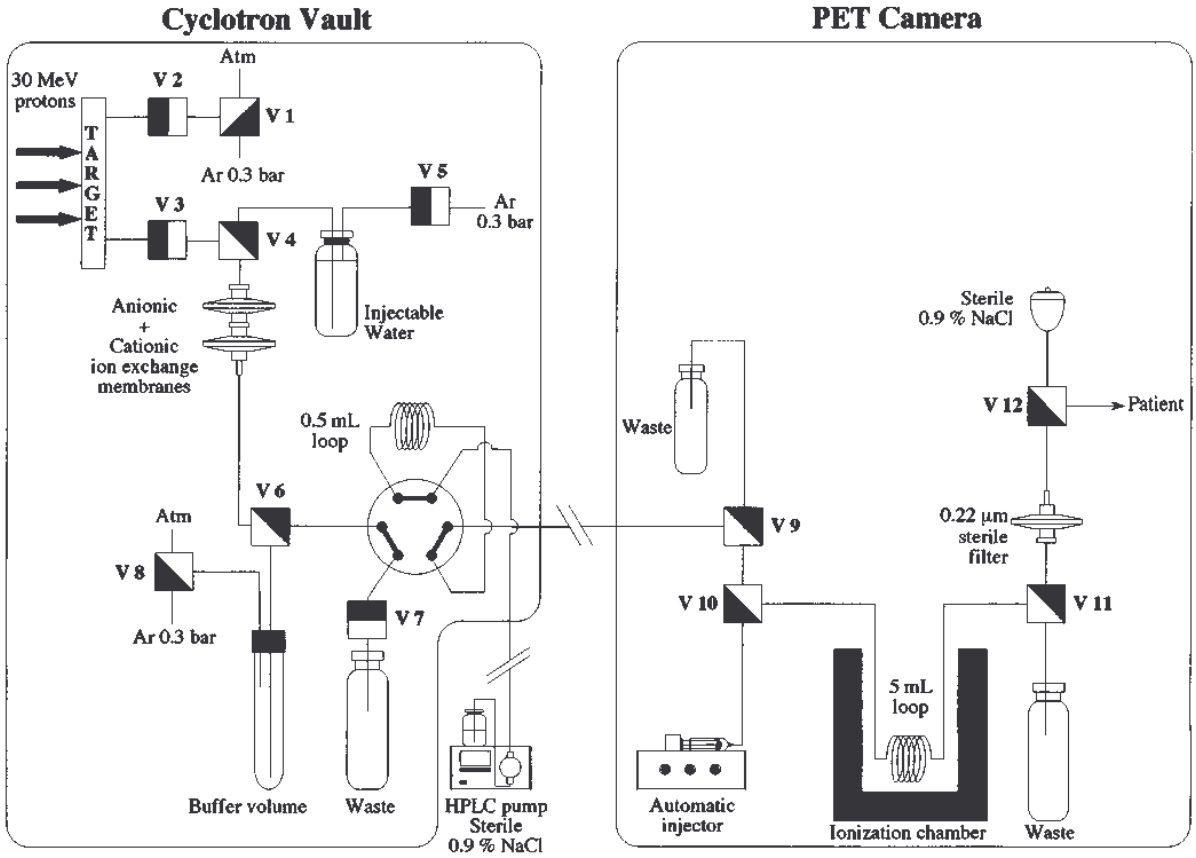

FIG. 1. System developed for the production, delivery, and bolus injection of oxygen-15-labeled water.

The activity was then loaded into a 0.5-mL loop mounted on a Rheodyne valve model 7000. This valve was pneumatically switched (actuator Rheodyne model 5701) and the labeled water was delivered through a 40-m PEEK tubing (o.d. 1.59 mm, i.d. 0.254 mm) using an HPLC pump with a constant flow rate of 2 mL/min of sterile 0.9% NaCl (pressure = 150 bars). The activity was collected directly in a 5-mL loop in an ionization chamber (Capintec, Ramsey, NJ) nearby the PET camera. Valve 9 was then manually switched and the activity was allowed to decrease until the desired value was obtained.

Injection

When the desired activity was reached, valves 10, 11, and 12 were manually switched and the automatic injector was turned on (20-mL syringe containing 15 mL 0.9% NaCl, flow rate: 15 mL/min). The activity was intravenously injected into the patient through a sterile 0.22-μm filter (Cathivex, Millipore-Waters).

Quality Controls

RADIOCHEMICAL PURITY. The radiochemical purity was determined during the set-up phase by gas chromatography as described by Clark *et al.* [3].

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RADIONUCLIDIC PURITY, STERILITY, APYROGENICITY, AND PH.

At each production, the half-life of the produced radioisotope was controlled over a 1-min period. Before each series of injections in one patient, a production was performed and the radioactive decay was measured for 30 min to check the radionuclidic purity. The same batch was used to check sterility and pyrogenicity (LAL). The pH of the final solution was measured on this batch and was always found to be of 6.5.

RESULTS AND DISCUSSION

Disposal of high-energy protons (obtained from a Cyclone 30 cyclotron, IBA, Louvain-la-Neuve, Belgium) allowed us to choose the $^{16}O\{p,pn)^{15}O$ nuclear reaction (threshold energy of 16.6 MeV; 5, 14). for the routine production of oxygen-15-labeled water. Indeed, irradiation of $H_2{}^{16}O$ with 30-MeV protons seems to be the simplest method for the direct production of this radiopharmaceutical. With this method, more than 800 μCi (EOB) of oxygen-15 can be produced (current: 25 μA; integrated current: 1 μAh). Under these conditions, nitrogen-13 was also produced via the $^{16}O(p,\alpha)^{13}N$ reaction. The labeled nitrogen oxide and ammonia as well as other cations or anions were removed by passing through both a cationic and an anionic ion exchange resins [11]. Decay control demonstrated the efficacy of the purification system: Before the two ion-exchange membranes, 97.3% (EOB) of the total activity was due to oxygen-15, 2.7% (EOB) was due to nitrogen-13, and less than 0.01% was due to fluorine-18. After the purification, the radionuclidic purity was found to be higher than 99.9% (EOB).
The $H_2{}^{15}O$ was delivered nearby the PET camera through a 40-m PEEK tubing using a pneumatically actuated injector and an HPLC pump.

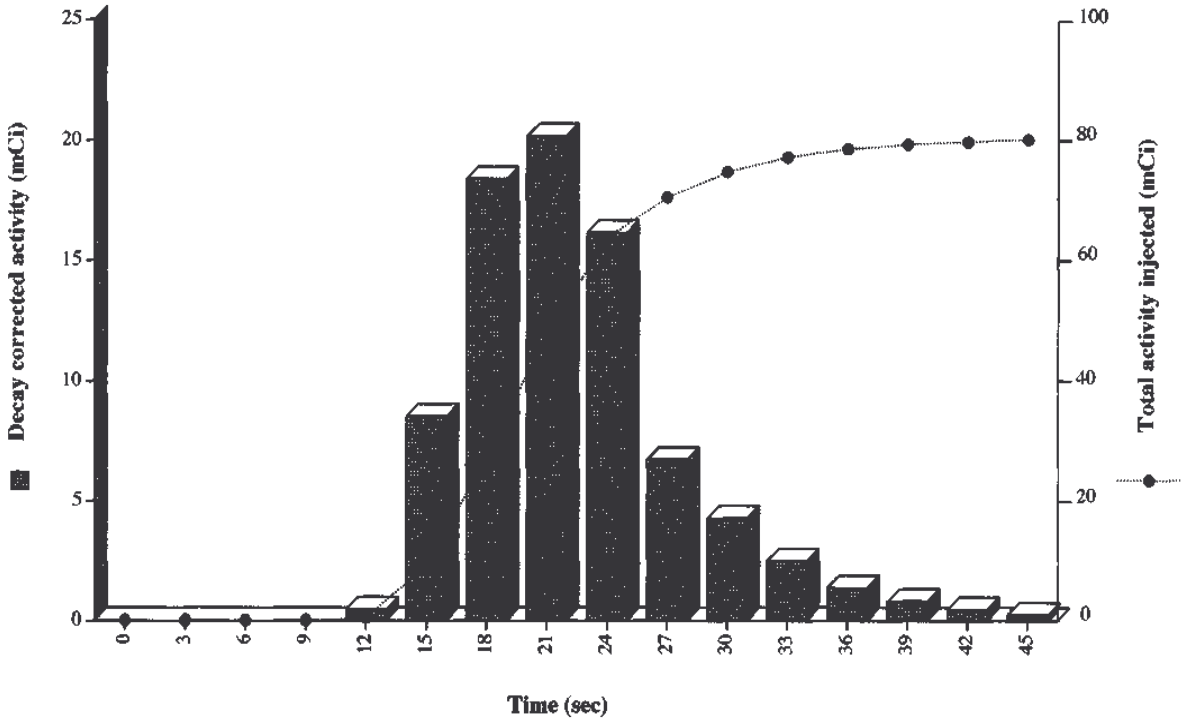

FIG. 2. Profile of the bolus injection (injection flow rate = 15 mL/min).

The activity was directly measured (typically 170 ± 50 mCi, n = 120) and was ready for injection. The profile of the injection bolus is depicted on Fig. 2 (injection flow rate = 15 mL/ min). Dilution was observed during the transfer: All the activity was collected in 4 mL (volume of the target: 280 μL). With this system, volume and timing of injection are compatible with the "slow bolus technique," which has been validated for the study of local cerebral blood flow distribution in humans [7, 15].
Table 1 summarizes the various steps and the total time of a typical production of $H_2{}^{15}O$. This system allows a new run every 6 min.
The quality controls including radiochemical and radionuclidic purity, pH, sterility, and pyrogenicity were performed according to the general guidelines published by Meyer *et al.* [9]. The radiopharmaceutical produced by the procedure described fulfilled these requirements. The radionuclidic purity checked by determination of the decay curve was found to be higher than 99.9% EOB. No trace of oxygen-15-labeled compound other than

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[^{15}O]water was detected by radiogas chromatography.

CONCLUSIONS

This procedure was developed to allow repetitive injections of $H_2{}^{15}O$ as often required in PET studies.

TABLE 1. *Typical Production of Oxygen-15-labeled Water*

Step	Total time
Filling of the target	38 sec
Irradiation	3 min 30 sec
Purification (ion-exchange membranes) + filling of the HPLC loop	4 min
Delivery to the PET camera	6 min

The system described permits the production, delivery nearby the camera, and the bolus injection of oxygen-15-labeled water for positron emission tomography with reduced exposure of the operator to the radiations. Mean activities of 170 mCi (ready for injection) can be obtained every 6 min. The labeled compound is in accordance with the quality criterion's required for a short-lived radiopharmaceutical.

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