ROUTINE PRODUCTION OF IODINE-123 AT THE KARLSRUHE ISOCHRONOUS CYCLOTRON

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Summary

Routine, twice-weekly, preparation of iodine-123 with the Karlsruhe Isochronous Cyclotron is achieved by bombardment of thin highly enriched $^{124}\text{TeO}_2$ (> 96 %) targets with protons of 26 MeV incident energy. This paper describes the experimental details of the targetry and radiochemical procedures have been in routine use at Karlsruhe for production and separation of ^{123}I for two years.

Introduction

In nuclear medical diagnostics short lived radionuclides which can only be produced by means of accelerators find increasing use. The reason is that quite a number of these nuclides meet the following requirements:

- When radionuclides are used in medicine, the radiation exposure of the patient should be kept as low as possible.
- The quality of scintillation pictures and hence the evidence of nuclear medical methods should be further improved.

Short-lived iodine-123 (half-life = 13.2 h) is an outstanding example of these attempts. As compared to iodine-131, iodine-123 offers major advantages both with respect to the radiation exposure and the quality of scintillograms. The great interest in iodine-123 becomes understandable if one knows that iodine-131 is one of the most frequently used radionuclides in nuclear medical diagnosis. For instance, in the Federal Republic of Germany every second nuclear medical examination (about 500.000 patients per year) is made with iodine-131.

It was extremely difficult to obtain iodine-123 in the Federal Republic of Germany since the production capacities available in other countries can hardly meet home demand and, on the other hand, a lengthy transport (e.g., from the USA) implies high losses in activity because of the short half-life and, consequently, high cost for the user. Moreover, a large time gap between production and application increases the relative portion of long-lived impurities, which reduces the advantages offered by iodine-123.

Knowledge of this situation as well as many discussions with nuclear medical experts have led to the development of a method at the Karlsruhe Isochronous Cyclotron, which allows routine production of iodine-123. The aim has been to supply this important radionuclide to some nuclear medical hospitals in southern Germany on a routine basis.

Choise of Nuclear Reaction

On account of the worldwide interest in iodine-123 more than 20 nuclear reactions have been studied during recent years for producing this element. However, if production on a routine basis at acceptable costs and for a large group of users is aimed at, only the reactions compiled in Table 1 are of interest.

At the Karlsruhe Isochronous Cyclotron protons and deuterons are accelerated to a maximum energy of 26 MeV per nucleon so that the indirect methods yielding ^{123}Xe as an intermediate product followed by B^+ -decay to ^{123}I , are not possible from the energetic point of view. Among the reactions possible energetically and involving highly enriched tellurium isotopes as the target substance the $^{124}Te(p,2n)^{123}I$ process is more favorable in our facility because of the higher yield and the lower cost of ^{124}Te (^{124}Te : DM 9/mg; ^{122}Te : DM 16/mg).

Table I: Possible nuclear reactions for iodine-123 production. Of the reactions we know, only those have been indicated which possess a large cross section and hence allow a high production rate per hour of accelerator operation and, moreover, produce iodine-123 at a purity sufficient for medical purpose 1.

Nuclear Reactions	Energy Range of Bombarding Particles (MeV)	Target Material (Enrichment)	Yields (mCi/µAh)	Impurities
¹²² Te (d,n) ¹²³ i	~11	¹²² Te (95 %)	<1	< 1 % ¹²⁴
¹²⁴ Te (p,2n) ¹²³ I	21 - 28	124Te (96 %)	10 - 25	< 1 % ¹²⁴ 1
¹²⁷ I (B,5n) ¹²³ Xe <u>β</u> *, EC ¹²³ I	> (\$8)	Nal, Kl	8 - 14	<0.2 % ¹²⁵ I
La/Cu (p,x) ¹²³ Xe <u>β*</u> , EC ¹²³ I (spallation)	> 450	Cu-La alloys	6 - 10	?

Target Technology and Iodine-123 Separation After Irradiation

Production of iodine-123 via the 124 Te(p,2n) reaction is described by Hupf e.a. 2 and Acerbi e.a. 3 . These authors used pressed metallic tellurium powder as target material. We found that the unfavorable physical and chemical properties of tellurium (poor thermal conductivity, melting point at 450°, high vapor pressure, available as a metallic powder only, gets easily oxidized) are extremely difficult for the development of an appropriate target configuration for a routine pro-duction $\overset{4}{\cdot}$. Especially the tellurium recovery procedure turned out to be very tedious in this case. Therefore we picked up the idea of Hagedoorn e.a.⁵, to use tellurium dioxide instead of tellurium metal. Tellurium dioxide has much more favorable properties (melting point at 735°, formation of a glassy substance after solidification of the melt, low vapor pressure, insoluble in water) which are used in the following way during production:

- Irradiation of a glassy TeO₂-crystal in a special 4π water cooled target arrangement with 26 MeV protons (Fig. 1). The radioisotopes of iodine so produced are retained in the TeO₂-matrix.
- Extraction of the radioiodine from the TeO₂-melt by dry distillation (Fig. 2).

The major advantages of this process are:

- The targets can be reused after dry distillation without any reprocessing.
- The losses of target substance are very low (< 3 mg per cycle).
- The time from the end of irradiation until the product is ready for shipment is less than 30 min.

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Fig. 2: Radioic/line extraction by means of a special quartz glass apparatus located in a hot cell. After the irradiated TeO₂ has been heated up to above the melting point (820^{OC}), the radioiodine isotopes escape quickly and quantitatively (< 5 min, > 95 %). A transport gas carries them into a recipient filled with medical caustic sodium solution where they are dissolved as iodides.



Fig. 1: Principle and mechanical design of the target configuration for iodine-123 production ⁶. The highly corrosive TeO₂ molten into a platinum support is irradiated directly in the cooling water. Note that more than half of the beam energy is lost in the cooling water behind the platinum backing. The irradiation position is chosen behind the first electrostatic extraction element inside the cyclotron in order to take advantage of a larger turn separation (\sim 10 mm). The target head is transported automatically between a hot cell and the irradiation position inside the cyclotron



Fig. 3: Typical quality test of iodine-123 produced in Karlsruhe using γ -spectroscopy. As extrapolated to the time immediately after the end of irradiation the iodine-124 fraction is < 1 %.

Radiochemical Quality and Example

of Application

Prior to delivery each batch is investigated for its radiochemical purity by γ -spectroscopy. A typical γ spectrum is shown in Fig. 3. The only significat impurity is iodine-124 (< 1 % after the end of irradiation) generated essentially by the 124 Te(p,n) 124 T-reaction. This quality turns out to be sufficient if the time of application is within 36 h after production.

An example where the purity is of minor importance is the dynamic renal function study by means of iodine hippuric acid (Fig. 4). On account of the extremely short life time of this compound in the kidneys (less than 5 min) high doses do not occur in this organ. By contrast, this test implies an undesired radiation dose for the thyroid gland if iodine-131 is used since the high energy &-radiation of iodine-131 splits off free iodine through autoradiolysis, which becomes bound by the thyroid. This effect is almost completely avoided in the case of iodine-123 ⁷.

Present Status of Routine Production

Since the middle of 1976 iodine-123 has been regularly produced once a week at the Karlsruhe Cyclotron (since 1978 twice a week). Within the frame of a pilot study the product was first made available to three large hospitals in Munich, Heidelberg and Homburg (Saar) and to a number of firms of the pharmaceutical industry. The present production parameters have been summarized in Table II.

Table II: Production parameters for iodine-123 at the Karlsruhe Isochronous Cyclotron.

Reaction:	$\begin{array}{rcl} {}^{124}\text{Te} (p,2n) & {}^{123}\text{I} \\ E_p &= 26 \ \text{MeV} \end{array} \\ & & & \\ {}^{124}\text{Te enriched up to 96.5\%} \\ & & & & \\ \text{Molten TeO}_2 \ \text{in a platinum support, } \varnothing \ 10 \ \text{mm} \\ & & & \\ 450 \ \text{mg/cm}^2 (\longrightarrow 5 \ \text{MeV energy loss of protons)} \end{array}$		
Target:			
Beam current:	10 - 20 μA homogenized by mechanical sweeping		
Separation:	Dry distillation at 820°C		
Yield:	8 - 12 mCi/ μ Ah (at the end of irradiation)		
Impurity:	< 1.0 % ¹²⁴ I (at the end of irradiation)		
Rate of	Twice a week; Tu and Th 0 ⁰⁰ - 2 ⁰⁰ a		
production:	present rate: 300 - 500 mCi		
A	possible rate: 1000 mCi		
Price:	DM 12.50/mCi leaving Karlsruhe		

One of the major requirements of users of short-lived radionuclides is the reliable delivery on schedule of the radiopharmaceutical product. Non-deliveries and even delays by more than one hour cannot be tolerated since in most cases the patients have been prepared for the medical examination long before production is started. The results now available show that these strict boundary conditions can be fulfilled.

During the period from mid-1976 until mid-1978 280 batches had been planned and 277 of them were delivered on schedule. Two of the three breakdowns were caused by the cyclotron (water leak in the dee-system, water leak in another isotope production target used a short time before the iodine production time). The third breakdown was caused by a pilot's error in the hot cell.

The extremely simple production process allows one to adapt the time of production to the respective user requirements in an optimum way. For instance, the batches for remote hospitals are produced during the night and are available for application in the early morning after

transportation by road whilst the batches for the less remote hospitals are produced in the early morning time and can be applied there as early as in the afternoon.

Since mid-1977 iodine-123 has been delivered to the hospitals mentioned above at a cost covering price of DM 12.50 per millicurie under long-term contracts (5 years). This price includes both the cost for the necessary accelerator times (DM 740,-- per hour) and for the staff required for the production process and its further development.



Fig. 4: Comparison of image qualities obtained for iodine-131 (upper picture) with that for iodine-123 (lower picture) produced in Karlsruhe by the example of a renal function diagnosis (Nuklearmedizinische Klinik und Poliklinik rechts der Isar der Technischen Universität München). The studies were performed using a gamma camera and 0.5 mCi iodine-131 hippurate respectively 3 mCi iodine-123 hippurate. The drastically reduced radiation dose on the thyroid also allows to apply higher quantities of radioiodine permitting statisticaly more accurate measurements of the rate of enrichment and elimination of o-iodine hippuric acid in the kidneys (timeactivity curves). The analysis of this process provides some important information about the metabolism in this organ. Although the pilot studies carried out together with industry were equally successful they have not yet resulted in signing a contract. The reasons include the very complex problems of logistics to be solved in marketing such a short-lived radionuclide. No efforts have been made to perform pharmaceutical processing in Karlsruhe. This practice does not involve drawbacks for the large hospitals supplied with this isotope because they are able to make the necessary simple chemical procedures on their own.

Conclusion and Prospects for the Future

The present state of iodine-123 production at the Karlsruhe Isochronous Cyclotron can be characterized as follows:

- A relatively simple and consequently cheap production method was developed for iodone-123 under realistic conditions.
- It was demonstrated that short-lived radionuclides to be produced only in particle accelerators can be made available to the users in a very reliable way.
- Since 1976 277 batches were produced on schedule for diagnostic procedures with a total activity of about 35 Ci. Examinations were performed on more than 8000 patients.
- The first delivery contracts for iodine-123 have been concluded with large hospitals; they guarantee long-term cost coverage.
- For iodine-123 production less than 3 % of the total irradiation time available of about 7000 h per year are used at the cyclotron so that current research projects have not been impeded.

It can be foreseen that in the medium term more large hospitals will use iodine-123 on a routine basis, above all for examinations on risk groups (pregnant women, new born babies, children). This demand can be met by a further improvement of the target technology (factor of 2 in the beam current seems possible) on the one hand, and by extension of the irradiation period for iodine production (no problem up to a factor of 3).

In the medium term it is highly desirable to build up a well performing network comprising several producers in order to gap loss of production which cannot be ruled out, but also extended accelerator shut-down phases. Since in the Federal Republic of Germany iodine-123 is presently not produced in major quantities by another establishment and this situation is not expected to change in the near future, at least in southern Germany, a first pilot test took place in January 1978 in cooperation with the manufactures at the injector cyclotron of SIN in Switzerland.

In the long run, the Karlsruhe Cyclotron will not be able to meet the requirements alone. In a market analysis concerning the demand of short-lived radioisotopes in the Federal Republic of Germany a demand in the order of 10 Ci per week is estimated in case of complete substitution of iodine-123 for iodine-131⁸. This demand can be satisfied only if at least one accelerator will be installed in the Federal Republic of Germany which serves exclusively for isotope production.

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