Applied Radiation and Isotopes 106 (2015) 166–170

Contents lists available at ScienceDirect

Applied Radiation and Isotopes

journal homepage: www.elsevier.com/locate/apradiso

Boron analysis for neutron capture therapy using particle-induced gamma-ray emission

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HIGHLIGHTS

- PIGE was evaluated for measuring blood boron concentration during clinical BNCT.
- PIGE detected 18 μgB/mL f-BPA in culture medium.
- All measurements of any given sample were taken within 20 min.
- Two hours of f-BPA exposure is required to create boron distribution image by PIGE.
- Boron on the cell membrane could not be distinguished from boron in the cytoplasm.

ARTICLE INFO

Article history:
Received 6 February 2015
Received in revised form
23 June 2015
Accepted 25 July 2015
Available online 29 July 2015

Keywords:
Boron
Particle-induced gamma-ray emission

ABSTRACT

The neutron source of BNCT is currently changing from reactor to accelerator, but peripheral facilities such as a dose-planning system and blood boron analysis have still not been established. To evaluate the potential application of particle-induced gamma-ray emission (PIGE) for boron measurement in clinical boron neutron capture therapy, boronophenylalanine dissolved within a cell culture medium was measured using PIGE. PIGE detected 18 μgB/mL f-BPA in the culture medium, and all measurements of any given sample were taken within 20 min. Two hours of f-BPA exposure was required to create a boron distribution image. However, even though boron remained in the cells, the boron on the cell membrane could not be distinguished from the boron in the cytoplasm.

1. Introduction

A clinical trial of boron neutron capture therapy (BNCT) for glioblastoma and other malignant tumors has been performed with promising results in Japan. The results from two separate groups were published in 2009 (Kawabata et al., 2009; Yamamoto et al., 2009). Each patient's dose was determined by neutron flux and blood boron concentration during irradiation in BNCT. The range of blood boron concentrations was approximately 10–40 μgB/g in our clinical trial (Yamamoto et al., 2009). The boron-10 concentration in a patient's blood has been said to be the most important parameter for clinical BNCT trials. Because it determines the neutron irradiation time and the patient's radiation dose, the measurement should be prompt and reliable. At least several different types of data should be available within 10–20 min. We previously used inductively coupled plasma-atomic emission spectroscopy (ICP-AES) and prompt gamma-ray neutron activation analysis (PGNAA) in JRR-4; however, because the neutron source has changed from nuclear reactor to accelerator, we required a new boron analysis method that does not include a reactor. Consequently, the proposed method uses a proton microbeam only. We previously reported that boron and gadolinium can be detected in the cultured cell and that two-dimensional images can be taken using micro-particle-induced X-ray emission (PIXE) and particle-induced gamma-ray emission (PIGE) (Yamamoto et al., 2014; Endo et al., 2006). PIXE/PIGE has been shown to provide a highly sensitive and multi-elemental analysis (Chhillar et al., 2014). In this report, we propose a method for measuring blood

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http://dx.doi.org/10.1016/j.apradiso.2015.07.035
0969-8043/

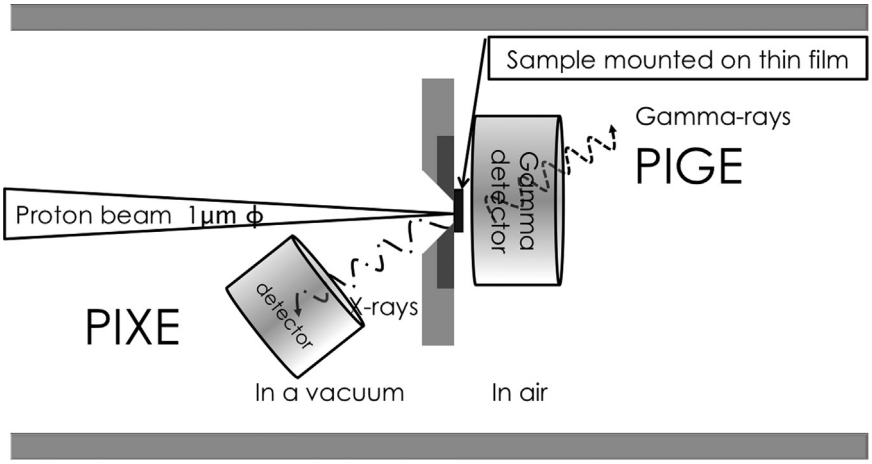

Fig. 1. Schema and principles of PIXE and PIGE.

boron concentration during a clinical BNCT trial, and examine the potential application of PIXE by using micro-PIGE. To evaluate the possibility of micro-PIGE for boron measurement, boronophenylalanine (BPA) resolved within a cell culture medium was measured. With respect to the required accuracy for a clinical dose-planning system, a statistical precision of 5% and a measurement time within 10–20 min is required in order to apply PIGE to clinical BNCT trials.

2. Materials and methods

BPA and fructose were dissolved and prepared as previously described (Yoshino et al., 1989). We use the term *f-BPA* here to refer to a complex mix of fructose and BPA. f-BPA was dissolved in a cell culture medium (Dulbecco's modified Eagle's medium containing 10% fetal bovine serum and 10 mg/L penicillin–streptomycin). The boron concentrations were 0, 18, 37.5, 75, 150, and 300 μgB/mL. One microliter of sample was dripped and dried onto 4-μm-thick polycarbonate membranes (SpectroCertified Thin-Film Sample Supports CAT. NO: 480 Chemplex Industries, Inc. USA) and fixed onto a sample holder.

U251 (human glioma) and CT26 (mouse carcinoma) cell lines were cultured on the polycarbonate membranes. These cells were treated with 0, 38, or 300 μgB/mL of f-BPA for 120 min. The samples were then analyzed using PIXE/PIGE after freeze-drying.

Micro-PIXE/PIGE analysis was performed at Takasaki Ion Accelerators for Advanced Radiation Application (TIARA, Takasaki, Japan). A 1.7 MeV proton beam, accelerated by the TIARA single-ended accelerator at TARRI, was emitted from an ion microbeam apparatus. The samples were attached directly to the window at the end of the microbeam system and bombarded by the proton beam in air. The beam spot was approximately 1 μm in diameter and the beam current was approximately 100 pA. The maximum scanning area was 800 by 800 μm^2. The emitted X-rays and gamma rays were detected (Fig. 1). A nuclear reaction, $^{10}B(p, p'\gamma)^{7}Be$, was used to measure ^{10}B concentration, and the gamma rays of this reaction were detected using a detector placed 5 mm behind the specimen. Concentrations of potassium and phosphorus, which were simultaneously detected with a detector placed in the vacuum, were measured using PIXE.

The data were analyzed using PIXEna, an application that was originally developed by TIARA. The application, which was developed for Windows PCs, is able to draw a spectrum and two-dimensional element distribution images. The positive control for boron was solid boron nitride, and the negative control was dried culture medium only. The range of gamma-ray energy from boron was determined by the spectrum of the positive control material and, to avoid contamination from the adjacent 440-keV sodium peak, which is from the $^{23}Na(p, p'\gamma)^{23}Na$ reaction, the boron peak range was set at the lower half of the peak area. We used a boron count ratio value twice that of the lower half range, and plotted the count ratio of boron yields versus total counts. Boron concentration in the samples was calculated based on an analytical curve created by using the count ratio of a sample with a known concentration. The presence of cells was confirmed if potassium and phosphorous were both detected (Endo et al., 2006). Two-dimensional images of potassium, phosphorus, and boron were composited using Photoshop CC (Adobe Systems).

3. Results

PIGE detected 18 μgB/mL of f-BPA in the culture medium; this is represented as a small peak (Fig. 2). The ratio of boron yields to total yields increased in a concentration-dependent manner (Fig. 3). All measurement periods were 5–17 min (data not shown). Two hours of f-BPA exposure was required to create a boron distribution image by PIGE. The boron atoms remained on the U251 cells (Fig. 4-1), and the distribution of boron was not localized in the CT26 cells (Fig. 4-2), but instead distributed over all the polycarbonate membranes.

4. Discussion

A proton beam is easier to handle than a thermal neutron beam, which is one advantage of the present method over other methods that use charged particle spectrometry (Bortolussi and Altieri, 2013). PIXE/PIGE has the potential to measure clinical concentration levels of blood (10–40 μgB/mL), which may help us to accomplish our objective. Further examination is needed to evaluate the accuracy of this method.

In the present analysis, the measurement time of each sample was within 20 min, which meets the basic requirements for clinical applications. The possibility of quantitative determination of boron concentration was suggested by the detection of 18–37.5 μgB/mL of f-BPA (Shibata et al., 2003). The micro-PIGE technique has several features: high sensitivity, good special resolution, and easy to prepare sample. On the other hand, owing to the small sample amount