Bone 50 (2012) 128–139

Contents lists available at SciVerse ScienceDirect

Bone

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

Review

Clinical utility of ^{18}F-fluoride PET/CT in benign and malignant bone diseases

Yuxin Li [a], Christiaan Schiepers [b], Ralph Lake [a], Simin Dadparvar [c], Gholam R. Berenji [a,*]

[a] VA Greater Los Angeles Healthcare System, Los Angeles, CA, USA
[b] Department of Molecular and Medical Pharmacology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA
[c] University PA Health System, Philadelphia, PA, USA

ARTICLE INFO

Article history:
Received 5 July 2011
Revised 26 September 2011
Accepted 28 September 2011
Available online 6 October 2011

Edited by: T. Jack Martin

Keywords:
^{18}F-sodium fluoride
Positron emission tomography, computed tomography, PET–CT
Bone scan

ABSTRACT

^{18}F labeled sodium fluoride is a positron-emitting, bone seeking agent with more favorable skeletal kinetics than conventional phosphate and diphosphonate compounds. With the expanding clinical usage of PET/CT, there is renewed interest in using ^{18}F-fluoride PET/CT for imaging bone diseases. Growing evidence indicates that ^{18}F fluoride PET/CT offers increased sensitivity, specificity, and diagnostic accuracy in evaluating metastatic bone disease compared to ^{99m}Tc based bone scintigraphy. National Oncologic PET Registry (NOPR) has expanded coverage for ^{18}F sodium fluoride PET scans since February 2011 for the evaluation of osseous metastatic disease. In this article, we reviewed the pharmacological characteristics of sodium fluoride, as well as the clinical utility of PET/CT using ^{18}F-fluoride in both benign and malignant bone disorders.

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Introduction

The clinical use of ^{18}F-fluoride as a bone imaging agent was initially demonstrated by Blau et al. in 1962 [1], and was approved by the U.S. Food and Drug Administration (FDA) as Positron Emission Tomography (PET) tracer in 1972. It was the standard bone-scanning agent during the early days when rectilinear scanning was widely used. However, with the introduction of the Anger gamma camera and the development of ^{99m}Tc labeled phosphate and diphosphonate compounds in 1970s, the ^{18}F-fluoride bone tracer was rapidly replaced by ^{99m}Tc labeled radiopharmaceuticals, primarily due to the optimal physical characteristics of ^{99m}Tc for the Anger camera. Although not routinely used in the clinic, ^{18}F-fluoride has more desirable skeletal kinetics as a bone-seeking agent than conventional phosphate and diphosphonate compounds [2]. With the expanding use of Positron Emission Tomography/Computed Tomography (PET/CT) and commercial availability of ^{18}F labeled PET tracers, there is renewed interest in using ^{18}F-fluoride for bone scan. The latest shortage of ^{99}Mo/^{99m}Tc generators further enhances the enthusiasm for ^{18}F-fluoride PET/CT study. Due to the growing evidence showing that a PET bone scan has substantial advantages over MDP bone scintigraphy, the Centers for Medicare & Medicaid Services (CMS) has started to reimburse sites participating in the National Oncologic PET Registry (NOPR) for ^{18}F sodium fluoride PET scans since February 2011.

Pharmacokinetics of ^{18}F fluoride

The biological nature of skeletal accumulation of fluoride has been recognized since 1937, and sodium fluoride had been used to treat metabolic bone disease [3]. Like most other radioactive tracers used in nuclear medicine, ^{18}F sodium fluoride is administered intravenously. Immediately after intravenous injection, fluoride is rapidly cleared from the plasma in an exponential manner, is accumulated in bone, and excreted through the kidneys. Under normal conditions, the plasma protein binding of fluoride is negligible. Fluorides are continuously filtered through glomeruli. The renal clearance of fluoride is dependent on urine flow rate, varying from 60 to 90% of glomerular filtration rate (GFR) at high urine flow, to 5% of GFR at low urine flow. To reach the skeletal structures, fluorides pass from the plasma, through the extracellular fluid space, and move into the bound water shell of bone surface. The principal mechanism for the movement of fluorides from plasma to the bone surface is mediated by passive diffusion based on chemical equilibrium, which is a very fast process with half times measured in minutes. Once reached to the bone surface, fluorides further migrate to bone crystal that is composed of hydroxyapatites. Fluorides exchange with hydroxyl ions (OH^-) to form fluoroapatites, and finally are incorporated into the bone crystal structure (Fig. 1). Although the ion-exchange is a slow process that may take days or even weeks, fluoride is considered localized in the bone structure once it entered the bound water shell of bone surface. Like other halides such as chloride and bromide, fluoride can concentrate in red blood cells, and also accumulate in immature blood cells and bone marrow. However, this does not affect skeletal accumulation of fluoride since fluoride can diffuse from a blood cell to the bone surface.

* Corresponding author at: VA Greater Los Angeles Healthcare System, Nuclear Medicine Service (115), 11301 Wilshire Blvd. Los Angeles, CA 90073, USA.
E-mail address: Gholam.Berenji@va.gov (G.R. Berenji).

8756-3282/$ – see front matter. Published by Elsevier Inc.
doi:10.1016/j.bone.2011.09.053

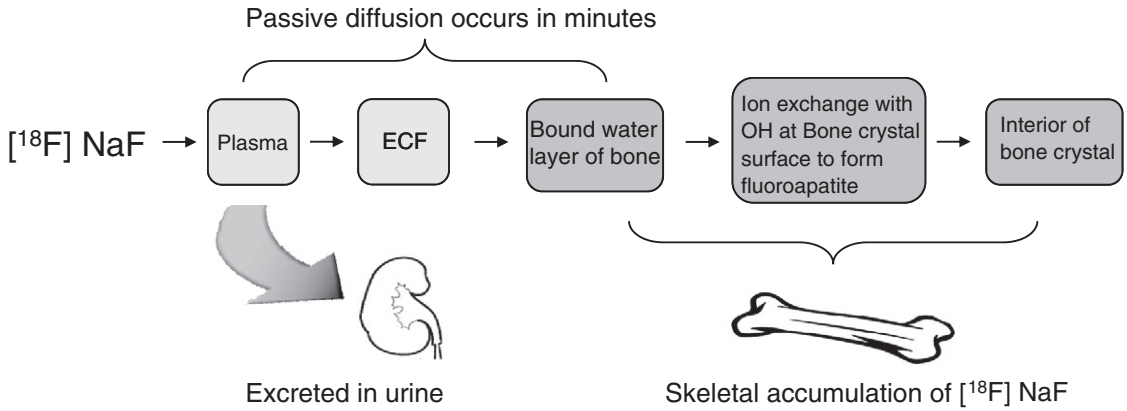

Fig. 1. Diagrammatic demonstration of skeletal uptake of sodium fluoride.

It has been suggested that the trans-membrane migration of bone-seeking tracers is proportional to molecular size. Smaller molecules such as fluoride cross more rapidly than larger agents such as MDP. Similarly, the first pass extraction fraction of fluoride in bone is close to 100% in the animal model [4]. Owing to the rapid renal clearance as well as fast bone accumulation rate, a high bone–soft tissue contrast can be obtained within 1 h after tracer injection, compared to 3–6 h for the MDP bone scan. Only 10% of fluoride remains in plasma 1 h after tracer injection. Similar to that of MDP, skeletal accumulation of fluoride is proportional to regional blood flow and rate of bone turnover. Blood flow is the rate-limiting step in the transfer of fluorides from blood to bone. The rapid skeletal accumulation rate of fluoride ion is demonstrated in Fig. 2.

Comparison between MDP bone scintigraphy and fluoride PET bone study

The difference between ^{18}F sodium fluoride PET bone study and conventional ^{99m}Tc MDP bone scintigraphy is summarized in Table 1. The major advantages of fluoride PET study are markedly improved image quality, increased sensitivity, and shorter examination time. The considerably improved image quality and sensitivity can be attributed to three reasons. 1. The Anger camera with collimator system for ^{99m}Tc MDP imaging is notorious for low geometric efficiency, in which only ~0.01% of emitted photons are acquired for imaging. In contrast, PET technology uses the coincidence-detection method to acquire photons without need of a collimator, resulting in the order of ~1% of emitted photons being detected [5]. This conveys to a much higher sensitivity (by approximately two to three orders of magnitude) for PET over Planar/SPECT imaging. 2. Fluoride PET bone scan has higher spatial resolution than that of MDP bone scan. 3. The favorable kinetic characteristics of sodium fluoride provide better bone–soft tissue contrast ratio than that of MDP imaging. All these properties of sodium fluoride PET study make it the perfect metabolic bone study with excellent image quality and extremely high sensitivity (Fig. 3).

Normal imaging pattern of ^{18}F-fluoride PET bone scan

Since the skeletal accumulation of fluoride is similar to that of MDP, the bio-distribution of fluorides also resembles that of MDP. Thus, the pattern of fluoride PET bone scan is very similar to the image pattern of a conventional MDP scan, in which the axial skeleton demonstrates higher tracer uptake than the appendicular skeleton (Fig. 4). The mean uptake values of fluoride in the humerus, tibia, and femur are about 15%–25% of the values in the spine. The kidneys and bladder are clearly visualized in a fluoride PET bone scan, and normally have the highest uptake.

Fluoride uptake can sometimes be observed in the vascular structures and the gastrointestinal tract, outside the physiological distribution in the skeleton and genitourinary tract. Vascular uptake of fluorides is frequently observed in older patients with atherosclerotic calcification, and is correlated with atherosclerotic burden [6,7]. Owing to the limited spatial resolution of PET imaging, vascular uptake of fluoride is usually observed in major arteries, such as aorta, carotid, iliac, and femoral arteries. It was suggested that atherosclerotic calcification is an active process similar to bone formation [8]. Therefore, the vascular wall uptake of fluoride may suggest active mineral deposition into atherosclerotic lesions. In our experience the fluoride uptake in arteries does not always overlap with vascular calcifications, suggesting that fluoride uptake and calcification represent different stages in the dynamic atherosclerotic process [9]. Similar to vascular calcifications, fluoride uptake is frequently observed in other tissues vulnerable to calcification, such as choroid plexus and mitral valves.

Bowel uptake of fluoride is common. In the veteran population at our institution, we observed that approximately 40% of patients demonstrate variable bowel accumulation of fluorides, either in the small or large bowel. We did not observe any correlations between the bowel uptake and gastrointestinal complaints from the patients. The mechanism of fluoride uptake in bowel is unclear. It may represent a normal variant given the higher incidence rate. In some patients, bowel uptake can be quite intense and extensive as demonstrated in Fig. 5.

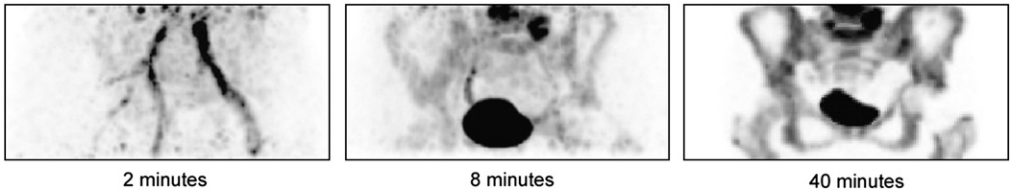

Fig. 2. Maximum Intensity Projection (MIP) images of the pelvis obtained with PET using ^{18}F fluoride PET. Images were acquired 2 min, 8 min, and 40 min after ^{18}F sodium fluoride injection for evaluation of hip prosthesis. Asymmetric blood flow was demonstrated 2 min after tracer injection, with more tracer in the left common iliac than the right. After 8 min, rapid clearance of tracer from the plasma shows low activity in the vessels, and early skeletal uptake of fluoride. There is significant urinary excretion of tracer in the bladder. Delayed image at 40 min demonstrates excellent bone–soft tissue contrast.