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Automated radiosynthesis of [¹¹C]morphine for clinical investigation

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Abstract

To meet a multiple-dose clinical evaluation of the P-gp modulation of [¹¹C]morphine delivery into the human brain, radiosynthesis of [¹¹C]morphine was accomplished on an automated system by *N*-methylation of normorphine with [¹¹C]CH₃I. A methodology employing optimized solid-phase extraction of the HPLC eluent was developed. Radiosynthesis took 45 min with a radiochemical yield ranging from 45 – 50% and specific activity ranging from 20 – 26 Ci/μmol (decay corrected to end-of-bombardment); radiochemical and chemical purities were >95% (n = 28).

Keywords

[¹¹C]Morphine; Automated radiosynthesis; Positron emission tomography

1. Introduction

Members of the ATP-binding-cassette (ABC) transporters play an important role in the multiple active transport systems that are involved in the protection of the human brain. ABC sub-family B member 1 (ABCB1), or the multidrug resistance protein 1 (MDR1), is called P-glycoprotein (P-gp), which is regulated by its substrates, genetic influence as well as affected by diseases such as stroke and epilepsy (Aller et al., 2009; Cordoncardo et al., 1989; Ueda et al., 1987). P-gp is considered a major drug efflux pump comprising the blood-brain-barrier, responsible for a broad range of xenobiotic transport. P-gp prevents the uptake of many classes of drugs in human brain, including a variety of analgesics including opioid receptor ligands. Morphine, the best known opioid receptor ligand, is widely used to treat both chronic and acute pain (Woodhouse et al., 1999). Its pharmacologic actions, tolerance and side effects have been studied in depth over decades. Morphine is reported to be a substrate for P-gp (Letrent et al., 1999b). In in vitro studies, using P-gp over-expressed cell line L-MDR1, morphine had significantly higher basal to apical transport and behaved like a P-gp substrate (Wandel et al., 2002). In MDR1a knockout mice, morphine exhibited a

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significantly greater antinociceptive effect compared to wild type mice (Hamabe et al., 2006). Assessing the response to heat pain stimuli found that P-gp genetic variants influenced central morphine effects in mice (Liang et al., 2006). The cyclosporine analogue, PSC833 (valsopodar), as a P-gp substrate, can block the transport system and increase the morphine concentrations in perfused mouse brain (Cisternino et al., 2004). In rats pretreated with another P-gp substrate, GF120918, the accumulation of unbound morphine in cerebral extracellular fluid was increased and the morphine-associated antinociception was enhanced (Letrent et al., 1999a). All together, the data from in vitro and in vivo studies demonstrated that morphine is a P-gp substrate in animals. However, it is not clear if morphine is a P-gp substrate in the human brain and how an effective P-gp inhibitor such as cyclosporine would modulate the delivery of morphine to human brain. Positron emission tomography (PET) is as an unique noninvasive method which has the capability of investigating drug delivery by studying radiolabeled drug with PET isotopes such as carbon-11 and fluorine-18 (Mintun et al., 2005; Sasongko et al 2005). In clinical investigation, cyclosporine increased by 80% human brain uptake of the P-gp substrate [^{11}C]verapamil (Hsiao et al., 2006; Sasongko et al., 2005). To investigate the cyclosporine modulation of morphine delivery to the human brain and help clarify how P-gp affects the uptake of morphine in human brain, an automated synthesis of [^{11}C]morphine that can deliver multiple high quality doses of [^{11}C]morphine is a high priority. In this article, we report the radiosynthesis and optimization of conditions for production of [^{11}C]morphine by an automated module.

2. Materials and methods

2.1. General

All commercial reagents and solvents were used as purchased unless otherwise stated. Production of [^{11}C]CH₃I on site with a cyclotron (JSW BC-16/8) followed the reported method (Tu et al., 2005). Normorphine was purchased from RTI (Research Triangle Park, NC). 5N sodium hydroxide aqueous solution and sodium hydroxide pellets (98%) were purchased from Fisher (Houston, TX). Anhydrous dimethylsulfoxide (DMSO) and potassium dihydrogen phosphate were purchased from Sigma-Aldrich (Milwaukee, WI). 10 mL sterile vials were purchased from Hospira (Lake Forest, IL). Unvented and vented 0.2 μm syringe filters were purchased from Millipore (Billerica, MA). Water was purified by a MilliQ integral water purification system (Millipore, Billerica, MA).

The radiosynthesis of [^{11}C]morphine was performed through *N*-methylation of the precursor normorphine by [^{11}C]CH₃I under basic conditions, heated in DMSO. After heating, [^{11}C]morphine was purified using a semi-preparative HPLC system and then processed by a solid-phase extraction methodology. The whole process was accomplished by a remotely-controlled automated synthetic module. The schematic diagrams of the methylation module for making [^{11}C]morphine are shown in Figure 1 and Figure 2. Due to the limitation of space in the lead-shielded hot cell, the synthetic module was built on the surfaces of a cube. The module components were primarily on the front and the left surfaces as shown in Figure 1 and Figure 2 respectively. This whole system was remotely controlled by a computer located outside of the hot cell. The delivery and transfer of solutions were manipulated via air-activated valves controlled by the computer remotely. The HPLC system consisted of a Rheodyne injector valve with a 2.0 mL sample loop, a Thermo Separations P200HPLC binary pump, a Spectra Physics Spectra 1000 UV variable detector (254 nm), and a Bioscan Flow counter radioactivity detector (NaI crystal).

2.2 Production of [^{11}C]Methyl Iodide

Production of [^{11}C]CH₃I followed the reported method (Tu et al., 2005). Briefly, [^{11}C]CH₃I was produced on-site from [^{11}C]CO₂ using a GE PETtrace MeI Microlab. Up to 1.4 Ci of

[¹¹C]carbon dioxide was produced from the JSW BC-16/8 cyclotron by irradiating a gas target of 0.5% O₂ in N₂ for 15 – 30 min with a 40 μA beam of 16 MeV protons in the Barnard Cyclotron Facility of Washington University School of Medicine. After the GE PETtrace MeI Microlab system converted the [¹¹C]CO₂ to [¹¹C]CH₄ using a nickel catalyst [Shimalite-Ni (reduced), Shimadzu, Japan P.N.221-27719] in the presence of hydrogen gas at 360°C; the [¹¹C]CH₄ was further converted to [¹¹C]CH₃I by reaction with iodine in the gas phase at 690°C. Approximately 12 min following the end-of-bombardment (EOB), [¹¹C]CH₃I were delivered in the carrier gas to the hot cell where the radiosynthesis was accomplished.

2.3.1 Synthesis of [¹¹C]Morphine—[¹¹C]CH₃I was bubbled for a period of 2–3 min into a solution of normorphine (1–2 mg) in DMSO (0.18 mL) containing 3 μL of 5N NaOH aqueous solution at room temperature. When the trapping of radioactivity was complete, the sealed reaction vessel was heated to 85°C for 5 min. After the heating source was removed, 1.8 mL of the HPLC mobile phase composed of acetonitrile/ 0.1 M ammonium formate buffer (8/92, v/v), pH = 4.5, was added into to the reaction vessel. The mixture was loaded onto a reversed phase HPLC system (Alltech Platinum EPS C18 column, 250×10 mm) to purify the [¹¹C]morphine. Under these conditions, the product was collected from 13.5 to 15.5 min into a vial that contained 50 mL of phosphate buffer (pH = 8.0). After finishing elution of the sample, the collected fraction containing the product was passed through a C-18 Plus Sep-Pak[®] cartridge to remove the mobile phase solvent, whereby [¹¹C]morphine was retained on the cartridge. Then the Sep-Pak cartridge was rinsed using 10 mL of sterile water. Finally, the [¹¹C]morphine trapped on the Sep-Pak[®] was eluted with 1.0 mL of ethanol into a sterile pyrogen-free glass vial containing 0.9% sodium chloride injection (8.5 – 9.5 mL) and the solution was passed through a 0.22 μm (Whatman Puradisc 13 mm syringe filter) sterile filter to form the final injection dose. The total synthesis time was 45 min.

2.4 Quality Control for [¹¹C]Morphine

An aliquot of sample was assayed by an analytical HPLC system (Alltech Platinum EPS C18 column, 250×4.6 mm), UV wavelength at 254 nm; mobile phase consisted of acetonitrile/ 0.1 M, pH 4.5 ammonium formate buffer (8/92, v/v). At this condition, the retention time for [¹¹C]morphine was approximately 5.5 min at a flow rate of 1.2 mL/min. The sample was authenticated by co-injecting with the cold standard morphine solution. The quality assurance of [¹¹C]morphine for human injection also included carbon-11 radionuclide purity, analysis of residual solvents, appearance, color, pH, bacterial endotoxins, and sterility. The release of [¹¹C]morphine for injection occurs only after the analytical HPLC results of the sample meet release criteria listed in Table 1. Because the short half-life of carbon-11, the bacterial endotoxins and sterility are released post-injection, and serve as track records for the future production of [¹¹C]morphine.

3. Results and Discussion

As shown in Scheme 1, [¹¹C]morphine was synthesized from *N*-[¹¹C]methylation of normorphine reacted with [¹¹C]CH₃I in the presence of 5 N NaOH aqueous solution and dimethyl sulfoxide (DMSO) as a solvent. DMSO is an aprotic solvent that can afford the high yield in suitable conditions.

Although the synthesis of carbon-11 labeled morphine was originally reported in the 1970's, either by reductive alkylation using [¹¹C]formaldehyde combined with sodium borohydride (Allen and Beaumier 1979) or by *N*-methylation using [¹¹C]CH₃I with a base in ethanol (Kloster et al., 1979) or dimethyl formate (DMF) (Långström et al., 1982), the reaction

conditions and processes have never been optimized. In addition, no automated radiosynthetic procedure of producing the [^{11}C]morphine for human studies was reported. Subsequently, our reported protocols will enable radiochemists to perform automated synthesis of [^{11}C]morphine and deliver high amounts of radioactivity for multiple-dose clinical investigations of [^{11}C]morphine.

In the synthesis of [^{11}C]morphine, dimethyl sulfoxide was chosen as the reaction solvent is due to its great solubility and aprotic nature. The great solubility renders a homogeneous solution even with the presence of an inorganic base; and the aprotic nature of DMSO facilitates the *N*-[^{11}C]methylation. Both effects accelerate the reaction and shorten the reaction time, which is critical for the radiosynthesis of carbon-11-targeted tracers because of its short half-life (20.38 min). To avoid radical temperature changing from dry ice-acetone cold bath of -78°C for efficiently trapping of [^{11}C]CH₃I, to the reaction temperature of approximately 85°C within a short time period (1 • 2 min), the [^{11}C]CH₃I was trapped in the DMSO solution at room temperature. Our studies demonstrated the room temperature trapping of [^{11}C]CH₃I was sufficient. The substrate for making [^{11}C]morphine is the hydrogen chloride salt of normorphine that was liberated in situ with small amount 5 N sodium hydroxide aqueous solution (3 μL). Using sodium hydroxide instead of another organic base can forestall the base from competing with normorphine to react with the [^{11}C]CH₃I, which usually leads to low yield (Långström et al 1982). We observed that the amount of sodium hydroxide affected the competing reaction of *O*-[^{11}C]methylation at the phenol hydroxyl group; if using more than 3 μL of 5N NaOH, the amount of *O*-[^{11}C]methylation by-product was increased, whereas by using 3 μL 5N NaOH, the by-product formation was minimized. Even when small amount by-product formed, under our HPLC conditions (a reverse phase HPLC system with optimized mobile phase of acetonitrile/0.1M ammonium formate buffer, pH ~ 4.5), the byproduct had a retention time of 27.2 • 30.1 min, thus its presence did not interfere the purity and quality of [^{11}C]morphine, which had a retention time of 13.5 • 15.5 min.

The HPLC collection fraction was passed through a C-18 Sep-Pak cartridge to remove the HPLC mobile phase and then formulate the final dose. The utilization of solid phase extraction (SPE) instead of rotary evaporation to remove the HPLC mobile phase and formulate the dose of [^{11}C]morphine favors the production of [^{11}C]morphine on an automatic radiosynthetic module. SPE methodology considerably shortened the synthetic time, substantially reduced the radiation received by the production staff, lead to high reproducibility and is highly compatible with automated production procedures (Zheng and Mock 2005; Zheng and Mulholland 1996). Unlike rotary evaporation, which usually needs heat for removing the solvents, SPE methodology processes the sample at room temperature, which may prevent the decomposition of some temperature sensitive samples. However, during the SPE processing of the sample, it was found that the sample was very difficult to retain on the Sep-Pak if the HPLC eluent was directly diluted with MilliQ water and then passed through the Sep-Pak. Different kinds of Sep-Paks packed with different packing material were tested; none of them worked well. The trapping efficiency of different Sep-Paks for [^{11}C]morphine is displayed in Table 2. It was found that at pH 4.5, the retaining rates are 26.2%, 25.1%, 18.8%, 10.0%, and 2.54% respectively for the Waters Oasis HLB Plus cartridge, Waters Sep-Pak C18 Plus cartridge, Waters Sep-Pak C18 Cartridge, Waters Sep-Pak Light C18 cartridge, and the Waters Sep-Pak Light Silica cartridges. To resolve this problem, considering the lipophilicity of [^{11}C]morphine could be affected by the pH value of the solution, we then optimized the pH value of the solution. We found over 98% of [^{11}C]morphine was able to be retained on the cartridge when the pH of the sample solution was around 7.5 as shown in Table 2. Analyzing the structure of the morphine, we concluded the lipophilicity of [^{11}C]morphine depends on the media pH which affects the trapping efficacy of [^{11}C]morphine on Sep-Pak cartridges. The solid phase extraction (SPE)

efficiency is determined by the distribution of substrates between the hydrophobic sorbent and the hydrophilic solvent. If the substrate is too hydrophilic, it cannot be retained on the hydrophobic sorbents, for example, at pH = 4.5, morphine lipophilicity is low, and the Sep-Pak cartridges were not able to retain the [^{11}C]morphine effectively; whereas at pH = 7.5, morphine lipophilicity increases and the Sep-Pak cartridges were able to retain the [^{11}C]morphine. Our observations are consistent with the results by using reversed phase-HPLC; the lipophilicity of morphine is relative low at pH 3.5, and relative high at pH 7.5 (Carrupt et al., 1991). To adjust the pH value for the HPLC fraction containing [^{11}C]morphine, either a strong basic solution such as 1 N NaOH aqueous solution or a relative mild basic buffer such as pH = 8.0 phosphate buffer can be used. Although there is no significant difference using either one, we prefer to use 50 mL of pH 8.0 phosphate buffers instead of a 1 N NaOH aqueous solution. More consistent results were generated using 50 mL of phosphate buffers (pH = 8.0) to adjust the pH value of the samples to around 7.5 instead of using a small volume of the stronger base, ie. 400–500 μL of 1 N NaOH aqueous solution.

Thus, pH adjustment was indispensable for the SPE process of [^{11}C]morphine and it is the key to the synthesis of [^{11}C]morphine on the automated radiosynthesis module. At the optimized pH condition, the SPE processing of the HPLC fraction containing [^{11}C]morphine and the formulation of the injected dose is a facile way to make [^{11}C]morphine on the automated module system for clinical applications.

Using the procedure reported here, ~55 mCi of [^{11}C]morphine was easily achieved in 45 min. The radiochemical yield ranged from 45 – 50% (decay corrected to EOB). To calculate the specific activity of [^{11}C]morphine, a 20 μL of aliquot of the dose was injected onto an analytical HPLC to determine the cold mass concentration of the dose (in ppm) by fitting to an established calibration curve that was built using a cold morphine standard. The specific activity (in Ci of [^{11}C]morphine per μmol of cold morphine) was then calculated using the radioactive yield (decay corrected to EOB), the concentration of cold mass in the radioactive dose, the molecular weight of morphine, and the total volume of the dose. Using our analytical HPLC system for quality control, the minimum detectable concentration of the cold mass is 0.1 ppm. Based on our calculations, the specific activity of [^{11}C]morphine ranged from 20 – 26 Ci/ μmol (decay corrected to EOB). The radiochemical purity is > 99% and chemical purity is > 95% respectively (n = 28).

4. Conclusions

[^{11}C]Morphine was successfully made by an automated system following USP chapter 823. The final processing of the product was optimized using solid phase extraction instead of rotary evaporation. The key technique in solid phase extraction is adjusting the pH to 7.5–8.0 for the HPLC fraction containing [^{11}C]morphine; the pH-adjusted, diluted eluent is then passed through a Sep-Pak which significantly improved Sep-Pak trapping efficiency. The automated synthesis of [^{11}C]morphine was approved by Radioactive Drugs Research Committee (RDRC) of our institute and was used for routine dose production for a clinical investigation of the effect of P-gp on human brain morphine uptake.

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Figure 1. Diagram of the automated methylation module for the synthesis of $[^{11}\text{C}]$ morphine, front surface. V1: Parker Valve Series 66 3-way. V2: CIP pinch valve. V3: pneumatically-operated 6-way PEEK injector valve (Rheodyne).

Figure 2.

Diagram of the automated methylation module for the synthesis of [^{11}C]morphine, left surface. V4, V5 and V7: Parker Valve Series 66 3-way. V6 and V8: CIP pinch valve.

Scheme 1.

Synthesis of $[^{11}\text{C}]$ morphine from normorphine and $[^{11}\text{C}]\text{CH}_3\text{I}$.

Table 1^[11C]Morphine release criteria

Tests	Release Criteria
Radiochemical Purity	• 90%
Radiochemical Identity (^[11C] Morphine)	Retention time of ^[11C] morphine and coinjected morphine must be within $\pm 10\%$
Radionuclidic Identity (¹¹ C)	19.37 to 21.40 (20.385 $\pm$ 5%)
Specific Activity (@ EOS)	• 500 Ci/mmol (for reference only, not a release criterion)
pH	4.5 to 8.0
Appearance; Color	Clear; Colorless
Bacterial Endotoxins	• 17.5 EU/mL
Residual Solvents	Acetonitrile: • 0.41 mg/mL, (4.1 mg/day max) DMSO: • 5 mg/mL, (50 mg/day max) Ethanol: • 100 mg/mL
Mass of ^[11C] Morphine	• 50 μ g/injected dose
Sterility	Sterile
Radionuclidic Purity	• 99.5%

Table 2

Effects of media pH on solid phase extraction efficiency.
Solid phase extraction efficiency affected by pH of media.

Cartridge Tested	Activity Applied (mCi)	Retained Activity* (mCi)	Retained rate
At pH 4.5			
Waters Oasis HLB Plus	6.90	1.81	26.2%
Waters Sep-Pak C18 Plus	1.67	0.42	25.1%
Waters Sep-Pak C18	1.44	0.27	18.8%
Waters Sep-Pak light C18	1.50	0.15	10.0%
Waters Sep-Pak Light Silica	1.74	0.034	2.54%
At pH 7.5			
Waters Sep-Pak C18 Plus	0.193	0.190	98.4 %

* Time corrected.