Original Article

FDG 합성 후 질소가스를 이용한 튜빙의 잔류 ^{18}F-FDG 최소화를 위한 방법의 유용성

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A Study on Minimizing the Residual ^{18}F-FDG in the Tubing Using Nitrogen Gas

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Purpose: In ^{18}F-FDG automated synthesizer, deliver is done in automated mode after synthesis until the dispenser. After the delivery, the yield is calculated from the radioactivity which was read by the dose calibrator located in the dispenser. However, when the distance between the automated synthesizer and the dispenser is far, there are ^{18}F-FDG residues, which results in loss of the amount of ^{18}F-FDG. This study investigated the usefulness of a method that minimizes ^{18}F-FDG residues. **Materials and Methods:** The structure of the tubing between the (TRACERlab Mx FDG; GE.) and the dispenser is that the distance is 8 m and the internal diameter is 1/16 inch. The synthesis process of The module goes through the synthesis process of trap, synthesis, delivery in the automated module. The time taken for synthesis is about 25 to 26 minutes, after which rinsing is done. However, after rinsing, as the distance of the tubing increased, there were 10~13% of ^{18}F-FDG residues. Therefore, a method of using push syringe and N_2 gas in manual mode to minimize ^{18}F-FDG residues is analyzed. **Results:** In manual mode, there were ^{18}F-FDG residues of 4~5% for the push syringe, and there were ^{18}F-FDG residues of less than 1% for the N_2 gas, which showed that the method using N_2 gas had superior usefulness. Also, there were no ^{18}F-FDG residues in the cleaning the next day. **Conclusion**: The distance between the synthesizer and the dispenser needs to be reduced as much as possible, to reduce the rate of loss of ^{18}F-FDG resulting from the distance of the tubing. However, in case the distance between the synthesizer and the dispenser has to be increased due to the system structure, using push syringe and N_2 gas simultaneously is a useful method for minimizing ^{18}F-FDG residues. **(Korean J Nucl Med Technol 2010; 4(1):8-12)**

Key Words : Delivery distance, N_2 gas

Introduction

^{18}F-FDG is the most commonly used radiopharmaceutical in the nuclear medicine field. High dose of ^{18}F-FDG is prepared more than once in most hospitals, and once it is produced, it is dispensed into vials or syringes. In such case, it is recommended to install the synthesizer and dispenser as close to each other as possible. However, it is sometimes inevitable to install the dispenser away from the synthesizer, which will reduce the final radiochemical yield of ^{18}F-FDG due to the ^{18}F-FDG dose remaining in the tubing between the two system. In the regard, we conducted this study to minimize the residual ^{18}F-FDG in the tubing.

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Materials and Methods

1. Materials

Cyclotron manufactured by GE Healthcare. Cyclotron energy is proton 16.5 MeV and duetron 8.4 MeV. ^{18}F-FDG synthesizer is Mx-module that installed six years ago. Synthesizer nitrogen pressure of 2 to 10 bar, compressed air of 6 to 10 bar. Dispenser is dispensing of ^{18}F-FDG into syringes via syringe dispenser manufactured by Comecer. Tubing used to connect our synthesizer and dispenser are made of Tefzel. Tubing outer diameter of 0.062 inch and inner diameter of 0.03 inch.

2. Methods

^{18}F has produced by cyclotron. The procedures consist of as follows: First, the negative ions come out of the ion source is accelerated up to 16.5 MeV by RF system. The electron is remained by the carbon foil of extraction system and only the positive ions are transferred to the target; Next, the beam is irradiation into the ^{18}O-water in the target. After a certain period of irradiation, the ^{18}O-water in which the nuclear reaction occurs passes through tubing to get into the synthesizer Tracerlab Mx-module.

Start of synthesis, QMA cartridge recovery of ^{18}O-water and ^{18}F-elution to reactor, dissolving of mannose triflate in acetonitrile and labeling with ^{18}F.

Trapping of TAcFG on tc18 cartridge and alkaline hydrolysis with NaOH on tc18 cartridge. Neutralization with buffering reagent and removal from tc18 cartridge. Tracer transfer and purification over tc18 and alumina cartridge on the way out. Lastly, rinsing and emptying of cassette. When the synthesis is completed, it is transferred to the dispenser along the tubing. At this time, a method to minimize the residual ^{18}F-FDG in the tubing is used.

The first method to transfer ^{18}F-FDG into the dispenser is operated automatically by the software program of the synthesizer and includes two system (Fig. 1).

Since this process is done in the Tracerlab Mx-module itself, there is no need for other operation for this process which

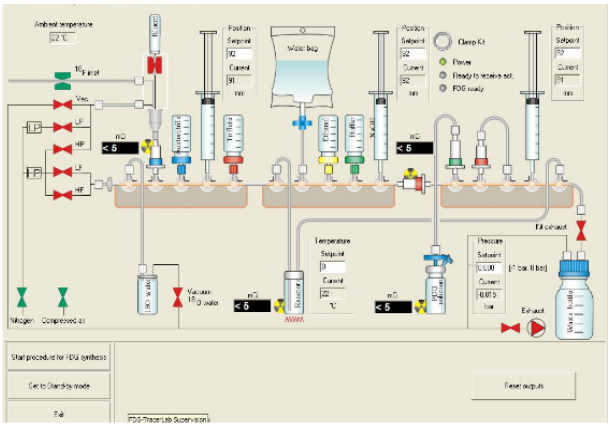

Fig. 1. FDG Tracerlab.

occurs automatically after the synthetic process is completed.

The second method is operated manually after the completion of the first method. In the middle of the synthesis, pressing the disable rinsing button is needed. Pressing the disable rinsing button will the rinsing is done in the cassette after the delivery process in the first method.

Since all processes are completed before the rinsing process, it is aimed to protect what is not supposed to be flown in from getting into the vial during the injection to the patient due to the rinsing when pushing the syringe. The second method consists of the following procedures; First, push down the right push syringe which in a vacuum stage; Next, open up the valve in the syringe and set up the set point at 90 to fill out the air into the syringe to transfer the ^{18}F-FDG remained in the tubing to the dispenser; After that, open up the purification sep-pak valve and change the set point in the right push syringe to 3 to push the air into the tubing. The reason to have it pass through the sep-pak is to protect the impurities in the cassette from being transferred into the vial in the dispenser. This procedures are repeated twice.

The third method is also operated after the first method. This method is similar to the second method, except that high flow nitrogen valve is open during this procedure. As in the second method, the disable rinsing button should be pressed during the synthetic process and the right push syringe which is in a vacuum stage should be also pushed down. Then, the high flow nitrogen valve should be opened. After these procedures, the other remaining procedures are same as in the second method.

After that, we performed quality control tests of ^{18}F-FDG to see whether the ^{18}F-FDG obtained using the third method is suitable for clinical use. First, we tested physical characteristics by looking at the clean and transparent liquid with bare eyes. For the test of pH, we dropped the sample onto a pH paper to check the color change. For the test of Radiochemical purity, we dropped the sample onto the silica-gel coated plate and soaked it into the solvent. After a certain period time has passed, we put it into the Radio-TLC detector and measured the radiolabelling efficiency. For the test of Radionuclidic purity, put the sample into gamma-detector and checked on the peak energy. For the test of residual kryptofix, observe a change in color by dropping standard solution kryptofix into TLC silica-gel plate saturated with iodoplatinate solution. For Residual solvents ran a check through Gas chromatography. For Endotoxin test, we put the sample into the LAL test reagent and measures the degree of solidification. Finally, test of Sterility test was referred to the department of clinical pathology.

Results

Using the first method ^{18}F-FDG yield was 42.22% based on the trapped radioactivity in QMA. Using the second method we obtained ^{18}F-FDG in 49.15% based on the trapped radioactivity in QMA and from the third method using the ^{18}F-FDG yield was 54.05% (Table 1, 2). Therefore, increase of ^{18}F-FDG yield 12.3% (Fig. 2).

Quality control tests showed that ^{18}F-FDG is suitable for clinical use no matter which transferring method is used ^{18}F-FDG is a clear and colorless liquid, and its pH is around 6.0 Radiochemical purity is higher than 98% based on TLC. Radionuclidic purity showed peak at 511 and 1022 keV. The residual kryptopix and residual solvents are less than the permissible limits. ^{18}F-FDG is endotoxin free and sterile, based on endotoxin test and sterility test.

Conclusion

The distance between ^{18}F-FDG synthesizer and dispenser

Table 1. Compare first method with second method

trapped in QMA(mCi)	pre-push(mCi)	pre-push Yield(%)	post-push(mCi)	post-push Yield(%)
3,824	1,610	42.1	1,916	50.1
1,691	711	42.0	829	49.0
3,692	1,544	41.8	1,802	48.8
3,831	1,610	42.0	1,889	49.3
3,604	1,571	43.5	1,824	50.6
3,637	1,566	43.0	1,855	51.0
1,419	577	40.6	700	49.3
1,700	700	41.1	816	48.0
3,187	1,377	43.2	1,549	48.6
3,198	1,355	42.3	1,532	47.9
3,175	1,389	43.7	1,575	49.6
1,513	589	38.9	746	49.3
1,839	792	43.0	916	49.8
2,032	901	44.3	990	48.7
1,401	598	42.6	702	50.1
1,750	732	41.8	886	50.6
3,026	1,285	42.4	1,492	49.3
1,163	478	41.1	590	50.7
2,046	899	43.9	1,017	49.7
2,001	871	43.5	1,003	50.1
2,298	964	41.9	1,170	50.9
2,099	896	42.6	1,056	50.3
1,271	511	40.2	641	50.4
1,223	503	41.1	624	51.0
1,956	845	43.2	955	48.8
average	994.96	42.27	1,163	49.67

Table 2. Compare first method with third method

trapped	in QMA(mci)	pre-push(mci)	pre-push Yield(%)	post-push(mci)	post-push Yield(%)
	1,301	570	43.8	733	56.3
	1,458	613	42.0	833	57.1
	1,392	588	42.2	742	53.3
	1,866	796	42.6	1,010	54.1
	1,628	705	43.3	868	53.3
	1,373	578	42.0	728	53.0
	1,764	720	40.8	960	54.4
	933	402	43.0	521	55.8
	686	270	39.3	378	55.1
	1,052	455	43.2	558	53.0
	1,044	426	40.8	567	54.3
	1,448	684	47.2	781	53.9
	2,100	847	40.3	1,134	54.0
	1,054	442	41.9	582	55.2
	1,361	611	44.8	761	55.9
	805	332	41.2	436	54.1
	810	368	45.4	449	55.4
	1,091	478	43.8	587	53.8
	1,622	677	41.7	881	54.3
	2,069	917	44.3	1,126	54.4
	831	339	40.7	460	55.3
	828	347	41.9	450	54.3
	2,227	902	40.5	1,225	55.0
	1,883	789	41.9	1,004	53.3
	average	577.33	42.48	740.58	54.52

should be short to recover maximum dose of ^{18}F-FDG. However, it is not always possible. In this case we would like to advise to use nitrogen gas along with syringe pushes to minimize the residual ^{18}F-FDG in the tubing between the two systems. Our results also showed that the quality of ^{18}F-FDG we synthesized using the third method is the same as those obtained using the other two method, indicating that ^{18}F-FDG is suitable for clinical use.

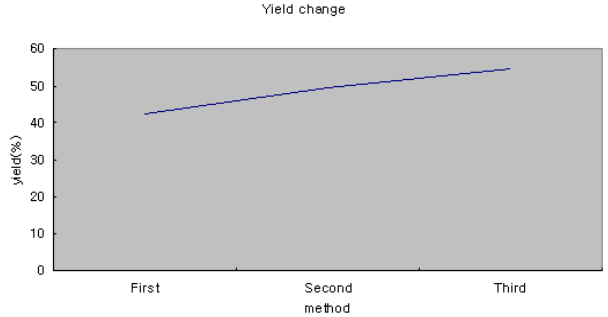

Fig. 2. Compare three methods to yield change.

요 약

^{18}F-FDG 자동합성장치에서 합성 후 자동분배장치까지는 자동모드로 delivery를 하게 되는데, delivery 후 자동분배장치에 있는 dose calibrator가 표시한 방사능으로 계산하여 수율이 계산되어진다. 그러나 자동합성장치와 자동분배장치의 거리가 증가하게 되면 튜빙에 ^{18}F-FDG 잔류량이 발생하게 되어 ^{18}F-FDG의 손실이 있다. 본 연구는 ^{18}F-FDG 잔류량을 최소화하기 위한 방법의 유용성에 관하여 알아보았다.

싸이클로트론에서 생산된 ^{18}F는 자동합성장치로 이동되고 자동합성장치에서 합성이 이루어지며, 합성 과정의 소요 시간은 25~26분이 소요된다. 그 후 dispenser로 ^{18}F-FDG를 delivery하고 자동합성장치 자체 rinsing으로 모든 과정이 끝마쳐진다. 자동합성장치와 자동분배장치 사이의 튜빙의 구성은 거리 8 m, 내경 1/16 inch로 되어 있다. 그러나 delivery 후 튜빙 거리 증가에 따라 ^{18}F-FDG 잔류량이 10-13%가 발생하게 되었다. 따라서 ^{18}F-FDG 잔류량을 최소화하기 위하여 첫

번째는 자동합성장치의 자동모드로 delivery, 두번째로 자동모드 delivery 후 push syringe 이용한 방법, 세번째로 자동모드 delivery후 push syringe와 질소가스를 병행한 방법을 시행하여 delivery 수율의 변화를 비교 분석하였다.

첫번째 방법에서 delivery 시에 QMA 기준으로 42.22%, 두번째 방법에서는 49.15%, 세번째 방법에서는 54.05%의 결과를 얻었다. Delivery 되어진 ^{18}F-FDG 의 품질관리평가상에서도 정상의 결과를 얻었다.

합성장치와 자동합성장치의 거리는 최대한 단축시켜 튜빙거리로 인한 ^{18}F-FDG 손실율을 낮추어야 한다. 그러나 시스템구조에 따라 자동합성장치와 자동분배장치의 거리가 증가되는 경우에 push syringe와 범용성 이동가스(질소 가스)를 병행하는 방법이 ^{18}F-FDG 잔류량을 최소화하는 방법으로 유용하다.

REFERENCES

1. 고창순 편저. 핵의학. 고려의학. 1991;55-62:63-67:77-79.
2. Mark S. Jacobson, Heather R. Dankwart, Douglas W. Mathony. Radiolysis of ^{18}F-FDG and the role of ethanol and radioactive concentration. ***Appl radiat Isot.*** 2009 Jun;67(6):990-995.
3. M. Asti, E. Grassi, R. Sghedoni, G. De Pietri, F. Fioroni, A. versari, G. borasi, D. Salvo. Purification by ozonolysis of ^{18}O enriched water after cyclotron and the utilization of the purified water for the production ^{18}F-FDG. ***Appl radiat Isot.*** 2007;Jul; 65(7):831-835.
4. S. M. Qaim. Use of cyclotron in medicine. ***Radiat phys chem*** 2004;Oct;71(3):917-926.
5. Ying Ma, Bill X. Huang, Michael A. Channing, William C. Eckelman. Quantification of kryptopix 2.2.2 in ^{18}F-FDG and other radiopharmaceuticals. ***Nucl Med Biol.*** 2002 Jan;29(1);125-129.
6. Michael A. Channing, Bill X. Huang, William C. Eckelman. Analysis of residual solvents in ^{18}F-FDG by GC. ***Nucl Med Biol.*** 2001May;28(4):469-471.
7. Bruce H. Mock, Wendy winkle, Michael T. Vavrek. A color spot test for the detection of kryptofix 2.2.2 in ^{18}F-FDG preparations. ***Nucl Med Biol.*** 1997 Feb;24(2):193-195.