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Technical Aspects and Administration Methods of Lutetium177 Lu Dotatate for Nuclear Medicine Technologists

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Disclaimer:

This article discusses different methods for Lu-177 dotatate Lutathera infusion. Nuclear Medicine professionals should choose the method that suits their departments needs in accordance with their respective institution's regulations and radiation safety standards. The protocol and drug referred to in this article has not been tested by Moog Medical, and Moog Medical did not contribute financially to the development of this protocol. No other potential conflicts of interest relevant to this article exist.

Abstract:

At Banner MD Anderson Cancer Center in Arizona, we gained valuable knowledge of the different infusion methods for 177 Lu-DOT-AO-Tyr3-Octreotate (Lutetium Lu-177 dotatate, Lutathera, PRRT). Our nuclear medicine department utilized two different methods of administration called the gravity infusion method and the infusion pump protocol. The experience we had with these methods allowed us to identify aspects of the gravity infusion method that were problematic which lead us to search for and implement the infusion pump protocol. The pump protocol ensured that the infusion process of administering Lu-177 dotatate was a safe and consistent dose delivery for every patient.

Keywords:

Lutathera, Neuroendocrine Cancer, PRRT, Pump Protocol, Gastroenteropancreatic Neuroendocrine Tumor

Introduction:

The NETTER-1 Clinical Trial#NCT01578239, AAA-177LU-103, Expanded Access Protocol (EAP) for therapeutic use of 177 Lu-DOT-Ao-Tyr3-Octreotate was established in Arizona during the year 2017 (3). Our center was the first in Arizona to administer the somatostatin analogue therapy, Lu -177 dotatate, to patients with inoperable, somatostatin receptor positive, gastroenteropancreatic (GEP-NET) neuroendocrine tumors of the foregut, midgut, and hindgut (2).

On October 2017, the first Arizona patient was treated with PRRT (peptide receptor radionuclide therapy) and, to date, we have treated twelve patients. On January 26, 2018, the Federal Drug Administration (FDA) approved Lutetium Lu-177 dotatate (Lutathera, Advanced Accelerator Applications USA, Inc.) (1). GEP-NET patients are traveling great distances to receive this now commercially available drug. The aim of this article is to describe our facility's experience with the SOP (standard of procedure) recommended gravity infusion method and our experience with the infusion pump protocol.

NETTER-1 Clinical Trial Exerience:

Twelve EAP patients were treated with Lu-177 dotatate (7.4GBq/200mCi +/-20%) and three of the twelve patients had their treatment discontinued due to toxicity (3). The remaining nine patients received a total of four Lu-177 dotatate infusions. There was an interval of eight weeks between each administration with a +1-week extension for those experiencing toxicity that resolved (3). Two methods of administration were utilized between 2017 and 2018 for delivery of Lu-177 dotatate into patients enrolled in the EAP clinical trial at our facility. These methods include: the gravity infusion method and the infusion pump protocol. In this paper we will discuss the methods used, the difficulties faced, and the current protocol created with the collaboration of fellow technologists at other facilities.

Recommended Gravity Infusion Method:

The first method of administration, derived from the NETTER-1 clinical study investigator's brochure, is the gravity infusion method (3). The Expanded Access Protocol for therapeutic use of Lu-177 Dotatate utilizes the gravity infusion method as the SOP to administer the liquid therapy agent. The premise of this method suggests that the flow of saline into the Lu-177 dotatate vial induces pressure, which in turn, pushes the radiopharmaceutical out of the vial and into the intravenous catheter of the patient. The gravity infusion method calls for an infusion pole, a 250 mL 9mg/mL NaCl saline solution bag, a long needle (90-100mm), a short needle (3cm, 18G) gravity IV infusion sets, and a pair of forceps (3). The Lu-177 dotatate vial is encased in a lead pig. A 250mL saline bag is hung and the tubing is connected to the short needle (3). The short needle is punctured into the Lu-177 dotatate vial at an angle with the needle tip sitting in the air pocket located at the top of the Lutathera vial (3). The short needle is used for the saline drip into the vial (3). Next, the long needle is attached to the intravenous catheter tubing and punctured into the Lu-177 dotatate vial at an angle with the needle tip sitting at the bottom of the vial and inside of the radiopharmaceutical liquid (3). The long needle is used to transfer the Lu-177 dose into the patient (3). Once the flow of saline begins, the radiopharmaceutical is pushed into the intravenous catheter of the patient (3). The flow of saline is controlled by a pump at a rate of 50-100mL/hour for 10minutes and then increased to 200-300mL/hour for an additional 30 minutes (3).

Challenges of the Gravity Infusion Method:

There were several challenges with this method. First, it was very difficult to assess how much of the radiopharmaceutical was administered over time. The infusion amount of dose over time was important to our facility because there were occasions in which our radiologist chose to infuse only a portion of the 200mCi dose to the patient due abnormal bloodwork/toxicity. In theory, the amount of saline administered should be directly related to the amount of radiopharmaceutical administered. However, in our experience, this was not the case. The amount of time it took to administer the dose varied significantly each time despite using the same rate and volume of saline flow for every infusion. The second difficulty of the gravity infusion method was loss of air pressure in the vial during four of the thirty-seven drug administrations. We found that the loss of air pressure could be avoided by stabilizing the needles and puncturing the vial at the outer/thicker portion of the septum. This adjusted technique ensures that the puncture holes of the vial do not get enlarged during infusion which can cause loss of air pressure. Loss of air pressure, in turn, can result in loss of air pocket. A loss of air pocket can cause the radiopharmaceutical to bubble out of the top of the vial and slow or stop the infusion. To remedy the loss of air pressure, we needed to infuse 5mL of air into the saline line which would recreate an air pocket in the vial. The constant monitoring of the vial due to the chance of losing the air pocket was also causing unnecessary exposure to the technologist. During one infusion, the loss of air pressure disabled us from infusing the dose. In this instance, the only alternative was to draw up and hand inject the remaining dose. The hand injection rescue method caused additional exposure to the physician as well as the surrounding personnel even when shielded.

Possible Solutions to the Challenges of the Gravity Infusion Method:

We corrected the issues of the gravity infusion method by placing the Lu-177 dotatate vial (with lead pig) into an acrylic box to prevent contamination exposure in case we had an instance where the radiopharmaceutical bubbled outside the top of the vial. We also placed a digital pocket dosimeter on top of the acrylic box to measure mR/hr and found that the reading was directly related to the mCi administered (as the PRRT decreased in the vial, the mR/hr reading decreased). Once these issues were resolved, we

found that this method was feasible but still increased exposure to the technologist having to closely monitor the vial throughout the duration of the infusion. The gravity infusion method was also difficult to reproduce successfully when attempted by all technologists.

The many challenges of the gravity infusion method and the high radiation exposure to the physician needing to hand inject the dose after a failed infusion, lead us to search for a more reliable method. Knowing this drug would soon be FDA approved and the demand for Lutetium Lu-177 Dotatate would increase, we decided to search for a more reliable method of infusion. For this reason we have found and successfully implemented the infusion pump protocol method at our facility. This protocol has proven to be very reliable and efficient, causing less exposure to all involved. It is a consistent method of liquid dose infusion with low possibility for contamination or error.

Alternate Method of Administration-Infusion Pump Protocol:

The infusion pump protocol method requires the use of any commercially available infusion pump, a male to male adaptor, a three way stop-cock, infusion pump tubing, an 18-gauge (3 ½ in) spinal needle, a micron filter, an 18-gauge (1 ½ inch vent needle), forceps, and a 10mL saline vial. The logic behind the infusion pump protocol method is very simple. The infusion pump pulls the liquid therapy out of the vial via 18-gauge spinal needle and infuses it into the patient. First, the Lu-177 dotatate vial is ventilated with a micron filter. Then, the infusion pump tubing is primed and inserted into the pump. The liquid therapy is infused at a rate of .8mL/min for a total of 30minutes. At the end of infusion, 10 mL of saline is injected into the Lu-177 dotatate vial through the micron filter and the pump is set to an infusion rate of 2mL/min for 5minutes total. The five-minute saline infusion is used to rinse the vial of any residual dose.

Challenges to the Infusion Pump Protocol:

The recommended SOP for Lu-177 administration requires the dose to be diluted with 250 mL NaCL saline solution throughout a thirty-minute infusion. This was the first major challenge of the infusion pump protocol. The NaCL dilution recommendation was not possible with the infusion pump protocol we developed. For this reason, we needed approval from our radiologist and physicians to alter the SOP and remove the need for saline dilution during infusion of the liquid therapy. Another minor

hurdle of this method is the need to allot extra time for set-up of the equipment prior to administration. Equipment set-up typically takes an additional ten-minutes. The final challenge of this method was the extra cost of an infusion pump. However, the need for a more efficient, reliable, and predictable method of administering Lu-177 dotatate justified the cost of purchasing the equipment. The decreased chance of contamination and radiation exposure to staff alone made the purchase worthwhile.

Discussion:

We have experienced great success with the infusion pump protocol, but believe this method needs further rigorous testing. Because there is a rise in demand for liquid nuclear therapies, we believe there is a worldwide necessity for proven standardized methods of administration.

Conclusion:

While the gravity infusion method is cost effective, we identified some challenges that increased the possibility for error, contamination, and excessive radiation exposure. Consequently, we developed the infusion pump protocol method. Our facility currently utilizes the Curlin pump manufactured by MOOG, however, this method can be done with any commercially available infusion pump. This new method also reduces error, the possibility of contamination, and most importantly radiation exposure. Our facility has utilized this method for six months and we have not experienced any of the contamination or leakage issues that we encountered with the gravity infusion method. It has proven to be beneficial to our patients and department staff and provides a safe and consistent dose delivery to our patients. The benefits of this method far outweigh the additional expense of purchasing an infusion pump.

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Figure 1:

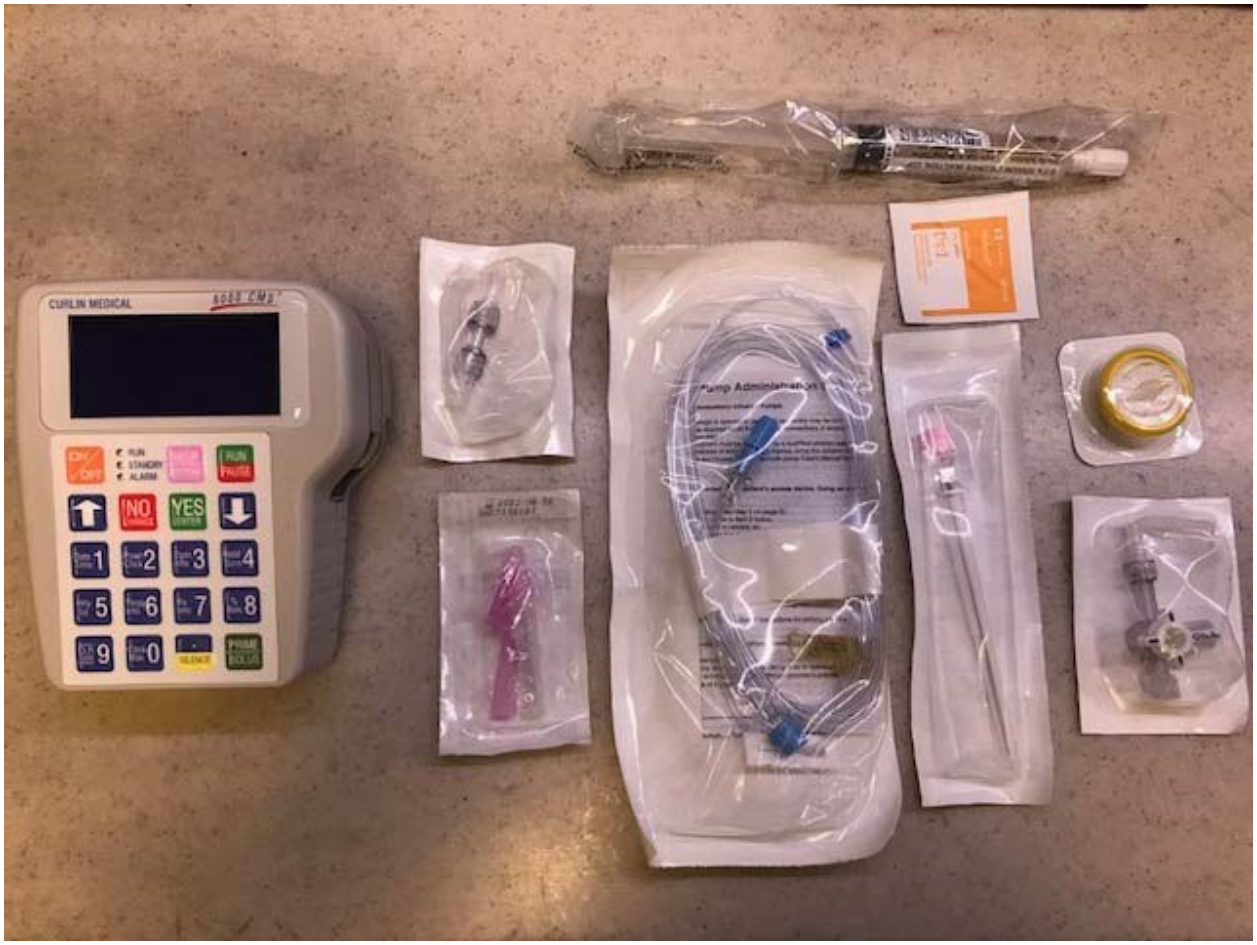

Figure 1: Materials for Pump Protocol. The Moog pump is shown on the left and the injection supplies on the right.

Figure 2:

Figure 2: Lutathera Patient Set-up using Pump Protocol

Figure 3:

Figure 3: Room Set-up for Pump Protocol

Figure 4:

Figure 4: Vent needle set up