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Temperature impact on [^{68}Ga]Ga-edotreotide for the shipping of radioactive material in shielded container

<https://doi.org/10.1515/ptph-2020-0007>

Received May 25, 2020; accepted July 22, 2020; published online August 17, 2020

Abstract

Introduction: To reduce costs of gallium-68 activity in nuclear medicine, a subcontracting activity has been settled for [^{68}Ga]Ga-edotreotide preparations. Cold kits are radiolabeled in our radiopharmacy and shipped out to nearby hospitals. According to the Summary of Product Characteristics (SmPC), preparations must be stored below 25 °C until expiration (4 h).

Objective: The aim of this study was to define the impact of high temperature on preparation quality during shipping.

Materials & methods: After radiolabeling, vials were placed in “type A” package until their expiry date. Four kits were stored in “Type A” container exposed to an outside temperature of 50 °C to represent extreme temperature conditions and one kit was kept at room temperature and used as a control. For each preparation, pH, organoleptic properties and radiochemical purity (RCP) were evaluated. RCP was measured using two radio thin layer chromatography, to evaluate the rates of gallium-68 colloids and free gallium-68. Samples were withdrawn at the end of preparation (t_0), at $t_0 + 1$ h or at $t_0 + 2$ h and at $t_0 + 4$ h.

Results: RCPs and pH of the radiopharmaceutical were all conform from t_0 to $t_0 + 4$ h. Four hours storage in “type A” package at 50 °C does not show any impact on physical and chemical quality of the preparation. Thanks to it expanded

polyethylene foam which absorbs impacts; “Type A” package might acts as thermal barrier and enables the temperature regulation of shipped vials.

Conclusion: A monitored expedition in temperature-controlled vehicle does not seem necessary in those conditions.

Keywords: gallium-68; radiopharmaceutical; shipment; stability study.

Introduction

In nuclear medicine, the radionuclide gallium-68 was introduced in 2009 to radiolabelled Positron Emission Tomography (PET) radiopharmaceuticals. The development of generator for the production of gallium-68 and the commercialization of labeling kits has increased the use of gallium-68 in nuclear medicine departments. However, the availability of gallium-68 is often restricted in France by the cost of germanium-68/gallium-68 generators and the equipment investment required for this activity [1].

To optimize production costs, a subcontracting activity of gallium-68 radiolabeled preparations has been settled in our radiopharmacy unit since October 2019. Cold kits are radiolabeled at the radiopharmacy of Institut Curie Saint Cloud site and shipped out to three nearby hospitals in Ile de France. Currently, those hospitals are less than one-hour drive from our institute. The first radiopharmaceutical prepared for this subcontracting activity is [^{68}Ga]Ga-edotreotide which is a somatostatin analog used in adult patients who are thought to have so-called well-differentiated gastro-entero-pancreatic neuroendocrine tumors [2]. The Summary of Product Characteristics (SmPC) of [^{68}Ga]Ga-edotreotide recommends storage up to 4 h below 25 °C after preparation. Being considered as the supplier of the preparation and to ensure radiopharmaceuticals quality during the expedition, a stability study was requested by the local French Health Authority (“Agence Régionale de Santé” (ARS)) of Ile de France as part of the subcontracting authorization [3, 4].

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The purpose of this study was to define the impact of high temperature (50 °C) during shipping on the quality of [^{68}Ga]Ga-edotreotide preparations stored into typical “Type A” packages (UN 2915).

Materials and methods

Materials

According to the “European agreement concerning the International Carriage of Dangerous Goods by Road” (ADR) [5, 6], radioactive material must be shipped in typical “Type A” packaging. Cases (model A33M-CWM®) were provided by Vortal (Seneffe, Belgium). These cases are composed by one wrapping made of plywood with steel corner and edge and polyethylene foam (Figure 1A, B), and one protection container made of stainless steel with inner core of lead (Figure 1C).

For the study, Heratherm™ oven OGH60-S provided by Thermo Fischer Scientific (Illkirch, France), with an external temperature sensor Digital Thermometer GTH 175/Pt provided by Greisinger Electronic (Remscheid, Germany) was used to subject cases to high temperature.

The radiopharmaceutical kits of edotreotide (SomaKit TOC®) were provided by Advanced Accelerator Applications a Novartis Company (Saint-Genis-Pouilly, France) and were radiolabeled with gallium-68 obtained from GalliaD® germanium-68/gallium-68 generator provided by IRE ELiT (Fleurus, Belgium). The activity was measured using a CRC®25R dose calibrator provided by Mirion Technologies – Capintec (Florham Park, New Jersey, USA).

For quality control, chemicals and solvents were obtained from Sigma-Aldrich (Saint Quentin Fallavier, France). Radio-thin layer chromatography (r-TLC) scanner Scan-RAM™ was provided by Lablogic ScienceTec (Villebon-sur-Yvette, France). Supports were instant thin layer chromatography paper impregnated with a silica gel (iTLC-SG) provided by Agilent (Les Ulis, France) and thin layer

chromatography silica gel 60 (TLC-SG) provided by Merck Millipore (Guyancourt, France). To estimate the preparation pH, paper pH provided by Macherey–Nage was used.

Dose calibrator and thin layer chromatographic system described previously were initially qualified and periodically re-qualified.

Methods

Temperature evaluation in “Type A” case: First, to evaluate the capacity of our containers to preserve the inner temperature, a vial of water was placed into a “Type A” case. This case was stored into an oven at 50 °C. Using a calibrated probe, the temperature inside the vial of water was measured before, during and at 4 h.

Radiolabeling and conservation: Kit was radiolabeled according to the SmPC and Good Practices for the Preparation of Medicinal Products in Healthcare Establishments [7]. When using GalliaD® generator, the first step of the radiolabeling process is the reconstitution of the radiopharmaceutical vial powder with water and the addition of buffer into the vial. After, the generator is directly eluted into the vial through a 0.2 μm sterile vent filter. Then, a heating step of the vial into a dry bath at 95 °C during 7–10 min is needed. After the heating step, the vial cools down at room temperature for approximately 10 min.

Then, for the study the vial was placed in “Type A” case until its expiry date, 4 h after the end of the preparation. Four preparations in “Type A” cases were exposed to an external temperature of 50 °C to represent extreme expedition conditions. One preparation was kept at room temperature (<25 °C) and used as a control [8].

Quality control: For each preparation, a sample was withdrawn at the end of preparation (t_0). Two other samples were withdrawn either at $t_0 + 1$ h or at $t_0 + 2$ h, then a final sample was taken for all preparations at $t_0 + 4$ h.

For each preparation, pH, organoleptic properties and radiochemical purity (RCP) were evaluated. According to the SmPC, pH must be between 3.2 and 3.8. RCP was controlled using two r-TLCs according to the SmPC. The first one was used to evaluate the rate of

Figure 1: “Type A” case – wrapping (A, B) and protection container (C).

free gallium-68. The support was a silica gel 60 layer (1.5 × 8 cm) eluted with citrate buffer 0.1 M, pH 5.0 as mobile phase. The second one was used to evaluate the rate of gallium-68 colloids. The support was an iTLC-SG (1.5 × 12 cm) eluted with ammonium acetate 1 M in water/methanol 50:50 v/v as mobile phase. Migrations last about 15–20 min.

According to the SmPC, free gallium-68 rate should be ≤2.0% and gallium-68 colloids rate should be ≤3.0% so that the RCP of [⁶⁸Ga]Ga-edotreotide should be ≥95.0%.

Results and discussion

When measuring the temperature in a vial of water placed in a “Type A” case stored at 50 °C, we observed that the vial at room temperature (22.6 °C) did not exceed 25 °C before at

least 2 h. After 2 hours and a half, the vial temperature was about 25.9 °C. The maximum temperature observed was 29.9 °C after 4 h.

Radiopharmaceutical vials are placed in shielded container for radioprotection restrictions. These containers are introduced in “Type A” cases which are composed by expanded polyethylene foam to absorb impacts. This foam also acts as thermal barrier. Therefore, the internal temperature of the package gradually rises even if it subjected to high temperature. Having made this general observation, we began tests on real radiopharmaceutical preparations.

According to the stability of [⁶⁸Ga]Ga-edotreotide, the study was performed until product expires. The preparations activity ranged from 679 to 1100 MBq. During this study, RCPs of the radiopharmaceutical were all over 95.0%

Figure 2: RCP evolution over time of five preparations of [⁶⁸Ga]Ga-edotreotide stored at 50 °C in “type A” package.

Table 1: RCP and pH values of four preparations of [⁶⁸Ga]Ga-edotreotide stored at 50 °C storage in “type A” package.

		Control	1	2	3	4	Mean (%)	Standard deviation (%)
Conservation temperature		25 °C	50 °C					
t ₀	RCP (%)	97.59	96.72	99.39	99.44	98.92	98.41	1.21
	⁶⁸ Ga colloids (%)	1.45	2.54	0.1	0.36	0.43	0.98	1.01
	Free ⁶⁸ Ga (%)	0.96	0.74	0.51	0.2	0.65	0.61	0.28
	pH	3.5	3.5	3.5	3.5	3.5	–	–
t ₀ + 1 h	RCP (%)				98.97	97.91	98.44	0.75
	⁶⁸ Ga colloids (%)				0.7	1.02	0.86	0.23
	Free ⁶⁸ Ga (%)				0.33	1.07	0.70	0.52
	pH				3.5	3.5	–	–
t ₀ + 2 h	RCP (%)	97.04	95.93	96.62			96.53	0.56
	⁶⁸ Ga colloids (%)	1.85	2.92	1.41			2.06	0.78
	Free ⁶⁸ Ga (%)	1.11	1.15	1.97			1.41	0.49
	pH	3.5	3.5	3.5			–	–
t ₀ + 4 h	RCP (%)	96.78	96.02	96.7	98.82	98.14	97.29	1.15
	⁶⁸ Ga colloids (%)	2.02	2.75	1.34	0.35	0.67	1.43	0.98
	Free ⁶⁸ Ga (%)	1.2	1.23	1.96	0.83	1.19	1.28	0.41
	pH	3.5	3.5	3.5	3.5	3.5	–	–

from t_0 to $t_0 + 4$ h. Figure 2 shows the RCP evolution over time of four preparations of [⁶⁸Ga]Ga-edotreotide stored at 50 °C in “type A” package. For all preparations, a slight decrease of less than 2.8% of RCP was observed at $t_0 + 1$ h or $t_0 + 2$ h and then the RCP remained stable until $t_0 + 4$ h.

For the four preparations, pH remained between 3.2 and 3.8 as well as the control (Table 1). All these preparations were compliant with the specifications of the SmPC, even 4 h at 50 °C.

It should be noted that according to the radio-labeling process which includes a heating step at 95 °C, the [⁶⁸Ga]Ga-edotreotide preparation seems to be stable even after high temperature exposition. Moreover, it has been proved that the [⁶⁸Ga]Ga-edotreotide is stable at 37 °C in human serum up to 4 h [2]. Nevertheless, as the subcontracting activity places us as the supplier, we are in charge of maintaining the pharmaceutical quality during shipment.

In addition, with the growing of this activity and the arrival of a second generator, we expect to send radio-labeled preparations to other customers which could be close to 2 hours’ drive from our hospital. Thus, we needed to know if temperature-controlled transport was necessary.

Lastly, as a sterile preparation for IV infusion, this radiopharmaceutical is produced in class A shield hood to prevent microbiological contamination. The short half-life of gallium-68 (68 min) conducts to a short shelf life of [⁶⁸Ga]Ga-edotreotide preparation. As a consequence, even if the storage conditions are compatible with a microbial breeding during expedition, this risk is considered as negligible due to this short shelf life. Thus, we decided to focus on the physical and chemical quality of the final product.

Conclusion

To conclude, “Type A” cases enable the regulation of temperature of shipped vials. Even if the external temperature is up to 50 °C, inside the case, vials are stored up to 2 h at a temperature below 25 °C thanks to the foam.

Moreover, 4 h storage at 50 °C of the “Type A” package does not show any impact on physical and chemical

quality of the preparation. It does not seem necessary to set a monitored expedition in temperature-controlled vehicle for [⁶⁸Ga]Ga-edotreotide preparation or for any other radiopharmaceuticals stored at temperature below 25 °C, especially when shipping time is less than 2 h.

Research funding: None declared.

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: Authors state no conflict of interest.

Informed consent: Informed consent was obtained from all individuals included in this study.

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