ORIGINAL ARTICLES

Aspects on radiolabeling of 177Lu-DOTA-TATE: After C18 purification re-addition of ascorbic acid is required to maintain radiochemical purity

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Abstract

Purpose: Radiolabeled peptides like 177Lu-DOTA-TATE are vulnerable to radiolysis, which results in decreased radiochemical purity (RCP) of these radiopeptides. Gentisic acid (GA) and ascorbic acid (AA) are well known ingredients to reduce the effects of radiolysis. Currently, there is a trend to change the procedure from a manual to a cassette-based automated labeling and to introduce a C18 solid phase extraction (SPE) post-radiolabeling in order to remove non-incorporated 177Lu from the injection solution. However, with the introduction of SPE purification, GA and AA might effectively be removed from injection solution with a concordant dramatically drop of the RCP. Therefore we investigated the impact of tC18 SPE purification on the RCP of 177Lu-DOTA-TATE.

Methods: We compared the manual radiolabeling procedure with the cassette-based automated radiolabeling procedure with/out tC18 SPE purification cartridge. The effect of tC18 purification on RCP of 177Lu-DOTA-TATE was investigated by HPLC as function of the post-radiolabeling time and the concentration of activity.

Results: After tC18 SPE purification, GA and AA were effectively removed and resulted in volume-dependent decrease in RCP, e.g. <95% after 5h in 20 mL. Re-addition of AA directly after tC18 SPE purification resulted in a RCP ≥95% at 72h. In addition, with the cassette-based automated radiolabeling procedure we also found 28% of the original activity remaining in the activity-containing vial and tubing vs. < 1% with the manual procedure.

Conclusion: Re-addition of AA post tC18 SPE purification is required to maintain RCP of 177Lu-DOTA-TATE.

Keywords

Lutetium-177, 177Lu-DOTA-TATE, Cassette-based, Automated radiolabeling, Radiochemical purity, Ascorbic acid, Quencher, Gentisic acid, Radiolysis

1 Introduction

Radiolabeled somatostatin analogues, such as [DOTA0,Tyr3]octreotate, further referred as DOTA-TATE have been subject of intensive research during the last 2 decades and play an important role in somatostatin receptor imaging and peptide receptor-targeted radionuclide therapy (PRRT) e.g. 177Lu-DOTA-TATE[1-7].

RCP of 177Lu-DOTA-TATE is an essential factor for successful PRRT. Because of the high doses of 177Lu-DOTA-TATE (7.4 GBq 177Lu per PRRT administration), the peptide is subject to radiolysis. The degree of radiolysis is influenced by several factors like the amount of DOTA-TATE, temperature, time, the total activity, the volumic activity, quencher(s) et cetera [8-12].

In the current publication we present a comparative study to investigate the effect of gentisic acid (GA) and ascorbic acid (AA) as quenchers during and after (manual and cassette-based automated) the radiolabeling 177Lu-DOTA-TATE procedures.

There is currently a trend to move from manual radiolabeling to a cassette-based automated radiolabeling procedure; therefore we investigated these two different procedures in parallel. Sep-Pak Light tC18 SPE purification (further referred as tC18) is included as default in the cassette-based automated procedure. However, the tC18 purification of the reaction mixture after radiolabeling potentially removes GA and/or AA effectively. The aim of this study was to compare radiolabeling procedures (manual vs. cassette-based automated) with and without tC18 purification and to investigate the impact on the RCP of 177Lu-DOTA-TATE as function of time until the moment of administration to patient.

Materials and chemicals

Reagents and solvents were used in the highest quality grade without further purification.

GA and water for trace analyses (Trace-SELECT®) were purchased from Sigma-Aldrich Chemie GmbH (Taufkirchen, Germany). Hydrochloric acid 30% (HCl) Ultrapur was obtained from Merck KGaA (Darmstadt, Germany). AA was purchased from WÖRWAG Pharma GmbH & Co. KG (Böblingen, Germany). DOTA-TATE as kit formulation [13] was provided by Erasmus MC Rotterdam (Rotterdam, The Netherlands). Ethanol (99.5%), Aqua ad iniectabilia and isotonic 0.9% NaCl (further referred as saline) were purchased from B.Braun Melsungen AG (Melsungen, Germany). tC18 cartridges were obtained from Waters GmbH (Eschborn, Germany). 177LuCl3 with specific activities in the range 740-1000 GBq/mg was bought from IDB-Holland (Baarle Nassau, the Netherlands).

2 General methods

The manual radiolabeling procedure was performed in a temperature-controlled heating block from CardiRad (Lohja, Finland) and cassette-based automated radiolabeling procedure was performed in a Modular-Lab Pharm Tracer module (EZAG, Berlin, Germany) using the C4-Y90-00-standard synthesis and C1-PR-00 pressure test cassette (EZAG, Berlin, Germany).

2.1 Cassette-based automated radiolabeling procedure

The cassette was prepared according to the Y-Lu-INCASSETTE-TEST protocol (EZAG, Berlin, Germany). For standard patient radiolabeling, 240 µg DOTA-TATE in 0.6 mL (400 µg/mL) of the DOTA-TATE kit formulation [13] was transferred automatically and quantitatively in to a glass reaction vial (RV) and eventually 7.5 GBq 177LuCl3 (0.3 mL) was added in to RV. Subsequent program steps are consecutively executed and the radiolabeling was running automatically according to the LU-177-DOTA-PEPTIDES-PT-V.X.X protocol (according EZAG). RV was heated for 30 min at 80°C. After 5 min cooling to ambient temperature the reaction mixture was transferred from the RV to the preconditioned tC18 cartridge. Pre-conditioning of the tC18 cartridge was performed with an ethanol/water mixture (5 mL, 50:50% v/v). This tC18 procedure was introduced in order to remove non-incorporated 177Lu from the final product. The content of RV was transferred to the tC18 cartridge and rinsed with 3 mL saline. 177Lu-DOTA-TATE was desorbed from the tC18 cartridge with 2.5 mL of ethanol/water (50:50% v/v). An aliquot of the final mixture was taken and subjected to quality control by ITLC and HPLC. The eluate plus 17.5 mL saline solution (final volume 20 mL) were

filtered with means of a sterile Millex-GV 0.22 µm filter into a 25 mL glass vial (product vial or PV). Finally, a filter integrity test was performed. The cassette-based automated radiolabeling procedure process takes about 60 min.

2.2 Manual radiolabeling procedure

The manual radiolabeling procedure was performed directly in the activity-containing vial (AV), containing 7.5 GBq 177LuCl3 in 0.3 mL. For standart patient radiolabeling 0.6 mL (240 µg DOTA-Tate) of the DOTA-TATE kit formulation [13] was added to the AV, and incubated for 30 min at 80 °C [13]. After cooling down to ambient temperature non-incorporated 177Lu was complexed by the addition of 0.25 mL DTPA-solution (4 mg/mL) to the reaction mixture [14-15]. An aliquot of the reaction mixture was taken and quality control was performed using ITLC and HPLC. The residual was diluted with 5 mL saline solution, filtered with means of a sterile Millex-GV 0.22 µm filter into PV and finally adjusted to a final volume of 20 mL. The manual radiolabeling procedure takes about 40 min.

3 Studies on RCP of 177Lu-DOTA-TATE

RCP is defined as the % of the activity of the radionuclide present in the desired radiopharmaceutical form of the total radioactivity. RCP of 177Lu-DOTA-TATE was investigated with/out tC18 purification and re-addition of quenchers as shown in experiments 1-4, see Table 1. In order to investigate the dilution of the quenchers two additional radiolabeling were performed (experiment 5-6, see Table 1). One radiolabeling included tC18 purification (experiment 5, see Table 1), while another radiolabeling (experiment 6) was performed without the tC18 purification. Both samples were diluted with saline up to a final volume of 20 mL, at constant concentration of ~ 0.5 GBq/mL. In addition, experiment 7 was performed without tC18 purification post radiolabeling and was diluted to a patient dose (7.4 GBq in 100 mL). RCP was determined by HPLC, as described below.

Table 1. Different post radiolabeling procedures of 177Lu-DOTATATE

Experiment	1	2	3	4	5	6	7
tC_{18} purification	-	+	+	+	-	+	-
Ethanol/H_2O 50/50% (2.5 mL)	-	+	+	+	-	+	-
Re-addition AA or GA (100 mmol/L)	-	-	AA	GA	-	-	-
Final volume (mL)	5	5	5	5	20	20	100
Total activity (GBq)	2.5	2.5	2.5	2.5	10	10	7.4
0.5 GBq/mL	+	+	+	+	+	+	-

Labelings were performed using 7.5 GBq of 177LuCl3 (0.3 mL) and 0.6 mL of kit Erasmus MC matrix. Thereafter post radiolabeling procedures were performed either with/out tC18 purification, re-addition of AA or GA, and diluted in different final volumes (5, 20 and 100 mL) with saline. RCP of 177Lu-DOTA-TATE was monitored as function of time

4 Analytical methods

4.1 Incorporation by ITLC

ITLC-SG glass fibre sheets were purchased from PALL Life Sciences (Port Washington, NY, USA). Small portions (1-3 µL) were added on the ITLC-SG strips and sodium citrate buffer (0.1 M, pH 5) was used as mobile phase as described [14, 16]. Activity was recorded by Gina Star TLC and analyzed using Raytest miniGita software (Straubenhardt, Germany). Calculation of incorporation was performed as described [16].

4.2 HPLC

HPLC methods were performed using a Dionex-3000 HPLC system with a variable wavelength Dionex GmbH detector (Idstein, Germany) containing a Waters 4.6 mm × 250 mm, 5µm Symmetry C18 column (Eschborn, Germany) . The gradient elution system utilized mobile phase A (methanol) and mobile phase B (0.06 M sodium acetate buffer, pH 5.5). Gradient was performed with a flow rate of 1 mL/min starting with 100 % B for 6.5 min; and was changed to 50% A and 50% B within 0.5 min and increased to 60% A over 20 min.

Thereafter, the mobile phase A was increased within 0.2 min to 100 % and was kept constant for 4.8 min. Finally, the gradient parameters returned to the initial starting conditions. The data were analyzed using Chromeleon Client Software Version 6.8.9. from Dionex GmbH (Idstein, Germany).

5 Results

5.1 Radiochemical yield

With the cassette-based automated radiolabeling procedure we obtained radiochemical yields of 71 ± 18 % (n=12). The manual labeling achieved radiochemical yields ≥ 99% (n=3), independent of activity (range 2.5-10 GBq) or final volume (range 5-20 mL).

5.2 Radiolabeling without tC18 Purification

RCP of 177Lu-DOTA-TATE was measured by HPLC up to 168 h post-radiolabeling. Fig. 1A shows a typical HPLC radiochromatogram of 177Lu-DOTA-TATE which was prepared as described [13]. Fig. 1B shows the HPLC radiochromatogram of 177Lu-DOTA-TATE in the absence of quenchers. Fig. 2A clearly demonstrates that 177Lu-DOTA-TATE without the tC18 purification post-radiolabeling remained stable (RCP ≥95% at 72h post radiolabeling, experiment 1 and 2, see Table 1).

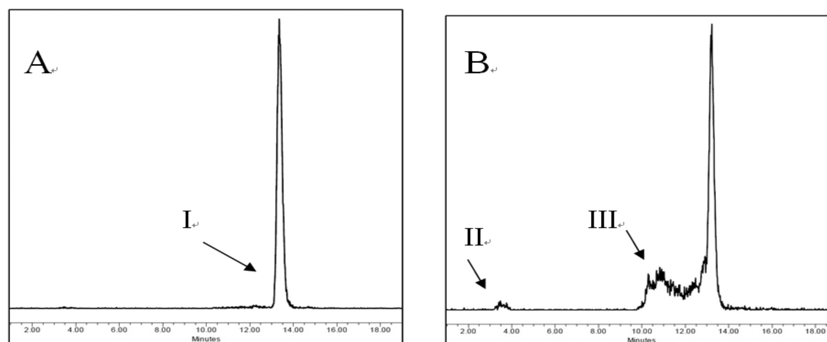

Figure 1. Typical RP-HPLC radiochromatogram of 177Lu-DOTA-TATE
(A) with a RCP of >95% and ^{177}Lu-DOTA-TATE (B) with a RCP <95%. Peaks (I): ^{177}Lu-DOTA-TATE, (II):^{177}Lu-DTPA and ^{177}Lu and (III): radiolysed fragments of ^{177}Lu-DOTA-TATE. These fragments were not further characterised. X-axes are expressed in time (min) and Y-axes in mV.

After increasing the volume up to 20 mL at constant volume activity (experiments 5, Table 1), 177Lu-DOTA-TATE remained stable (RCP ≥95% ~ 24h post-radiolabeling) as shown in Fig. 2B, while the RCP of 177Lu-DOTA-TATE in a patient dose (7.4 GBq/100 mL) rapidly decreased below 95% within 12 h (Fig 2C, experiment 7, see Table 1).

5.3 Radiolabeling with tC_{18} purification

tC18 purification of reaction mixture containing 177Lu-DOTA-TATE totally removed both AA and GA (>99%), as confirmed by HPLC (data not shown). The tC18 purified fraction without re-addition of quencher in total volume of 5 mL resulted in a 95% RCP after ~ 35h and 92% at 72h post radiolabeling (Fig. 2A, experiment 2, see Table 1). While RCP of 177Lu-DOTA-TATE in 20 mL final volume decreased much more rapidly and resulted in a RCP of < 95% after ~5h and 74% at 24h post radiolabeling (Fig. 2B, experiment 6, see Table 1).

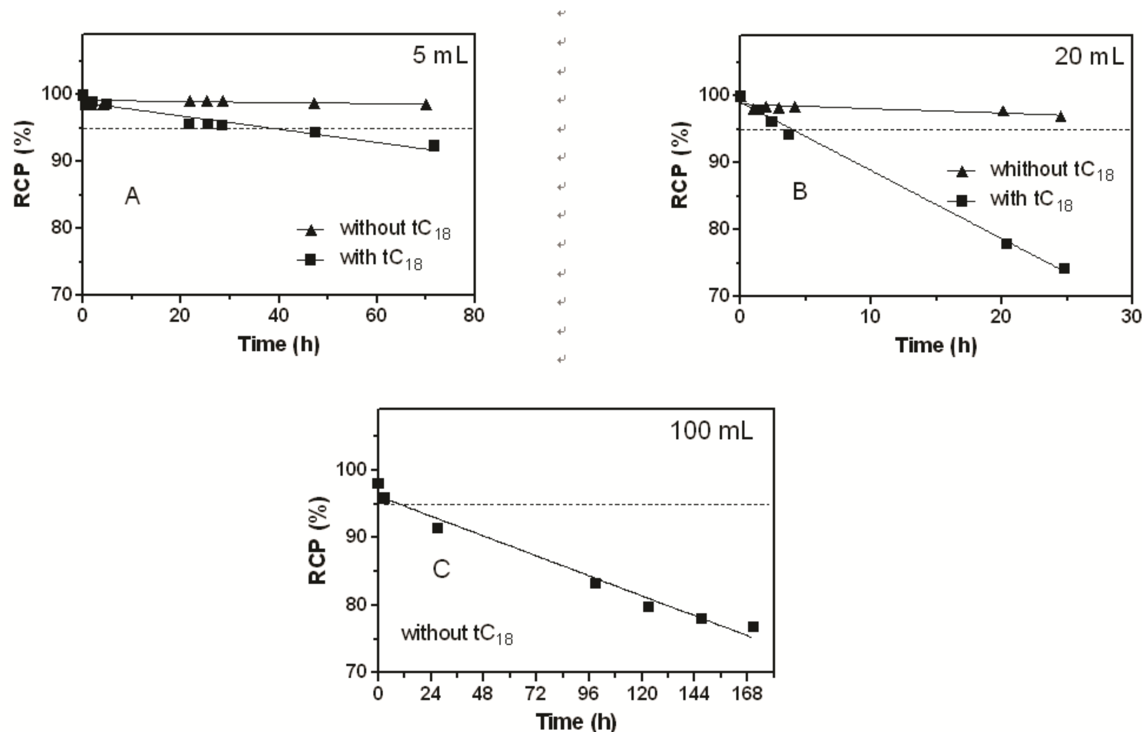

Figure 2. RCP of tC18 purified 177Lu-DOTA-TATE as function of time in a final volume 5 mL (A, see experiments 1 and 2, Table 1) and 20 mL (B, see experiments 5 and 6, Table 1), both at 0.5 GBq/mL. (C): represents a patient dose (7.4 GBq/100 mL) without tC_{18} purification diluted with saline to a final volume of 100 mL (experiment 7, Table 1). X-axes are expressed in time (h) and Y-axes in RCP (%). Dotted lines represents 95% RCP and is taken as lowest level suitable for patient administration.

5.4 Re-addition of AA or GA post tC_{18} purification

RCP of 177Lu-DOTA-TATE with the re-addition of AA (100 mmol/L) post tC18 purification was ≥95% at ~ 72h post radiolabeling (Fig. 3, experiment 3, see Table 1). Re-addition of GA (100 mmol/L, experiment 4, see Table 1) had only minor stabilizing properties, RCP of 177Lu-DOTA-TATE decreased below <95% within ~ 24h post radiolabeling (data not shown). Fragments observed in HPLC radiochromatogram as peaks prior to the main peak were caused by radiolysis of 177Lu-DOTA-TATE (Fig. 1B), were not further characterised. Fragments observed were not caused by formation of ionic 177Lu, 177Lu-DTPA or 177Lu-DOTA, since they have no retention on C18 column and are eluted from the HPLC system directly after void volume (Fig 1B, fragment II).

5.5 Activity loss, localisation of activity

Performing the manual radiolabeling including tC_{18} purification resulted in 5.2 ± 0.5 % (n=3) loss of activity in the tC_{18} purification cartridge. Whereas with the cassette-based automated radiolabeling procedure, loss of activity in the cassette was 28 ± 18 % (n=12), mainly caused by adhesion in the RV, tubing and tC_{18} cartridge.

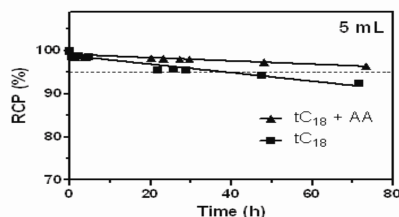

Figure 3. RCP of tC_{18} purified ^{177}Lu-DOTA-TATE as a function of time in a total volume 5 mL with/out re-addition of AA (see experiments 2 and 3, Table 1). X-axes are expressed in time (h) and Y-axes in RCP (%). The dotted line represents 95% RCP and is taken as lowest level suitable for patient administration.

6 Discussion

Liu et al. reported the addition of GA and AA as quenchers for radiolabeled DOTA-biomolecules in order to prevent radiolysis [8, 10]. They clearly demonstrated factors which influence RCP, factors such as presence and the relative amount of quencher, as well as the activity amount and the activity/quencher ratio. These data are in accordance with our studies. AA and GA-containing DOTA-TATE kit formulation was used and radiolabeled as described [13]. With regards to the production of radiopharmaceuticals, the existing GMP requirements as well as the reduction of the radiation exposure for the employees, Petrik et al.[18] reported radiolabeling of peptides for diagnostic and therapeutic purposes using a cassette-based automated radiolabeling procedure. They also showed radiochemical yields of 89% and RCP of ≥95%, however, without presenting data on RCP as function of time post radiolabeling, whereas in daily practice radiolabeled peptides will be administered hours after radiolabeling. We used the same cassette-based automated radiolabeling procedure and a DOTA-TATE kit formulation and were also able to maintain RCP at ≥95%. However, we observed 28 ± 18 % loss of activity in the cassette-based procedure (n=12), and, in addition, a decrease of RCP after tC18 purification as function of the volumic activity.

To investigate this phenomenon, we performed parallel manual and cassette-based automated radiolabeling syntheses. In the latter, tC18 purification is included as a safty-net system, to remove possible to free non-incorporated 177Lu ions from the reaction solution. Therefore, a tC18 purification step was also included in the manual radiolabeling. In two identical performed radiolabeling syntheses the initial RCP was ≥95%, however, since tC18 purification of eluate after radiolabeling resulted in total elimination of AA and GA and resulted in a decreased RCP of < 95% (Fig. 2A, experiments 1 and 2, Table 1). The experiments were repeated and after tC18 purification step GA or AA (final concentrations of 100 mmol/L) were added directly in to 177Lu-DOTA-TATE containing labeling mixture (experiments 3 and 4, Table 1).

Additional experiments were performed in 20 mL total volume, (experiments 5 and 6, see Table 1), while keeping the volume activity constant (0.5 GBq/mL). These experiments showed a much more rapidly decrease in RCP of 177Lu-DOTA-TATE (<95% RCP after ~5h and 74% at ~ 24h post radiolabeling, Fig. 2B,). Further dilution (5→20 mL) resulted in concordant dilution of quencher and might explain the decrease of RCP of 177Lu-DOTA-TATE.

As shown in Fig. 2A and B, experiments 2 and 6, Table 1, both after C18 purification, we found a more rapid decrease in RCP in 20 mL vs 5 mL. Without C18 purification the difference in decrease of RCP was less clear, experiments 1 and 5, Table 1, Fig. 2A and B. However, there is a difference between experiments 2 and 6: after the C18 purification (and 2.5 mL (50:50 water:ethanol)) the residual is diluted with 2.5 mL saline solution (experiment 2) or 17.5 mL saline solution (experiment 6). In consequence, the final ethanol concentration is different, 0.25 mL ethanol per mL or 0.062 mL ethanol per mL (1 mmoles/L ethanol in experiment 2 (5 mL) and 0.25 mmoles/L) in experiment 6 (20 mL).

Based on these results we can conclude that the standart implementation of a tC18 purification, which are generally effective for eliminating non-incorporated 177Lu ions, needs the re-addition of a quencher to maintain RCP of 177Lu-DOTA-TATE, although when ethanol is also known as an effective quencher in the mmoles/L range [17-18].

In daily practice, performing a manual radiolabeling as described [13], without tC18 purification, patient doses are diluted to 100 mL with saline. However, without the re-addition of quenchers, the RCP decreases time-dependent, while the RCP could be maintained > 95% up to 12h after radiolabeling (Fig. 2C). Thus, the dilution to 100 mL after radiolabeling, even without using tC18 purification, is preferably performed by the addition of AA up to a final concentration of 100 mmol/L. The re-addition of GA under the same conditions showed only minor stabilizing properties. To our knowledge RCP data on GA addition on 177Lu-labeled DOTA-peptides are not available in literature, however, Liu et al.[8, 10] reported a beneficial effect on the addition of GA to 90Y-DOTA-biomolecules.

When therapeutic doses of 177Lu-DOTA-TATE are administered (7.4 GBq for PRRT), radiolysed 177Lu-labeled fragments will most likely not bind to somatostatin receptor-positive tumor tissue. Here, however, it should be clarified, that 1% loss in RCP represents 74 MBq 177Lu non-characterised radiolysed peptide (and 370 MBq at 95% RCP), adding undesired radiation dose burden to the patient. As a consequence, we strongly advise re-addition of AA post tC18 purification. In addition, dilution after radiolabeling, even without using tC18 purification, should be performed with addition of AA.

Although not investigated here, the decrease in RCP of all 177Lu-labeled DOTA-biomolecules in the absence of quencher can be anticipated, and thus requires further study [17].

7 Conclusion

Re-addition of AA post tC18 SPE purification is required to maintain RCP of 177Lu-DOTA-TATE. RCP of tC18 purified 177Lu-DOTA-TATE, either labeled manually or cassette-based automated, decreases time- and volume-dependent.

Conflict of interests

The authors declare no conflicts of interests.

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