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# Stability of Stabilized $^{99m}\text{Tc-D,L-HMPAO}$ Stored in Vials and Syringes

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Our objective was to determine the stability of stabilized  $^{99m}\text{Tc}$ -hexamethylpropylene amine oxime ( $^{99m}\text{Tc-D,L-HMPAO}$ ) dispensed by vial and syringe, with the storage time and labeling activity varied. **Methods:**  $^{99m}\text{Tc-D,L-HMPAO}$  was labeled according to the manufacturer's instructions, but with modification of the  $^{99m}\text{TcO}_4\text{Na}$  activity. Two groups were prepared: 1,110 MBq (30 mCi) and 2,600–3,700 MBq (70.3–100 mCi). Five minutes after labeling, the radiochemical purity (RCP) of the vial content was determined. Afterward, the same activity was distributed into two 2-mL syringes and into the manufacturer's vial. In one of the syringes, the radiopharmaceutical stayed in contact with the needle for 4 h. At 2 and 4 h after labeling, the RCP of the vial and syringe content was checked and compared. **Results:** The mean RCP of stabilized  $^{99m}\text{Tc-D,L-HMPAO}$  labeled with 1,110 MBq (30 mCi) and stored in a vial decreased from 93.1% at 5 min to 92.1% at 2 h and to 91.1% at 4 h. With storage in a syringe, the RCP decreased from 89.8% at 2 h to 88.7% at 4 h. This diminution increased for labeling with higher activities (2,600–3,700 MBq [70.3–100 mCi]), ranging from 91.4% at 5 min, 89.0% at 2 h, and 85.3% at 4 h in a vial and from 85.9% at 2 h to 80.2% in a syringe.  $^{99m}\text{TcO}_2$  and secondary  $^{99m}\text{Tc-HMPAO}$  were the main impurities at  $t = 0$ .  $^{99m}\text{TcO}_4^-$  was an impurity that increased with time in both vials and syringes but significantly so in syringes. All these impurities were higher with labeling activities in the range of 2,600–3,700 MBq (70.3–100 mCi). Contact of the needle with  $^{99m}\text{Tc-D,L-HMPAO}$  sharply decreased the RCP to 57.1% at 4 h. **Conclusion:** The RCP of stabilized  $^{99m}\text{Tc-D,L-HMPAO}$  decreases significantly in both vials and syringes with high labeling activities. The product is less stable when stored in a syringe than in a vial. The fraction of dose in contact with the needle affects the RCP results.

**Key Words:** stabilized  $^{99m}\text{Tc-D,L-HMPAO}$ ; stability in vial; stability in syringe

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**H**examethylpropylene amine oxime labeled with  $^{99m}\text{Tc}$  ( $^{99m}\text{Tc-D,L-HMPAO}$ ) is a radiopharmaceutical used in

regional cerebral perfusion studies (1).  $\text{D,L-HMPAO}$  is the active principal of the specialty pharmaceutical sold under the name *Ceretec* (GE Healthcare Bio-Sciences) in the form of a freeze-dried vial for reconstitution with sodium pertechnetate ( $^{99m}\text{TcO}_4\text{Na}$ ). The stereoisomer  $^{99m}\text{Tc-D,L-HMPAO}$  is a neutral and lipophilic complex able to cross the intact blood–brain barrier. Once in the brain, it experiences a transformation mediated by glutathione (2,3), becoming a less lipophilic complex. This complex is unable to recross the blood–brain barrier and remains retained in the brain, allowing the tomographic study.

The reconstitution of a freeze-dried  $\text{D,L-HMPAO}$  vial with technetium generates 3 forms of radiochemical impurities: secondary  $^{99m}\text{Tc-HMPAO}$ , free technetium ( $^{99m}\text{TcO}_4^-$ ), and reduced hydrolyzed technetium ( $^{99m}\text{TcO}_2$ ). The ratio between them varies rapidly with time according to labeling conditions (4), determining the radiopharmaceutical stability. This parameter limits the  $^{99m}\text{Tc-D,L-HMPAO}$  administration to 30 min after labeling (5).

The manufacturer recommends that the RCP of this radiopharmaceutical be at least 80%. Actually, an RCP of at least 85% is needed to obtain a high-quality image (6,7).

There are different methods of stabilizing  $^{99m}\text{Tc-D,L-HMPAO}$ : addition of gentisic acid (8), preparation of the radiopharmaceutical in ethanol (9,10), and addition of methylene blue (11) or cobalt chloride (11–14). Of these methods, the addition of cobalt chloride after labeling has shown the best results. This form of stabilization had led to the commercialization of another specialty pharmaceutical, named *stabilized Ceretec*, which is stable for 6 h after labeling (15) according to the manufacturer.

This specialty pharmaceutical can be prepared in centralized units far from where it is going to be administered. Because stabilized  $^{99m}\text{Tc-D,L-HMPAO}$  is prepared several hours before its administration, 2 variables can potentially influence its stability: the labeling activity and the length of storage time in plastic syringes (16).

We occasionally have noticed some problems in the interpretation of perfusion images obtained with monodoses supplied in plastic syringes by radiopharmacy centralized units. We have observed a rise in the background and extracerebral activities related to cortical activity. In all cases, the RCP proved to be less than 85%. Variability in

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**TABLE 1**  
Effect of Labeling Activity and Storage Form on RCP of Stabilized  $^{99m}\text{Tc-D,L-HMPAO}$  over Time

Time (h)	1,110 MBq			2,600–3,700 MBq		
	Vial	Syringe	Needle	Vial	Syringe	Needle
0	93.1 ± 1.6	NA	NA	91.4 ± 1.0	NA	NA
2	92.1 ± 0.9	89.8 ± 2.1	74.2 ± 5.0	89.0 ± 1.4	85.9 ± 1.4	73.3 ± 8.5
4	91.1 ± 1.0	88.7 ± 2.0	59.8 ± 5.1	85.3 ± 3.0	80.2 ± 3.1	57.1 ± 4.5

NA = not applicable.

Values represent percentage of RCP (mean ± SD);  $n = 10$ .  $P < 0.01$  for vials between both groups of labeling activities at all times.  $P < 0.01$  for syringes in both groups of labeling activities at 2 and 4 h.  $P < 0.01$  between vials and syringes in both groups of labeling activities at 2 and 4 h.  $P < 0.01$  between vials and needles in both groups of labeling activities at 2 and 4 h.  $P < 0.01$  between syringes and needles in both groups of labeling activities at 2 and 4 h.

extracerebral activity has been attributed to a decrease in RCP that has occasionally been described when labeling activity for  $^{99m}\text{Tc-D,L-HMPAO}$  exceeds the specifications of the manufacturer (7). It is also known that stabilized  $^{99m}\text{Tc-D,L-HMPAO}$  is less stable when stored in syringes than in vials (16).

Our objective was to determine the stability of stabilized  $^{99m}\text{Tc-D,L-HMPAO}$  dispensed by vials and syringes, according to the storage time and the labeling activity.

#### MATERIALS AND METHODS

We prepared 10 vials of stabilized Ceretec labeled with the maximum activity recommended: 1,110 MBq (30 mCi) of  $^{99m}\text{TcO}_4\text{Na}$  (15). Another 10 vials were labeled with higher activities: 2,600–3,700 MBq (70.3–100 mCi). All manufacturer specifications (except activity) were followed in all 20 preparations.

The RCP of  $^{99m}\text{TcO}_4\text{Na}$  was determined by instant thin-layer chromatography using silica gel strips as a support and butan-2-one as a solvent.

We studied the stability of stabilized  $^{99m}\text{Tc-D,L-HMPAO}$  in the vial (where it is originally supplied) and in the plastic syringe (Becton-Dickinson) where it is stored from the moment of its preparation in the radiopharmacy centralized unit until it is administered.

Immediately after the RCP of the vial had been determined, the total activity was equally distributed among the vial and two 2-mL plastic syringes, and the vial and syringes were stored at room temperature. The RCP of the vial and syringes was also determined after 2 and 4 h.

To determine the influence of the needle on the RCP of the stabilized  $^{99m}\text{Tc-D,L-HMPAO}$ , in one of the syringes the radiopharmaceutical was never allowed to contact the needle. In the other syringe, stabilized  $^{99m}\text{Tc-D,L-HMPAO}$  was in contact with the needle (19-gauge; 8.9 cm [3.5 in] long) from the beginning to the end of the study.

The RCP was assessed using 2 strips of instant thin-layer chromatography silica gel as a support and butan-2-one as a solvent in the first chromatogram to quantify secondary  $^{99m}\text{Tc-HMPAO}$  and  $^{99m}\text{TcO}_2$ . Sodium chloride (0.9%) was the solvent used in the second chromatogram to quantify  $^{99m}\text{TcO}_4^-$ . The activity in the strips was determined with a miniGITA radiochromatography scanner (Raytest).

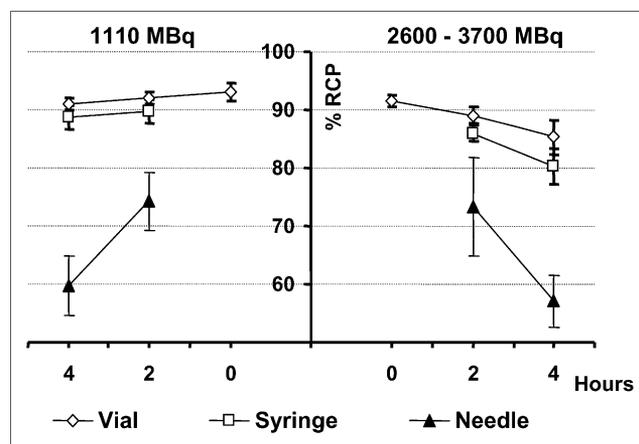
The Student  $t$  test was used to compare results between the mean value of each group. A  $P$  value of less than 0.05 was considered statistically significant.

#### RESULTS

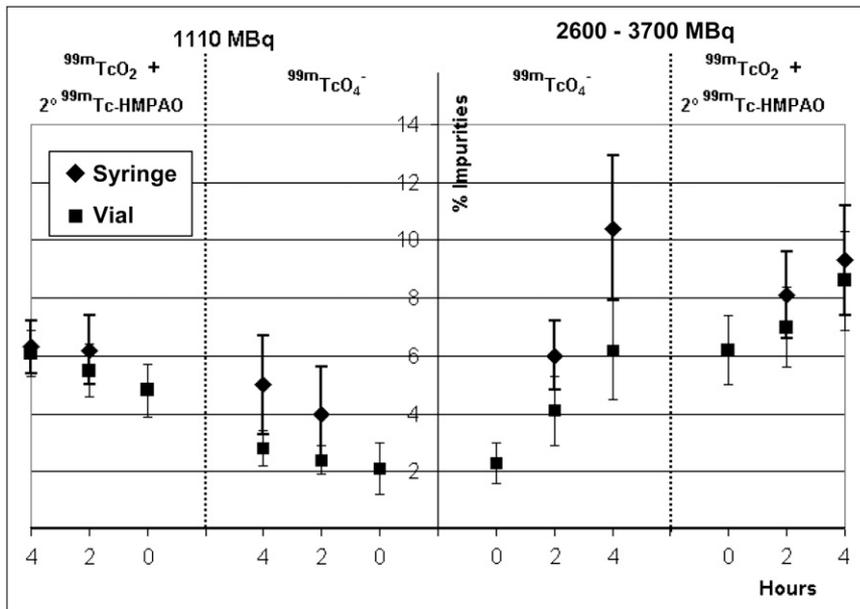
The RCP of the  $^{99m}\text{TcO}_4\text{Na}$  used in the labeling was  $97.8 \pm 1.5$ . The RCP of the stabilized  $^{99m}\text{Tc-D,L-HMPAO}$  showed significant differences between vials and syringes for both groups of labeling activities at all times studied. But the RCP decreased significantly ( $P < 0.01$ ) in vials and in syringes as labeling activity increased (Table 1). This diminution was more important in syringes, resulting in values of 80.2% after 4 h in the high-activity group (Table 1; Fig. 1). This RCP value was in the limit permitted for administration according to the manufacturer. The RCP in vials remained higher than 85% for both groups of activities at 2 and 4 h.

The solution of stabilized  $^{99m}\text{Tc-D,L-HMPAO}$  in contact with the needle was unstable, and the RCP dropped to values lower than 80% at 2 h and lower than 60% after 4 h (Table 1). Accordingly, to correctly determine the RCP of the stabilized  $^{99m}\text{Tc-D,L-HMPAO}$ , one should discard the radiopharmaceutical solution in contact with the needle.

The initial RCP of the stabilized  $^{99m}\text{Tc-D,L-HMPAO}$  in vials was higher than 90% (Fig. 1).  $^{99m}\text{TcO}_2$  and secondary  $^{99m}\text{Tc-HMPAO}$  were the main impurities (Fig. 2). The



**FIGURE 1.** Percentage of RCP of stabilized  $^{99m}\text{Tc-D,L-HMPAO}$  over time in both groups of labeling activities and forms of storage.



**FIGURE 2.** Percentage of radiochemical impurities in stabilized  $^{99m}\text{Tc-D,L-HMPAO}$  over time in vials and syringes (mean  $\pm$  SD;  $n = 10$ ).

quantity of impurities formed at 2 and 4 h in vials and syringes for both groups of activities is detailed in Table 2.

Quantities of  $^{99m}\text{TcO}_2$  and secondary  $^{99m}\text{Tc-HMPAO}$  were significantly higher when the vials were labeled with activities of 2,600–3,700 MBq. In contrast, low quantities of  $^{99m}\text{TcO}_4^-$  were found at  $t = 0$  for both groups of activity.  $^{99m}\text{TcO}_4^-$  increased with time in vials and in syringes, being significantly higher ( $P < 0.01$ ) in syringes at 2 and 4 h for both groups of activities (Table 2; Fig. 2).

We also observed that the value of RCP obtained from the fraction of the dose in contact with the needle decreased significantly with time independently of the labeling activity (Fig. 1).

## DISCUSSION

Stabilized  $^{99m}\text{Tc-D,L-HMPAO}$  as prepared by the hospital radiopharmacy is intended to be injected immediately. The

radiopharmaceutical is stored in a vial, and the time of storage in a syringe is minimal. In contrast, radiopharmacy centralized units prepare the dose several hours before it is administered in the nuclear medicine department, implying the use of higher labeling activities and longer storage in a syringe, which is the dosage form provided by these centralized units.

We have found that cerebral perfusion studies performed with stabilized  $^{99m}\text{Tc-D,L-HMPAO}$  supplied in a syringe by the radiopharmacy centralized unit have occasionally shown a decrease in relative cerebral cortical uptake because of an increase in background activity. This problem poses some difficulties when interpreting the images.

The aim of this study was to determine whether the stability of stabilized  $^{99m}\text{Tc-D,L-HMPAO}$  is affected by the amount of labeling activity and by the storage form (vial or syringe).

**TABLE 2**  
Effect of Labeling Activity and Storage Form on Radiochemical Impurities in Stabilized  $^{99m}\text{Tc-D,L-HMPAO}$  in Vials and Syringes over Time

Time (h)	1,110 MBq				2,600–3,700 MBq			
	$^{99m}\text{TcO}_2$ + secondary $^{99m}\text{Tc-HMPAO}$		$^{99m}\text{TcO}_4^-$		$^{99m}\text{TcO}_2$ + secondary $^{99m}\text{Tc-HMPAO}$		$^{99m}\text{TcO}_4^-$	
	Vial	Syringe	Vial	Syringe	Vial	Syringe	Vial	Syringe
0	4.8 $\pm$ 0.9	NA	2.1 $\pm$ 0.9	NA	6.2 $\pm$ 1.2	NA	2.3 $\pm$ 0.7	NA
2	5.5 $\pm$ 0.9	6.2 $\pm$ 1.2	2.4 $\pm$ 0.5	4.0 $\pm$ 1.6	7.0 $\pm$ 1.4	8.1 $\pm$ 1.5	4.1 $\pm$ 1.2	6.0 $\pm$ 1.2
4	6.1 $\pm$ 0.8	6.3 $\pm$ 0.9	2.8 $\pm$ 0.6	5.0 $\pm$ 1.7	8.6 $\pm$ 1.7	9.3 $\pm$ 1.9	6.2 $\pm$ 1.7	10.4 $\pm$ 2.5

NA = not applicable.

Values represent percentage of radiochemical impurities (mean  $\pm$  SD);  $n = 10$ .  $P < 0.01$  for  $^{99m}\text{TcO}_2$  + secondary  $^{99m}\text{Tc-HMPAO}$  and  $^{99m}\text{TcO}_4^-$  between both groups of activities in vial and syringe at all times.  $P > 0.05$  for  $^{99m}\text{TcO}_4^-$  between both groups of labeling activities in vial at  $t = 0$ .

After determining the results of this study, we have observed that the RCP of stabilized  $^{99m}\text{Tc-D,L-HMPAO}$  decreases both in vials and in syringes when labeling activity increases. This instability is higher in syringes (16): when the labeling activity is in the range of 2,600–3,700 MBq (70.3–100 mCi), the RCP after 4 h is 80%. This value is within the limit for administration, with  $^{99m}\text{TcO}_4^-$  being the main impurity. Obviously, stabilized  $^{99m}\text{Tc-D,L-HMPAO}$  labeled with a high activity and stored in a syringe cannot, at 6 h, attain the RCP recommended by the manufacturer (15). Some authors report that RCP values of at least 85% must be attained to obtain a good-quality image (6,7). The increase of  $^{99m}\text{TcO}_4^-$  may be due to the increased rate of reoxidation of stabilized  $^{99m}\text{Tc-D,L-HMPAO}$  to  $^{99m}\text{TcO}_4^-$  (16). It is unclear if reoxidation is related to the material constituting the container (plastic syringe) or to air in the product.

Stability can possibly be improved by enhancing the manufacturer-established conditions of the technetium elution used for the labeling. Ballinger et al. (7) showed that the RCP (time = 0) of  $^{99m}\text{Tc-D,L-HMPAO}$  was not affected by the effect of generator ingrowth or by the time elapsed from elution to labeling. Nevertheless, they did not determine the RCP at different times after labeling but instead only the initial RCP. This fact may relate to our finding that  $^{99m}\text{TcO}_4^-$  is initially low and then gradually increases.

The radiopharmacy unit that makes the preparation must look for possible improvements to obtain a final RCP of at least 80% at the time of administration. Among these improvements are optimizing the elution quality, choosing the vial as the dosage form, and, if necessary, reducing the time between labeling and administration.

RCP must be determined from a solution of stabilized  $^{99m}\text{Tc-D,L-HMPAO}$  that has not been in contact with the needle. The instability of stabilized  $^{99m}\text{Tc-D,L-HMPAO}$  in contact with a needle, compared with that in a vial or syringe, is probably related to metallic compounds.

## CONCLUSION

The RCP of stabilized  $^{99m}\text{Tc-D,L-HMPAO}$  decreases in both vials and syringes when labeling activities higher than 2,600 MBq (70.3 mCi) are used. The stabilized  $^{99m}\text{Tc-D,L-}$

HMPAO is more unstable in syringes than in vials. When high activities are used, the syringe as a dosage form should be rejected, specially if storage time exceeds 2 h. The fraction of the dose in contact with the needle should be discarded in the determination of RCP.

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