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Validation of an ergonomic method to withdraw [^{99m}Tc] radiopharmaceuticals

Short running title: Method to withdraw radiopharmaceuticals

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ABSTRACT

The main objective of the present work was to ensure quality of radiopharmaceuticals syringes withdrawn with a spinal needle/obturator IN-Stopper system.

Methods

Visual examinations and physicochemical tests are performed at T0 and T+4h for [99mTc]albumin nanocolloid and T+7h for [^{99m}Tc]eluate, [99mTc] HydroxyMethylene DiPhosphonate and [99mTc]Human Serum Albumin. Microbiological validation was performed according to European pharmacopoeia. Fingertip radiation exposure was evaluated to confirm the safety of the system.

Results

Results show stable visual and physicochemical properties. The integrity of the connector was not affected after 30 punctures (no cores). No microbiological contamination was found on tested syringes. Concerning radiation safety, no overexposure was reported with the system.

Conclusion

The system could be used 30 times. The stability of syringes drawing with this method is guaranteed up to 4 hours for [99mTc]albumin nanocolloid and 7 hours for [^{99m}Tc]eluate, [99mTc]HydroxyMethylene DisPhosphonate and [99mTc]Human Serum Albumin.

Introduction

To reduce personal exposure to gamma radiation, [^{99m}Tc]radiopharmaceuticals vials are placed in tungsten shields with lead glass. Dose preparation is usually done by reversal of the vial in order to withdraw the prescribed dose in a syringe. Shielded vials weigh between 900 grams and 2 kilograms. Syringes are also manipulated with a shield device whose weight is almost 200 grams. Due to the heaviness of the material, the repetition of these actions induces serious physical demands on the staff.

In our department, a method avoiding reversal has already been validated for fluorine-18 radiopharmaceutical dispensing. It consists of introducing a spinal needle connected to a membrane obturator IN-Stopper (B Braun) (*1*) into the vial. The length of the needle allows for the withdrawal of the totality of the liquid contained in the vial without reversal. The doses are dispensed by inserting the assembled needle and syringe into the obturator.

The use of the spinal needle/IN-Stopper would improve ergonomics but a validation must be carried out to guarantee the quality of the syringes drawn. Several interactions between medical device and radiopharmaceuticals have been amply described (*2*) and process validation is necessary (*3*).

According to manufacturer's recommendations, the obturator in stopper can only be punctured 10 times by a 0.6 mm diameter needle, which corresponds to our practice for fluorine 18 radiopharmaceuticals. [^{99m}Tc] radiopharmaceutical preparations are multidose vials and in our department, 10 doses could be filled from one vial. So the recommended number of uses of the connector would be exceeded because of the readjustment of the dose needed to obtain the prescribed dose. Thus, the obturator integrity is not guaranteed and a microbiological risk exists.

To ensure radiation safety, an evaluation is also necessary before routinely use by staff.

The use of this method to withdraw [^{99m}Tc]radiopharmaceutical preparations (up to now used for [^{18}F] radiopharmaceuticals) requires a visual examination, physicochemical and microbiological validation and a radiation safety evaluation.

Materials and methods

Tests were performed in a class A shielded hood (TEMA Sinergie).

To limit the risk of forming rubber cores, a Quick needle, 18 G and 90 mm length (Vygon) was put into the vial's cap using the stylet. The stylet was removed and an obturator top, IN-Stopper was connected to the spinal needle. The system is represented in figure 1.

The dose was drawn in a syringe (Plastipak BD) connected to a needle Microlance 3, length 25 mm, 23 G (Becton Dickinson) by piercing the rubber part of the connector.

Shielded vials (Medisystem) weigh 915 grams and shielded syringes (Medisystem) 172 grams.

Visual examination and physicochemical controls

The system was tested with the following solutions: [^{99m}Tc]pertechnetate eluate, [^{99m}Tc]HydroxyMethylene DiPhosphonate HMDP (Osteocis®, IBA molecular), [^{99m}Tc]albumin nanocolloid (Nanocoll®, GE Healthcare), Human Serum Albumin HSA (Vasculocis®, IBA molecular).

[^{99m}Tc]sodium pertechnetate was eluted from a Drytec® 99Mo/99mTc generator (GE Healthcare). The [^{99m}Tc]radiopharmaceuticals were prepared following the manufacturer's instructions. The studied system was introduced into vials before drawing the syringe used for the first quality control test (T0). The stability study was performed for 7 hours for [^{99m}Tc]eluate (n=5), [^{99m}Tc]HMDP (n=5), [^{99m}Tc]HSA (n=5) and for 4 hours for [^{99m}Tc]albumin nanocolloid (n=5). Luer slip connector syringes, capacity 1 mL (Plastipak BD) were used for sampling. Vials were stored at room temperature throughout the study. Organoleptic specifications detailed in the product characteristic summary were checked by a visual examination. pH was determined by pH indicator strips (MColorpHast, Merck Millipore).

Radiochemical purity (RCP) was performed by Instant Thin Layer Chromatography (ITLC). For [^{99m}Tc]pertechnetate eluate, [^{99m}Tc]HSA (*4*) and [^{99m}Tc]albumin nanocolloid (*5*), the method required Whatman 31 ET strips (Biodex, Clerad) and acetone as solvent (GPR Rectapur, VWR). Concerning [^{99m}Tc]HMDP the RCP was determined by a two strips procedure (*5*): ITLC-SG strips and distilled water as solvent were used to determine percentage of reduced or hydrolyzed technetium-99m and Whatman 31 ET strip and acetone as solvent were used to evaluate percentage of free pertechnetate.

After migration of the solvent, paper strips were scanned with a sodium iodine crystal detector on a MiniGita Star (Elysia Raytest). Chromatograms were recorded and analyzed with Gina Star TLC (Version 5.8).

Visual examination of the IN-Stopper connector

The IN-stopper membrane was examined to check its integrity and the absence of small cores or plugs.

Sterility test

The sterility tests were performed on three different days by three different operators.

Each day, 10 syringes were prepared with the spinal needle/IN-Stopper system as following. The rubber cap of the growth medium vial was cleansed with a chlorhexidine sterilized pad before being punctured by the system. Each day, 10 syringes were prepared (total, n=30) up to 7 hours after the introduction of the system into the growth medium vial. Syringes were withdrawn at regular time intervals. Each 2,5 mL luer slip connector syringe was prepared following the same protocol to simulate volume readjustment : IN-Stopper connector cleaning with a chlorhexidine sterilized pad; 1,5mL broth withdrawal into the syringe ; needle removal and then, insertion; withdrawal of 1 mL into the growth medium vial; needle removal and then, insertion ; 0,5mL broth withdrawal into the syringe (final volume is 1 mL) ; disassembling of the needle and assembling with a 0,22nm Perifix filter (B. Braun) ; hood air withdrawal ; disassembling of the filter and assembling with a cap (Vygon).

The growth medium vials were stored at room temperature during the study.

Experimental conditions were validated by a positive control (PC) and a negative control (NC). The PC syringes were inoculated with *Staphylococcus aureus* and *Aspergillus brasiliensis* growth. Sterile water was used for NC.

A positive transport sample (T+) and a negative transport (T-) were also prepared in syringe to validate transport conditions.

Each day, syringes were collected by Bioclin laboratory (Saint Aubin, France).

Microbiological cultures were performed by Bioclin laboratory according to European Pharmacopoeia VIIIth edition(*6*).

Samples (spinal needle/IN-Stopper tests, PC, NC, T+, T-) were divided into two equal parts and directly inoculated onto two different media. Fluid thioglycolate medium and soybean casein digest broth were respectively incubated at 30-35°C and at 20-25°C during 14 days with the exception for the PC witch were incubated during 5 days.

Fingertip radiation exposure and contamination

A fingertip radiation dosimeter, Nuclear Educational Dosimeter (Unfors Instruments) was attached to the distal medial aspect of the index finger and covered with a pair of latex examination gloves. Tests were performed on the right index, and then to the left index of each operators.

Dosimetry was measured and compared for three operators for both procedures; routine process which involves disinfection of the vial cap followed by reversal withdrawing of one syringe; and spinal needle/obturator process which consists of insertion of the system into the vial followed by disinfection of the obturator and withdrawing of one syringe. The vial used for the tests were filled with a [^{99m}Tc]pertechnetate eluate. Vials were measured using a dose calibrator CRC 25R (Capintec) in order to calculate the received dose per MBq for each hand.

Spillage and radioactive contamination were also studied. A contamination detector LB 124 (Berthold) was used to measure radioactive on shielded hood, gloves, vials and syringe shields. Areas that register more than twice the previously determined background level are considered contaminated.

RESULTS

Characteristics of the tested preparation

The product characteristic summary recommendations were followed for all the preparations. Table 1 summarizes all preparation characteristics (activity, volume).

Visual examination and physicochemical controls

The eluates and the preparation remained limpid and free from rubber coring. Physicochemical results are specified in table 2. Results met the specifications of the product characteristic summary and show 7 hours stability for [^{99m}Tc]eluate, [^{99m}Tc]HMDP, [^{99m}Tc]HSA and 4 hours stability for [^{99m}Tc]albumin nanocolloid according to those parameters.

Visual examination of the IN-Stopper connector

No cores or plugs were observed on the vial caps and the integrity of the obturator was not affected after 30 punctures.

Sterility test

The PC and the T+ showed a microbiological contamination in both media for all samples.

Syringes withdrawn with spinal needle/IN-Stopper system, NC and T- remained free of microbiological contamination in both media.

These results proved the microbiological stability of the syringes drawn with spinal needle/IN-Stopper system up to 7 hours.

Fingertip radiation exposure and contamination

The results showed an important reduction in the cumulative fingertip radiation dose for the dominant hand when using the spinal needle/IN-Stopper system compared to the reversal method.

Only the dominant hand received a dose during the introduction of the system in the rubber cap. This dose remains low compared to that received during the reversal procedure.

Results are summarizes in Table3.

There was no spillage of the radioactive solution during the tests and no contamination was found.

DISCUSSION

[^{99m}Tc]Radiopharmaceutical withdrawal is usually performed by vial reversal. To avoid these reversal movements, long needles are ideal and allow for withdrawal of the quasi total of the preparations. We previously used Sterican needles (60mm, 23 G, Braun). Withdrawal was done by puncturing the vial cap several times to adjust the dose to obtain the prescribing activity. However, the needles were flexible and oscillated during removal of the vial's cap causing radioactive micro droplets and staff extremity radiation exposure.

As a result, we finally chose a spinal needle to put into the vial's cap. To prevent air contamination of the preparation, other teams tried to connect bi-directional valve on the spinal needle. But, this presents drawbacks: impossibility of using them with luer slip syringe, radiation exposure increase (*7*), risks of radioactive contamination of the work environment (*8*). IN-Stopper connectors were chosen because they allow both luer slip and user lock slip syringe utilization. Luer slip syringes are preferred by technologists for peripheral injection but luer lock slip syringes are preferred for securing central injection. The 23G needle diameter allows

for an easy withdrawal and reduces the risk of forming rubber cores (*9,10*). In our study, we proved that although the manufacturer recommended only 10 uses, the IN- Stopper connector could be used safely 30 times.

The conditions of the study followed the routine practices. [^{99m}Tc]radiopharmaceuticals tested were the most often prepared in the department. In fact, we dispense syringes for up to 7 hours for [^{99m}Tc]HMDP, [^{99m}Tc]HSA and [^{99m}Tc]eluate and for up to 4 h for [^{99m}Tc]albumin nanocolloid. A maximum of 10 syringes could be withdrawn from one multidose preparation. Eluate withdrawal is necessary for [^{99m}Tc]radiopharmaceuticals preparation. Thus, we also performed tests on it. Levigoureux et al. had already proved the non-microbiological contamination of multi dose radiopharmaceuticals when the rules of hygiene are applied (*11*). Furthermore, the radioactive nature of radiopharmaceuticals cannot guarantee sterility (*12*). The study was performed under worst case conditions: vials stored at room temperature and disinfection of the obturator cap only once for a syringe preparation. The cap obturator was not disinfected before dose adjustment and a new puncture.

Syringes were filled with air to allow aerobic microbial growth. Air was filtered to avoid external microbial contamination during the tests. Assessments on vials would have been easier but to ensure the quality of the radiopharmaceuticals injected to the patient, microbiological tests on syringes were preferred.

Concerning radiation safety, the system does not increase the fingertip dose even if there is an additional step: insertion of the spinal needle in the rubber cap before first drawing. Furthermore, the non-dominant hand is not in touch with the vial containing the radioactive solution.

Furthermore, the non-dominant hand is not in touch with the vial containing the radioactive solution.

The cost of the system (IN-Stopper obturator and spinal needle) is calculated at € 0.815 excluding taxes which corresponds to an annual cost of less than € 1,300 for 1500 preparations.

Staff immediately accepted this new withdrawal method which improves ergonomics. In spite of all these benefits, 2 risks remain: needle stick injury and internal radioactive contamination. These risks could be reduced by needle recapper use (*13*).

This study shows that eluate and preparation characteristics (visual, physicochemical) are not influenced by the system. Furthermore, we prove that administrated syringes remained sterile and free from rubber coring.

CONCLUSION

When syringes are withdrawn with the spinal needle/IN-Stopper system, stability of [^{99m}Tc]eluate, [^{99m}Tc]HMDP and [^{99m}Tc]HSA syringes is guaranteed up to 7 hours and 4 h for [^{99m}Tc]albumin nanocolloid. This method strikes a good balance between both recommendations for radiopharmaceutical preparation, radiation safety, hygiene and ergonomics. This method must be validated for other radiopharmaceuticals before widespread use.

Conflict of interest:
All the authors have no conflict of interest to declare.

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Figure 1. Photo of the withdrawal system: spinal needle assembled to a membrane obturator IN-Stopper.

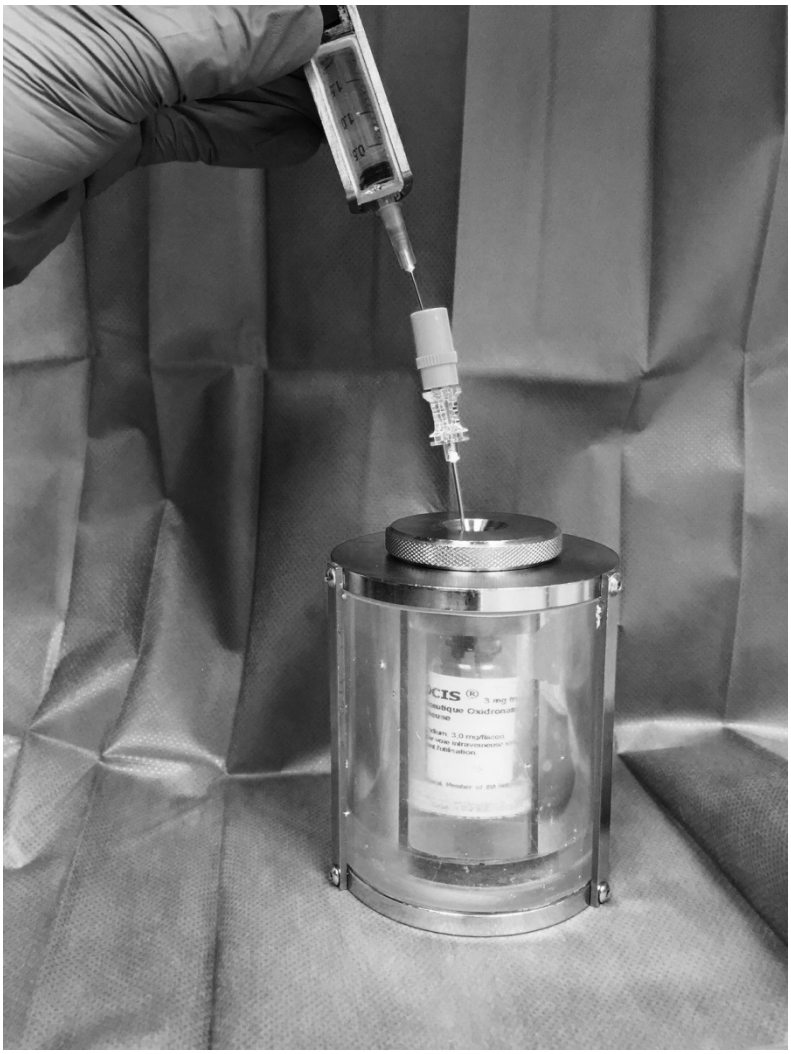

Table 1. Activity and volumes of preparations (mean, minimum and maximum).

	Activity (MBq) Mean (Minimum- Maximum)	**Volume (mL)** Mean (Minimum- Maximum)
[^{99m}Tc]HMDP (*1*)	10,930 (10,220-11,600)	5.0 (5.0-5.0)
[^{99m}Tc]HSA (*2*)	2,068 (1,995-2,376)	3.52 (3.3 à 3.7)
[99mTc]albumin nanocolloid	1,634 (1,368-1,814)	4.78 (4.8-5.0)

(*1*) [^{99m}Tc]HMDP : [^{99m}Tc] HydroxyMethylene DiPhosphonate

(*2*) [^{99m}Tc]HSA : [^{99m}Tc]Human Serum Albumine

Table 2. Physicochemical results of controls performed on [^{99m}Tc]pertechnetate eluate, [99mTc] HydroxyMethylene DiPhosphonate, [99mTc]Human Serum Albumin and [99mTc]albumin nanocolloid.

	pH mean (minimum - maximum)			**RCP (%)** mean (minimum - maximum)		
[^{99m}Tc] pertechnetate eluate (n = 5)	**Conformity**	**T0**	**T+7h**	**Conformity**	**T0**	**T+7h**
	4-8	5.84 (5.8-6.0)	5.80 (5.8-5.8)	*> 95 %*	99.63 (99.37-99.99)	99.56 (99.34-99.99)
[^{99m}Tc]HMDP(*1*) (n = 5)	**Conformity**	**T0**	**T+7h**	**Conformity**	**T0**	**T+7h**
	5-7	5.36 (5.0-5.5)	5.36 (5.0-5.5)	*> 95 %*	99.63 (99.34-99.79)	99.05 (98.42-99.57)
[^{99m}Tc]HAS(*2*) (n = 5)	**Conformity**	**T0**	**T+7h**	**Conformity**	**T0**	**T+7h**
	2-6.5	5.4 (5.0-6.0)	5.4 (5.0-6.0)	*> 95 %*	99.70 (99.05-99.99)	99.51 (99.13-99.76)
[^{99m}Tc]albumin nanocolloid (n = 5)	**Conformity**	**T0**	**T+4h**	**Conformity**	**T0**	**T+4h**
	4 à 7	5.0 (5.0-5.0)	5.0 (5.0-5.0)	*> 95 %*	99.55 (99.31-99.99)	99.67 (99.10-99.99)

(*1*) [99mTc]HMDP : [99mTc] HydroxyMethylene DiPhosphonate

(*2*) [99mTc]HSA : [99mTc]Human Serum Albumine

Table 3. Activities of the [^{99m}Tc]pertechnetate eluate vials and dosimetry of dominant and non dominant hand measured for routine process in comparison with spinal needle/IN-Stopper system.

	Activity of the vial (MBq) minimum - maximum	**Dose (µSv/MBq) Dominant hand** mean ± SD	**Dose (µSv/MBq) Non dominant hand** mean ± SD
Routine process Disinfection of the vial cap, reversal of the vial and syringe drawing	7,170-10,600 MBq	12.3 x 10-5 ± 8.69 x 10-5	17.5 x 10-5 ± 9.92 x 10-5
Spinal needle/IN-ptopper system Insertion of the spinal needle/IN-Stopper system into the vial	10,218-11,800 MBq	6.65 x 10-5 ± 3.68 x 10-5	0
Disinfection of the obturator cap and syringe drawing spinal needle/IN-Stopper system	6,790-11,215 MBq	6.85 x 10-5 ± 6.81 x 10-6	12.1 x 10-5 ± 4.89 x 10-5