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Administration accuracy of automated infusion device

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Comparison of three devices for automated infusion of positron-emitting radiotracers

Abstract

Objective: The administration accuracy and precision of automated infusion device for positron-emitting radiotracer is directly associated with bias and variance in standardized uptake values (SUV) of ^{18}F-FDG PET/CT. Therefore, the accuracy of such devices must be confirmed and calibrated at locations where they are used. The present study aimed to validate the administration accuracy of three automated infusion devices for quantitative PET assessment.

Methods: Temporal variations as well as variations in radioactive concentrations and dispensed volumes of ^{18}F-FDG were determined for the M-130, the AI-300 (both Sumitomo Heavy Industries Ltd., Japan), and the UG-05 (Universal Giken Co. Ltd., Japan) automated infusion devices. The total test dispensed volumes were 25, 20 and 18.5 mL, respectively. A reference value was generated by measuring amounts of radioactivity using a standard dose calibrator. Administration accuracy was validated according to the criteria of the Japanese Society of Nuclear Medicine (JSNM).

Results: Temporal variation in the M-130 and UG-05 for specified 185 MBq was a relatively stable in the range -1.60 to 0.92% and 1.16 to 5.35%, respectively, whereas that in the AI-300 was -0.55 to 8.68%. For M-130 and UG-05, the difference between measured and reference value was in the range -5 to 5%. The values measured by the AI-300 deviated from the reference values by a maximum of 30%, which depends on radioactive concentration and dispensed volume of ^{18}F-FDG..

Conclusions: The administration accuracy of the AI-300 varied considerably under different conditions, but a software update might somewhat improve this. Our findings indicate that dispensed volumes of ^{18}F-FDG should be carefully considered when the radioactive concentration is high. Administration accuracy should be regularly confirmed at each location to maintain the quality of quantitative PET assessment. The present study provides useful information about how to confirm the administration accuracy of automated infusion devices.

infusion device, quantitative PET, dose calibrator, radiation exposure

Introduction

Positron emission tomography/ computed tomography (PET/CT) with

^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG) has become increasingly important for the initial

staging, differential diagnosis, treatment response and prognostic prediction of various

malignancies (*1-3*). The incidence of ^{18}F-FDG PET/CT evaluations is increasing worldwide,

and thus exposing nuclear medicine workers to increasing amounts radiation during

increasingly frequent administrations of ^{18}F-FDG to patients is problematic (*4-6*).

Automated infusion devices for positron-emitting radiotracer have recently been developed

to reduce radiation exposure. Schleipman et al. showed that an automated infusion device

resulted in an estimated 10-fold reduction in whole-body and extremity exposure among

nuclear medicine workers (*7*). Automated infusion devices have been installed in most

(87.1%) Japanese PET facilities (*8*), but their quantitative performance and longitudinal

accuracy have not yet been evaluated.

The accurate and reproducible administration of ^{18}F-FDG is directly associated

with bias and variance in standardized uptake value (SUV) because the administration

accuracy to the patient is used directly in the SUV equation (*9*). Boellaard reported that

variations of factors affecting ^{18}F-FDG PET quantification ranged from 0% to 50% or more

depending on quality of administration (*10*). Regular quality control of the administration

accuracy and precision of automated infusion devices is essential to maintain their

performance. Accuracy may vary within 3% between automated infusion devices and dose

calibrators according to the European Association of Nuclear Medicine (EANM) guidelines

for ^{18}F-FDG imaging (*11*). That is, the actual amount of administered radioactivity may not

deviate by more than 3% from that indicated by automated infusion devices.

Lecchi et al. recently compared the accuracy of ^{18}F-FDG radioactivity

administered by the Intego[TM] automated infusion device (MEDRAD Inc., Warrendale, PA,

USA) with that administered using a manual dose-delivery system (*12*). Although they

found that variation in the accuracy of the ^{18}F-FDG radioactivity administered by the

Intego[TM] was within 3% (*12*), the quantitative accuracy of a wide range of radioactive

concentrations and dispensed volumes was not clear. The administration accuracy of

automated infusion devices depends on the radioactive ^{18}F-FDG concentration and the

dispensed volume of ^{18}F-FDG (*13*). Therefore, the administration accuracy of all automated

infusion devices must be confirmed and calibrated at the location where they are used.

The present study aimed to validate the administration accuracy of three

automated infusion devices for quantitative PET assessment. To our knowledge, this is the

first attempt to verify the administration accuracy of more than one device based on the

same rigorous validation criteria.

Materials and methods

Device operational characteristics of automated infusion devices

We compared the M-130, the AI-300 (Sumitomo Heavy Industries, Ltd., Tokyo,

Japan) and the UG-05 (Universal Giken Co. Ltd., Kanagawa, Japan) automated infusion

devices (Fig. 1). Figure 2 shows their operational characteristics. Scheme of measurement

and administration process of each device is roughly performed by 4 steps. First step,

radioactive concentration in a multidose vial is automatically measured by each sensor or

scintillator. Second step, the requested activity through a touchscreen computer interface is

automatically withdrawn from the multidose vial by a motor-driven to each syringe. Third

step, to check on the accuracy of the requested activity in each syringe is reconfirmed by

each sensor or scintillator. Final step, to flush the extracted request, ^{18}F-FDG with saline is

injected into patient via three-way cock.

Administration procedure by the M-130 consists of basic processes. The

radioactive concentration in a multi-dose vial is automatically measured by the Thallium

activated Cesium Iodide (CsI(Tl)) scintillator and a motor-driven 10-mL syringe withdraws

a specific amount of radioactivity from the vial determined through a touchscreen computer

interface. The amount of radioactivity in the syringe is reconfirmed by the plastic

scintillator. Finally, a solution containing ^{18}F-FDG and physiological saline for flushing and

washing is injected into patients via a three-way stopcock. The other devices have a broadly

similar device operational characteristics that differs slightly according to each integrated

measurement mechanism. The radioactive concentration in multi-dose vials is

automatically measured by the semiconductor sensor in the AI-300 and that in 5-mL

syringes is adjusted by two semiconductor sensors that are adjacent to the syringe. The

radioactive concentration in multi-dose vials is also automatically measured in the UG-05.

A specified amount of radioactivity withdrawn from a 5-mL syringe into a 10-mL vial is

confirmed by the semiconductor sensor, and then the specified amount is withdrawn from

the 10-mL vial using a motor-driven 20-mL syringe. Table 1 shows the main technical

features of the automated infusion devices compared herein. If the dispensed volume of

^{18}F-FDG solution is > 0.25 or 0.3 mL in the M-130, AI-300 or UG-05, respectively, then the

manufacturers can guarantee the administration accuracy of each device.

Validation of administration accuracy

Preparation of measurements

We measured amounts of radioactivity using CRC-25PET and CRC-712 external

dose calibrators (Capintec Inc., Ramsey, NJ, USA) to validate the administration accuracy

of the automated infusion devices. These dose calibrators have been standardized using the

National Institute of Standards and Technology (NIST) traceable germanium-68/gallium-68

(^{68}Ge/^{68}Ga) standard sources as ^{18}F surrogates (*14*). We set the same time on dose calibrator

and each device because the quantitative value of ^{18}F changes by about 0.6% per minute due to differences in time between dose calibration and automated infusion devices. The external dose calibrator and all internal detectors of the automated infusion devices were directly cross-calibrated using ^{18}F. We also confirmed the total administered volume using the LA230S (Sartorius Corp., Goettingen, Germany) electronic balance as real volume.

Measurement of administration accuracy

We validated administration accuracy based on the confirmation procedure of the Japanese Society of Nuclear Medicine (JSNM) that is based on the EANM guidelines for ^{18}F-FDG imaging (*11*). Difference of measured value in internal detector of each device and external dose calibrator were confirmed. We determined temporal variations, variations in radioactive concentrations and dispensed volumes of ^{18}F-FDG for the AI-300, M-130 and UG-05. Total volumes of physiological saline containing ^{18}F-FDG in sealed 30-mL vials for the M-130, AI-300 and UG-05 were 25, 20 and 18.5 mL, respectively. A reference value comprised a specific amount of radioactivity in a sealed vial measured using the external

dose calibrator. The average of five measured values was defined as the reference value, with which all radioactivity values determined by the automated infusion devices were compared. Temporal variations in specified amounts of 50 and 185 MBq of radioactivity were measured six times on different days. The results of sample No. 6 in M-130 were excluded because it did not fulfil the criteria. Variations in radioactive concentrations and dispensed volumes of ^{18}F-FDG were also confirmed with 100 - 1000 MBq/mL and 0.15 - 3.5 mL, respectively. Radioactive concentrations were calculated by dividing the actual administered volume by the desired amount of administered radioactivity.

The amount of radioactivity measured by automated infusion devices must be corrected to the value at the time of the external measurement using a dose calibrator to account for radioactive decay. The administration error of the automated infusion device was as follows:

$$\text{Administration error } [\%] = \left\{ \frac{A_a}{A_m} \times exp\left(-\frac{T_m}{109.8} \times \ln(2)\right) - 1\right\} \times 100,$$

where A_a is the amount of radioactivity recorded by automated infusion device, A_m is the amount of radioactivity measured using the dose calibrator, T_m is the difference

between the time of administration by the automated device and the time when the amount

of radioactivity was measured by the dose calibrator (min), and *109.8* is the half-life of ^{18}F

(min).

The manufacturer released updated software for the AI-300 during in 2015 to

improve administration accuracy. We compared administration error before and after the

software release.

Results

Table 2 summarizes temporal variations in administration error on different days.

The mean administration accuracy of the AI-300 was 7.43% (range, 1.52 to 14.42%) and

5% (range, -0.55 to 8.68%) under conditions of specified amounts of 50 and 185 MBq of

radioactivity, respectively. The variability was appreciably higher than that of the others

devices. The mean administration error of the M-130 for 50 and 185 MBq of radioactivity

was stable within -2.86% (range, -3.79 to -1.59%) and -0.80% (range, -1.60 to 0.92%),

respectively, whereas that of the UG-05 was 4.26% (range, -0.13 to 6.37%) and 3.48%

(range, 1.16 to 5.35%), respectively.

Figure 3 shows the administration error of the devices as a function of the radioactive concentration and the dispensed volume of ^{18}F-FDG. The administration error of the AI-300 reached a maximum of 30% at high radioactive concentration of 700 MBq/mL and bias appeared proportional to the radioactive concentration (Fig. 3A). The M-130 and UG-05 were relatively stable at -5% and 5%, respectively. On the other hand, bias to the dispensed volume of ^{18}F-FDG was inversely proportional in the AI-300 (Fig. 3B). The percent deviation was large when the dispensed volume was < 0.5 mL, reaching a maximum of 30%. The M-130 and UG-05 achieved stability to the dispensed volume of ^{18}F-FDG in the range of -5 to 5%.

Figure 4 shows the administration error of the AI-300 before and after the software update. The administration error improved to within 5% after the update, but was worse by -10% when the dispensed volume was < 0.2-mL volume; this is not covered by a warranty.

Discussion

Although manufactured automated devices for infusing positron-emitting radiotracers have common features, many points differ and their administration accuracy and precision under various administration conditions is not understood in detail. We validated the administration accuracy of three automated infusion devices. The results indicated that the radioactive concentration and dispensed volume of ^{18}F-FDG affected the administration accuracy of the devices to various degrees and that the AI-300 was unstable.

Values were measured under various conditions on different days to exclude factors such as the impact of operator error and hardware. Temporal variations in desired amounts of radioactivity adversely affected all automated infusion devices more at 50, than at 185 MBq. The administration accuracy at 50 MBq deviated from the accuracy of each device guaranteed by manufacturers and the EANM criteria (*11*). We consider that the measurement accuracy of the devices is limited at lower levels of ^{18}F-FDG radioactivity and thus the administration accuracy might be reduced. The degree of temporal variation differed depending on the device. The administration error of 185 MBq was stable for the

M-130 and UG-05 at -0.80% (range, -1.60 to 0.92%) and 3.48% (range, 1.16 to 5.35%), respectively, which was closer to the accuracy in a previous study of the Intego^{TM} system that met the EANM criteria (*12*). These results indicated that the M-130 and UG-05 devices were stable and offered highly reproducible administration accuracy.

The desired volume of ^{18}F-FDG dispensed by each device declines as a function of a higher radioactive concentration when extracted from multi-dose vials (*13*). Therefore, a dispensed volume below 0.5 mL conspicuously worsened the administration error of the AI-300, which was already overestimated compared with the other devices. The device operational characteristics of the AI-300 is a key factor in the overestimation. The manufacturer of the AI-300 has publicly announced that this was primarily caused by the ^{18}F-FDG solution and physiological saline adhering to the boundary of the three-way stopcock. Systematic error can be explained by the ^{18}F-FDG solution mixing with saline at the boundary of three-way stopcock over time, or a small amount of ^{18}F-FDG detaching from a stock ^{18}F-FDG during flushing with saline. Thus, we considered that an overestimated amount of radioactivity administered by the AI-300 as a function of a smaller

dispensed volume of ^{18}F-FDG would increase uncertainly relative to the total administered

volume.

The manufacturer of the AI-300 updated the software to suppress overestimation.

It automatically adjusts the dispensed volume of ^{18}F-FDG to improve the accuracy of

dispensed volumes below 0.5 mL. The dispensed volume of radioactivity after updating the

software was stable within 5% (Fig. 4). Systematic error in the AI-300 should therefore

have a much smaller effect after the software update. However, since correction by

software cannot improve the integrated device operational characteristics, systematic error

in the AI-300 cannot be completely resolved in this manner. A new device with refinements

is currently under development to replace the AI-300.

Although none of the three automated infusion devices barely met the EANM

criterion of ± 3% (*11*), we confirmed that the administration error of the M-130, AI-300 and

UG-05 was within the assurance range stated by the manufacturers (± 10%, ± 5% and ± 5%,

respectively). A method of managing the administration accuracy of automated infusion

devices has not yet been defined, but the present study provides useful information about

how to confirm it. We suggest that consistent administration accuracy can be achieved in

the following three ways. The tendency of error inherent in each device at each location

should be confirmed. Users and manufacturers should regularly correct, maintain and

implement quality control measures for automated infusion devices by rigorous

cross-calibration between the dose calibrator and the integrated detectors within each

device. The optimal radioactive concentration should be determined and then the dispended

volume of ^{18}F-FDG should be adjusted taking into consideration the operational aspects of

clinical practice. We do not believe that these ways are sufficient to resolve all issues

associated with the administration accuracy of automated infusion devices and will require

further investigation.

This study is limited by our comparison of three automated infusion devices and

focusing on their administration accuracy. Further study is required to evaluate the radiation

protection ability and operational aspects of automated infusion devices (*4,7,12,13*).

Conclusions

The administration accuracy of the AI-300 was unstable under various conditions, but a software update provided some improvement. Our results indicate that the dispensed volumes at high radioactive concentrations is important. The elimination of administration error from high radioactive concentration make it possible to reflect mainly the level of guideline required for the intended clinical use of quantitative PET. In addition, administration accuracy should be regularly confirmed at each location to maintain the quality of quantitative PET assessment. The present study provides useful information about how to confirm the administration accuracy of automated infusion devices.

Conflicts of interest

The authors declare that they have no conflict of interest.

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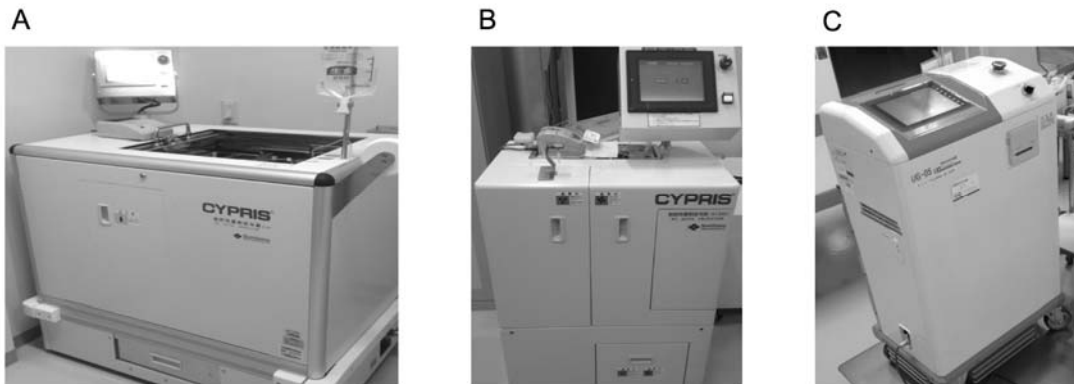
Figure legends

FIGURE 1. Manufactured automated infusion devices evaluated in this study. (A)

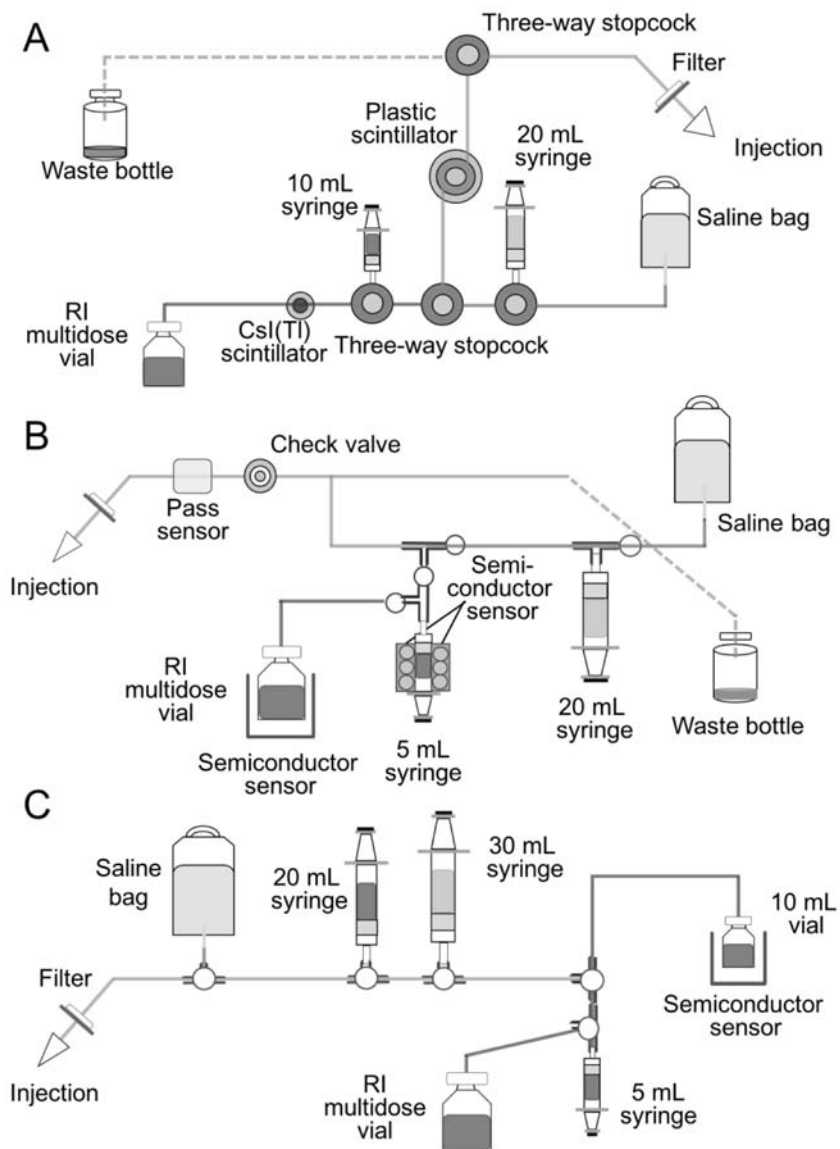M-130; (B) AI-300; (C) UG-05.

FIGURE 2. Scheme of measurement and administration process of each device. (A) M-130; (B) AI-300; (C) UG-05.
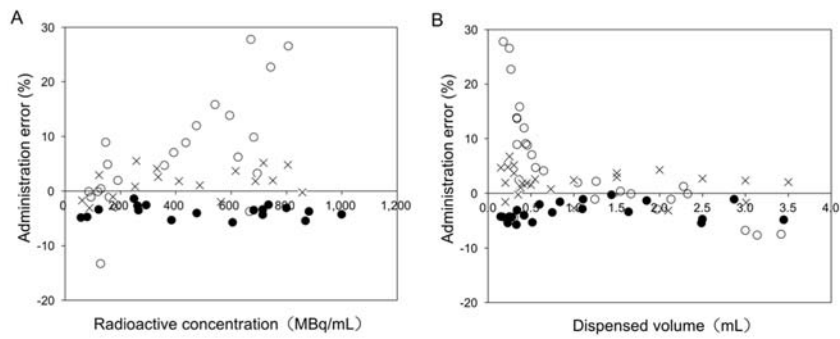
FIGURE 3.   Variations in (A) radioactive concentrations and (B) dispensed volumes. ○, AI-300; ●, M-130; ×, UG-05.

FIGURE 4. Administration accuracy of AI-300 before and after software update. ○, original; ●, update.

Table 1. Main technical features of automated infusion devices.

Automated infusion device	M-130	AI-300	UG-05
Maximum radioactivity of multi-dose vial (MBq)	18,500	37,000	37,000
Maximum radioactive concentration of multi-dose vial (MBq/mL)	1,500	1,500	1,200
Range of net administration (MBq)	100 - 740	50 – 740	- 740
Measurement accuracy of radioactive concentration (%)	± 10	± 5	± 5
Measurement accuracy of radioactivity (%)	± 10	± 5	± 5
Administration accuracy (%)	± 10	± 5	± 5
Variation of volume	constancy	variability	constancy
Measurement sample	tube	syringe	vial

Table 2. Comparison of accuracy of administered FDG radioactivity between automated infusion device and external dose calibrator

Devices	Sample	Radioactive concentration (MBq/mL)	Dispensed volume of FDG (mL)	Radioactivity recorded by devise (MBq)	External measurement (MBq)	Administration accuracy (%)	Radioactive concentration (MBq/mL)	Dispensed volume of FDG (mL)	Radioactivity recorded by devise (MBq)	External measurement (MBq)	Administration accuracy (%)
M-130	1	294.12	0.17	48.42	50.33	-3.79	225.94	0.84	189.79	192.89	-1.60
	2	121.95	0.41	48.40	49.76	-2.72	127.32	1.40	178.25	179.58	-0.74
	3	200.00	0.25	49.26	50.05	-1.59	202.31	0.87	176.01	178.43	-1.36
	4	147.06	0.34	48.52	49.84	-2.66	152.30	1.17	178.20	180.36	-1.20
	5	166.67	0.30	48.19	49.97	-3.56	167.53	1.04	174.23	172.64	0.92
	6	142.86	0.35	24.07	24.42	-1.42	59.61	1.54	91.80	94.27	-2.63
AI-300	1	104.17	0.48	48.87	47.87	2.09	118.80	1.42	168.70	169.63	-0.55
	2	131.58	0.38	50.09	49.34	1.52	165.57	1.12	185.44	170.62	8.68
	3	147.06	0.34	50.61	44.54	13.64	178.59	1.04	185.73	175.66	5.73
	4	131.58	0.38	52.01	46.88	10.94	161.71	1.14	184.35	173.83	6.05
	5	151.52	0.33	49.01	42.83	14.42	177.28	1.05	186.14	171.39	8.61
	6	161.29	0.31	48.93	47.98	1.99	183.62	1.01	185.46	182.75	1.48
UG-05	1	90.79	0.60	54.48	51.27	6.26	92.04	2.01	180.23	174.92	3.04
	2	154.73	0.34	52.61	50.16	4.87	181.37	1.02	147.90	141.92	4.21
	3	205.09	0.26	53.32	52.14	2.27	205.56	0.90	185.01	175.61	5.35
	4	206.85	0.26	53.78	50.56	6.37	179.61	1.03	179.35	177.29	1.16
	5	224.45	0.25	56.11	52.98	5.92	212.64	0.87	182.29	173.10	5.31
	6	108.58	0.39	42.34	42.40	-0.13	411.11	0.45	191.05	187.63	1.83