Bladder Wall Radiation Dose in Humans from Fluorine-18-FDOPA

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PET, in conjunction with ^{18}F-fluorodopa (FDOPA), has become the standard technique to assess basal ganglia degeneration in patients with movement disorders. Based on published dosimetry data, the injected dose of FDOPA is limited to 111 Mbq (3 mCi) because of exposure to the bladder wall, which is the critical organ for such studies. These dosimetry studies are based on mathematical models for the bladder radioactivity accumulation and clearance when the subjects were asked to void approximately 2 hr after the intravenous injection of FDOPA. In this study, we improved the radiation dose estimate to the bladder wall using dynamic PET to image the bladder during the uptake phase as well as before and after voiding. **Methods:** The subjects were tested on a new protocol. They were hydrated preinjection and given a first bladder void break at 40 min postinjection and a second void at the end of study at 120 min. **Results:** The MIRD model, applied to the data collected from 10 adults of both sexes, yielded an average absorbed dose of 0.15 ± 0.08 mGy/MBq (0.57 ± 0.28 rad/mCi). **Conclusion:** This absorbed dose is significantly lower than previous estimates and allows for FDOPA injections up to 333 Mbq (9 mCi).

Key Words: PET; fluorine-18-FDOPA; dosimetry

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Dopaminergic function in humans has been studied using ^{18}F-fluorodopa (FDOPA) and PET (*1,2*). The parameters obtained from these studies provide disease discrimination as well as an objective measure of disease severity (*3*). Harvey et al. (*4*) placed a limit of 74 MBq (2 mCi) FDOPA injection based on a bladder wall radiation dose of 6.95×10^{-10} Sv/Bq (2.57 rem/mCi). This dose estimate was based on tissue biodistribution studies in mongrel dogs and urine data obtained from human studies assuming that 80% of the bladder activity was voided at 2 hr postinjection. Mejia et al. (*5*) obtained the tissue distribution data from mice and bladder data from human subjects using a heavily collimated CsI detector placed 5 cm above the bladder during the PET studies. Their dose estimate to the bladder wall was half that of Harvey et al. because of the difference in the assumed bladder content volume. Mejia et al. assumed a bladder content volume of 200 ml recommended by the ICRP and MIRD Committee, instead of the 110 ml used by Harvey et al. (*4,5*). Recently, Lu et al. (*6*) demonstrated a 35% reduction in the absorbed dose to the bladder wall by prehydrating the subjects with soft drinks. They modeled the bladder content curve as the complement of the plasma curve and calibrated this curve by a urine sample obtained at the first void 2 hr postinjection. These improvements increase the maximum FDOPA injected dose to 156 MBq (4.2 mCi). We wanted to further increase the injected dose as well as increase the accuracy of bladder absorbed dose estimates. Therefore, we developed a new PET study protocol that allows for a break at 40 min postinjection to achieve an early bladder void. In addition, we dynamically imaged the bladder during the first 40 min to accurately define the bladder content curve.

MATERIALS AND METHODS

Subjects

The study population consisted of 10 subjects (8 men, 2 women; mean age 50 ± 8.8 yr). Four men and one woman were normal volunteers and the remaining subjects had a diagnosis of typical/atypical Parkinson's disease. No known renal dysfunction conditions were noted among the subjects. All participants were asked to refrain from taking any medication or eating for 6 to 8 hr before the PET study. All subjects gave informed consent and the study protocol was approved by the NSUH investigational review board. In addition, we dynamically scanned the bladders of two normal subjects for 125 min to define the shape of the bladder uptake curve for the duration of the PET study and to validate our assumptions.

Scanning Protocol

All studies except one were performed on the Scandatronix Super-PETT 3000 Time-of-flight barium fluoride detector tomograph with an axial field of view (FOV) of 10.5 cm and a resolution of 7.5 mm FWHM (*7*). One study was performed on the GE Advance tomograph with a FWHM of 4.5 mm. This tomograph has an axial FOV of 15.2 cm and generates 35 slices of 4.3-mm thickness (*8*).

The following study protocol was used: (a) a 10-min bladder transmission scan to correct for attenuation; (b) a dynamic emission bladder scan consisting of twenty 2-min scans starting at injection time; (c) a 10-min break for voiding and full urine collection; (d) a static scan of the bladder for 5 min; (e) a dynamic emission brain scan of 48 min, comprised of six 8-min scans; (f) a 10-min brain transmission scan; (g) a final static bladder scan of 5 min; and (h) a second void with full urine collection immediately after the scan. The subject's head was positioned in the scanner using a stereotaxic headholder and a three-dimensional laser system (*9*). Repositioning for bladder scans was achieved by marking the subject's abdomen with laser crosshairs. Arterial blood samples were taken to quantify the brain data. The total volume of urine was measured for each void and small aliquots were weighted and counted for ^{18}F radioactivity. All subjects were asked to drink at least 350 ml of water before the start of the study. For the additional two normal subjects, we dynamically scanned their bladders for 125 min (using GE Advance scanner) but included two bladder voids at 40 min and 110 min postinjection.

Bladder Dose Calculation

The following equation is used to determine the activity excreted during the first and second void:

$$A_{exc} = C_{cnt} * (V_{tot}/V_{cnt}) * (1/C_{eff}) * (1/T_{cnt}) * EXP(.693 * \Delta T/110)/222 \times 10^{7},$$

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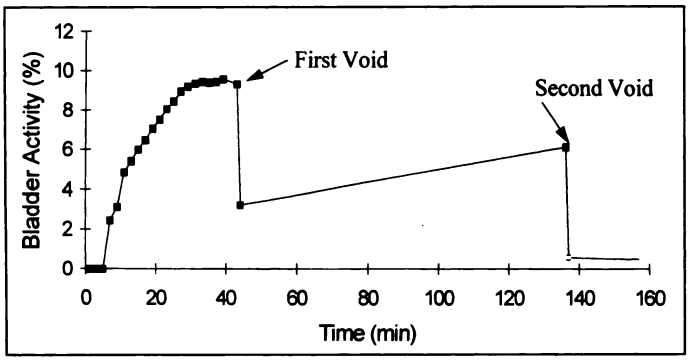

FIGURE 1. FDOPA percent activity in the bladder is shown as a function of time. The first 40-min data were collected in dynamic mode followed immediately by a bladder void. The second void took place after the end of brain scans and a prevoid bladder scan. All individual data points (■) refer to a bladder scan except the last data point (○) that was obtained from the activity of the post-void urine aliquot. The line after the second void is an extrapolated estimate of the bladder content based on ^{18}F decay.

where A_{exc} = activity excreted (mCi); C_{cnt} = number of counts in urine sample; V_{cnt} = urine volume counted (ml); V_{tot} = total urine collected (ml); C_{eff} = well counter efficiency; T_{cnt} = counting duration (min); and ΔT = time elapsed between excretion and urine counting (min).

In the above equation, the half-life of ^{18}F is taken as 110 min and the factor of 222×10^7 is dpm/mCi.

With reference to Figure 1, the rising curve before the first void was obtained from a region of interest (ROI) placed over the bladder from a 40-min dynamic PET scan of the pelvic region. The rise from the first void to the second void resulted from a linear fit of counts in the bladder obtained immediately after the first void at 40 min and the scan preceding the second void. The final washout phase was obtained assuming physical decay of residual activity in the bladder after the second void. The percent excreted activity during the first void was calculated as the ratio of the activity excreted (from the equation above) and the total injected activity. These data were used to scale the y-axis as shown in Figure 1. In the exclusive bladder studies, we used a procedure similar to that used for the previous 10 subjects to define the time-activity curve (TAC) for the bladder. All planes, where the bladder was visible, were added together. A large ROI, slightly bigger than the bladder, was selected and the TAC obtained using a thresholding technique (spatially varying the top 50% of the pixels).

Statistical Analysis

The mean bladder dose was compared with published data using the Student's t-test. The relationship between the bladder wall dose and the volume of urine output in the first void was tested by using regression analysis. Similarly, the relationship between the urine concentration and the urine volume was also tested using regression analysis.

RESULTS

Table 1 shows the bladder wall radiation dose to each patient in the study. Note that the maximum bladder wall radiation dose is 0.31 mGy/MBq (1.13 rads/mCi) while the minimum is 0.07 mGy/MBq (0.27 rads/mCi). Based upon Version 3 of the MIRDDOSE program (*10*), an average dose to the bladder wall in humans was found to be 0.15 ± 0.08 mGy/MBq (0.57±0.28 rads/mCi). Table 2 provides the radiation dose received by the organs in close proximity to the bladder (gonads and lower large intestine).

The two exclusive bladder studies demonstrated similar uptake curves and Figure 2 illustrates one of them. The curve in the second phase (40 min to 100 min) follows a step exponential rise with a rate constant of (36.3 min^{-1}) and the difference in the area under this curve and the linear assumed curve is 3%.

Figure 3 demonstrates the lack of correlation between bladder wall dose and the volume of urine output in the first void (R^2 = 0.006, $p > 0.1$). Figure 4 shows a statistically significant inverse relationship between the urine concentration and the volume of urine output from the first void (Urine concentration = $-0.0006 \times$ Urine volume + 0.556; $R^2 = 0.56$, $p < 0.001$).

TABLE 1
Total Bladder Wall Radiation Dose to Each Patient Resulting from FDOPA Injection

	Age (yr)	Sex	First void urine volume (ml)	Dose (mGy/MBq)	Dose (rad/mCi)
	41	M	725	0.15	0.55
	42	F	650	0.21	0.79
	51	M	775	0.12	0.46
	43	M	180	0.18	0.65
	62	F	395	0.11	0.40
	60	M	325	0.12	0.43
	46	M	215	0.21	0.79
	54	M	225	0.05	0.18
	61	F	420	0.31	1.13
	40	M	350	0.07	0.27
Mean ± s.d.	50 ± 8.8		426 ± 217	0.15 ± 0.08	0.57 ± 0.28

DISCUSSION

A few methodological issues with our study protocol are addressed below. First, the use of a different scanner in one study may have a small influence on the dosimetery data. This was avoided by using a large ROI (>5 cm^2) covering the bladder so that the variable resolution of the two scanners (7.5 mm versus 4.5 mm) would have a negligible effect. Furthermore, the bladder content concentration was calibrated by the measured radioactivity from the urine aliquot. Even though PET measures radioactivity concentration accurately, our Scandatronix scanner (FOV 10.5 cm) did not cover the whole bladder in some studies and, therefore, the only way to determine the total bladder radioactivity accurately was to directly measure the total urine output and activity. Second, the repositioning of the pelvic area for the second and third scans was not critical to the dosimetery because the counts were summed over all slices. Moreover, repositioning was achieved by marking the laser crosshairs on the subject's skin. In addition, the postvoid scan had enough urine left in the bladder to select an ROI > 5 cm^2 to make an accurate measurement. The assumption of linear buildup of urine radioactivity is

TABLE 2
Estimated Radiation Dose to Various Organs Resulting from FDOPA Injection

Target organ	Bladder contents (mSv/MBq)	Total dose* (mSv/MBq)	Total dose* (rad/mCi)
Bladder wall	152.60 ± 10^{-3}	159.30 ± 10^{-3}	589.41 ± 10^{-3}
Uterus	9.53 ± 10^{-3}	16.01 ± 10^{-3}	59.24 ± 10^{-3}
Lower large intestine	4.40 ± 10^{-3}	11.42 ± 10^{-3}	42.25 ± 10^{-3}
Ovaries	4.02 ± 10^{-3}	10.50 ± 10^{-3}	38.85 ± 10^{-3}
Testes	2.94 ± 10^{-3}	9.69 ± 10^{-3}	35.85 ± 10^{-3}
Effective dose equivalent		17.87 ± 10^{-3}	66.12 ± 10^{-3}

*Total organ doses are computed from the data of Harvey et al. (*4*) by substituting our bladder content data.

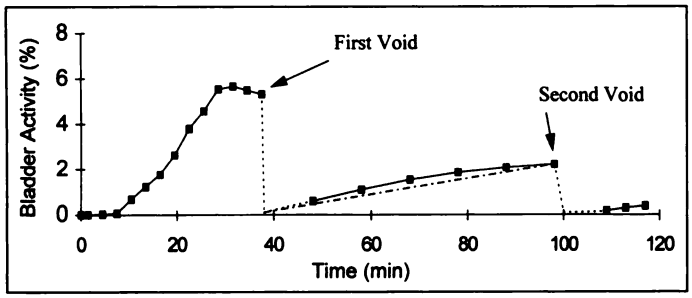

FIGURE 2. FDOPA percent activity in the bladder is shown as a function of time for one of the two normal subjects in whom the bladder was scanned for 125 min. The dotted lines represent the two bladder void periods and all individual data points (■) refer to a bladder scan. The difference in bladder dose calculated by the use of a linear buildup assumption as shown by the straight line (-.-.-) and the actual observed step-exponential curve was <3%.

justified based on the experimental data (Fig. 2), as well as the fact that urine radioactivity accumulation peaks at about 30 min postinjection and the blood activity is small and decreasing slowly at this time. Moreover, the underestimation of the bladder dose, due to this assumption, is very small (<3%). The worst case scenario would be to assume a step-exponential rise for the second phase similar to the rate constant observed in the first phase. This unlikely situation would increase the bladder dosimetry by 13%. In addition, a break at 40 min postinjection does not in any way interfere with the calculation of FDOPA influx constant, K_i, in the striatum using the Patlak approach or the striato-occipital ratio (*3,11*). Finally, the assumption that the last phase (post-second void) follows an exponential decay with the ^{18}F half-life is justified based on: (a) a small rise observed in the bladder activity (Fig. 2) and (b) the negligible contribution (<5%) of this phase to the total area under the curve for bladder uptake and by integrating this last phase to infinite time provides a conservative estimate considering that there will be multiple bladder voids even when the subject leaves the PET facility.

The average radiation dose to the bladder wall of 0.15 mGy/MBq (0.57 rads/mCi) observed in this study was significantly lower ($p < 0.03$) than both values published by Lu et al. (*6*) of 0.32 mGy/MBq (1.21 rads/mCi) when patients were

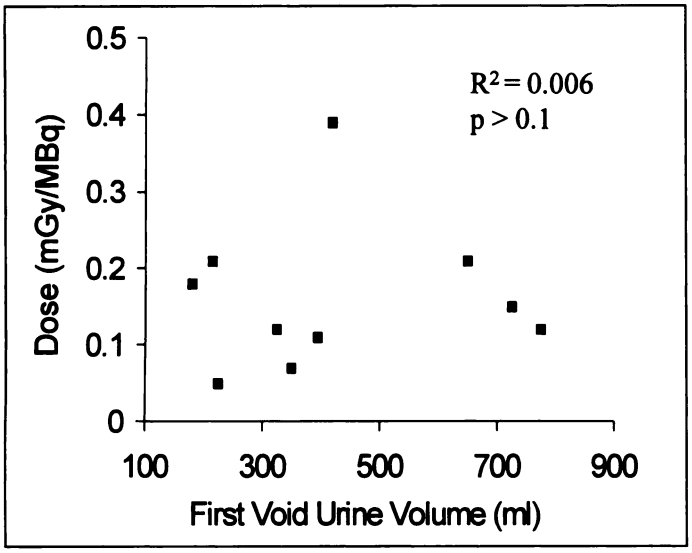

FIGURE 3. The dose to the bladder wall is shown as a function of urine volume from the first void. No significant relationship was found between the two variables. This suggests that the decrease in radiation dose to the bladder wall occurs even with a small volume of urine output from the first void. Concentration of urine compensates for the decrease in volume (Fig. 4).

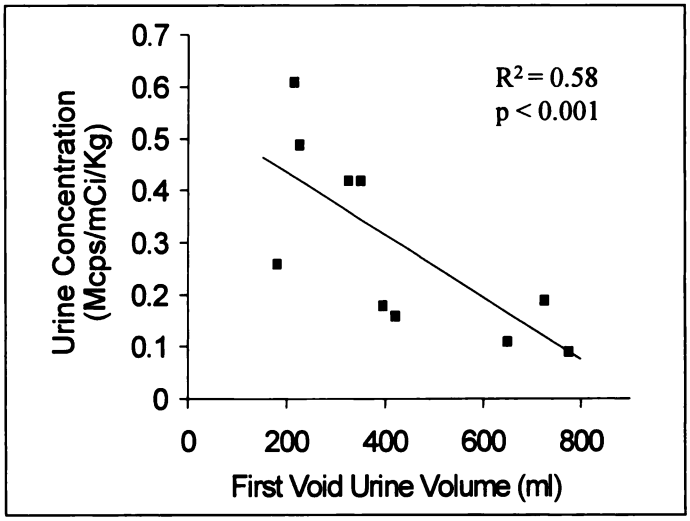

FIGURE 4. Statistically significant inverse relationship was observed between urine concentration and urine volume from the first void ($R^2 = 0.56$, $p < 0.001$). The line of regression is superimposed on the data points (Urine concentration = −0.0006 × Urine Volume + 0.556).

hydrated and 0.497 mGy/MBq (1.84 rads/mCi) when no hydration was used. The lower average wall radiation dose obtained in our study is the result of having subjects void 40 min postinjection as opposed to a 2-hr void in other protocols. The dose to the bladder wall is reduced by more than 50% by the use of a single void before the brain scanning phase. This reduction in bladder wall absorbed dose, by voiding, allows injection of a larger FDOPA activity yielding a larger signal-to-noise ratio and better quality images. Our data also show that, within the normal range, the absolute amount of urine output in the first void is not critical to the reduction of bladder dose; a small urine volume was associated with a higher concentration (Figs. 3 and 4).

CONCLUSION

Our study demonstrates that an injection of 333 MBq (9 mCi) FDOPA is the upper limit and should not be exceeded to comply with the 50-mGy (5-rad) maximum dose permitted by the FDA for research subjects.

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