Optimization of Urinary FDG Excretion During PET Imaging

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Accumulation of fluorodeoxyglucose (FDG) activity in the urine interferes with the visualization of pelvic and, sometimes, abdominal abnormalities. Although this is a major problem, there are few data on the physiological variables affecting FDG urinary excretion that are critical to minimizing urinary FDG interference during PET imaging. **Methods:** The excretion of FDG in urine was determined during 90 min in four groups of rats (n = 24) under the following conditions: normal, hydrated, hydrochlorothiazide treated and phlorizin treated. FDG clearance rates were measured in both normal and phlorizin-treated animals and compared with the glomeruler filtration rate measured with ^{99m}Tc-diethylenetriamine pentaacetic acid. We measured FDG excretion in 10 patients who had no known renal disease and were undergoing PET scanning (divided into two groups: hydrated and dehydrated) to relate the animal data to humans. **Results:** The hydrated and phlorizin-treated animals had the highest excretion of FDG (39.68 ± 5.00 % injected dose (%ID) and 45.64 ± 9.77 %ID, respectively). Animals given the hydrochlorothiazide had the highest urinary volume, but the percentage excreted was comparable with the normal rats. Measurement of the clearance of FDG in animals before and after the administration of phlorizin determined the amount of FDG reabsorbed in the proximal tubules to be 56% ± 9.15%. The hydrated patients had a higher excretion of FDG than dehydrated patients (16.98 ± 1.99 %ID versus 14.27 ± 1.00 %ID, $P < 0.021$), and the volume of urine voided was significantly higher ($P < 0.020$). **Conclusion:** Hydrochlorothiazide increases urine volume without enhancing FDG excretion. The hydration of patients before PET scanning may lead to more FDG reaching the bladder. Reduction of bladder activity by more frequent voiding facilitated by increased urine volume in hydrated patients may be offset by increased delivery of FDG to the bladder. A preferable means of increasing urinary volume without increasing delivery of FDG to the bladder may be the use of a diuretic.

Key Words: fluorodeoxyglucose; PET; excretion

J Nucl Med 1999; 40:1352–1357

Fluorodeoxyglucose (FDG) PET scanning is widely used in the evaluation of patients with tumors (*1*). FDG is an analog of glucose in which the hydroxy group in the 2 position has been replaced with a fluorine atom. FDG is taken up in cells and phosphorylated to FDG-6-phosphate mediated by hexokinase. Because FDG-6-phosphate is not a substrate for glycolysis and does not undergo further metabolism, it remains trapped in the cell (*2*). Although glucose is completely reabsorbed in the proximal tubules of the kidney, FDG is not; this results in accumulation of radioactivity in the urine. Accumulation of FDG activity in the urine interferes with the visualization of pelvic and, sometimes, abdominal abnormalities even when the patients empty their bladders before the scan (*3–5*). Although this is a major problem, there are few data on the physiological variables affecting FDG urinary excretion that are critical to minimizing urinary FDG interference during PET imaging (*6*). To study this problem, we measured the amount of FDG excreted in the urine of animals under different physiological conditions. The clearance rate of FDG was measured in normal animals and animals treated with phlorizin (an agent that blocks reabsorption of glucose) to determine the amount of FDG reabsorbed in the proximal tubules. FDG excretion in patients who have no known renal disease and are undergoing PET scanning was carried out to relate the animal data to humans.

Received Jul. 31, 1998; revision accepted Feb. 4, 1999.

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MATERIALS AND METHODS

Excretion of Fluorodeoxyglucose in Sprague-Dawley Rats

Twenty-four female Sprague-Dawley rats (180–200 g, Charles River, Boston, MA) were divided into four groups. Each animal had catheters placed in the bladder for collection of urine, in the femoral vein for administration of FDG (PETNET, Palo Alto, CA) and the femoral artery for collection of blood. All animals were given food and water ad libitum before receiving approximately 3.7 MBq FDG. The normal group received only FDG. The hydrated group was infused with normal saline (1.5–3.0 mL/h until the urine flow rate was constant for 5 min) before the administration of FDG. The saline infusion (1.5 mL/h) continued throughout the experiment. The third group was given hydrochlorothiazide (0.1–0.2 mg/mL; Sigma, St. Louis, MO) in their drinking water for 5 d before the study. On the day of the study, a single injection of hydrochlorothiazide (1.5 mg) in 0.3 mL water was given 15 min before FDG administration. The fourth group was given a prime dose of phlorizin (0.88 mg; Sigma) in 0.2 mL saline 15 min before FDG administration and infused with phlorizin (4.4 mg/mL at 1.5 mL/h) for the remainder of the experiment. Urine was collected at

30-min intervals, and the amount of FDG present was determined and expressed as percentage of injected dose (%ID). At the conclusion of each experiment, the animals were killed and their kidneys and bladder were harvested. The amount of FDG present was determined and expressed as percentage of injected dose per gram of tissue (%ID/g).

Clearance Rate of Fluorodeoxyglucose

The clearance rate of FDG was measured in 6 normal female Sprague-Dawley rats that were catheterized as described above. Clearance measurements were made simultaneously using FDG and ^{99m}Tc N,N′,N″-diethylenetriamine pentaacetic acid (DTPA) using the continuous infusion

$$\frac{\text{(urine concentration)(volume urine)}}{\text{plasma concentration}}$$

method (*7*). To minimize spill down of ^{18}F counts into the ^{99m}Tc window, the ^{18}F activity was counted first and the ^{99m}Tc activity was counted after the samples had decayed for 1 d. The FDG clearance rate was also determined in 6 animals that were given a priming dose of phlorizin (0.88 mg) in 0.2 mL saline and infused with 4.4 mg/mL at 1.5 mL/h for the remainder of the experiment.

Urinary Excretion of Fluorodeoxyglucose in Humans

The study population consisted of 10 consecutive patients who had no known renal disease (excluding diabetics) and were scheduled to undergo PET. The patients were randomly divided into two groups; Group 1 (hydrated) patients were told not to eat after 8:00 PM the night before imaging but were allowed to drink ad libitum. Group 2 (dehydrated) patients were told not to eat or drink after 8:00 PM the night before imaging. All patients received the standard dose of FDG (111–130 MBq). Urine was collected at 60 and 150 min postinjection. The volume, specific gravity and total activity of each urine sample were determined.

RESULTS

Urinary Excretion of Fluorodeoxyglucose in Rats

In three of the groups of rats, the majority of the overall excreted FDG appeared in the urine during the first 30 min: hydrated (70%), hydrochlorothiazide (63%) and phlorizin (57%) (Fig. 1). The hydrated and phlorizin-treated animals had the highest overall excretion of FDG (39.68 ± 5.00 and 45.64 ± 9.77 %ID, respectively). Both groups of animals had statistically higher excretion of FDG than the normal and hydrochlorothiazide-treated groups ($P < 0.001$). However, the difference between the hydrated and phlorizin-treated animals was not statistically significant ($P < 0.112$). There was no significant difference in the overall excretion of FDG between the normal and hydrochlorothiazide-treated animals ($P < 0.226$). In the normal group, there was no significant difference in the amount of FDG excreted in the first 30 min and the second 30 min.

Figure 2 shows that hydrochlorothiazide had the greatest effect on volume of urine voided over 90 min (6.47 ± 2.14 mL), followed by hydration (4.92 ± 1.35 mL) and phlorizin (4.15 ± 1.43 mL), compared with the normal animals (3.23 ± 1.51 mL). Although the total voided volume for the hydrochlorothiazide-treated animals was higher than the normal and phlorizin-treated animals ($P < 0.008$ and $P <$

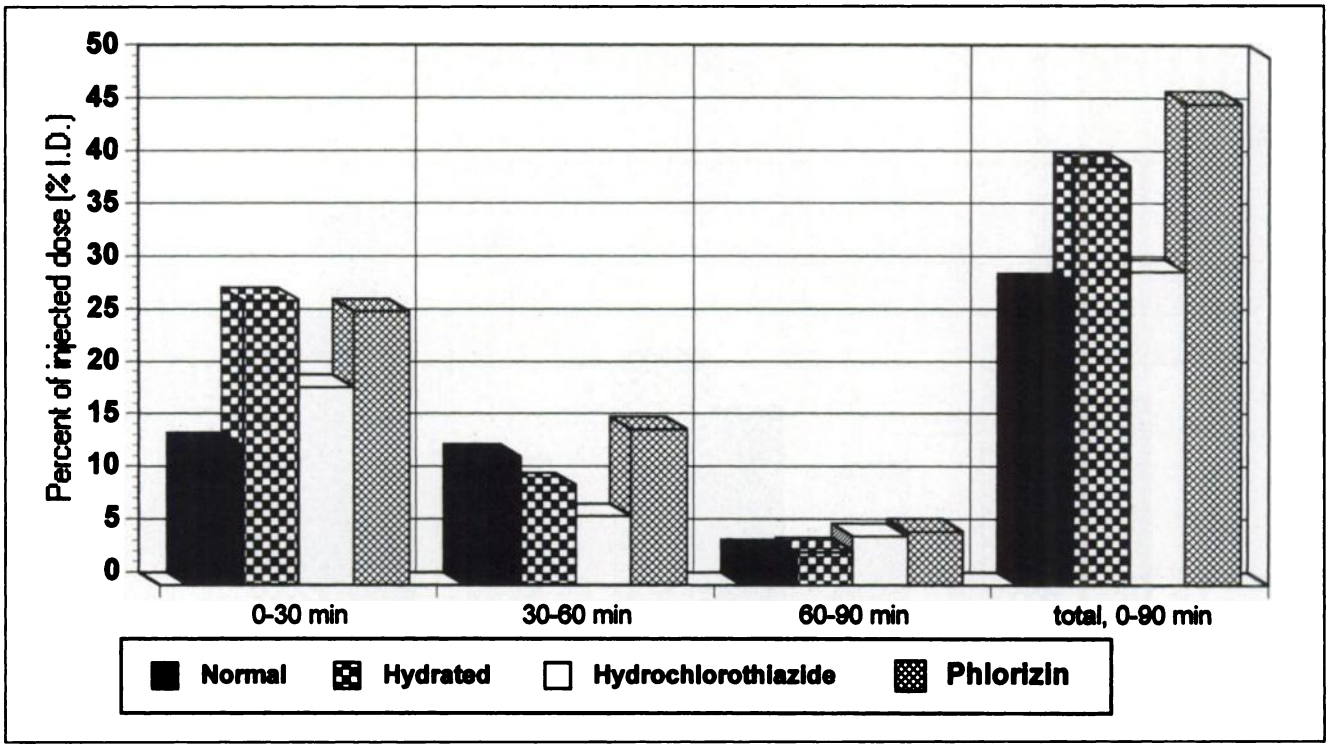

FIGURE 1. Urinary excretion (%ID) of FDG in four groups of Sprague-Dawley rats: normal (FDG only), hydrated (saline infusion at 1.0 mL/h), hydrochlorothiazide (single injection of 1.5 mg) and phlorizin (prime dose of 0.88 mg and infused 4.4 mg/mL).

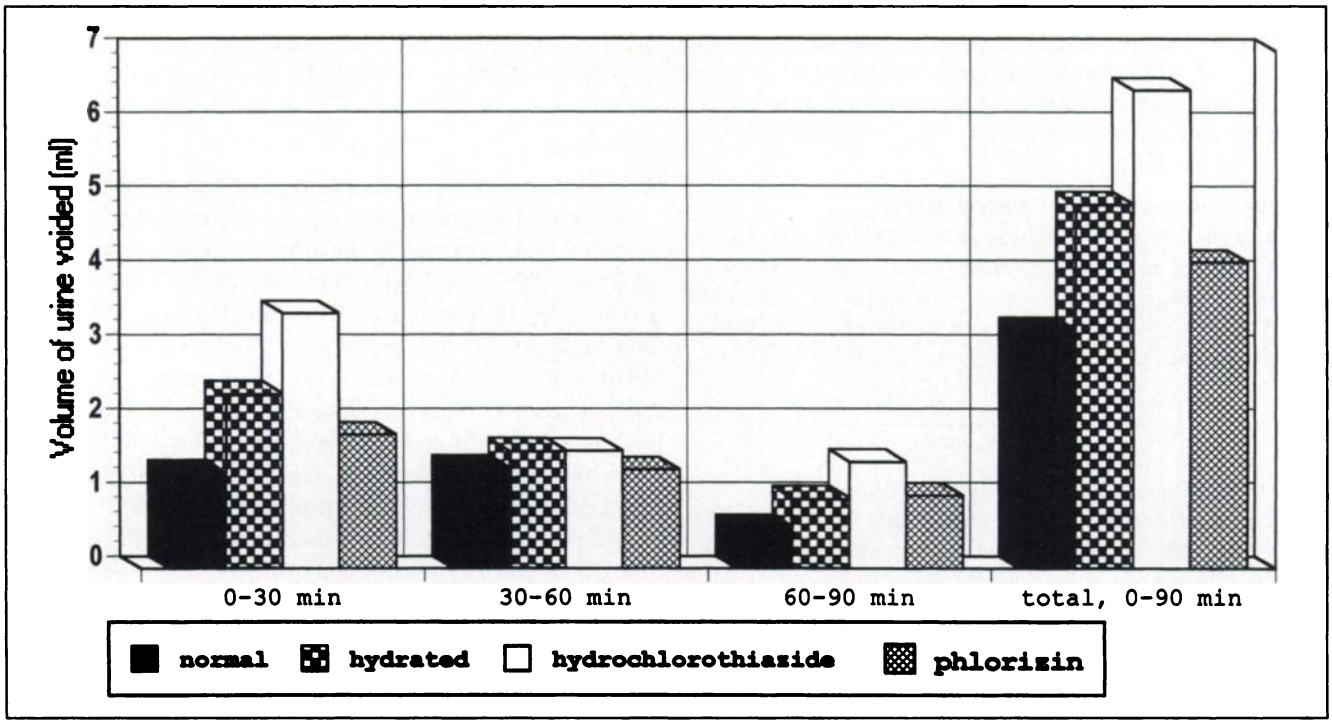

FIGURE 2. Comparison of volume of urine collected (mL) at 30, 60, 90 min and total for four groups of animals.

0.030, respectively), it was not statistically different than the hydrated animals ($P < 0.085$). Analysis of the kidneys at the end of each experiment showed that there was significantly lower residual renal FDG activity in the phlorizin group (0.31 ± 0.110 %ID/g) than the other three groups (hydrated 0.54 ± 0.113% ID/g, normal 0.42 ± 0.058% ID/g, hydrochlorothiazide 0.40 ± 0.166% ID/g; $P < 0.017$, $P < 0.030$ and $P < 0.048$, respectively). The lowest postmortem bladder activity was in the hydrochlorothiazide group (Fig. 3).

Clearance Rate of Fluorodeoxyglucose

The clearance rates of FDG and ^{99m}Tc-DTPA were determined simultaneously in both normal and phlorizin-treated animals using the continuous infusion method. In

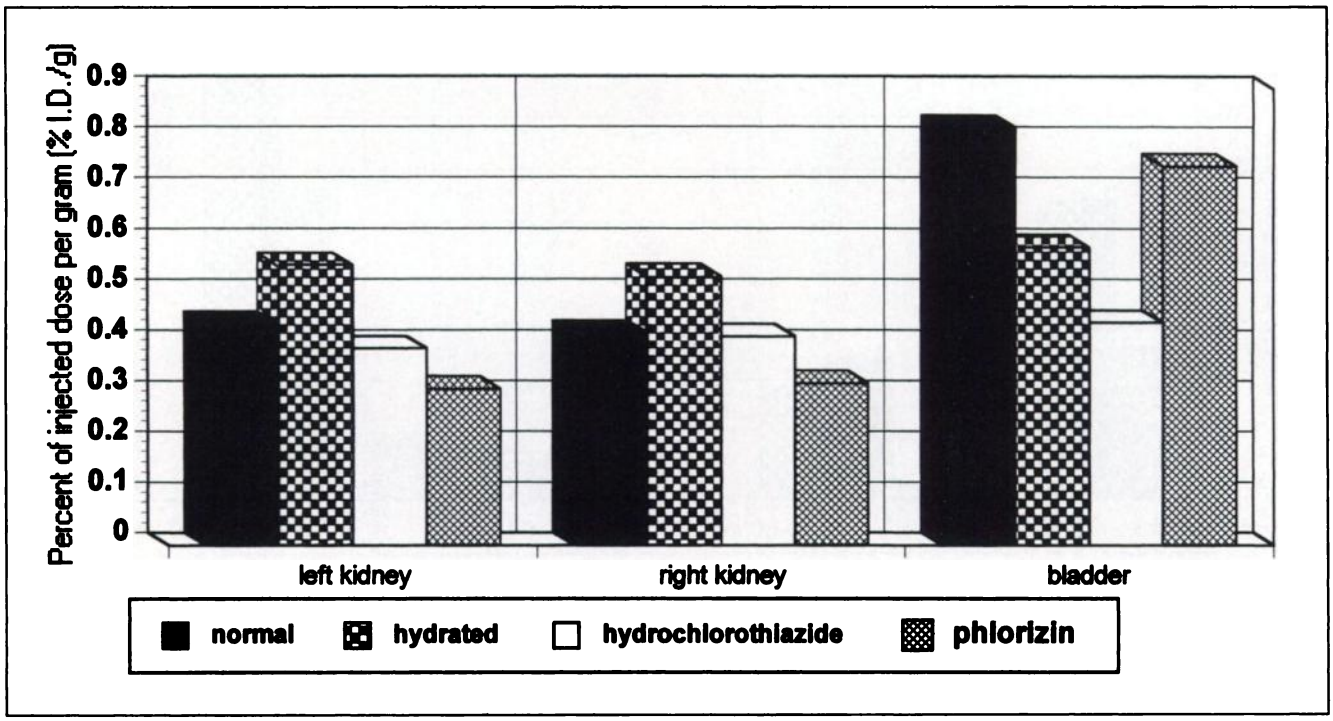

FIGURE 3. FGD uptake (%ID/g) in kidneys and bladder of four groups of animals at 90 min after intravenous injection of FDG.

normal animals, the clearance rate of FDG was 0.348 ± 0.089 mL/min/100 g body weight. This is approximately half the clearance rate measured with ^{99m}Tc-DTPA in the same animals (0.701 ± 0.091 mL/min/100 g, $P < 0.00004$). In the animals given phlorizin, the clearance of FDG increased to 0.785 ± 0.137 mL/min/100 g (not significantly different than normal DTPA clearance, $P < 0.106$). The administration of phlorizin resulted in an increase by a factor of 2.25 in the clearance rate of FDG.

Urinary Excretion of Fluorodeoxyglucose in Humans

The state of hydration of the two groups of humans was determined by volume of urine voided and the specific gravity of the urine. Results from the patient study are listed (Table 1). The state of hydration of the two groups is well differentiated based on urine volume (681.40 ± 135.24 mL versus 192.00 ± 88.65 mL, $P < 0.0002$) and specific gravity (1.005 ± 0.008 g/mL versus 1.019 ± 0.006 g/mL, $P < 0.010$). The hydrated patients had a higher excretion of FDG in their urine than the dehydrated patients (16.98 ± 1.99 %ID versus 14.27 ± 1.00 %ID, $P < 0.021$).

DISCUSSION

As PET imaging becomes used more frequently, the problem of FDG accumulation in the kidneys and urinary bladder needs to be addressed. Urinary FDG activity has the potential to interfere with tumor detection causing both false-positives and -negatives (*3–5*). Because FDG is not completely reabsorbed in the kidney, to optimize visualization of pelvic abnormalities, it is necessary to determine what physiological conditions reduce the accumulation of FDG in the urine. Hydration with voiding before scanning has been advocated with little supporting data as a means of reduction of bladder activity. Among the four groups of animals studied, the hydrated and phlorizin-treated groups had the highest excretion of FDG in the urine. This creates doubt of the efficacy of this approach. The use of a diuretic had no effect on the amount of FDG excreted into the urine compared with the control group. In three of the groups (hydrated, hydrochlorothiazide and phlorizin), the majority of the excreted FDG was excreted in the first 30 min. In all groups, less than 5% of the injected dose was excreted in the last 30 min of the experiment. This indicates that the FDG that remains in the blood is rapidly filtered by the kidneys and accumulates in the urine. The percentage of FDG excreted in the urine appears to be independent of the volume of urine voided. This is illustrated by the fact that the hydrochlorothiazide-treated animals, which had the highest urine void volume, had one of the lowest percentages of FDG excreted in the urine. As expected, the hydrochlorothiazide-treated animals had the lowest concentration of FDG in the urine (%ID/mL of urine) (Fig. 4). Somewhat unexpected is the fact that normal and phlorizin groups had similar overall concentration of FDG in the urine, despite the phlorizin group having a statistically higher excretion of FDG. This probably reflects the diuretic effect of the FDG molecule itself. These results are comparable with the findings of Kosuda et al. (*6*). Although using different experimental conditions, they reported that the concentration of FDG in the urine was highest for the control group, followed by a group given Lasix (furosemide; Hoechst-Roussel, Somerville, NJ) and then a group given Lasix and saline. In our experiments, the normal and phlorizin-treated groups had the highest concentration of FDG in the urine, followed by hydrated and the hydrochlorothiazide-treated group. The nature of the diuretic does not appear to be important because both hydrochlorothiazide and Lasix gave similar results.

TABLE 1
Fluorodeoxyglucose (FDG) Excretion in Patients

	FDG (%ID)	Void volume (mL)	Specific gravity (g/mL)
Hydrated	16.98 (1.99)*†	681.40 (135.24)‡	1.005 (0.008)‡
Dehydrated	14.27 (1.00)§	192.00 (88.65)	1.019 (0.006)

*$P < 0.05$.
†8.21 %ID 0–60 min, 9.17 %ID 60–150 min.
‡$P < 0.001$.
§6.67 %ID 0–60 min, 7.59 %ID 60–150 min.

The uptake of FDG in renal tissue was lowest for the phlorizin group. This is consistent with the supposition that FDG is a substrate for the sodium-dependent glucose transporter. If phlorizin blocks reabsorbtion of FDG in the proximal tubules, then the amount of FDG trapped in renal tissue should be lower than any other group. The average renal uptake in the two kidneys of the phlorizin group was 0.313 %ID/g. This was statistically lower than the other three groups (normal 0.423, hydrated 0.541 and hydrochlorothiazide 0.400 %ID/g; $P < 0.030$, $P < 0.017$ and $P < 0.045$, respectively).

Glucose transport in the kidney is a two-step process, with the active accumulation of glucose by an Na^+-dependent transporter on the apical membrane transporting glucose against its concentration gradient (*8*). The accumulated glucose is subsequently released into the capillaries by high-capacity, low-affinity GLUT 2, which is present at the basolateral borders (*9*). The low-affinity cotransporter SGLT-2 is abundant in the proximal convoluted tubule and is responsible for ~90% of glucose reabsorption. The remaining glucose is reabsorbed by the high-affinity SGLT-1 cotransporter present in the straight part of the proximal tubule (*10*). The hydroxy groups in D-glucose play a critical role in the recognition and transportation of glucose out of the proximal tubules of the kidney. Removal of the hydroxy group at the 2 position of D-glucose diminishes the affinity of this molecule for the sodium-dependent glucose transporter in the proximal tubules (*11,12*). However, atoms other than oxygen are capable of hydrogen bonding, and a fluorine atom substituted for a hydroxy group in the 2 position of

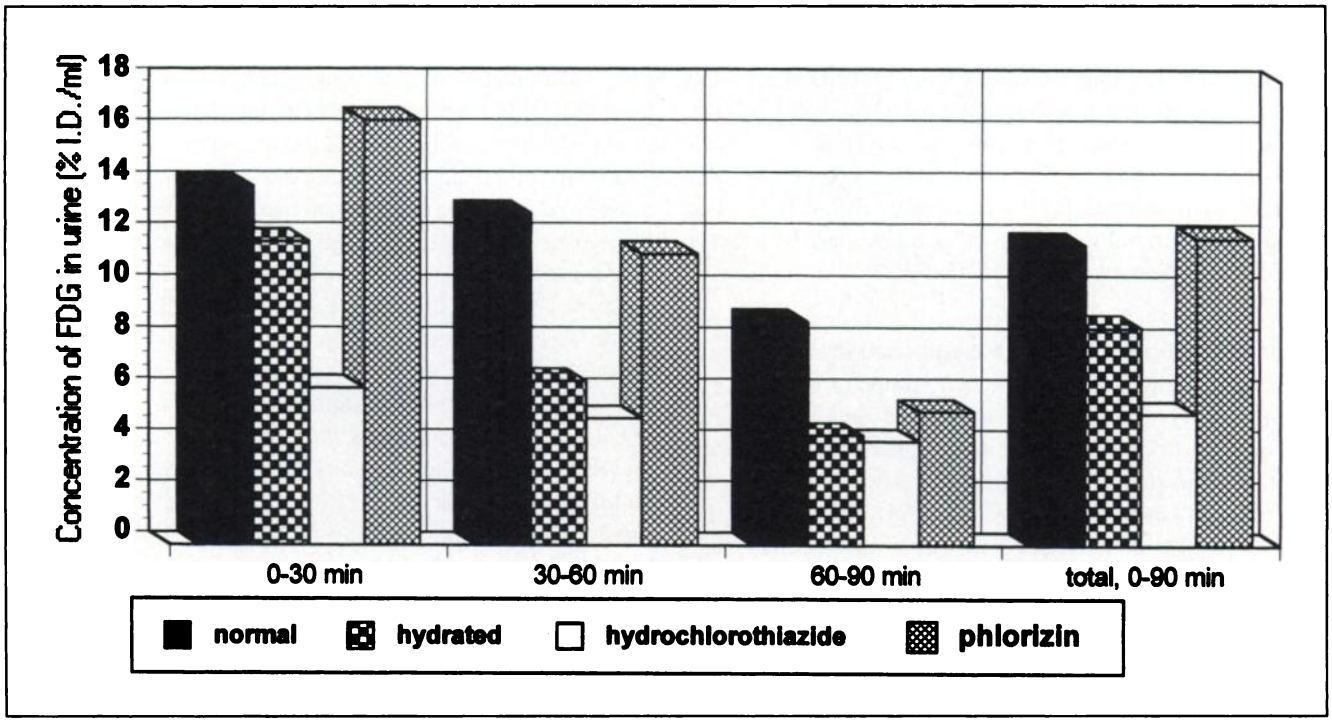

FIGURE 4. Concentration of FDG in urine (%ID/mL) at 30, 60, 90 min and total for four groups of animals.

D-glucose has been shown to be a substrate for the glucose carrier (*12*). This has been confirmed in our experiments measuring the clearance of FDG in normal and phlorizin-treated animals. In normal animals, the clearance of FDG was 0.348 mL/min/100 g; this is approximately half the clearance rate of ^{99m}Tc-DTPA measured in the same animals (0.701 mL/min/100 g). The clearance of FDG in the phlorizin-treated animals increased to 0.785 mL/min/100 g. These results indicate that in normal animals, 56% of filtered FDG is reabsorbed in the proximal tubules. Based on intratubular microinjection experiments, approximately 16% of 2-deoxy-D-glucose is reabsorbed in the early proximal tubules (*13*). The difference in reabsorption among D-glucose, FDG and 2-deoxy-D-glucose is due to the hydrogen bonding ability of the atoms in the 2 position. As the ability of these atoms to hydrogen bond decreases, the affinity for the receptor decreases, resulting in increased accumulation of the sugar in the urine.

In the animal study, the state of hydration had a marked effect on the amount of FDG excreted in the urine. When this observation was tested in humans, the hydrated group had the significantly larger urinary volume (681 mL) compared with the dehydrated group (192 mL), as well as a lower specific gravity (hydrated 1.005 g/mL, dehydrated 1.019 g/mL). Based on these criteria, there were significant differences in the state of hydration between the two groups. As was seen in the animal study, the hydrated group had a higher excretion of FDG in the urine than the dehydrated group (16.98 and 14.27 %ID, respectively). The difference between the two human groups was not as great as seen in the animals, which may reflect the fact that we were able to exert greater control over the physiological conditions of the animals than the patients.

CONCLUSION

Replacement of a hydroxy group in D-glucose with a fluorine atom causes significantly greater urinary accumulation of FDG, resulting in problems in image interpretation. The decrease in reabsorption of FDG is a result of lower affinity of FDG for the glucose transporters in the proximal tubules of the kidney. Moving the ^{18}F label to another position is not an option because the resulting molecules are not metabolically trapped in cells. Therefore, alternative methods must be developed to reduce the amount or concentration of FDG in the urine. The hydration of patients before PET may lead to more FDG reaching the bladder. More frequent voiding facilitated by increased urine volume in hydrated patients may be offset by increased delivery of FDG to the bladder. A preferable means of increasing urinary volume without increasing delivery of FDG to the bladder may be the use of a diuretic.

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