Effects of Dipyridamole Infusion on Human Renal Function Observed Using Technetium-99m-DTPA

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Our observation that a prolonged dipyridamole infusion reduced or eliminated blood clearance of Gd-DTPA in dogs led us to investigate if dipyridamole, infused intravenously at rates comparable to those used in thallium myocardial perfusion tests, would alter renal filtration in humans. Renal filtration was assessed using a bolus injection of 10 mCi of ^{99m}Tc-DTPA in five males (19–63 yr old) with normal serum urea and creatinine. Twenty minutes following the bolus injection a 10-min intravenous infusion of either dipyridamole (0.14 mg/kg/min) or saline sham was given. Four to 10 min following the start of the dipyridamole infusion, a paradoxical rise in counts in the kidney region of interest was observed and persisted for 10 to 27 min. During this time, a 13% to 52% (mean±s.d., 40%±16%, p<0.007) reduction in the exponential slope defining the clearance of counts from the cardiac region of interest occurred (implying a reduction of glomerular filtration rate), mean heart rate increased 27±5 bpm, p<0.002 and mean diastolic pressure decreased 12.9±6.4 mmHg, p<0.028. This finding indicates that renal clearance of tracers such as thallium or contrast agents such as Gd-DTPA is reduced during dipyridamole infusion.

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I n our laboratory, dipyridamole has been used to induce cardiac hyperemia in a beagle dog model to facilitate the use of magnetic resonance imaging for the determination of regional cardiac blood flow (*1*). Since Gd-DTPA (gadolinium-diethylenetriaminepentaacetate) is used as a contrast agent in these studies, ^{99m}Tc-DTPA was used to perform renograms on dogs to observe any effect that dipyridamole might have on renal elimination of the DTPA molecule. (We have already established that Gd-DTPA and ^{99m}Tc-DTPA have similar biodistribution and clearance (*2*).) The renograms indicated that dipyridamole had a dramatic effect on the renal clearance of ^{99m}Tc-

DTPA. Since dipyridamole is frequently used in pharmacologic stress testing, with and without an exercise component, of patients with coronary artery disease (*3*), it was decided that normal humans should be investigated to see if the effect observed in the dog also occurred in humans.

METHOD

Five human volunteers between the ages of 19 and 65 yr were studied. Ethical acceptability of this study was obtained from the University of Western Ontario Review Board for Health Sciences Research Involving Human Subjects. They were previously screened for cardiovascular health by a cardiologist and their renal function was assumed normal since serum creatinine and blood urea fell within the normal range.

Each volunteer underwent two infusions, one a sham infusion of saline and the other an experimental infusion of dipyridamole. The subjects were randomized as to which infusion they would receive first, with the two separated in time by 5–7 days.

The subjects received a 10-mCi bolus injection of ^{99m}Tc-DTPA into an intravenous catheter in the antecubital vein. The ^{99m}Tc-DTPA was prepared from an in-house radiopharmaceutical kit formulation. Instant thin-layer chromatography indicated that the amount of free ^{99m}Tc was less than 2%. Beginning at the start of the isotope injection, images were collected at a rate of 30 per minute for the initial 2 min of the study and then at a rate of 5 per minute for the subsequent 58 min. A scintillation camera system (General Electric Maxi 61, Milwaukee, WI) with a high-efficiency collimator was used and images were acquired using a computer (Digital Equipment Corporation Gamma-11, Marlboro, MA). Twenty minutes following the bolus injection of ^{99m}Tc-DTPA, a 10-min continuous infusion of either dipyridamole or saline was begun. The dipyridamole/saline sham was infused into a peripheral intravenous site in the right antecubital vein using a Harvard Infusion pump. The dipyridamole was infused at a rate that would deliver a dose of 0.14 mg/kg/min. This dose was used because it is the same dose used in our previous animal experiments and it is also the same dose used in thallium stress testing (*3*). To eliminate any volume effect the infusion of dipyridamole might have had, the same volume infusion rate was used in the saline sham. Blood pressures were acquired every 2 min during the 10-min infusion and every 5 min for all other times using a sphygmomanometer on the subject's left arm. Heart rate was sampled at the same time as the blood pressure using the digital read out of an electrocardiogram

monitor (Honeywell Inc., telemetry transmitter and receiver TT-31, Fort Washington, PA).

Using the computer, regions of interest (ROIs) were drawn around the heart and left and right kidneys. In drawing the regions around the kidney, an effort was made to avoid including the renal pelvis. The cardiac region was drawn to include primarily left ventricle. Curves of counts in the ROI were plotted against time for the three defined regions.

In the case of the dipyridamole infusions, an unusual rise in the activity of the kidneys was noted following the onset of the dipyridamole infusion. To quantitate the effect of dipyridamole on renal clearance of DTPA, the cardiac curve was evaluated for a change in logarithmic slope, i.e. the cardiac curve was fitted to a single exponential and then the time constant in the exponent (here called the logarithmic slope) was considered proportional to the glomerular filtration rate (GFR) (4,5). The left and right kidney curves were used to objectively define the time interval to be used in the slope analysis of the heart curve. The start of this interval was defined as the time at which the counts began to rise in the kidney renal ROI, and the end defined as when the counts began to fall (see Fig. 1A).

RESULTS

The most interesting result of this experiment was the curve generated by the kidney ROI for the dipyridamole infusions (Fig. 1A). The curve resulting from the analysis of the saline infusions were characteristic of a normal renogram (Fig. 1B). Four to 10 min following the initiation of the infusion of dipyridamole, the counts in the kidneys began to rise and continue to rise for 10 to 27 min, depending on the patient (see Fig. 1A and Table 1). Comparison of the saline-to-dipyridamole heart curves (Fig. 1C) showed a significant decrease in the slope during dipyridamole infusion, which varied from 13% to 52% (mean±s.d., 40%±16%, p<0.007). The individual subject results are shown in Table 1. This decrease in logarithmic slope strongly suggests that a similar decrease in GFR occurred (4,5).

Figure 2 shows the relative activity of the kidneys compared to the activity in the remainder of the thorax and abdomen. In this figure, the 12-sec frames during the rise in renal activity (24–46 min) were added together for both

TABLE 1
Heart Curve Logarithmic Slope During Kidney Curve Rise Period

Subject	Saline (min⁻¹)	Dipyridamole (min⁻¹)	%Change	Interval (min)
1	0.011	0.006	48%	19
2	0.009	0.008	13%	10
3	0.007	0.003	52%	22
4	0.011	0.006	46%	27
5	0.010	0.006	41%	15

the dipyridamole and saline control. The maximum grey scale values was set equal to the maximum pixel activity in the kidney. Note how much greater the relative kidney activity appears in the dipyridamole image (left) compared to the saline control image (right).

In order to determine if the kidney ROIs were the only regions where this unique effect of increased counts was noted, we drew multiple ROIs on each dipyridamole study and plotted time-activity curves. Regions were drawn over the left and right kidney, heart, liver, peri-renal, aorta, spleen, splanchnic bed, ureters and bladder. Only the time-activity curves for the left and right kidneys showed the distinctive pattern of increased counts. Some of the curves did show a flattening effect paralleling the effect seen in the heart curve. Figure 3 shows time-activity curves for the left kidney and a splanchnic ROI.

The mean heart rate increased 27±5 bpm, p<0.002, and the mean diastolic pressure decreased 12.9±6.4 mmHg, p<0.028, in comparison to mean preinfusion values. The changes in systolic pressures were not significant.

To estimate the reproducibility of the slopes reported in Table 1, one of the authors blind to these results, reanalyzed the slopes of the saline curves using redrawn ROIs and the previously determined time intervals. Values were reproducible to within 4%, 9%, 2%, 1.5% and 0.3%, respectively, for the five subjects. Note that in all cases the dipyridamole effect exceeded these estimates of reproducibility.
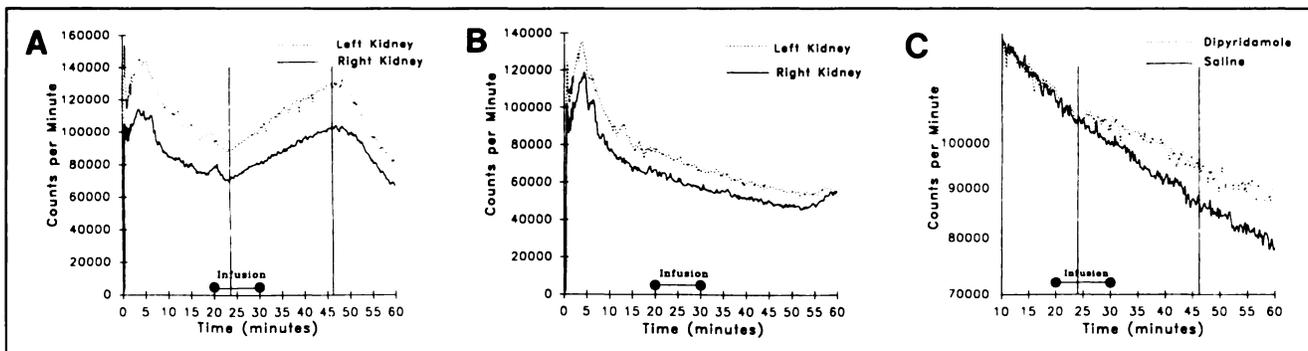
FIGURE 1. Time-activity curves of left and right kidneys showing the increase in counts due to a dipyridamole infusion (A) which did not occur during the saline infusion (B). The corresponding heart curves (C) show the logarithmic slope decrease from 0.007 min⁻¹ to 0.003 min⁻¹ due to the dipyridamole infusion. The vertical lines in (A) and (C) correspond to the time interval over which the altered heart slope was calculated. All results are for Subject 3 in Table 1.
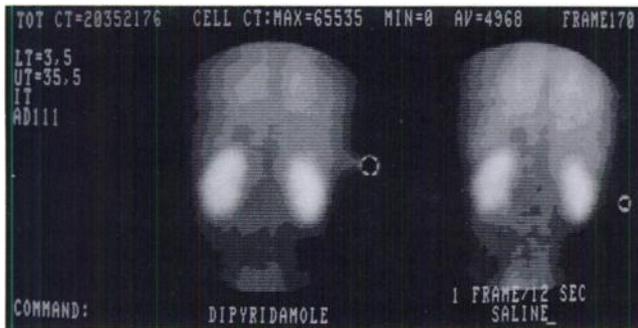
FIGURE 2. These images correspond to the addition of 12-sec frames from the start of the increase in renal activity to the time it begins to decrease in Subject 3, i.e. summed over 22 min. The image on the left corresponds to the dipyridamole study and the image on the right corresponds to the saline control. In each image, the maximum of the grey scale has been set equal to the maximum pixel occurring in the kidneys. Note the relative increase in kidney to background ratio seen in the dipyridamole study.

DISCUSSION

Dipyridamole is known to antagonize cellular adenosine uptake which results in increased concentration of extracellular adenosine due to decreased inactivation. Adenosine is postulated to be a major mediator in tubuloglomerular feedback (6). Thus, increased extracellular adenosine concentration provides the basis for the explanation for our results.

Administration of exogenous adenosine is known to significantly dilate vessels of the brain, heart, muscles and intestine (7,8). Therefore, the decrease in blood pressure observed during the dipyridamole infusion is the result of peripheral vasodilatation and the heart rate increase a compensatory mechanism for the fall in peripheral resistance.

The decreased GFR is caused by an adenosine induced constriction of the afferent glomerular arterioles in the kidney (9-11). Although dipyridamole-induced reduction of GFR has been demonstrated previously, it has never,
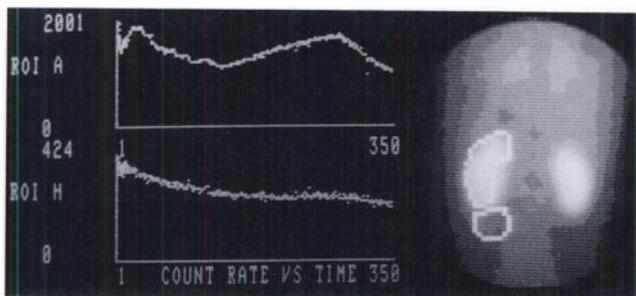
FIGURE 3. Time-activity curves for Subject 3 for the left kidney and a region of the splanchnic bed below the left kidney. Note that the increase in the renal activity after the dipyridamole injection is not paralleled by an increase in splanchnic bed activity. Rather the splanchnic bed activity continued to decrease, albeit at a slower rate, which reflects the slower blood plasma clearance during this period of time.

to our knowledge, been documented in humans using nuclear medicine techniques.

The rise in the counts of the kidney curves is also explained by the effects of adenosine on the renal vasculature. Distal to the afferent glomerular arteriole constriction, hydrostatic pressure is decreased in the glomerulus and the vasa recta (9,10). The decreased hydrostatic pressure is responsible for the decreased GFR. The decreased hydrostatic pressure in the vasa recta facilitates increased reabsorption of water from the filtrate (11) as it flows through the nephron. In addition, with the diminished GFR, a lesser sodium load is presented to the tubular cells resulting in a higher percentage of the filtered sodium being reabsorbed. As a result, a higher percentage of the filtered water will be reabsorbed due to osmosis. This markedly reduces the tubular flow resulting in renal parenchymal retention of the ^{99m}Tc-DTPA. With both a decreased GFR and increased reabsorption, one is left with a very concentrated, slow flowing, low volume of urine (12) containing ^{99m}Tc-DTPA since the ^{99m}Tc-DTPA itself is not reabsorbed. When dipyridamole is discontinued, the adenosine metabolism returns to normal followed by renal function. This hypothesis of concentrated ^{99m}Tc-DTPA is reinforced by the visual pattern of increased activity in the renal regions seen in the dipyridamole studies, as compared to the saline controls, of all five subjects and exemplified in Figure 2.

There is also the possibility that this observed effect of decreased plasma clearance might be due, at least in part, to an increase in the size of the vascular compartment produced by the dipyridamole-induced vasodilation in the splanchnic bed. That is, our interpretation of decreased renal filtration based on a decrease in the slope of the blood curve assumes that the intravascular volume of distribution has not increased since, to a fist approximation, renal clearance is equal to the logarithmic slope times the volume of distribution. If this occurred, we would have expected an increase in detected activity in a splanchnic ROI during the dipyridamole-induced increases in renal activity. Analysis of the time-activity curves for all five subjects generated from multiple ROIs which included the kidneys, heart, liver, peri-renal region, aorta, spleen, ureters, bladder (when it was included in the field of view) and splanchnic bed strongly suggests that there is no significant increase in the intravascular volume of distribution. This is because during the increase in renal activity, no increase in activity in any of these regions was observed. In fact, as shown in Figure 3, the activity in the splanchnic bed continued to decrease; albeit at a slower rate reflecting the general decrease in clearance of the plasma activity. If the vascular volume was significantly increased, one would have expected the activity in the splanchnic bed to have increased rather than continue to reflect changes in the blood plasma activity.

A close examination of Figure 1C shows that the blood clearance, i.e. the logarithmic slope, does not increase back

to saline values once the increase in renal activity has stopped. On analysis of this slope following the point in time when the kidney activity begins to decrease, we found that: (1) in two subjects (including Patient 3 shown in Fig. 1C) there was no significant change in slope; (2) in two others there was a significant increase; and (3) in one, the results were unknown since there was insufficient data to analyze. What is probably happening is that plasma clearance returns to normal gradually with individual variability. Also, the rate of urine formation will vary in a complicated manner with increases if filtration increases and increases if water re-absorption decreases. Furthermore, renal activity should start to decrease once the tubules are full, i.e. renal transit times would have increased with the administration of dipyridamole but not increased to infinity. As urine formation slowly recovers, a bolus front of 99mTc-DTPA would move towards the collecting ducts and finally the activity in the kidney would start to decrease once this bolus passed out of the kidney.

Another possible explanation for part of this reduced plasma clearance would be a dipyridamole increase in the rate constants between intra- and extravascular volumes of distribution. Such an interpretation is dependent on the assumption that at the time of dipyridamole administration, i.e. 20 min, a significant equilibrium between the compartments had not been achieved. This assumption was tested by analyzing the logarithmic slopes in the saline controls at 60 min and comparing them to those determined at 20 min. It was found that at 60 min, the slopes were further reduced on average by 10% and at maximum by 15%. However, such an increase in the rate constants would have initially decreased the blood curve as tracer movement to the extravascular space was accelerated. This would have then been followed by a decrease in the logarithmic slope. As can be seen in Figure 1C, no such initial decrease is seen. Therefore, if this rate constant effect exists, it is an extremely small effect.

SUMMARY

The reduction of GFR is consistent with the known effect of dipyridamole on endogenous adenosine causing constriction of the afferent glomerular arterioles. The increased renal retention of 99mTc-DTPA is the result of decreased urine flow rate due to decreased GFR and increased water reabsorption resulting from decreased hydrostatic pressure in the vasculature distal to the glomerulus. This finding would have to be considered if one was examining renal data obtained during dipyridamole thallium stress tests. As well, the use of dipyridamole for stress testing in place of exercise in Gd-DTPA enhanced cardiac MRI (13) should be interpreted with caution since filtration, i.e. blood clearance of the contrast agent, could be delayed.

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