Effects of Cyclosporine in Lowering Red Blood Cell Technetium-99m Labeling Efficiency

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Cyclosporine, an immunosuppressant drug taken by many transplant patients, has been found to significantly lower red blood cell (RBC) labeling efficiency to an unacceptable level (below 50%.) We have observed an intermittent RBC ^{99m}Tc labeling problem in our cardiac transplant patients. After closely examining our in vitro labeling technique and finding no obvious errors, we began to check for a chemical interference from patient medications. We reviewed a detailed list of all medications these transplant patients were taking and felt the immunosuppressant drugs, cyclosporine and Immuran, to be the most suspect. We have currently studied 10 cardiac transplant patients who were undergoing radionuclide ventriculogram (RVG) examinations at our institution. We discovered that peak concentrations of cyclosporine in whole blood of greater than 100 ng/ml significantly decreased RBC labeling efficiency. We found no labeling interference from the other medications, including Immuran.

We have identified that recent cyclosporine administration will cause a significant decrease in red blood cell (RBC) labeling. A technically superior blood-pool study is directly related to the RBC labeling efficiency of the RBCs with technetium-99m (^{99m}Tc). Two basic methods of labeling are generally used, in vivo (*1*) and in vitro (*2*). There are variations on these two techniques, but we primarily use the in vitro labeling method available as a commercially supplied kit*, which yields a consistently higher labeling efficiency (90%–99%) and therefore produces better image quality (*3*). Using both methods, we have encountered intermittent labeling problems regardless of the method used. These labeling problems led us to examine our labeling technique, which revealed no known errors.

The majority of these labeling problems involved our cardiac transplant patients. We examined the medications these patients were taking to identify a possible source of interference with our in vitro labeling process. We suspected the immunosuppressant drug cyclosporine, as the other drugs had previously shown no interference with RBC labeling. Cyclosporine-A was introduced in the early 1980s and is one of the most common immunosuppressant drugs used to prevent the rejection of transplant organs and treat diseases of autoimmune origin. We sought to answer the questions: (1) Does cyclosporine act alone in causing a decrease in RBC labeling efficiency?; and (2) At what levels of cyclosporine do we see interference with RBC tagging?

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METHODS

We examined the RBC tagging efficiencies from heart transplant patients pre- and post-cyclosporine dosing. We randomly selected ten male cardiac transplant patients who were at least 1 yr post-transplant for our initial study. This would ensure that these patients were on a stable maintenance dose of cyclosporine. The patients were instructed to remain on all daily medications (see Table 1) with the exception of the immunosuppressant drugs, cyclosporine (Sandimmune) and Azathioprine (Immuran.) The first patient in the series was currently taking all other medications, including Azathioprine, with the exception of cyclosporine. A 15-cc sample of whole blood was taken to our in-house nuclear pharmacy for in vitro labeling using a commercially available RBC labeling kit* (*3*). The labeling efficiency was 97% despite the presence of the immunosuppressant drug, Azathioprine. The patient was then instructed to take his normal dose of cyclosporine. Another blood sample was taken approximately 2 hr later and revealed a labeling efficiency of 47%.

Nine other male cardiac transplant patients were studied. These patients took all daily medications except cyclosporine and blood samples were drawn and labeled using the in vitro labeling method. These patients then took their normal oral dose of cyclosporine and blood samples were drawn at 2 hr postadministration, because pharmacokinetic studies performed by Sandoz Corporation (*4*), manufacturer of cyclosporine, indicate peak concentrations in the blood and plasma occur 2–4 hr after administration.

To determine at what cyclosporine blood levels RBC labeling interference was observed, a dilution study was set up using five test tubes with 5 cc of whole blood and 100 units of heparin in each. The whole blood was obtained from a control volunteer who was on no medications. Tube 1 was a

TABLE 1. Common Medications Taken by Cardiac Transplant Patients

Drug	Amount	Action
Cyclosporine	5.0–10.0 mg/kg/day	Immunosuppressant
Azathioprine	1.0–3.0 mg/kg/day	Immunosuppressant
Prednisone	7.5–30 mg/day	Anti-inflammatory
Nifedipine	10–20 mg 3 x/day	Calcium channel blocker
Captopril	25–50 mg 2 x/day	Antihypertensive
Labetalol Hcl	200–400 mg 2 x/day	Alpha/beta blocker

control tube with no cyclosporine and to the other tubes were added 500, 1,000, 1,500 and 2,000 ng/ml of cyclosporine, respectively. These levels were selected because average through whole-blood concentrations of cyclosporine range from 200 to 800 ng/ml and peak concentrations may be as high as 4000 ng/ml (*4*). The five tubes were then incubated for 3 hr. This is the same method used for producing controls for the cyclosporine radioimmunoassay. After 3 hr, we labeled these five samples using the in vitro method. Any changes in labeling efficiency from this sample in these dilutions should only be related to the effects of cyclosporine since no other drugs were present.

RESULTS

Red blood cell labeling efficiencies were recorded and plotted for all 10 cardiac transplant patients pre- and 2-hr post-cyclosporine administration (Fig. 1.) Labeling efficiencies for pre-cyclosporine administration had a mean value of 96%, a standard deviation (s.d.) of 2.5, and a range of 91.7%–98.9%. Samples drawn 2 hr after an oral administration dose of 100–400 mg of cyclosporine showed a mean value of 44%, a s.d. of 11.9, and a range of 22.3%–62.1%. These results are presented in Table 2.

TABLE 2. In-Vitro ^{99m}Tc-RBC Labeling Values from Pre- and 2-Hr Post-Cyclosporine Patients

Patient number	Pre-cyclosporine	Post-cyclosporine
1	92.3	46.7
2	98.9	37.6
3	98.1	52.1
4	94.3	22.3
5	95.6	31.4
6	96.6	42.3
7	97.4	40.3
8	96.8	57.8
9	91.7	47.2
10	98.6	62.1

Results from our control dilution study revealed that cyclosporine whole blood concentrations up to 1,000 ng/ml produced an acceptable RBC labeling efficiency. The 1,500- and 2,000-ng/ml concentrations showed a rapid and continual decline of labeling efficiencies to around 60% (Fig. 2.)

DISCUSSION

The kit for in vitro RBC labeling should provide between 85%–99% labeling efficiency. This range will provide acceptable gated cardiac images for analysis. However, with tagging efficiencies below 85%, image quality begins to drop and suffers drastically as tagging efficiencies decrease (Fig. 3.) It is, therefore, most important to obtain the highest RBC tagging efficiency possible so that image resolution as well as processing techniques, such as automatic left ventricular edge detection, do not suffer.

In patients who are on a maintenance level of cyclosporine (100–400 mg twice daily), normal trough values should range from 100–500 ng/ml, with postadministration peak concen-

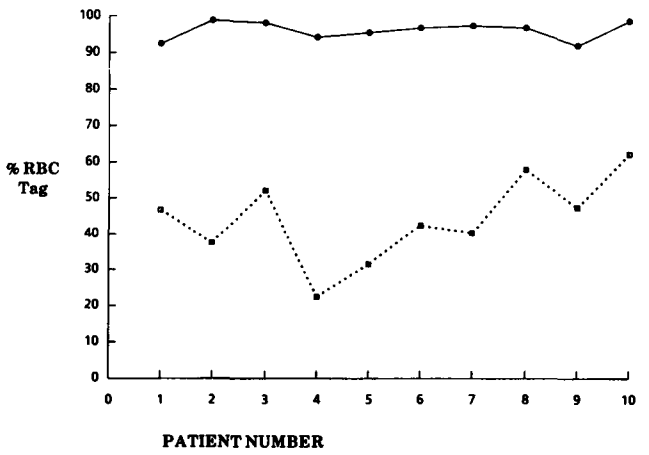

FIG. 1. Pre-cyclosporine ^{99m}Tc-RBC labeling efficiency (●——●) versus 2-hr post-cyclosporine dosing (■- - -■) in ten cardiac transplant patients.

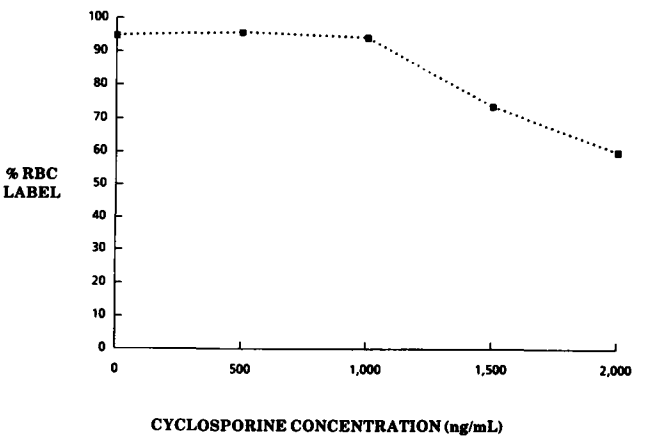

FIG. 2. Red blood cell labeling efficiencies at increasing concentrations of cyclosporine in whole blood. Samples range from a control with no cyclosporine up to 2000 ng/ml.

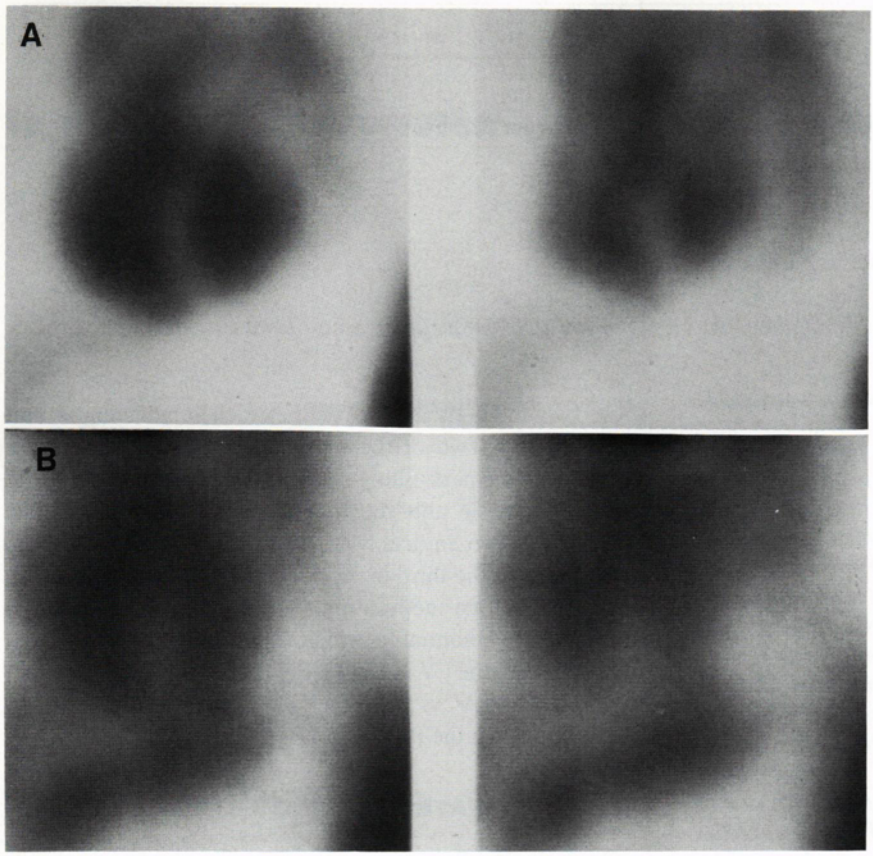

FIG. 3. (A) Gated, diastolic, and systolic cardiac blood-pool images in 45° LAO projections on a cardiac transplant patient with RBC labeling efficiency of 96%. (B) Same patient 2 hr post-cyclosporine dosing with a RBC labeling efficiency of 42%.

trations reaching as high as 4,000 ng/ml. It has been our experience that patients on maintenance doses of cyclosporine that fall within the average trough range of 100–500 ng/ml will usually have very acceptable RBC tagging efficiencies. However, the blood concentration of cyclosporine 1–6 hr after oral administration, reaches a level that can cause significant interference in RBC tagging and drastically decrease image quality.

We have obtained good results by having patients refrain from taking their daily cyclosporine dose until after we have labeled and completed their cardiac gated blood-pool procedure. We have even experienced good RBC tagging results (above 90%) as long as 1 hr after oral cyclosporine dosing. This is primarily due to the fact that peak concentrations are not reached in the blood until 2–4 hr after dosing. There may be a competitive binding phenomenon between the ^{99m}Tc and cyclosporine for RBCs, which causes the degrading of the RBC labeling efficiency.

Erythrocytes are the primary binding components for as much as 70% of the cyclosporine found in whole blood (*4*). Oral cyclosporine is absorbed from the upper bowel, extensively metabolized, and excreted primarily through the biliary and urinary systems (*4*).

CONCLUSIONS

There are multiple studies in nuclear medicine that require RBC labeling, including cardiac gated studies and gastrointestinal bleed detection, that can be adversely affected by the presence of peak amounts of cyclosporine. With more research being done in organ transplantation, including heart, kidney, liver etc., patients should be screened to determine if cyclosporine levels are sufficiently high to interfere with RBC tagging procedures.

As a general guideline in order to avoid RBC labeling problems in transplant patients, we would suggest that RBC labeling not be performed for 1–6 hr after an oral cyclosporine dose. This time frame may vary, depending on the patients dosage and metabolic rate.

NOTE

* Cadema Medical Products, Inc., Middletown, NY.

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