TEACHING EDITORIAL

Radionuclide Evaluation of Renal Transplants

The evaluation of renal function has long been fertile ground for the application of nuclear medicine techniques. Dr. Clorius in this issue of the Journal (1) has retrospectively compared dual-isotope studies, I-131 or I-123 Hippuran and bolus pertechnetate, with the clinical course of renal transplantation and has found this method useful.

There have been numerous attempts in the past ten years to use nuclear medicine techniques to evaluate transplant function and to differentiate between acute tubular necrosis (ATN) and rejection, but there are divergent opinions as to our ability to make the differentiation with certainty (2). Some groups have approached the problem on an a priori basis and suggested that graft dysfunction in the first week be termed ATN, whereas graft dysfunction that occurs beyond the first week is termed rejection. The incidence of disease occurrence suggests that this "gamesmanship" approach will produce the correct answer 80 to 90% of the time. The false-positive rate for this a priori approach is difficult to determine, but the incidence of hyperacute rejection or ATN of delayed onset from any cause or the incidence of surgical complications may approach 8%. We must now improve the diagnostic performance with radionuclide investigation.

Ten years ago we checked the uptake and excretion of Hippuran and were pleased to show the clinician that the renal artery, the renal vein, and the ureter were patent and urine was entering the bladder. When graft dysfunction occurred, it soon became clear that with Hippuran as the tracer neither visual nor graphic methods could separate the two most common problems, ATN and rejection, although it was possible to follow the course of the process and determine the direction of change. Some success however has been attained by numerical methods based on physiologically reasonable multicompartmental models (3, 4).

One difference between rejection and ATN can be determined by blood flow (5). Generally ATN is characterized by relatively normal blood flow whereas rejection is characterized by poor blood flow; and this difference in blood flow can be demonstrated by the proper bolus injection of a technetium-labeled radiopharmaceutical. The choice of which technetium-labeled radiopharmaceutical to use is not a critical one. Ten to 20 mCi of pertechnetate, Tc DTPA, or basic Tc penicillamine (6) produce essentially the same results when used to estimate renal blood flow on the first pass following bolus injection. Film or magnetic media may record the activity distribution at rates of from 1 to 5 sec per frame for 60 sec. The usual approach is to obtain activity/time curves from the transplant, iliac artery, either proximal or distal to the graft, and a background area. Slopes, heights, and transit times may then be measured from the activity/time curves with or without background correction. Regardless of the parameters measured, the variability of the bolus injection plays a major role in the introduction of variability in the resultant parameters.

The importance of a compact bolus cannot be overemphasized. Injection through convenient i.v. tubing almost always results in an elongated nonbolus; however, there are two approaches we have used to minimize the problem. These techniques may become important. The first involves the injection of the radiopharmaceutical into a dilated antecubital vein proximal to an AV shunt that is often in place for long-term dialysis. A small volume, usually 0.1 cc containing 15 to 20 mCi, is injected into the dilated vein through a 25-gauge needle on a tuberculin syringe. No tourniquet is ever applied to the arm, although an assistant may gently compress the mid-humeral area to cause slight distention of the vein to be injected. The syringe is not rinsed with blood. Bleeding from the very small wound is minimal and can be controlled with gentle pressure of a cotton pledget, but never apply pressure sufficient to occlude the vein. Using this technique a bolus of excellent quality is routinely accomplished and exceeded in quality only by injection through a catheter in the superior vena cava. Injection into an antecubital vein followed by arm raising as mentioned by Dr. Clorius is often satisfactory as long as axillary veins are not kinked. A standardized method we have
adopted involves the insertion of a butterfly needle, the careful injection of Tc DTPA through a three-way stopcock into a short piece of tubing with rapid injection into a peripheral vein, followed by injection of 30 cc of saline. This technique is discussed in detail in Chapter 4 of Quality Control in Nuclear Medicine (7).

A method to correct for bolus shape was the subject of a teaching editorial in the June issue of this Journal (8). Application of the deconvolution method to the renal transplant bolus problem may be of great help in decreasing the fluctuations in measured curve parameters so that the three classes of renal transplants—normal, ATN, and rejection—may be identified. Thus, despite the bolus problem, nuclear medicine can provide valid information.

The method I have found most useful to separate ATN from rejection requires a good intravenous bolus injection of pertechnetate or Tc DTPA, the image recording on magnetic media at one per second for 60 sec, and generation of an activity/time curve from the region of the graft (9). Three parameters are measured (Fig. 1). The washout parameter is the time in seconds for the declining counts of the first 6 to 10 sec following the peak to reach one-half their initial value. Originally activity/time curves from background and iliac artery were obtained, area corrections made, and appropriate curves subtracted from the renal curve. Subtraction of curves, calculation of differences in transit times, and ratios of curves failed to produce better discrimination between ATN and rejection than the washout parameter, which is a measure of the steepness of the initial washout phase. The measurement of the washout parameter does not require a computer although we have routinely used one. It is sufficient to take the raw counts from the first 6 to 10 sec following the peak of the renal curve, plot the counts on semilog paper, and fit a straight line to the curve. Goodness of fit values are almost always above 0.9, which indicates that a monoexponential curve is a quite reasonable assumption for those 6 to 10 sec following the peak. We also carefully assess the initial uptake phase of the curve, because these initial 6 sec should have a T1/2 of 1 sec or less. Curves that double every 2 sec on the average will produce a washout parameter that is falsely evaluated, and normal and ATN graphs will be falsely classified as rejection. Sample values for three parameters are recorded in Table 1.

I have used this washout parameter in clinical situations for over 10 yr in more than 300 patients and more than 900 flow studies. Washout parameters less than T1/2 = 17 sec rarely indicate rejection. ATN is characterized by values less than T1/2 = 28 sec, whereas rejection is characterized by values greater than T1/2 = 28 sec. Reports based on this parameter are accurate and usually predictive of clinical events to follow, and I do not hesitate to indicate that rejection is present in a patient who shows no clinical signs or symptoms. Interpretation of the sequential images is not a sensitive or accurate replacement for the washout parameter.
Clinicians recognize the limitations of our methods. The washout parameter considers the entire diagnostic universe of transplant possibilities to consist of normal, ATN, and rejection—an unrealistic situation. Clinicians recognize the physiological implications of normal and decreased blood flow upon which our simplistic method is based, realize the dynamic nature of the rejection process, and will obtain sequential studies. The severity of rejection may be estimated by the magnitude of the washout parameter. Values greater than 100 sec approach a horizontal line and indicate severe rejection. Response to massive i.v. steroid therapy can be seen by the washout parameter even when the Hippuran renogram remains essentially unchanged.

Although the rejection process is much more complex than reduction of blood flow, the identification of a decreased blood flow provides a valid point that can be measured in any nuclear medicine laboratory with a recording system and the ability to generate activity/time curves from a region of interest. I have no doubt that radiopharmaceutical advances will provide us with other more specific diagnostic means in the next several years.

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### REFERENCES