EDITORIAL

Quantitation of Renal Function Using MAG_3

Although a number of investigators have shown strong correlation between MAG_3 clearance and orthoiodohippurate (OIH) clearance, there has been no agreement on the exact value for the proportionality constant. Taylor, using a single-injection technique with HPLC-purified MAG_3, found a value of 0.70 (simultaneous 0–90-min data) (*1*). Bubeck found a value of 0.67 using a continuous-infusion technique with HPLC-purified MAG_3 in a series of 124 patients (*2*). Single-injection techniques using unpurified commercial kits have led to somewhat lower values, ranging from 0.51 to 0.61 (*3–5*). Whether these differences should be ascribed to the purity of the radiopharmaceutical or to the methodology of the studies has been unclear. In this issue, Prenen and co-workers report a value of 0.47, the lowest yet, using a continuous infusion method with an unpurified commercial kit, and argue that impurities are not significant. Their report will ensure that the debate continues.

ERPF VERSUS GFR—OR BOTH?

The two classical physiologic measures of renal function are inulin clearance (or GFR) and PAH clearance (or ERPF). Of these two, GFR is more familiar, being approximated (very crudely) by the widely available creatinine clearance. However, clinicians can learn to monitor renal function using ERPF in much the same way that they now use GFR. The compelling advantage of ERPF, from the standpoint of the nuclear medicine clinic, is that ERPF can be accurately measured in less than an hour in conjunction with an imaging study. Comparable accuracy in GFR requires a three-hour study, because the GFR agents are cleared much more slowly.

We are fortunate at the University of Alabama at Birmingham that Tauxe introduced his ERPF measurement here nearly two decades ago, so that our clinicians are accustomed to it, and our medical students and residents are exposed to it from the start (*6*). Our clinic offers both GFR and ERPF measurements, but ERPF is usually requested for routine patient care, and the more time-consuming GFR measurement is reserved for research studies.

The difference between ERPF, *effective* renal plasma flow, and RPF, the true renal plasma flow, should be recalled. The ERPF depends on the extraction fraction, which can be reduced in disease states. When ERPF is used to monitor disease activity, any disease-induced fall in extraction fraction will increase the measured fall in ERPF and thus increase the sensitivity of the measurement.

Ideally both ERPF and GFR should be measured and the (effective) filtration fraction calculated. The procedures are simple enough for routine clinical practice, although to date the combined measurement has been requested at our clinic only for research studies. Some disorders, such as acute transplant rejection, are characterized by a fall in filtration fraction, so that the severity of disease may not be reflected by the ERPF value. However, this can be readily identified on MAG_3 imaging studies by a distinctive pattern of parenchymal retention that is believed due to tubular stasis resulting from the fall in GFR. MAG_3 studies thus furnish an indirect qualitative measure of GFR as well as a direct quantitative measure of ERPF.

DOES MAG_3 CLEARANCE MEASURE ERPF?

A number of studies, cited above, have documented the close correlation between MAG_3 clearance and ERPF (taking OIH clearance as an approximation to ERPF). However, the relationship is empirical, and there is a possibility that it might fail in certain disease states or with the use of certain drugs. Time will tell. Patients with very high levels of renal function, in whom poorly excreted impurities in the radiopharmaceutical will cause the greatest numerical error, have not been carefully studied. It has been asserted that the relationship between MAG_3 clearance and OIH clearance fails in the presence of proteinuria (*7*), but few patients were studied and the conclusion is contrary to our experience. Our own studies (*8*) included five patients with +3 or +4 proteinuria (not mentioned in our published report), which caused no noticeable discrepancy between MAG_3 and OIH measurements. Even though not all possibilities have been explored, it is clear that ERPF can be estimated from MAG_3 clearance in most clinical contexts.

HOW DO YOU MEASURE MAG_3 CLEARANCE?

MAG_3 clearance can be measured by conventional single-injection multisample plasma clearance methods or by any of several simplified methods based on a single timed plasma sample. We believe the simplified methods are adequate for routine clinical use. Simple methods have been published by Russell (*8,9*), Claessens (*10*), and Müller-Suur (*5*). An additional method, developed by Bubeck, is available directly from that author and in some commercial software, but has not yet, to our knowledge, been published. All these methods give similar results and we are not aware of differences that would be consequential in routine clinical use.

HOW DO YOU INTERPRET MAG_3 CLEARANCE?

MAG_3 clearance can either be used directly as a measure of renal function or it can be converted to an ERPF

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estimate. The former is more defensible scientifically, but the latter seems more readily accepted by clinicians. The conversion depends on an empirical correlation between MAG_3 clearance and OIH clearance. A further refinement would be to correct for the small difference between OIH clearance and PAH clearance.

Different authors, as cited above, have reported different factors relating MAG_3 clearance to OIH clearance. Our own value, which has not been previously reported, is 0.59 ± 0.02. This has been calculated from single-injection multisample data obtained after simultaneous injection of MAG_3 and OIH in 19 patients; the clinical study has been described elsewhere (*11*). More exactly, regression of OIH clearance on MAG_3 clearance gave slope 1.45 ± 0.12, intercept 51 ± 35 ml/min, and correlation coefficient 0.94. Since the intercept did not differ significantly from zero, and, since the true curve should pass through the origin (corresponding to an anephric patient), the data were refitted to a line forced through the origin to give a calculated slope of 1.69 ± 0.04. (If one intends to predict OIH clearance from MAG_3 clearance, the preferred practice is to use regression of OIH on MAG_3, not of MAG_3 on OIH, since the least square error in OIH clearance is thereby minimized.) We arrive at the MAG_3/OIH ratio of 0.59 ± 0.02 by taking the reciprocal.

However, the method we are now using routinely in our clinic is based on a slightly different approach. It is based not on calculating MAG_3 clearance and dividing by 0.59, but instead on multiplying the MAG_3 plasma concentration by 0.56 and then applying the Tauxe formulas for OIH (*8*). No further correction is required to estimate ERPF, because the Tauxe formulas were originally designed to slightly overestimate OIH clearance and thus approximate PAH clearance (by adopting 60 min as the termination time for the multisample reference data for the Tauxe formulas) (*12*). Our choice of this method was based on the fact that many of our patients have years of previous ERPF values in their medical records. Consistency with our previous measurements was given top priority.

MAG_3 has not been compared directly with PAH. To be convincing to all nephrologists, the comparison PAH clearance should be measured by classical continuous infusion. This would be a lot of work, and nobody seems eager to pay for it. However, moderate error in the correction factor relating MAG_3 clearance to PAH clearance is not of great practical importance. Clinically, it is the changes in renal function that usually matter. If all values were off by a constant factor of 20%, the error would probably go unnoticed unless the measurements were compared with those from another laboratory. The whole issue could be avoided if clinical users could be persuaded to use MAG_3 clearance directly instead of converting it to ERPF. In that case, one of the formulas intended for direct estimation of MAG_3 clearance should be used (*5,9,10*), and not the method we are now using.

The user should be aware that single-sample methods may be unreliable in the presence of ascites or edema. He should also be aware that the percentage error can be large when renal function is very poor (below 25 ml/min for GFR or 125 ml/min for ERPF). The absolute error is not excessive, so that the single-sample method will correctly indicate that function is poor, but the relative error is large, so that the single-sample method should not be used to monitor changes at this level. (There are ways to get around this, but they involve prolonging or complicating the study.) Whenever renal function is poor enough that the serum creatinine is markedly elevated, the serum creatinine level itself becomes a sensitive indicator of changes in function, and there is less need for ERPF measurement. The ERPF is most useful in the range of renal function where serum creatinine is insensitive.

Normal values for MAG_3 clearance have not been well established. Renal clearances decrease with age, and any attempt to define normal values must take this into account. The "normal value" for MAG_3 clearance attributed to us by Prenen and co-workers (this issue) was in fact merely a value we assumed for an illustrative calculation, in a sentence that began "Taking as normal..." In practice, we use MAG_3 to estimate ERPF and then apply the age- and sex-dependent normal values for ERPF derived from a series of well-studied renal transplant donors at this center (*6*). However, normal values are not of great importance, since it is the changes on serial studies that are usually of most interest. The value of an accurate quantitative measurement is greatly diminished whenever there is no baseline measurement in the patient's record. To be used to best advantage, these measurements should be used repetitively.

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SELF-STUDY TEST

Gastrointestinal Nuclear Medicine

Questions are taken from the *Nuclear Medicine Self-Study Program I*, published by The Society of Nuclear Medicine

DIRECTIONS

The following items consist of a heading followed by numbered options related to that heading. Select those options you think are true and those that you think are false. Answers may be found on page 2125.

A 70-yr-old man was seen in the emergency room with episodes of intermittent melena and maroon-colored stools. The patient's vital signs were stable; his hematocrit was 35% and his hemoglobin was 10.2 g/dl. Images from a ^{99m}Tc-red blood cell study (Fig. 1) at 5, 30, and 90 min are shown along with a mucosal photograph obtained during subsequent colonoscopy (Fig. 2).

True statements concerning this patient include which of the following?

1. An air-contrast barium enema likely would be diagnostic.
2. A ^{99m}Tc-sulfur colloid study would likely have shown similar findings.
3. Angiodysplasia of the colon is present.
4. Selective magnification angiography of the superior mesenteric artery likely would be diagnostic.
5. The bleeding site is in the hepatic flexure.

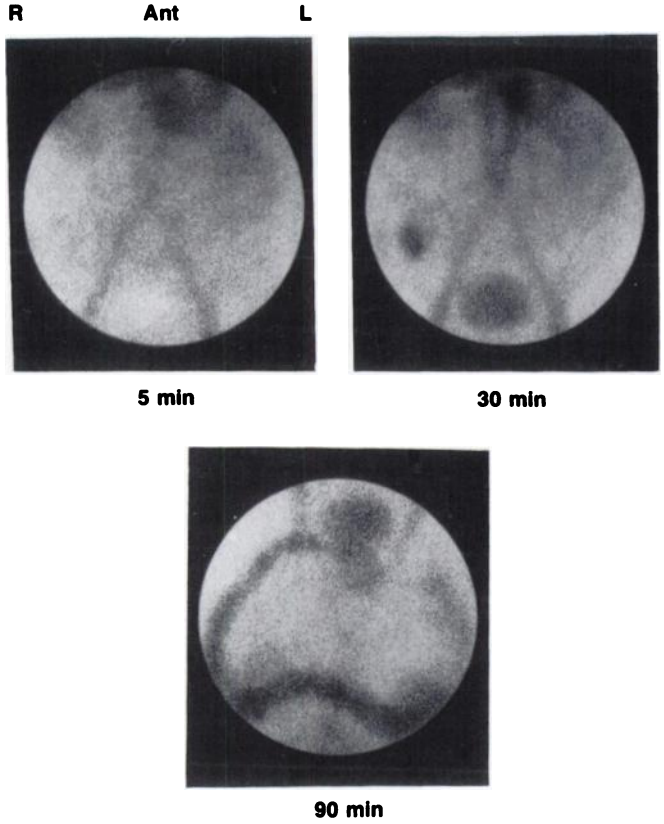

Figure 1

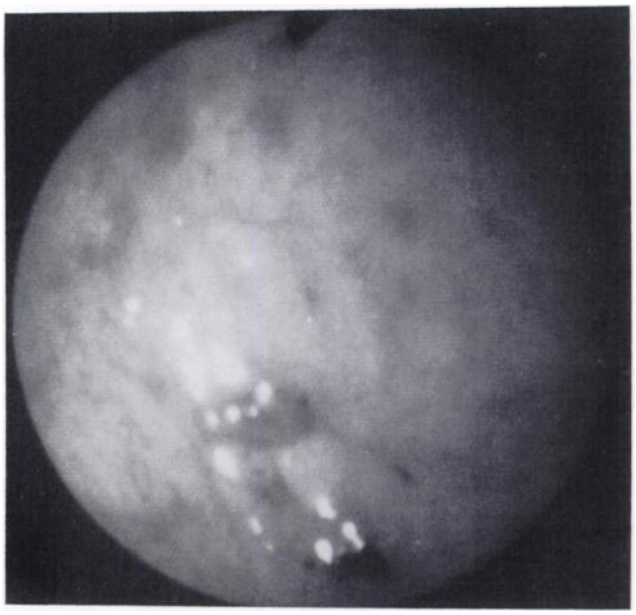

Figure 2

(continued on p. 2078)