Current Status of Renal Clearances*

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ABSTRACT

Determination of renal clearances continues to have value in clinical situations. Current knowledge of renal function permits expansion of the clearance concept to include non-excretory mechanisms by which kidneys clear substances from blood. Measurement of clearances is useful in quantifying renal function, progression of renal disease, response to therapy, demonstrating asymmetrical renal function, prescribing certain drugs or determining the amount of dialysis required. Because accurate chemical methods are clinically cumbersome, isotopic techniques are under development and simple, accurate methods are approaching routine availability.

Introduction

The clearance concept evolved over many years (10) but as classically presented, describes only excretory clearances and does not apply to non-excretory clearance mechanisms. It is important to restate the concept in terms which reflect all mechanisms by which renal parenchyma clears substances from blood. To determine a renal clearance is to determine the rate (amount per time) at which a substance is removed from circulation by the kidneys. This statement is explicitly different from the classical formulation that clearance equals the amount of a substance recovered from a timed urine collection divided by the plasma concentration of the substance. The difference is emphasized to bring out the importance of non-excretory renal clearance phenomena, in addition to classical excretory clearance mechanisms.

Substances may be cleared by: (1) glomerular filtration—e.g., inulin; (2) tubular secretion—e.g., para-aminohippuric acid; (3) tubular reabsorption and catabolism—e.g., B-2 microglobulin; and (4) tubular reabsorption and storage—e.g., amino-glycoside antibiotics.

Reasons for measuring a renal clearance include: (1) quantification of renal function; (2) measurement of rate of progression of a disease; (3) determination of a therapeutic or natural response; (4) com-

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parison of one kidney to another, as in renovascular hypertension; (5) obtaining data required to prescribe drugs appropriately—e.g., digoxin; and (6) determining the appropriate "dose" of dialysis.

Excretory clearances all begin with glomerular filtration. Factors involved in glomerular filtration rate (GFR) include the filtration barrier itself, perfusion pressure, oncotic pressure, ionic charge on the membrane, and molecular size, shape, flexibility, deformability, and electrical charge of the solute. There is disagreement as to whether or not there exists a functional reserve of filtering capacity, a question of some importance as the presence of a reserve capacity would imply that significant renal damage might occur before a measurement of glomerular filtration would reveal the presence of disease. Although amphibia have been observed to have intermittent perfusion of glomeruli, Thompson et al argued that "under normal conditions, all glomeruli are functional and no reserve of inactive nephrons exists." This statement avoids the issue of whether or not a glomerulus always functions to capacity. There are clear-cut examples of supranormal levels of glomerular filtration, implying either that more glomeruli are filtrating than usual, or that each glomerulus is filtering more than usual.

Most clinicians and physiologists are familiar with the dramatic changes in filtration rate that occur during normal pregnancy. It is less well-known that diabetic patients tend toward a raised GFR. Patients who have suffered major burns but are not septic or in shock have been found to have an endogenous creatinine clearance that averaged 172 ml per min, and was confirmed in half the cases by inulin or iothalamate clearance. Patients who have donated a kidney rapidly recover a clearance more than half the preoperative level, and recipients may achieve a filtration rate of more than 100 ml per min, and often reach rates above 75 ml per min from a single kidney. These four examples would lead one to suspect that there must be a functional reserve capacity for glomerular filtration.

Machensen-Haen et al have demonstrated that in patients with membranoproliferative glomerulonephritis, changes in cortical interstitial volume are related to filtration rate. They speculate that interstitial pressures affect cortical hemodynamics, thus altering filtration, even though serum creatinine may not rise until the reserve capacity is destroyed by the disease process. In short, tests of filtration rate, although useful to document what is happening at a given time, may not reflect total parenchymal capacity to filter or the rate of progression of disease.

Clearance tests that reflect tubular function must also be interpreted with some care. The most widely used is the clearance of para-amino hippuric acid (PAH) to determine renal plasma flow. Since it is difficult in clinical circumstances to measure renal extraction of any substance, and since secretion of PAH may vary with GFR, it is understandable that this procedure has not found widespread clinical application. Understanding of tubular excretory mechanisms is incomplete. For example, it is known that phenol red and diodrast share the same excretory mechanism but are "cleared" at very different rates. Infusion of sodium acetate will lead to augmented clearance of phenol red.

In today's era of polypharmacy, the ways by which one drug may affect the metabolism and/or excretion of another are just being discovered. We are also beginning to understand that facilitated clearance may reflect disease. It has been known for some time that the clearance of amylase relative to creatinine is augmented during acute pancreatitis. Recent work, using B-2 microglobulin as a marker of proteins usually reabsorbed by normal tubules, has demonstrated an increase of C_{B-2}/C_{cr} by a factor of 80. This
implies that tubular damage has occurred disproportionate to any change in glomerular function so that an acute and partial glomerulo-tubular imbalance exists in that circumstance. Thus, clearance tests of tubular function may reflect not only the integrity of the tubule but the effects of circulating substrates or specific rather than global disruption of tubular activity. The tests, therefore, must be selected and interpreted with care.

Non-excretory clearances by the kidney are particularly associated with proteins and drugs. Small molecular weight proteins, such as insulin, amylase, and B-2 microglobulin, are relatively freely filtered and are then reabsorbed and catabolized by tubular cells. As parenchymal mass is reduced, there is a reduction in the amount of insulin required because of a decreased removal rate of insulin from plasma. This decreased non-excretory renal clearance may result in severe hypoglycemia requiring glucose infusions. The altered insulin requirement was not predictable from changes in serum creatinine, suggesting that excretory and non-excretory clearance rates may not change in strictly parallel fashion.

It is increasingly apparent that accurate measurement of renal clearances is important in order to prescribe appropriately such drugs as digoxin and aminoglycoside antibiotics. Both excretory and non-excretory clearance mechanisms may contribute to renal clearances of drugs, so that measurement of drug levels as well as glomerular filtration are indicated.

Accurate determination of renal clearances has also been determined to be necessary to define an individual patient's residual renal function so that dialysis requirements can be individualized appropriately. It was found that the clearance of creatinine was more accurate than the clearance of urea, that the average of the two was better than either, and that the clearance of iothalamate agreed with the clearance of inulin.

Because clearance techniques that are accurate are difficult to apply to clinical circumstances, a number of investigators have tried to adapt isotopic techniques to quantification of GFR. It was demonstrated several years ago that iothalamate sodium I125 was a suitable substance and gave results comparable to inulin. Techniques were awkward, and multiple venipunctures were needed, as methods using a single injection and a single sample were not accurate over the entire range of GFR. It was noted that in patients with a GFR below 15 ml per min, 51Cr-EDTA clearances correlated closely with inulin despite the fact that there is a significant extra-renal clearance of this substance. An accurate but somewhat cumbersome technique requiring blood samples at two min, 10 min, and two, three, and four hours has been described but seems unsuitable for general clinical use. This type of technical difficulty with nuclear medicine methods may be obviated by combining computer and isotopic techniques. Further development of this concept may lead to practical quantification of both excretory and non-excretory renal clearances as suitable isotopes are identified and utilized.

Renal clearances continue to be of value to quantify GFR in clinical and research situations. Additional benefits of clearance techniques include quantification of pharmacokinetic phenomena, assessment of requirements for dialysis, and non-excretory clearances of endogenous small proteins and exogenous drugs. Current techniques that meld computer technology with advanced nuclear medicine techniques may yield more accurate and useful clearance data than have been available in routine circumstances before.

References


