Comparative Studies on Dialysance and Renal Clearance of Various Cardiac Glycosides

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We have pointed out in previous studies (Kramer et al, 1970a) that the accumulation of the different cardiac glycosides in renal insufficiency is inversely related to their binding to plasma proteins. Whereas the serum half-life of ouabain, of which only about 8% is bound to plasma proteins, increased from 14 hours in normal subjects to 60 hours in anuric patients, no such changes were found in the case of the highly protein-bound digitoxin. Methyldigoxin showed only a moderate accumulation, thereby taking an intermediate position. The serum half-life of methyldigoxin increased from 43 hours in normal subjects to 97 hours in anuric patients. Plasma protein binding of this glycoside as measured by means of ultracentrifugation was 32%, thus lying between the values of digitoxin (96%) and ouabain (8.5%).

So far we have two conceivable explanations for the inverse relationship between plasma protein binding and accumulation in renal insufficiency:

1. The buffer action of plasma proteins increases proportional to the protein binding of a cardiac glycoside.
2. Highly protein-bound glycosides are highly lipid soluble as well, and therefore more readily excreted by the liver.

The present study was actually started to prove a third explanation. The movement of molecules from blood to protein-free fluid across a semipermeable membrane as in the dialyser or in the glomeruli is hindered by protein binding. This phenomenon has in fact been used as a method for determining plasma protein binding of a drug, so-called 'equilibration dialysis'. As in the case of dialysance the renal clearance should be correlated inversely to protein binding, provided that neither reabsorption nor secretion takes place in the renal tubules. Renal clearance of a cardiac glycoside excreted only by glomerular filtration is given by

$$(1) \qquad C_{\text{cardiac glycoside}} = GFR \times \left(1 - \frac{\beta}{100}\right),$$

where β is the protein-bound part of the glycoside expressed as per cent of total plasma concentration. With the assumption that the renal clearance of cardiac glycosides approximately follows this equation, the third explanation for the inverse relation between plasma protein binding and accumulation in renal insufficiency would be given by the fact that the kidney would contribute less to total excretion of a cardiac glycoside which is highly bound to plasma protein.

METHODS

Four different tritiated cardiac glycosides: ouabain, methyldigoxin, peruvoside and digitoxin were selected for the present studies. Ouabain, peruvoside and digitoxin were labelled randomly according to Wilzbach (1957). Methyldigoxin was specifically labelled at the 12α position according to the method of Wartburg et al (1965).

Dialysance of these glycosides was determined in anuric patients who were given a single intravenous injection during regular haemodialysis using a Ultraflo 145 coil in a recirculating system.

Elimination of radioactivity was estimated in two different ways:

1. From the blood passing the dialyser as judged by the decrease of plasma radioactivity corrected for fluid loss.
2. From the rinsing fluid as judged by the increase of radioactivity.

Renal clearance of the cardiac glycosides was determined in healthy subjects after a single intravenous dose. Radioactivity in serum, urine and rinsing fluid was measured by liquid scintillation counting according to Kragelung and Dyrbye (1966).

RESULTS AND DISCUSSION

The results of the present study are summarised in Table I. Renal clearance

Table I. Renal clearance and dialysance of radioactivity after i.v. injection of various cardiac glycosides. Mean + SD. (n = number of single values; t.p. = test person; hr = hour after injection)

	Ouabain	Methyldigoxin	Peruvoside	Digitoxin
Renal clearance [ml/min]	97 ± 18 (n = 29)	73 ± 16 (n = 29)	60 → 19 [2.hr] [8.hr] (3 t.p.)	2 → 1 (5 t.p.)
Dialysance [ml/min]	40 ± 11 (n = 23)	25 ± 6 (n = 23)	27 → 7 [2.hr] [8.hr] (3 t.p.)	< 1 (3 t.p.)

of radioactivity was about 2-3 times greater than dialysance obtained with the Ultraflo 145 coil. Thereby both dialysance and clearance showed an inversely proportional relationship to plasma protein binding of the glycosides. The decrease of tritium dialysance from 27 ml/min during the 2nd hour to 7 ml/min during the 8th hour following administration of ^{3}H-peruvoside must be due to formation of highly protein-bound metabolites. It is reasonable to assume that a similar mechanism is responsible for the decrease of renal clearance. As illustrated in Figure 1, clearance of radioactivity was constant after injection of ^{3}H-ouabain and ^{3}H-methyldigoxin, but dropped after administration of ^{3}H-peruvoside from 94 to 8 ml/min within 24 hours. This decrease goes further than expected. As calculated from protein binding of radioactivity 24 hours after injection of ^{3}H-peruvoside (62%) and from creatinine clearance of the test persons (115 ml/min), renal clearance should amount to about 40 ml/min. The fact that renal clearance falls below this value must

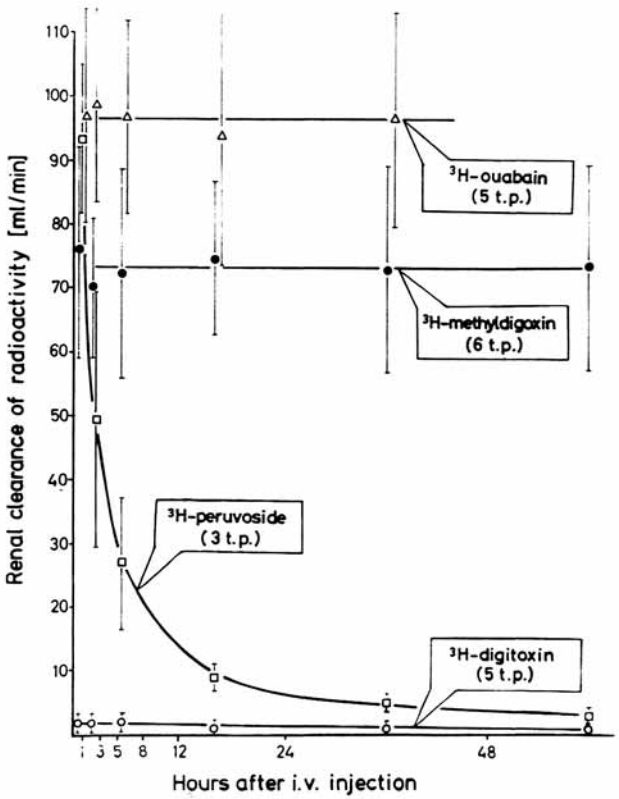

Figure 1. Renal clearance of radioactivity measured at different times after the injection of different cardiac glycosides

be explained by additional formation of metabolites, which are readily reabsorbed by the kidney. A similar explanation may hold true in the case of digitoxin, which showed a decrease of tritium clearance from 2 to 1 ml/min after administration. Tubular reabsorption of the highly lipid soluble digitoxin is rather likely since the renal clearance of the drug should amount to 4 ml/min according to equation (1). Renal clearance of radioactivity after the injection of ^{3}H-ouabain (97 ml/min) and ^{3}H-methyldigoxin (73 ml/min) very closely approximates the calculated values of 104 ml/min and 78 ml/min respectively. It is therefore reasonable to assume that renal excretion of these two glycosides depends almost completely on glomerular filtration.

Unfortunately renal clearance of a drug does not provide enough information about the quantitative role of the kidney in total excretion. Clearance is equal to elimination per plasma concentration and plasma levels are much higher with highly protein-bound cardiac glycosides. Thus, our third explanation for the inverse relation between plasma protein binding and accumulation in renal insufficiency would be questionable if not supported by similar results concerning per cent excretion of cardiac glycosides (Kramer et al, 1970b).

Renal clearance may, however, serve as an excellent parameter in judging the efficiency of an artificial kidney with respect to the elimination of cardiac glycosides. Plasma levels in anuric patients and in cardiac patients with normal renal function should not differ too much under optimal treatment. A comparison between dialysance and renal clearance therefore seems reasonable in judging a dialyser. According to Table I it may be concluded, that the Ultraflow 145 coil is able to eliminate 30-50% of the amount excreted during the same period of time by normal kidneys. Since haemodialysis is commonly performed twice a week for 12 hours, the artificial kidney has only 1/7 of the time available to normal kidneys for elimination of substances normally contained in the urine. This great performance of a dialyser is simply explained by elevated plasma levels due to accumulation of the substances during the interval. Because of the narrow therapeutic tolerance range of cardiac glycosides, enhanced elimination due to elevated plasma levels should play an unimportant role unless proper dosage in patients with renal insufficiency was exceeded. From these considerations it may be estimated that in the state of regular haemodialysis less than 10% of the amount of cardiac glycosides normally excreted by the kidneys are extracted from the patient's blood. This loss of cardiac glycosides is so small that it does not need to be taken into consideration, when digitalising an anuric patient. For the treatment of overdosage symptoms, however, haemodialysis may be recommended since plasma levels in this case are elevated. Great care should be taken in this kind of treatment that plasma potassium is not depressed, otherwise signs of overdose may be enhanced.

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