EXCRETION OF UREA FROM HIGH BLOOD CONCENTRATIONS

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Of all the precise methods of estimating renal function which are available in a modern clinic, the determination of the urea clearance is the simplest, and therefore, of the greatest practical importance.

In diureses exceeding 2 ml per minute per square meter of body surface, the urea clearance is on the average, 70% of the true filtration, and its value is an indication of renal filtration capacity.

Theoretically this test is based on results which show that the renal tubules are purely passive with respect to urea: it is only filtered in the glomeruli and neither secreted nor reabsorbed actively, and is partially reabsorbed only through simple diffusion as the filtrate passes through the nephron [3,4,5]. The above is the commonly held view concerning the excretion of urea in mammals.

However, certain authors have held a different view. Thus, E. A. Asratyan [1] found in experiments on dogs that with high concentrations of urea in the blood, its clearance in certain cases might be almost twice as great as the total filtration. From this he concludes that there is an additional mechanism for the excretion of urea.

Recently K.M. Shteingardt [2] reached the same conclusion, after having repeated Asrayan's experiments and obtained results agreeing with his in every detail. The conclusions of these authors, which contradict the generally accepted view of the mechanism of the excretion of urea, have been often quoted in Soviet literature, and may cause doubt about the soundness of the method of determining the urea clearance as a means of estimating renal function.

With this in view, we carried out the work reported here.

EXPERIMENTAL METHOD

The experiments were carried out on dogs weighing 8-12 kg with the normal opening of the ureters brought out on to the skin of the belly. For the whole of the period under observation the animals were maintained on their usual liquid and solid diet.

The investigation consisted of a simultaneous determination of the filtration rate (inulin clearance) and urea clearance both with a raised blood urea, and under conditions of rapid diuresis, induced by other osmotically active substances. The animal was given a continuous intravenous injection of a solution containing 2% inulin and 2-10% urea at a rate of 3-5 ml/minute, or 2% inulin with 20-45% glucose solution. Urine and blood samples were taken after the injection had been maintained for 30-40 minutes, when steady concentrations of the substances in the blood had been reached.

Inulin in the urine and plasma was determined using a colorimetric resorption method, and urea – by the urease method as modified by Conway. From these results the filtration rates and urea clearances were calculated. The results were referred to $1 m^2$ of body surface, as this allowed comparison of results between dogs of different size and weight.

EXPERIMENTAL RESULTS

The results of 33 experiments on 4 dogs have been divided into three groups according to the blood urea concentrations which occurred with the loads used (Table 1).

TABLE 1

Average Values and Limits of Variation of the Ratio of Urea Clearance (C_u) to the Inulin Clearance (C_{in})

Number of experiments in the group	Limits of the observed concentrations of urea in the plasma (mg/ml)	Limits of variation of the ratio urea clearance (C_u) to inulin clearance (C_{in})	Average value of ratio C_u/C_{in}
9	from 0.11 to 0.30	from 0.57 to 0.91	0.72
11	" 0.31 " 0.50	" 0.60 " 0.97	0.77
18	" 0.64 " 2.20	" 0.72 " 0.98	0.85

As can be seen from Table 1, the average value of the ratio increases with increase in the concentration of blood urea. However, even with high concentrations up to 220 mg%, i.e. 10 times higher than normal, the ratio C_u/C_{in} remains less than 1, which shows that no active excretion occurs. At the same time with normal and moderately raised blood ureas this ratio varies considerably, sometimes reaching values of 0.91-0.97. Evidently there is no direct relation between the blood urea and the ratio of the two clearances. The increase in the average value of the ratio with increasing values of blood urea is probably not due to any specific effect of the urea on the tubules, but to the diuretic effect it produces. When diuresis is rapid, and when the rate of flow of the primary urine along the canals increases, conditions are less favorable for the reabsorption of urea, so that its clearance rises and approximates the true filtration rate.

It is known that over very wide limits of diuresis rates the filtration rate in dogs remains constant; however, the rate of flow of fluid along the canals, which clearly will be higher the greater the rate of urine excretion, is entirely determined by the rate of reabsorption of water. A convenient expression for the reabsorption process is the value of the ratio of the inulin content of the urine (u) to that of the plasma (p). The unreabsorbed inulin increases in concentration in proportion to the amount of water reabsorbed, and the ratio u/p increases. We would expect that the ratio C_u/C_{in} will depend on the ratio u/p.

In order to demonstrate this relationship in general, we altered the amount of water reabsorbed by injecting not only urea but also another osmotic diuretic which changes the value of u/p, namely glucose. The results of the experiment are shown graphically in the figure. The results of the experiments with intravenous injection of urea are shown by the open circles, while the closed circles show the results for glucose. It can be seen that by altering the concentration index of inulin from 40 to 15, the value of C_u/C_{in} varies from 0.8 to 0.6; however, with a concentration index less than 15, the value of C_u/C_{in} shows a steady increase, with a value of approximately 1.0 at a u/p ratio of approximately 4.0.

The four points lying above the dotted line must be noted. In these experiments the ratio C_u/C_{in} exceeds 1.0, and this can only occur if urea is actively excreted.

Table 2 shows the figures corresponding to these four points.

TABLE 2

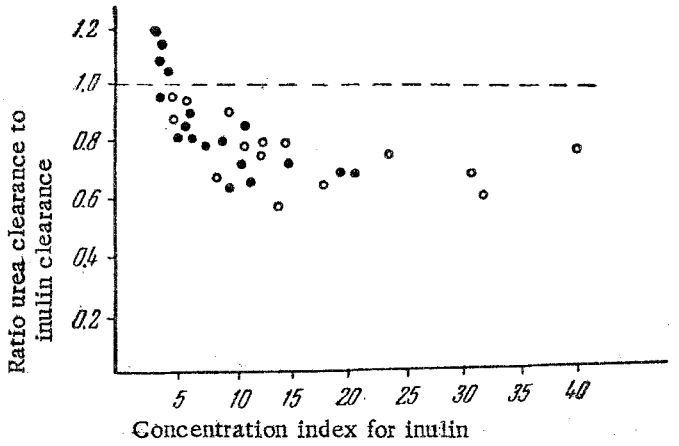
Excretion of Urea in Osmotic Diuresis Caused by Injecting Glucose

Concentration of urea in plasma (mg/ml)	Concentration index of inulin (u/p)	Diuresis in ml per m^2 per minute	Ratio of urea clearance to inulin clearance
0.35	4.5	22.0	1.05
0.35	4.7	23.8	1.08
0.20	3.9	24.7	1.16
0.32	4.0	20.4	1.20

Are we to conclude from these four experiments that under certain known conditions urea is actively excreted as E.A. Asratyan and K.M. Shteingardt suppose?

First of all it is to be observed that these exceptional values are not associated with a high blood urea, but were obtained in experiments with injection of glucose. In these experiments the diuresis was particularly high, and the u/p ratio for inulin particularly low; under these conditions the passive reabsorption of urine approximates zero, and the urea clearance approximates the filtration rate. We consider that under these conditions the true value of C_u/C_{in} is equal to unity. Values exceeding this amount in two experiments by 5-8%, and in two by 16-20%, are evidently due to an error, the most probable being failure to stabilize the ratios in the plasma during the collection of urine. In each instance the amount by which the ratio C_u/C_{in} differs from unity is in no way comparable with the differences found by E.A. Asratyan and K.M. Shteingardt which were of the order of 200%.

Their results are probably due to the fact that they measured filtration rate in terms of endogenous creatinin, which in dogs gives values which are too low, while for urea measurements they used the nonspecific methods of Foss and Borodin which are not capable of yielding sufficiently accurate quantitative results. Our results support the findings of those who hold that urea is excreted purely by filtration. Excretion is not an active process either in normal or in very high concentrations in the plasma.



Relation between concentration index for inulin and the ratio of urea clearance to inulin clearance. Open circles show results of experiments with injection of urea, dots – results of experiments with injection of glucose.

SUMMARY

The value of filtration by inulin method (C_{in}) and urea clearance (C_u) in its increased concentration in the blood were determined simultaneously. It was established that C_u/C_{in} ratio increases with reduction of concentration index of inulin caused by the loading of urea. The C_u/C_{in} ratio almost equals 1, but is never over it. Concentration of urea in the blood does not stimulate its excretion by the tubular epithelium.

LITERATURE CITED

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