KINETICS OF UREA DIFFUSION IN THE ORGANISM DURING HAEMODIALYSIS.  
A QUANTITATIVE CONTROL OF ELIMINATION OF UREA

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The analytical findings, concerning the kinetics of urea diffusion, are derived from repeated measurements of the urea concentrations in the arterial inflow and venous outflow of a dialysing coil, as well as in the dialysate inflow and outflow. These findings provide the theoretical basis for the quantitative control of elimination of urea.

A coil dialyser is put into an open-end, low volume dialysate system (Kopp and Grossmann, 1966). Samples are taken from blood inflow and outflow, and from dialysate inflow and outflow for enzymatic determination of urea. The flow-rates of the blood and of the dialysate are kept strictly constant under the control of a blood pump and a flowmeter. The margin of error of the accuracy of the enzymatic analysis of urea is ±2% for each value. The amounts of urea eliminated are thereby determined in two independent ways.

Total amount of urea eliminated is equal to

1. the product of blood flow rate multiplied by the difference of urea in serum before and after passage of the coil, and
2. the product of dialysate flow rate multiplied by the difference of urea concentration in dialysate inflow and outflow.

Urea concentrations in the arterial blood do not show a continuous decrease with the time of dialysis. As illustrated in Fig. 1, we find definite steps in the decrease of the arterial serum-urea concentrations with the time of dialysis. These steps are equidistant and the difference between their plateaux is approximately 30 mg% of serum urea corresponding to 5 mmol/l. The general pattern of these steps varies with the blood flow rate. Slow blood flow in the region of 150 ml/min shows an initial fluctuation of the serum urea concentrations, which then decrease in a stepwise function. The plateaux remain constant for periods between a half to one and a half hour. The steps extend over a period of 15 to 30 minutes. Rapid blood flows in the region of 250 ml/min show rapid falls and rapid increases of serum urea concentrations at intervals of 10 to 15 minutes, as illustrated in curve D.

Fig. 2 shows very precisely the concentration step at the blood flow rate of 160 ml/min and an initial blood urea concentration of 140 mg% in a case of maintenance dialysis treatment. It is obvious that the extraction of urea at different times at a strictly constant blood flow rate is not constant with constant blood flow against time. The calculated values of the theoretical distribution space or extraction volume of urea shows a stepwise increase. Finally, it reaches values which are in the range of the total body water.

From this it is recognised, that urea is not distributed uniformly over the total body water. This indicates the existence of chemical bindings of urea. The stepwise decrease during haemodialysis proves, furthermore, that the process of urea diffusion itself is not free, but follows a particular mechanism, corresponding to a stepwise binding-affinity.

The urea diffusion rate from tissue to blood is necessarily greater during the periods when
Fig. 1. Examples of the stepwise decrease of serum urea levels during maintenance dialysis treatment with the TRAVENOL Twin Coil Kidney. The blood flow rates were constant during the whole period of dialysis.

Fig. 2. Maintenance dialysis treatment with the TRAVENOL Twin Coil Kidney. Serum urea levels are plotted from arterial inflow and venous outflow, i.e., before and after passage of the coil. No urea was added to the dialysate. Blood flow: 160 ml/min, constant. The distribution space of urea, calculated from the arterial urea concentration, climbs up in a step to 95% of the volume of total body water. Correspondingly the serum urea level drops off in a step. Haemodialysis is carried out in circulated single pass. Urea concentrations are determined in the dialysate outflow.

the serum urea concentrations remain on a plateau, compared with the short period, when the concentrations fall steeply. There, the diffusion from the tissues to the blood is impeded.

We analysed therefore the kinetics of urea extraction from a two-phase-system, which is
the blood contained in the cellophane tubing in the coil. Phase 1 is the serum, phase 2 are the erythrocytes. The two phases are separated by the membranes of the erythrocytes.

Immediately after the arrest of the blood flow, the 23 windings of the cellophane tubing of a coil were clamped and separated. The serum urea concentrations in each winding were then determined. We found the same stepwise decrease of serum urea concentrations over the length of the coil, as in the arterial blood of the patient during haemodialysis (Fig. 3). Creatinine, however, decreases in an exponential function as the creatinine serum levels do during haemodialysis. The absence of diffusion in the first 5 windings is explained by a thermo-osmotic effect (Grossmann and Kopp, 1966). Here only small amounts of water migrate from the bath into the blood, when the blood is slightly cooler than the bath.

![Graph of urea and creatinine concentrations](Image)

**Fig. 3.** Serum urea and serum creatinine concentrations are shown from the 23 windings of a Travenol Twin Coil Kidney, which was immediately withdrawn from dialysate after arrest of the blood flow. When the temperature equilibrium between blood and dialysate after the first five windings is reached, the effect of thermo-osmotic diffusion-block disappears and urea concentration drops stepwise according to the stepwise pattern of urea diffusion out of the erythrocytes. Creatinine decreases as an exponential function.

The conclusion to be drawn from this last experience is as follows: It is the biological membrane itself, which is responsible for the diffusion pattern in a stepwise fashion. This applies for all compartments separated by biological membranes. Therefore the concentration steps in the arterial blood, which have been found during haemodialysis, reflect the effect exercised by the biological membranes on the diffusion of urea.

The mechanism, which in that way impedes the diffusion of urea through biological membranes, finds its explanation as follows: Urea forms complex-compounds in a peculiar chemical bond with the n-alkyl-chains, called ‘urea-addition-compounds’, in that urea molecules wrap around the alkyl-chains. These addition-compounds are well known in the chemical field for over 15 years (Bengen, 1951; Schlenk Jr., 1949, 1950; Cramer, 1952; Redlich, Gable, Dunlop and Millar, 1950). The binding mechanism follows a stepwise
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pattern and is very tight, provided the n-alkyl-chains are arranged in a crystalline order. This is the case in the double layer of all biological unit membranes. However, n-alkyl-chains contained in serum lipoids in non-crystalline order have a poor binding capacity for urea. Only 3% of the serum urea is bound in that way. The diffusion of urea through a unit membrane is impeded by the fact that the urea molecules change their binding sites slowly, in accordance with the loading of the n-alkyl-chains with urea, which depends of course on the urea concentration. The presence of different concentrations of urea between the different compartments during haemodialysis creates an important osmotic gradient. Water has to migrate towards the sites of elevated concentrations of urea, which is clinically demonstrated by brain swelling and the associated symptoms. The osmotic water shift itself, which is directed against the urea flux, is a further hindrance to the diffusion of urea from the tissues. The symptoms generally described as ‘disequilibrium’ are therefore due to the extraction of urea. Disregarding its fixation in the membranes, urea is extracted in the greatest osmolar amounts during haemodialysis, compared with all other substances dialysed.

The theory has been applied clinically in a procedure to avoid the disequilibrium syndrome. It is based on considerations of how to control the extraction of urea from the tissues. The amounts eliminated have to be just below those which cause the water shift to the tissues. This could be accomplished by a slow decrease of the serum concentration of urea. In terms of distribution volume, this means, that it should at no time be less than the total body water.

These conditions are realised when decreasing amounts of urea are added to the dialysate, the initial concentration of urea being up to 50-60% of the initial serum urea concentration.

Fig. 4. Maintenance dialysis treatment with addition of urea to the dialysate. The fluctuations in the level of serum urea appear as a consequence of the kinetics of urea diffusion in a multi-compartment system, separated by unit membranes. The amounts of urea eliminated per unit of time slowly drop, as the arterial level does. Consequently, the distribution volume of urea is found to be higher than the volume of total body water during the whole period of dialysis. Compare with Fig. 2.
with the highest blood flows (Fig. 4). Elevation of the blood flow rate over 250 ml/min is then tolerated, and no clinical symptoms of disequilibrium are encountered. The total amounts of urea extracted during several hours of haemodialysis are even greater than with a haemodialysis of the same duration without urea in bath and running at a reduced blood flow rate to avoid clinical complications.

In conclusion, the efficiency of haemodialysis is solely indicated by the total amount of substances removed during dialysis, and not by the arterial concentrations before and after haemodialysis. The possibility of increased synthesis of urea as a result of haemodialysis, which has been postulated several times, can be safely excluded, since inhibition of an enzymatic reaction can not be released by the diminution of only 25-30% of the inhibitor, in this case urea. On the contrary, the smallest decreases of serum urea level during haemodialysis correspond to the highest theoretical distribution-volumes of urea and vice versa, demonstrating the chemical binding of urea in the organism.

REFERENCES

KOPP, K. F. and GROSSMANN, D. F. (1966): Method and apparatus for a quantitative control of urea extraction for hemodialysis without disequilibrium syndrome. This Volume, p. 303
DISCUSSION

The CHAIRMAN: Il faut être reconnaissant au Docteur Kerr de nous avoir confirmé qu’il ne fallait pas céder à la tentation de dialyses trop rapides et également être reconnaissant au Docteur Grossmann de nous avoir montré une fois de plus l’inégalité de la répartition de l’urée dans l’organisme.

Avant de passer la parole à notre Président, le Professeur Traeger, je voudrais lui renouveler nos remerciements pour l’excellente organisation de cette session et pour l’accueil exceptionnel qu’il a bien voulu nous réserver.

TRAEG: Messieurs, le IIIème Congrès de l’E.D.T.A. se termine. Avant de nous séparer, je voudrais simplement vous rappeler le contrat que nous avions passé ensemble l’an dernier, à la fin du Congrès de Newcastle.

Je vous avais promis le soleil, le ciel bleu. Je crois avoir tenu mon contrat! Vous m’aviez promis de venir nombreux, avec beaucoup de communications, vous avez également tenu votre contrat, et je vous en remercie vraiment très vivement. C’est grâce à vous que le Congrès a pu fonctionner.

Je dois maintenant résigner mes fonctions de Président, et le Docteur Thaysen va être notre nouveau Président pour l’année qui vient.


Je sais qu’il sera très difficile de succéder au Professeur Traeger qui a arrangé ici une Conférence qui a eu un grand succès, dans cette belle ville.

Néanmoins, nous voulons concentrer nos efforts pour ne pas créer un trop grand ‘anti-climax’. Soyez les bienvenus à Copenhague!