METHOD AND APPARATUS FOR A QUANTITATIVE CONTROL OF UREA EXTRACTION FOR HAEMODIALYSIS WITHOUT DISEQUILIBRIUM SYNDROME

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Disequilibrium syndrome is most frequently encountered during rapid haemodialysis with dialysers of high extraction capacity, e.g., the twin coil kidney. It is less severe, when dialysers of lower extraction capacity like the Kiil-kidney are used, necessitating however long-lasting dialyses. The addition of glucose to the bath did not show satisfying results in reducing these symptoms (Javid and Anderson, 1959; Bennhold, Kubicki and Kessel, 1965; Drukker, Alberts and Jungerius, 1965). The extraction of urea has been recognised by many authors to be responsible for the symptoms composing the disequilibrium syndrome (Scheitlin and Hunziker, 1962; Kennedy, Linton and Eaton, 1962; Freeman, Sheff, Maher and Schreiner, 1962; Kleeman, Davson and Levin, 1962; Kennedy, Linton, Luke and Renfrew, 1963; Dossetor, Oh and Pappius, 1965).

The study of this problem led us to conceive a procedure to control quantitatively the extraction of urea during haemodialysis. The procedure is based on the observation of the following effect: During several haemodialyses a comparison has been made between the total amounts of urea eliminated when:

1. no urea was added to the dialysing fluid. The blood flow rate through the dialyser was kept small in the range of 150 ml/min, as it was found that higher blood flows were not tolerated for longer periods of time, otherwise headaches, rise of blood pressure, vomiting were frequently observed after 2 to 3 hours from the onset of dialysis;

2. urea was added to the dialysing fluid at a concentration up to 50-60% of the initial serum urea concentration. The blood flow rate was constantly kept high in the range of 300 ml/min, which was very well tolerated.

The haemodialyses were carried out with the twin-coil on circulated single pass for durations up to 8 hours.

It has been found that the total amounts of urea eliminated under the conditions of number (2) were up to 20% higher than dialysing without urea in the bath, as in condition number (1). Signs of disequilibrium remained constantly absent, when dialysing against urea. After dialysis the concentrations of urea in the serum were found low in the case of the bath free of urea, and high in the case where urea was added (Fig. 1).

Figure 1 shows a rapid decrease of the curve, which illustrates the amounts of urea eliminated per unit of time in the case of the bath without urea. The corresponding values of the distribution space of urea are then found even lower than the volume of total body water. This implies that urea does not diffuse as readily from the tissues to the blood as it diffuses from the blood to the dialysate.

Explanation of the effect: The rapid fall of urea-concentrations in the blood when dialysing against a urea free dialysate establishes an important osmotic gradient between tissues and blood. This causes water to migrate towards the compartments with elevated urea concentration. This has been demonstrated clinically and experimentally for the central nervous
system with brain swelling and deterioration of cerebral functions, recognized by many authors as the origin of most symptoms composing the disequilibrium syndrome.

We are considering the double layer of lipoids, which are preferentially present in all biological membranes, as the site of the selective accumulation of urea (Grossmann and Kopp, 1966). Urea is chemically bound to the n-alkyl-chains of lipoids as an addition compound. This by itself reduces the diffusibility of urea and consequently the osmotic gradient between the intracellular compartment and the extracellular compartment is built up by haemodialysis. As a result the osmotic water-shift, which is directed against the urea-flux, reduces once more the migration of the urea molecules through the membranes. Therefore, during rapid haemodialysis the intracellular compartment is only partially emptied of urea. Low serum concentrations are obtained; this however does not reflect the efficiency of the procedure. An important rise of blood urea concentrations many hours post dialysis takes place (rebound phenomenon), when the diffusion barrier due to the osmotic water shift ceases to be effective.

In reverse, addition of urea to the bath diminishes the osmotic gradient from the tissues to the blood which has passed the dialyser. The osmotic water uptake of the tissues then remains small and the diffusion of urea molecules through the membranes, which is slow, is not markedly impeded. At the same time the well effect of tissue hydration, e.g. disequilibrium syndrome, remains absent. This allows the elevation of the blood flow rate to the degree which was previously found intolerable for longer periods of dialysis-time. The extraction of urea will be sufficiently high and remain high for the whole duration of dialysis. The final serum-urea concentration, although relatively high, will for this reason reflect to a certain degree the true condition of all tissues.
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The consequences of the effect described are of course most marked in dialysers of high extraction capacity with rapid lowering of the blood urea concentration, like the twin coil. They are less marked in slow extracting dialysers like the Kiil-dialyser (Alberts and Drukker, 1965). Hence the difference of the clinical results obtained with these two types of dialysers can be explained.

These considerations have led us to conceive a method for the quantitative control of the extraction of urea during haemodialysis. The elevation of the blood flow rate, which is tolerated by the patient when urea is added to the dialysate at a concentration, which is constant, raises the dialysances of all other dialysable substances. The procedure of adding a constant concentration of urea to the bath proved to be sufficient for the treatment of acute cases and in the beginning of maintenance dialysis treatment. For the purpose of chronic intermittent dialysis the continuous lowering of the urea concentration in the bath fluid during dialysis proved to be most effective, leading to a quantitative control of urea extraction.

The procedure necessitates a strictly constant dialysate flow in a low volume, open-end system, in which a gradually decreasing volume of a concentrated urea solution is allowed to run in. The apparatus shown on demonstration is simultaneously circulating and heating the cold dialysate inside the core of a dialysing coil (Fig. 2).

![Diagram](image)

*Fig. 2.* Low volume, open-end system for controlled extraction of urea. The urea concentrate runs in from a long cylindric reservoir. A heater and a pump for the circulation of the dialysate are in the core of a twin-coil.

Bacterial growth has never been a problem. A concentrated urea solution is stored in a long cylindrical reservoir, and the inflowing volume continually diminishes in a decreasing function, according to the lowering of its hydrostatic pressure. The outflow rate is adjusted.
to the time of dialysis. A specially designed infusion pump for this purpose is in development.

The limits between which the elimination of urea is tolerated in maintenance-dialysis treatment are illustrated in Figure 3. The tolerance of urea elimination is increased in acute renal failure, depending on how early or how late the dialysis treatment is begun.

![Fig. 3. Elimination of urea (g/h) and the limits of tolerance at different serum-urea-concentrations.](image)

The efficiency of the procedure in maintenance dialysis is shown by low values of serum urea that are obtained as they are representative for the whole organism. The daily increase of the urea concentrations in the blood during the interval between two dialyses and the absence of

![Fig. 4. The behaviour of serum urea levels during the interval between several haemodialyses—with controlled extraction of urea and without addition of urea to the bath.](image)
the rebound effect demonstrate that these values extend over the whole distribution space of urea throughout the body. Correspondingly the clinical condition of the patients is very good indeed. Eight hours of dialysing time twice a week or less proved to be sufficient for all cases treated (Fig. 4).

Conclusion

Highly efficient, rapid dialysis with dialysers of high extraction capacity is very well tolerated and shows elimination of the highest amounts of all dialysable substances including urea, when the extraction of urea is quantitatively controlled. It is the method of choice to avoid disequilibrium syndrome in acute and maintenance dialysis. The tendency to reduce the dialyser surface or the blood flow rates for this purpose is considered to be of net disadvantage.

REFERENCES


