CHANGES OF PLASMA CONCENTRATION AND ELIMINATION OF VARIOUS HORMONES BY HAEMOFILTRATION

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Summary

When we started to treat uraemic patients exclusively by haemofiltration at the end of 1974 in Hann. Münden and at the beginning of 1975 in Göttingen, all of us were afraid of causing deficiency syndromes as a result of the anticipated loss of essential substances such as hormones. Meanwhile the well-being of our patients has convinced us that haemofiltration is a possible way of treating uraemic patients.

Haemofiltration is performed by means of membranes with a cut-off for substances with a molecular weight of 20,000 Daltons. Since most hormones have a molecular weight between 500 and 30,000 it was of particular interest to study the elimination of hormones by this new way of treatment.

Materials and Methods

In five male uraemic patients haemofiltration was performed by means of an RP-6-haemofilter (Rhône-Poulenc, Paris) three times per week. All patients had been at least four weeks on intermittent haemofiltration treatment. During a six-hour haemofiltration treatment 20 L of ultrafiltrate were produced. The substitution fluid administered into the venous line was composed of: Na⁺ 144 mEq/L, K⁺ 3.0 mEq/L, Ca⁺⁺ 3.75 mEq/L, Mg⁺⁺ 1.5 mEq/L, Cl⁻ 118 mEq/L and lactate⁻ 34 mEq/L.

There was no dietary restriction for the patients during the treatment-free interval and during haemofiltration. Samples of blood and ultrafiltrate were withdrawn at the onset ('before') and at the end ('after') of the treatment. One additional sample was taken from the total ultrafiltrate at the end of each haemofiltration. In order to avoid rapid concentration changes of the hormone levels three samples were taken at ten-minute intervals and pooled. Pooled samples of the plasma and ultrafiltrate were rapidly deep-frozen after withdrawal and thawed at the time of hormone determination. For more details about radioimmunological determination of the hormones see Matthaei et al.
Results and Discussion

The relationship between concentration in the ultrafiltrate and the plasma has been expressed as a quotient and plotted as a function of the molecular weight for various substances and the investigated hormones in Figure 1. The interrupted line describes the permeability characteristics of the RP-6-haemofilter under clinical conditions. The target symbols stand for the hormones testosterone, cortisone, gastrin, insulin, gastric inhibitory polypeptide (GIP), somatomedin B, human growth hormone (HGH) and thyroid stimulating hormone (TSH). The concentrations in the filtrate were very low for testosterone and unmeasurable for cortisone, HGH and TSH. In the case of testosterone and cortisone the concentrations in the ultrafiltrate were low or not measurable, most likely as a result of their high plasma protein binding. In the case of HGH and TSH most likely the high molecular weight on the one hand and plasma protein binding on the other prevented penetration of the membrane. The effect of haemofiltration on the plasma concentration of those hormones, which were not eliminated by haemofiltration to a significant extent, is shown in Figure 2. The plasma concentrations of testosterone, cortisone and TSH remained unchanged. Only the plasma concentration of HGH showed a significant decrease which may be explained in part by food intake during haemofiltration.

We were particularly interested in the polypeptide hormones gastrin, insulin,
Figure 2. Effect of haemofiltration on the plasma concentration of testosterone, cortisone, HGH and TSH

GIP and somatomedin B, because the molecular weight of these hormones falls in the middle molecule range and one might assume that immunoreactive fragments of these hormones belong to the so-called peak-6 or peak-7 polypeptides. As shown in Figure 3 the concentration of the total IR-gastrin was elevated as has been observed by other authors in uraemic patients. 2,3 Apparently the total IR-gastrin concentration was not changed by haemofiltration. However, we must

Figure 3. Concentration in plasma and ultrafiltrate of IR-gastrin

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admit that we do not know the different components of the total IR-plasma-gastrin. It might well be that during haemofiltration the concentration of the most effective component, the G-17-gastrin⁴, was elevated and some other less effective hormone component was reduced.

According to Figure 4 the concentration of IR-insulin was elevated before onset of haemofiltration and there was a further increase of this hormone during haemofiltration which cannot be explained solely by food intake. Most interesting was the high concentration in the ultrafiltrate which indicates the elimination of some smaller immunoreactive fragment. The increase of the plasma concentration during haemofiltration indicates that the capacity of the endocrine cells for

![Figure 4. Concentration in plasma and ultrafiltrate of IR-insulin](image)

secretion of hormones is much greater than the elimination capacity of haemofiltration.

In Figure 5 the plasma concentrations of the gastric inhibitory polypeptide (GIP) were eight times higher than that of normal patients and a further increase during haemofiltration was observed. The concentrations of GIP in the ultrafiltrate were much lower than in the plasma, which may be explained by plasma protein binding.

The plasma concentration of the IR-somatomedin B according to Figure 6 were at the lower level of the normal range and there was a considerable loss of this hormone through haemofiltration. Since somatomedin B is necessary for growth and development this loss might eventually limit the usefulness of haemofiltration in uraemic children who are known to have very low plasma levels⁵. In our patients the plasma concentration of somatomedin B did not fall during haemofiltration.

The final interpretation of our results on hormone metabolism in uraemic patients under haemofiltration is rather difficult. We know very little about
the biological activity of hormone degradation products. Nevertheless we think it is possible to conclude that hormone deficiency in adult uraemic patients as a result of haemofiltration treatment is unlikely to occur because of the high secretory capacity of endocrine cells. One might go on to speculate that the elimination of hormone degradation products with disturbing biological activity through haemofiltration may have a favourable effect on the uraemic syndrome.
However, for further evaluation of haemofiltration and further understanding of the uraemic syndrome it will be necessary to develop methods for screening of hormone degradation products.

Figure 7 represents such an approach for investigation of hormone degradation products. The monosulphate fraction of the steroids in the ultrafiltrate were analysed by a combination of glass capillary column gas chromatography and mass spectrometry. It is obvious that the uraemic patient retains a great number of steroids which are not found in normal subjects. Nothing is as yet known about the biological activity of these steroids.

References
Open Discussion

CAMBI (Parma) We should divide fast-acting hormones like catecholamines from the slower-acting hormones like testosterone for example. Only the fast-acting hormones are actually important during dialysis because they may influence the dialysis run itself. The slow-acting hormones depend on so many variables that their activity in relation to dialysis treatment is unpredictable.

KRAMER The selection of these hormones for study was based simply on molecular size and molecular weight.

COBURN (Los Angeles) Since most hormone changes demonstrated were due to endogenous factors (eating, glucose, $K^+$, etc), you have no control for the effect of haemofiltration, per se. Regular haemodialysis with similar eating patterns would be an appropriate control for the effect of haemofiltration. Your conclusion about lack of 'hormone depletion' may not apply equally to all hormones. For example, exhaustion of insulin secretion can occur after prolonged over secretion, while this is not the case for parathyroid hormone.

KRAMER We would agree. It is just that we expected a deficiency syndrome with haemofiltration which does not appear.

ANDERTON (Edinburgh) In this group of patients with haemodialysis-resistant hypertension it has been shown by some workers that the circulating levels of renin and angiotensin are raised. Have you measured the angiotensin levels after haemofiltration?

KRAMER We have measured the plasma renin activity in our patients during haemofiltration and haemodialysis and the mean plasma values are lower in patients on haemofiltration.

MARUMO (Yamato) Could I ask why plasma IR-insulin levels are higher after the haemofiltration? Did you measure the glucagon level in plasma?

KRAMER We did not measure glucagon levels.