INTRAPERITONEAL ADMINISTRATION OF INSULIN DURING PERITONEAL DIALYSIS OF DIABETIC PATIENTS WITH TERMINAL RENAL FAILURE

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Summary

The effect on plasma glucose and serum insulin of varying amounts of insulin added to the dialysis fluid was studied in a total of 10 diabetic patients on peritoneal dialysis (PD). Addition of 12 and 24 U/L of immunoreactive insulin (IRI) resulted in a significant rise in serum insulin. With the use of 1.5% solution no insulin was required to control plasma glucose during PD, whereas use of 4% solution required addition of 12U/L IRI for optimal control of plasma glucose concentrations.

Introduction

Chronic peritoneal dialysis (PD) of patients with diabetic nephropathy may cause large fluctuations in blood glucose concentrations as a result of the absorption of glucose from the dialysis fluid. As these changes may lead to severe hyperglycaemia and hyperosmolality [1,2] it is important to maintain blood glucose control during PD by administration of adequate doses of insulin. By addition of glucose to the dialysis fluid a precise control of blood glucose would be achieved, provided that the insulin was absorbed and effective in lowering plasma glucose.

Material and methods

Three day model

To evaluate variations in plasma glucose during PD a 3-day model was set up. Five diabetics with end-stage renal failure (ESRF) were studied. Under standard conditions samples of ear blood for determination of plasma glucose and samples of arm venous blood for determination of serum insulin were taken before initiation of dialysis, after each cycle and after dialysis of 10L. The studies were carried out on three consecutive days: day 1 – no dialysis; day 2 – PD with the use of isotonic (1.5%) dialysis fluid with no insulin added (I°); day 3 – PD with addition of 8U/L of crystalline insulin (≈6U/L IRI) to the isotonic dialysis fluid (I°).
Fourteen day model

In a randomised experiment another five diabetics were studied under standard conditions over a period of 14 days. They dialysed three times weekly using 20L of either isotonic (I) or hypertonic (H) (4%) dialysis fluid per dialysis. The dialysis fluid contained either no insulin (I₀), or 12 (I₁₂), or 24 (I₂₄) U of IRI per litre. The patients then dialysed with each of the dialysis fluid compositions I₀, I₁₂, I₂₄, H₀, H₁₂ and H₂₄ in a random order. Before the start of each dialysis, and at 8am, 11am and 2pm (corresponding to the course of a normal PD) blood samples were taken for determination of serum insulin and plasma glucose. In addition plasma glucose was measured after PD at 5pm and 11pm. For each cycle the outflow volume was measured and representative specimens were taken for insulin and glucose estimations. PD was performed through an indwelling Tenckhoff catheter at a dialysis fluid flow rate of 4L/hr. An automated dialysis equipment was used for the fluid exchange and maintained the inflow volume at 2L/cycle. No insulin adsorption occurred in the containers or lines [3]. Insulin concentrations were measured by a radioimmunoassay, whereby 75% of the added insulin was determined as immunoreactive insulin (IRI) [4]. For statistical evaluation two-way analysis of variance and paired t-test were performed.

Results

Three day model

The changes in mean plasma glucose occurring in the 3-day model are illustrated in Figure 1. Before dialysis there was no demonstrable difference between patients or between days (F = 1.6 and F = 0.6, respectively). Analysis of variance showed

![Graph](image-url)

Figure 1. Mean plasma glucose concentrations in the 3-day model

Day 1: No dialysis
Day 2: PD with 1.5% solution without addition of insulin
Day 3: PD with 1.5% solution and addition of 6U/L IRI
a significant difference in plasma glucose concentrations between the 3-day study 
\(F = 4.0\) with the changes being significant between day 1 (no dialysis) and day 
2 (I\(^9\)) \(t = 4.20; p<0.001\). With regard to serum insulin concentrations at the 
start of the study there was considerable variation between patients (range 19.7– 
365\(\mu\)U/ml). There was a significant difference in the initial values between patients 
\(F = 14.5; p<0.001\) but none in the individual values between the 3 days \(F = 1.5\). 
Further analysis of variance of the difference between initial and final values for 
the three days revealed no significant difference either between patients or between 
days.

**Fourteen day model**

Figure 2 shows mean plasma glucose concentrations versus time for the five 
patients during the six treatment sessions. Figure 2A illustrates PD without 
addition of insulin to the isotonic \(I^0\) and hypertonic \(H^0\) dialysis fluid. 
Figure 2B illustrates PD with addition to the dialysis fluids of 12U/L of IRI 
\(I^{12}\) and \(H^{12}\), and Figure 2C shows PD with addition of 24U/L of IRI \(I^{24}\) 
and \(H^{24}\). Analysis of variance revealed that while there was no difference in 
the individual initial values between days \(F = 0.38\) there was a significant 
difference in start values between patients \(F = 12.9; p<0.01\). During PD with 
isotonic fluids \(I\) there was no difference in plasma glucose concentrations 
between start and end values (at 2pm) whether insulin was added or not. By 
comparing plasma glucose concentrations during PD with isotonic to those 
during PD with hypertonic fluids the only significant difference was demon-
strated at 2pm (Figure 2A).

During PD with hypertonic dialysis fluids \(H\) plasma glucose rose significantly 
from the start to the end of PD \(t = 3.08; p<0.02\) followed by a fall, but the 
post dialysis values never returned to pre dialysis levels. During PD with \(H^{12}\) 
(Figure 2B) plasma glucose rose insignificantly and then returned to initial values. 
During PD with \(H^{24}\) (Figure 2C) plasma glucose increased significantly \(t = 2.77; 
p<0.05\) and then decreased to a level below the initial value after PD had been 
completed \(t = 2.76; p<0.10\).

Serum insulin concentrations during PD are shown in Figure 3. Figure 3A 
illustrates PD with \(I^0\) and \(H^0\), Figure 3B PD with \(I^{12}\) and \(H^{12}\) and Figure 3C 
with \(I^{24}\) and \(H^{24}\). While there was no difference in the start values between 
days there was a significant difference between patients \(F = 15.4; p<0.01\). By 
addition of increasing doses of insulin to the dialysis fluids a significant increase 
in serum insulin occurred \(F = 7.24; p<0.05\). During PD with \(I^0\) there was no 
change in serum insulin, but with \(H^0\) a significant rise occurred \(t = 3.06; 
p<0.05\). By comparing PD with \(I^{12}\) to PD with \(H^{12}\) (Figure 3B) significant 
differences in serum insulin were demonstrated in both at 8am and 11am 
\(t = 3.58\) and \(t = 3.24; p<0.5\). However, there was no difference by the end 
of PD. During PD with \(I^{12}\) and \(H^{12}\) a significant increase occurred between the 
start and 11am, while there were no further changes during the remaining PD period. 
A comparison between PD with \(I^{24}\) and PD with \(H^{24}\) (Figure 3C) revealed no 
difference between serum insulin concentrations. Again there was a significant 
rise between the start and 11am \(t = 3.55; t = 3.04; p<0.05\).
Figure 2. Plasma glucose concentrations in the 14-day model
A: PD with isotonic (1.5%) or hypertonic (4%) solution without intraperitoneal administration of insulin
B: Same as A with addition of 12U/L IRI
C: Same as A with addition of 24U/L IRI
Figure 3. Serum insulin concentrations in the 14-day model
A: PD with isotonic (1.5%) respective hypertonic (4%) solutions without added insulin
B: PD with addition of 12U/L IRI
C: PD with addition of 24U/L IRI
Discussion

During PD treatment a considerable amount of glucose is absorbed from dialysis fluid. In the present study we found the amount of glucose absorbed each dialysis to be 80–128mmol with the isotonic and 480–707mmol with hypertonic dialysis fluid. Consequently, it is of great importance to be able to control plasma glucose during PD for example by addition of insulin to the dialysis fluid.

The present studies have shown that addition of 6U/L IRI does not affect plasma glucose concentrations. By addition of 12U/L IRI it was possible to control plasma glucose during both isotonic and hypertonic PD. Addition of 24U/L IRI to the isotonic PD caused a post dialysis fall in plasma glucose with the development of hypoglycaemic symptoms in two patients.

References

3 Andersen KEH, Pedersen FB. *Int Urol Nephrol* 1979; 11: 239
4 Wide L, Porath J. *Acta Biochem Biophys* 1966; 130: 257

Open Discussion

ROTTEMBOURG (Paris) What is the blood glucose level of your patients after they have received 24 units/litre, that is to say more than 400 units during the dialysis and when the plasma free insulin level is very high? Do they become hypoglycaemic?

HEMMELØFF ANDERSEN Only two of the patients became hypoglycaemic when we used the 24 units insulin infusion.

PARSONS (London) If I can take up the hypoglycaemic problem, the thing is that your peritoneal dialysis must go well. If you land up with two litres of intraperitoneal glucose plus 48 units of insulin and the peritoneal dialysis chooses to go wrong, at that moment you will suffer the most profound hypoglycaemia in some patients. I think this must be a warning that these high levels of insulin look very nice in the controlling of blood sugar, but they also carry a hazard if the peritoneal dialysis goes wrong, and not all of them go well. At that point you may have very sick patients at the end of your peritoneal dialysis session.

GAHL (Chairman) Did you measure the insulin absorption in the dialysis system and if so, how much was it?

HEMMELØFF ANDERSEN Yes, I did. We measured the absorption both in the container and in the PVC tubing and we found no absorption of practical relevance.