Elimination of Hexamethylene Diisocyanate Cross-Linked Polypeptides in Patients with Normal or Impaired Renal Function

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Summary. Infusions of 3.5% isocyanate cross-linked polypeptide solution 500 ml were given to 52 patients with normal or impaired renal function: glomerular filtration rate (GFR) = 0–133 ml/min. The serum concentration and urinary excretion of hydroxyproline were measured and the equivalent polypeptide concentrations were calculated from the results. In patients with normal renal function (GFR > 90 ml/min) the proportion of polypeptide excreted in the urine up to 12 h was 45.4 ± 2.6% (X ± SEM), up to 24 h 47.7 ± 2.9% and up to 48 h 49.3 ± 3.4%. In patients with moderate renal insufficiency (GFR = 30–90 ml/min) there was no decrease in polypeptide excretion and even in patients with more serious impairment of GFR (11–30 ml/min) 48-h urinary polypeptide excretion was still 40.6 ± 5.9%. In patients with GFR of 2–10 ml/min polypeptide excretion fell to 10.7 ± 3.2% during the first 12 h, although there was an increase in later collection periods as compared to patients with normal renal function – 19.9 ± 3.9% in 24 h and 27.0 ± 3.5% in 48 h. The elimination half-life (t½) calculated from serum concentrations was 505 ± 30 min (X ± SEM) in patients with normal renal function (GFR > 90 ml/min). Only when the GFR fell below 30 ml/min did it slowly begin to increase. In patients with minimal residual renal function (GFR = 0–0.5 ml/min), who were on haemodialysis, the elimination half-life was 985 ± 49 min, i.e. approximately twice the normal. Twice weekly infusion of 3.5% polypeptide solution 500 ml over a period of 6 weeks did not produce any significant cumulation in haemodialysis patients (GFR = 0–0.5 ml/min). A weekly dose of polypeptide 35 g appeared to be quite safe when given for several weeks, even to anuric patients. As no significant amount of polypeptide was lost during haemodialysis, the dose can be chosen without taking into account any effect of intermittent haemodialysis.

Key words: Colloidal plasma substitutes, cross-linked polypeptides, Haemaccel®, pharmacokinetics, renal failure.

Colloidal plasma substitutes may be given to patients with renal insufficiency for any of the usual indications, just as in patients with normal renal function, but they also find a use in special situations, for instance repeated correction of a circulating volume deficit caused by haemodialysis. As colloidal plasma substitutes are largely excreted via the kidneys [1, 10, 14, 21], and as extrarenal elimination mechanisms may possibly be deranged in advanced renal failure, administration of conventional doses to patients with renal insufficiency might lead to delayed elimination and toxic cumulation. This possibility also exists for isocyanate cross-linked polypeptide 1, a colloidal plasma substitute now in wide spread clinical use, as plasma substitutes derived from gelatin are mainly excreted via the kidneys by patients with normal renal function [7]. The present investigation was undertaken to study the urinary excretion and elimination half-life of isocyanate cross-linked polypeptide in patients with normal or impaired renal function. Attention was also directed to the question whether this substance, when given repeatedly in conventional clinical doses to patients with advanced renal failure, might lead to cumulation or to undesirable effects.

1 (Haemaccel®, 3.5%) Behringwerke AG, Marburg an der Lahn. Polymerized polypeptides derived from degraded gelatin and cross-linked with hexamethylene diisocyanate; abbreviated to polypeptides. Mean molecular weight (Mw) 35,000.
Patients and Methods

1. Determination of Polypeptide in the Serum and Urine of Patients with Normal or Impaired Renal Function

The elimination half-life ($t_{1/2}$) and urinary excretion were determined in 52 patients with normal or impaired renal function (glomerular filtration rate = 0–133 ml/min) after a one-hour intravenous infusion of 3.5% isocyanate cross-linked polypeptide 500 ml. Blood samples were taken before the infusion ($t_0$), at the end of the infusion ($t_{60}$ min) and after 2, 3, 4, 6, 8, 12, 24, 36, 48 and 72 h. The polypeptide in the urine was measured over three collection periods: the first 12 h, from 12 to 24 h and from 24 to 48 h.

The isocyanate cross-linked polypeptides in serum and urine were determined by measuring the imino acid hydroxyproline, which constitutes 14.5% of gelatin, by the method of Stegemann [19], as modified by Stegemann and Stalder [20]. In this method the imino acid is treated with chloramine-T in approximately neutral solution to oxidize it to a chromogen, which, when treated with p-dimethylaminobenzaldehyde in strong perchloric acid, yields a characteristic coloured substance, that can be evaluated photometrically at 550 nm. As the colour reaction is given only by free hydroxyproline, preliminary hydrolysis of the isocyanate cross-linked polypeptide is necessary. This was done either by heating with 6 N HCL at 105–107 °C for 18 to 20 h, or by the use of a commercially available reagent (Hypronostieon, Organon Teknika, Munich) based on the strongly acid ion exchange resin Amberlite CG 100. Hydrolysis on the ion exchange resin has technical advantages. It was checked for completeness in a large number of tests by examination in parallel with the hydrochloric acid hydrolysis technique.

The serum hydroxyproline level in patients with chronic renal failure (converted into polypeptide concentration) is approximately 5 mg/l higher than in normal persons [2, 6]. After intravenous infusion of isocyanate cross-linked polypeptide 17.5 g, the hydroxyproline concentration found was equivalent to approximately 2000 mg polypeptide/l, so the error caused by individual variation in endogenous hydroxyproline concentration was less than 1% in patients with a high exogenous serum concentration due to infusion, and below 3% even in patients with a low exogenous serum concentration; it can therefore be disregarded. Within the range of concentrations studied, the recovery rate amounted to 102.4 ± 3.1%. When the serum concentration was less than 10 μg/ml the error became larger, and these values, which were generally reached after 36–48 h by patients with normal renal function, were disregarded in the calculations.

2. Glomerular Filtration Rate

The glomerular filtration rate (GFR) was determined by $^{51}$Cr-EDTA clearance [4]. In patients on haemodialysis, the GFR was determined by combined urea-creatinine clearance [15] in the interval between dialyses; in a patient with a low level of residual renal function this gives more a precise value than the isotope clearance method.

3. Serum Polypeptide Concentration after Repeated Administration and after Increasing Doses

To detect any cumulation resulting from conventional clinical doses, five patients on chronic intermittent haemodialysis (GFR = 0–0.5 ml/min) were given 3.5% polypeptide solution 500 ml within a 30 minute period at the commencement of each haemodialysis for a period of 6 weeks. Serum samples for determination of polypeptide concentration were taken at the beginning and end of dialysis, and for a further 4 weeks immediately after the last dialysis.

Tests were carried out in two patients with normal renal function to ascertain whether there was any change in the half-life of the polypeptide after an increase in dose, or after repeated administration. On the first day the patients were given 3.5% polypeptide solution 500 ml (17.5 g), on the third day 35 g and on each of the fourth, fifth and sixth day 17.5 g polypeptide. Serum was collected after each infusion at the times listed above, and the pharmacokinetic data were calculated from the results.

4. Investigations During Haemodialysis Treatment

In order to ascertain whether the polypeptide was dialysable, four haemodialysis patients, who were being treated by ultradiffusion, were given 3.5% polypeptide solution 500 ml intravenously during the first 30 min of dialysis. During a $21/2$-h ultrafiltration phase, with a transmembrane pressure of 500 mm Hg (dialyser: Gambro Lundia Optima, 1.0 m²), the polypeptide concentration in serum and the ultrafiltrate were determined at 30 minute intervals. In addition, the serum polypeptide concentration in five other patients was measured during an 8-h conventional haemodialysis on the same dialyser.

5. Calculation of Pharmacokinetic Data and Statistical Correlates

The mean value of duplicate estimates of serum concentration for each patient was plotted on semi-