PAPERS AND SHORT REPORTS

Intraperitoneal insulin in uraemic diabetics undergoing continuous ambulatory peritoneal dialysis

ALESSANDRO BALDUCCI, GÉRARD SLAMA, JACQUES ROTTEMBOURG, ALAIN BAUMELOU, ANNE DELAGE

Abstract

The kinetics of absorption of intraperitoneally administered insulin were studied in nine uraemic insulin-dependent diabetics undergoing continuous ambulatory peritoneal dialysis (CAPD). In each of three studies 20 U of regular insulin was directly injected as a bolus into the peritoneal cavity through an indwelling Tenckhoff catheter. In two procedures the insulin injection was followed by the instillation of either 2 litres of 1.5% dextrose dialysate or 2 litres of 4.5% dextrose dialysate. In the third 20 ml of saline was used to flush the tubing. Plasma free insulin values rose more rapidly and reached significantly higher concentrations (55.6 ± 18.8 mU/l) when the insulin had been injected into an empty peritoneal cavity than when it was followed by dialysate. These differences were observed despite the fact that most of the insulin injected was retained by the patients.

Since the plasma insulin values did not differ after instillations of dialysate containing 1.5% and 4.5% dextrose, the osmolality of the dialysate seemed not to affect insulin absorption, and the dilution of the insulin probably delayed its transfer through the peritoneum. These findings suggest that insulin given intraperitoneally to patients undergoing CAPD will be most effective if it is given into an empty peritoneal cavity at least 30 minutes before the dialysate is instilled.

Introduction

Continuous ambulatory peritoneal dialysis (CAPD) is a valuable alternative to haemodialysis in treating end-stage renal failure,¹⁻⁴ and it is routinely used to dialyse uraemic diabetics.^{5, 6} In 1971 Crossley and Kjellstrand⁸ proposed adding insulin to the dialysate to maintain adequate blood glucose concentrations and prevent hyperosmolarity,⁷ and several groups have since used this technique.⁹⁻¹³ Such a technique, which avoids subcutaneous insulin injections, is favoured by many patients and now widely used in many dialysis units.

We studied the absorption kinetics of intraperitoneally injected insulin in uraemic diabetics undergoing CAPD to assess the effects of the presence or absence of dialysate in the peritoneal cavity and the dextrose concentration in the dialysate.

Patients and methods

Nine insulin-dependent diabetics with end-stage renal failure (creatinine clearance 0.8 ml/min) who were undergoing CAPD were investigated after they had given their informed consent to the study. Their mean body weight was $64.1 \pm (\text{SEM}) 3.1$ kg, mean age 58 ± 2.5 years, and mean duration of insulin treatment 16 ± 2.8 years. Plasma C-peptide concentrations after stimulation with 1 mg intravenous glucagon were below the threshold of sensitivity for the assay in eight patients and 0.04 ng/l in one. Seven patients had regularly had insulin added to the dialysate for a mean of nine months (range 1-13) before the study and received an average of 81 units/day of intraperitoneal insulin. Two other patients were receiving insulin subcutaneously at the time of the study.

Three procedures were tested in each patient, in random order: one in the morning, another in the afternoon of the same day, and the third in the morning of the next day. In each study 20 units of regular neutral insulin (Actrapid) were injected in all patients through the connecting tube and the Tenckhoff catheter after careful drainage of the previous dialysate exchange.

Procedure 1—Immediately after the insulin injection 2 l of dialysate with 1.5% of dextrose was instilled. The solution was then left in the peritoneum for 180 minutes.

Procedure 2—Insulin was injected as in protocol 1 but followed by the instillation of 2 l of dialysate with 4.5% of dextrose.

Procedure 3—The insulin injection was followed by only 20 ml of isotonic saline (enough to flush out the 5 ml dead space of the tubing).

Dialysis Unit, San Giacomo Hospital, Rome
ALESSANDRO BALDUCCI, MD, physician

Department of Diabetology and INSERM, Hôtel-Dieu Hospital,
75181 Paris
GÉRARD SLAMA, MD, physician

Department of Nephrology, La Pitié Hospital, Paris
JACQUES ROTTEMBOURG, MD, physician
ALAIN BAUMELOU, MD, physician
ANNE DELAGE, technician

The peritoneal cavity was then left empty during the 180-minute study period.

Blood samples were drawn from an indwelling catheter at regular intervals for 180 minutes after the insulin administration. Plasma free insulin concentration was measured by a radioimmunological assay according to the method of Nagakawa¹⁴ with a talcum powder separation. Dextrose concentration and total insulin were measured in the dialysate on two outflow samples (one recovered at the beginning, the other at the end of the drainage) after the three-hour exchange. Blood glucose and dialysate dextrose were measured using a polarographic electrode (Yellow Spring Instrument Co, USA).

Statistical analysis was performed using Student's *t* test for paired data.

Results

Plasma free insulin concentrations—Fig 1 shows mean plasma free insulin concentrations in nine patients during the 180 minutes after the administration of insulin in all three procedures. After procedure 1 the mean plasma free insulin concentrations rose from a basal value of $11 \pm (\text{SEM}) 4.5$ mU/l to a peak at 20 minutes of 20 ± 4.5 mU/l, then declined steadily to the basal value by 180 minutes (9.8 ± 2.1 mU/l).

FIG 1—Mean plasma free insulin concentrations in nine insulin-dependent diabetics injected with 20 U of insulin intraperitoneally followed by 20 ml of saline solution, 2 l of 1.5% dextrose dialysate, or 2 l of 4.5% dextrose dialysate. Values are means $\pm$ SEM.

After procedure 2 the pattern was similar: insulin values rose from 8.3 ± 2.9 mU/l to a peak at 20 minutes of 15.5 ± 6.3 mU/l and returned to the starting value by 180 minutes. There were no statistically significant differences between the insulin values after these two procedures. After procedure 3, the insulin injection alone, insulin concentrations rose sharply from 5.6 ± 2.1 mU/l and attained a higher level at 10 minutes than the peak value obtained at 20 minutes after procedures 1 and 2. The maximum value (55.6 ± 18.8 mU/l) was reached at 45 minutes. Insulin concentrations then fell steadily to 17.5 ± 5.2 mU/l at the end of 180 minutes. The mean value at 180 minutes was significantly higher than the starting value ($p < 0.05$). Mean insulin values after procedure 3 were significantly higher than those after procedures 1 and 2 at 45, 60, 90, and 120 minutes ($p < 0.05$). The mean area under the curve after procedure 3 (3299 ± 523 (arbitrary units)) was also significantly greater than after pro-

cedures 1 (1428 ± 116) and 2 (1206 ± 70) ($p < 0.001$). The difference between procedures 1 and 2 was not significant.

Insulin and dextrose in fluid drained from the peritoneum amounted to 3.8 units of insulin and 11 g of dextrose after procedure 1 and 3.1 units of insulin and 18 g of dextrose after procedure 2.

Blood glucose concentrations after the three procedures are shown in fig 2. Baseline values were similar before the three procedures. As expected values increased after intraperitoneal glucose instillation with no difference between procedures 1 and 2. Glucose concentrations fell after procedure 3, reaching a plateau after 45 minutes.

FIG 2—Variations in blood glucose concentration in nine insulin-dependent diabetics injected with 20 U insulin intraperitoneally followed by 20 ml of saline solution, 2 l of 1.5% dextrose dialysate, or 2 l of 4.5% dextrose dialysate. Values are means $\pm$ SEM.

Conversion: SI to traditional units—Glucose: 1 mmol/l $\approx$ 18 mg/100 ml.

Discussion

This study was designed to estimate the absorption kinetics of intraperitoneally administered insulin in diabetics; we made no attempt to bring blood glucose concentrations to normal during the study. A fixed amount of insulin was thus used to facilitate comparison between the patients.¹⁵

Our results show that the rate of absorption of intraperitoneal insulin is much greater when the insulin injection is not followed by the introduction of dialysate. The small increase in plasma free insulin concentrations when dialysate was present in the peritoneal cavity may have several explanations. Lack of absorption of the insulin can be ruled out because of the small amounts of insulin recovered in the drainage fluid after procedures 1 and 2 (3.8 and 3.1 units respectively). Increased clearance of plasma insulin caused by glucose loading is also unlikely but cannot be ruled out. Increased absorption of insulin to the peritoneum or its inactivation by the dialysate is possible. A delay of insulin transfer through the peritoneum as a result of the intraperitoneal dilution of the insulin is the most likely explanation. The dextrose concentration and hence the osmolality of the dialysate had no influence on plasma insulin values or insulin recovery, which suggests that insulin resorption through the peritoneum depends mainly on its concentration. The results suggest that peritoneal insulin transfer is a passive mechanism influenced by the insulin gradient between both sides of the peritoneal membrane.

Low plasma free insulin values after the simultaneous peritoneal administration of insulin and dextrose-containing dialysate contribute to the increase in blood glucose concentrations during peritoneal dialysis even when a 1.5% dextrose dialysate is used, as illustrated in fig 2.

Our results agree with those of Shapiro *et al* in dogs.¹⁶ They showed that the absorption and action of insulin added to dialysate were delayed. On the other hand, Poulsen *et al*¹⁷ observed only a small increase in plasma insulin in pigs when insulin was continuously infused into an empty peritoneal cavity. In their experiment, however, the total amount of insulin per kg of body weight was two to three times smaller than in our study and infused over 90 minutes instead of being injected as a bolus. Nevertheless, they also showed that the increase in plasma insulin concentration was, for the same amount of insulin infused, much higher when injected into the portal vein or into a peripheral vein than into the peritoneal cavity.¹⁷ In man our results agree with those of Shade *et al*,¹⁸ who reported a sharp increase in plasma insulin concentrations when insulin was injected intraperitoneally. They also observed that this increase was much higher after intraperitoneal than after subcutaneous insulin injection.

Intraperitoneal administration of insulin, which is preferred by patients undergoing CAPD, is now used routinely. Most dialysis units recommend adding insulin to the dialysate bags but such a technique carries the risk that insulin will be adsorbed to the surface of polyvinyl chloride containers.¹⁹ We prefer the direct administration of insulin through the catheter. Although the current method of administering insulin and dialysate at the same time has already improved blood glucose control in diabetics on CAPD, the results of our pharmacokinetics study suggest that it would probably be better, at least in the prandial period, not to dilute insulin in the dialysate but to inject insulin (followed by a small amount of a flush solution) into an empty peritoneal cavity. At each dialysate exchange, coinciding with the beginning of a meal, the new bag, although connected to the catheter, could be kept clamped for at least 30 minutes after the intraperitoneal insulin injection. The rapid insulin absorption would then help to control postprandial increases in blood glucose concentration. The effectiveness of this procedure in improving glucose control is under investigation in our department.

Nevertheless, studies in patients with and without renal insufficiency and the results of our study suggest that the intraperitoneal route may be an appropriate site for long-term insulin delivery by means of an artificial pancreas or a simpler device, as this route of administration may be more physiological, with the insulin being mainly absorbed through the portal system.²⁰

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SHORT REPORTS

Acute arthritis associated with *Clostridium difficile* colitis

Acute arthritis is well documented in association with gastrointestinal disease. We report the first case, to our knowledge, of arthritis complicating *Clostridium difficile*-associated antibiotic colitis.

Case report

A previously fit 45-year-old woman with no history of gastrointestinal or joint disease received a seven-day course of oral clindamycin (150 mg four times daily) for an infected finger. Within 24 hours of starting the antibiotic she experienced transient nausea and vomiting and watery diarrhoea 10-14 times a day, which persisted until admission 26 days later. Five days before admission her right knee and right ankle had become acutely swollen and painful.

On examination she was feverish (37.8°C) and the right knee was hot, red,

and tensely swollen, with restricted, painful movement. There was a small effusion in the right ankle, and the calf was oedematous but cool. Examination showed no other abnormality. Sigmoidoscopy showed red granular mucosa without ulceration or pseudomembrane, and the histological picture was non-specific inflammatory change. Stool culture grew *Cl difficile*, and neutralisable faecal enterotoxin was detected by its cytopathic effect in tissue culture. Faecal culture for other recognised enteric pathogens, including campylobacter, was negative.

Aspiration of the knee produced a slightly turbid fluid (five neutrophils per high-power field) with no crystals detected under polarised light and negative Gram stain and culture. No cytopathic toxin was detected in the synovial fluid. Tests for rheumatoid factor, antinuclear factor, and HLA-B27 were negative, and plasma urate concentration was normal. No increase in viral antibody titres was detected, and a test for yersinia antibodies was negative. Radiography of the knee and ankle showed no bony abnormality. She was treated with oral metronidazole 400 mg thrice daily for seven days and aspirin 900 mg four times daily. The diarrhoea settled within two days, and after aspiration of 90 ml fluid from the knee the arthritis also improved. On discharge 10 days after admission bowel habit was normal, the rectal mucosa was macroscopically normal, and no faecal toxin was detectable. There was a small residual effusion in the knee with some stiffness but a full