

Administration of Insulin by Continuous Ambulatory Peritoneal Dialysis

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Many patients with diabetic nephropathy undergoing continuous ambulatory peritoneal dialysis (CAPD) use their peritoneal access to administer insulin. Compared with the subcutaneous route, intraperitoneal (IP) insulin may display more consistent absorption, produce more physiologic insulin concentrations, and be more convenient to administer. However, there are no well-controlled trials that have demonstrated a clinically significant difference in glycemic control between IP and subcutaneous administration. For patients who choose to begin IP insulin at the time CAPD is initiated, the starting dose is 2–3 times the previous subcutaneous dose. For patients previously stabilized on CAPD, the conversion factor may be less. Doses are divided equally between bags. Some authors recommend adding more insulin to bags with a higher concentration of dextrose. In addition, the dose should be decreased when added to a bag used for an overnight dwell. Exchanges performed during the day may be timed to start 30 minutes before a meal. Unless clinical trials demonstrate a difference in efficacy between subcutaneous and peritoneal insulin administration, the route will remain a matter of patient preference.

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OUTLINE

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Diabetes mellitus is the third leading cause of end-stage renal disease (ESRD) in the United States. Approximately 5% of people with noninsulin-dependent diabetes mellitus (NIDDM) and 30–40% of those with insulin-dependent diabetes mellitus (IDDM) develop ESRD.¹ Options for sustaining life in these patients include renal transplantation, hemodialysis, and peritoneal dialysis. Transplantation is an attractive option for all patients with ESRD, and is the treatment of choice when possible for those whose ESRD is due to diabetes mellitus.²

For those who choose dialysis, continuous ambulatory peritoneal dialysis (CAPD) may offer

some advantages over hemodialysis, such as no need for routine vascular access, and continuous control of fluid status and blood pressure with a reduced risk of hemodynamic instability.¹ In the United States, over 25% of patients beginning CAPD have ESRD secondary to diabetic nephropathy.³ Many of these patients who require insulin administer it through the peritoneal access.

Rationale

Compared with the subcutaneous route, several possible advantages to the administration of insulin by peritoneal dialysate have been cited. Absorption of insulin is erratic after subcutaneous administration.⁴ One factor that may contribute to this is degradation at the site of injection.⁵ After subcutaneous administration of equivalent doses of insulin, the inpatient variability in peak plasma concentration and extent of absorption is 20–30%.⁴ The rate of absorption varies by as much as 50%,^{4,6} but it is not clear that absorption pharmacokinetics after intraperitoneal administration are any more consistent.

Peripheral hyperinsulinemia is another concern cited with subcutaneous insulin administration. Hepatic clearance of insulin released by the pancreas averages approximately 50%.⁷ After intraperitoneal administration, the majority of

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insulin is delivered directly to the liver by the portal circulation, mimicking physiologic secretion.^{7, 8} After subcutaneous injection, insulin reaches the peripheral circulation before the liver. Therefore, peripheral concentrations are relatively high in these patients compared with healthy individuals and also possibly those receiving intraperitoneal insulin.⁷

Hyperinsulinemia has been implicated as contributing to atherogenesis.^{9, 10} Its atherogenic potential is speculated to be due to its stimulation of lipid synthesis, with subsequent proliferation and deposition of lipid in arterial smooth muscle cells.¹¹ However, no clinical data associate high peripheral insulin concentrations with an increased risk of atherosclerotic disease. Therefore, this potential advantage of intraperitoneal insulin administration remains speculative.

A final advantage of peritoneal insulin administration is convenience. Some patients may prefer this route over subcutaneous injections.

Pharmacokinetics

Drugs are generally absorbed from the peritoneal cavity by passive diffusion. The extent of absorption is dependent on an agent's molecular weight, lipid solubility, protein binding, volume of distribution, ionic charge, and concentration gradient between the peritoneum and the peripheral circulation.¹²

Drugs can be absorbed directly from the peritoneal cavity into the peritoneal viscera, including the liver, or into the portal circulation.¹³ Insulin that is absorbed into the portal system or directly into the liver undergoes significant and variable hepatic clearance. Therefore, peripheral concentrations are not ideal for evaluation of its absorption from the peritoneum.¹⁰

Studies in dogs indicated that approximately 26% of a dose of insulin is absorbed from peritoneal dialysate.¹⁴ In three patients with diabetes who received insulin in their CAPD solution, the mean percentages absorbed after 2, 4, and 8 hours were approximately 22%, 28%, and 46%, respectively.¹⁵ Both of these studies used ¹²⁵I-labeled insulin to evaluate absorption kinetics. The influence of the insulin species source on intraperitoneal absorption has not been studied.

The rate of insulin absorption after intraperitoneal administration depends on the transperitoneal concentration gradient and the absorptive surface area.¹⁶ Insulin may be detected in the peripheral blood within 15 minutes, with the peak concentration occurring at 15–60 minutes.¹⁷ The onset of the hypoglycemic effect after instilling insulin and dialysate depends on the relationship between the insulin concentration and the glucose concentration; the blood glucose can decrease within 30 minutes.^{14, 15, 18}

Because of case reports of decreased insulin requirements in patients with peritonitis, controlled animal studies were conducted.^{19–21} Insulin disappeared more rapidly from the dialysate in rats with peritonitis than in those without peritonitis (mean half-life 84 ± 18 min vs 107 ± 28 min), but the difference was not significant.²⁰ However, the uptake of glucose from dialysate was increased significantly (mean half-life 70 ± 24 min vs 99 ± 18 min; $p < 0.05$). Overall, the results did not suggest that an alteration in intraperitoneal insulin requirements due to permeability changes would be expected during peritonitis. The issue remains controversial.

The effects of various dialysate dextrose concentrations and the presence of dialysate solution in the peritoneum on insulin transfer have also been studied.^{18, 22} Two concentrations of dextrose in dialysate, 1.5% and 4.5%, were evaluated in nine patients with IDDM receiving CAPD.¹⁸ After insulin 20 U was injected intraperitoneally, the dialysate was instilled. The time to free peak insulin concentration was later after insulin was injected into an empty peritoneum than when it was followed by dialysate (45 vs 20 min). After injection into an empty peritoneum, the insulin concentration was at all times higher than after injection with dialysate. The peak plasma insulin concentration was higher ($p < 0.05$) after injection into an empty peritoneal cavity (55.6 ± 18.8 mU/L) compared with administration with either 1.5% dextrose (20 ± 4.5 mU/L) or 4.5% dextrose (15.5 ± 6.3 mU/L). The area under the plasma insulin concentration-time curve (AUC) was significantly greater when insulin was injected directly into an empty peritoneal cavity (3299 ± 523 mU • min/L) than when it was administered as an additive to peritoneal dialysate solution containing either 1.5% dextrose (1428 ± 116 mU • min/L) or 4.5% dextrose (1206 ± 70 mU • min/L) ($p < 0.001$). There was no significant difference in the AUC between the two concentrations of dextrose. However, absorption of increasing amounts of glucose is associated with increasing dextrose concentrations in the dialysate, and alterations in insulin requirements may result from adjustments in dextrose concentrations.¹⁵ Overall, these findings demonstrate that insulin is more extensively absorbed when administered into an empty peritoneal cavity than when instilled concurrently with dialysate, probably as the result of convective fluid movement into the peritoneal cavity when dialysate is instilled.

Another factor that may affect absorption is the binding of insulin to the plastic tubing and bags in the CAPD system.^{23, 24} When added to the dialysate solution, up to 20% of the total amount of insulin may be adsorbed to the polyvinyl chloride container and another 5% may be lost as a result of adsorption to the administration set and filter

device.^{23, 24} Adsorption decreases with increased insulin concentration and decreased temperature.²⁵ The loss due to adsorption may be compensated for by administering higher doses of insulin. Some authors recommend direct administration of insulin through the catheter rather than into the dialysate bag to avoid its binding to the surface of containers.¹⁹

In summary, intraperitoneal insulin is absorbed rapidly.¹⁷ The extent of absorption is approximately 25–50% of an administered dose. In addition, absorption is not affected by the dextrose concentration of the dialysate and probably not by peritonitis.

Clinical Studies

No well-controlled studies have assessed the clinical utility of intraperitoneal insulin administration. A comparison of the efficacy of this route with subcutaneous injection should include patients with stable CAPD regimens. Both regimens should be maximized according to a defined algorithm. Measurement of glycemic control should include blood glucose and glycosylated hemoglobin concentrations. In addition, the study should be conducted over at least 6 weeks to allow for glycosylated hemoglobin concentrations to reach equilibrium. Several reports describing insulin administered by CAPD have been published, but none included rigorous controls, and many lacked adequate monitoring values.^{15, 19, 26–29}

Intraperitoneal administration of insulin was studied in 20 patients with diabetes and ESRD.²⁶ Fourteen patients had IDDM; five of the remaining six had been previously treated with insulin. They were treated with CAPD for 2–36 months. Insulin was added to the dialysate bag immediately before the fluid was infused through an indwelling Tenckhoff catheter. The initial dose was determined according to the concentration of dextrose in the dialysate. It was then adjusted to achieve a fasting blood glucose concentration of 7.7 mmol/L (140 mg/dl) and a postprandial concentration of less than 11.1 mmol/L (200 mg/dl). Glycosylated hemoglobin concentrations were measured monthly. All patients were followed for more than 1 year.

At the end of the study, the daily insulin dose ranged from 70–200 U. The mean glycosylated hemoglobin concentration was $182 \pm 38\%$ of the normal value, which was similar to that in dialysis patients without diabetes. Hyperglycemia was reported to occur only in association with peritonitis or 1–3 days after discontinuation of dialysis; neither nonketotic hyperosmolar coma nor ketoacidosis was reported. Symptomatic hypoglycemia occurred rarely; however, two patients were admitted to the hospital with

hypoglycemia. Intraperitoneal administration of insulin was concluded to have potential for treatment of patients with diabetes on CAPD.

Another study involved 24 patients with IDDM and ESRD.¹⁹ The average duration of CAPD treatment prior to enrollment was 10.6 months. Insulin was injected through the catheter immediately before instillation of the new dialysate solution. Patients were maintained on a standardized diet, and the dose of insulin was adjusted according to the blood glucose concentrations of the previous day. Preprandial blood glucose concentrations were measured twice a day for 1 year. Serum glycosylated hemoglobin concentrations were measured at the start of the study and after 1 year of treatment. At the end of the study, the daily dose of insulin ranged from 60–130 U. The mean fasting glucose concentration during treatment decreased from 11 mmol/L (198 mg/dl) to 5.8 mmol/L (104 mg/dl); this decrease was not significant. The mean serum glycosylated hemoglobin concentration at 1 year did not change significantly from that in the pretreatment period ($10.3 \pm 2.0\%$ vs $9.6 \pm 1.4\%$). Insulin requirements increased during episodes of peritonitis. The results of this study support the intraperitoneal route as an acceptable mode of insulin administration for patients with diabetes, but do not provide any evidence that it is superior to the subcutaneous route.

Thirteen patients, seven with diabetes and six without, were enrolled in a study that evaluated glycemic control with intraperitoneal administration of insulin.²⁷ Five of the seven patients with diabetes had IDDM and two had NIDDM. Insulin was given intraperitoneally to the patients with diabetes and subcutaneous insulin was discontinued. The dose was titrated depending on the time of day of the CAPD exchange and the concentration of dextrose in the dialysate. The duration of CAPD ranged from 2–7 months. Glycosylated hemoglobin and triglyceride concentrations were measured before and after CAPD. Both were higher after CAPD for all patients; however, baseline levels were reported only for those with diabetes. The lack of reported data makes it difficult to assess the conclusion that intraperitoneal insulin can provide satisfactory glycemic control in patients with diabetes.

Another trial assessing glycemic control studied the plasma concentrations of insulin and glucose in four patients with diabetes and ESRD who had been undergoing CAPD for 2–7 months.²⁸ The patients received either intraperitoneal insulin alone (added to the dialysate) or in combination with subcutaneous insulin. The dose of intraperitoneal insulin was adjusted according to the dextrose concentration of the dialysate, the time of day of the exchange, and an algorithm based on blood glucose concentrations. There

were no dietary carbohydrate restrictions. After the dose was stabilized, blood glucose concentration was measured before each exchange. On the study day, subjects maintained their usual activities; serum glucose and insulin concentrations were measured frequently. The frequency of glycosylated hemoglobin measurements and the values were not reported. Over 24 hours, mean plasma glucose concentrations for each patient ranged from 6.5 mmol/L (118 mg/dl) to 9.1 mmol/L (164 mg/dl). Glycosylated hemoglobin values, available for only three patients, ranged from 8.3–9.4%. Clinically significant hypoglycemic episodes were not reported. The study suggests that intraperitoneal insulin may result in satisfactory control of hyperglycemia, at least over short periods of time.

In another study, metabolic control was compared in six patients with IDDM receiving CAPD with intraperitoneal insulin (group 1), six nondiabetic patients on CAPD (group 2), and six healthy subjects (group 3).²⁹ The mean duration of CAPD was 7.2 months and 11.8 months for patients in groups 1 and 2, respectively. In groups 1 and 2, four dialysis exchanges were performed daily, before meals and at bedtime. In patients with diabetes, regular insulin was added to the dialysis solution. The daily insulin doses ranged from 36–70 U (mean 59.5 U). In groups 1 and 2, blood glucose was determined 7 times/day—before meals (which coincide with daytime exchange times), after meals, and before the bedtime exchange. As expected, the mean blood glucose concentration was higher in group 1 than in groups 2 or 3: 9.4 ± 8 mmol/L (169 ± 14.4 mg/dl), 6.5 ± 3 mmol/L (117 ± 5.4 mg/dl), and 4.9 ± 16 mmol/L (88.2 ± 2 mg/dl), respectively ($p < 0.001$). The mean glycosylated hemoglobin concentration was 6.7% in group 1 and 3.7% in group 2. The investigators concluded that intraperitoneal insulin may enable diabetic uremic patients to have satisfactory glycemic control throughout the day.

The efficacy of intraperitoneal insulin was compared with that of subcutaneous insulin in three patients with diabetes and three without.¹⁵ All six had previously been treated with hemodialysis or intermittent peritoneal dialysis. The study consisted of two 10-day phases. During phase 1, subjects with diabetes received subcutaneous insulin. In phase 2, CAPD was started and the subjects with diabetes were given intraperitoneal insulin at a daily dose 2.5 times the subcutaneous dose. The daily dose was divided equally among each of four dialysate bags with the exception of the evening bag, for which it was reduced by 25%. The dose was not altered based on dextrose concentration in the dialysate. After 1 week of CAPD, it was adjusted based on blood glucose concentrations from the previous week. Thereafter, it was left constant, and blood glucose

concentrations were measured 4 times/day for the next 10 days. The mean daily baseline dose of subcutaneous insulin was 30 U (28–32 U). By the end of phase 2, the dose ranged from 2.4–4.8 times the subcutaneous dose, with a mean daily dose of 107 U.

The maximum variation in glucose concentration each day during phase 2 was significantly smaller than during phase 1, 2.8–4.3 mmol/L vs 7.1–11.8 mmol/L, respectively ($p < 0.001$). Glycosylated hemoglobin concentrations were not measured. It was concluded that intraperitoneal administration of insulin improved glycemic control compared with the subcutaneous route, although individual requirements varied considerably more.

Thus administration of insulin in the peritoneal dialysate solution may be an alternative to subcutaneous insulin in patients with diabetes and ESRD; however, it must be noted that no well-controlled trials demonstrated a clinically significant difference in glycemic control between the two routes. Specifically, intraperitoneal administration has not been compared with several daily subcutaneous injections.

Complications

Aside from the usual adverse effects associated with insulin, other complications may result from intraperitoneal administration. One is subcapsular hepatic steatosis. In one series, steatosis was reported in 10 of 11 patients treated with intraperitoneal insulin, but in none of the 9 controls receiving CAPD without insulin.³⁰ It was thought to be caused by the unusually high concentrations of insulin saturating the liver capsule with intraperitoneal administration. It was speculated that this disrupted the local regulation of lipid metabolism, resulting in an abnormal accumulation of triglycerides in the liver.³¹

Another potential complication is peritonitis. The addition of insulin to the dialysate requires manipulation of the fluid, which could increase the frequency of bacterial contamination. This concern has not been borne out in clinical trials, possibly because the extensive training undertaken by patients using intraperitoneal insulin may improve their aseptic technique and reduce the risk of peritonitis. In one series, the frequency of peritonitis in patients receiving CAPD and intraperitoneal insulin was one episode/20.6 patient-months.²⁶ The risk of a first episode by the end of the first year of treatment was 46%, which was not significantly different from that in patients without diabetes undergoing CAPD.^{26, 32} Equal frequency of peritonitis was reported in patients receiving intraperitoneal and subcutaneous insulin.³³

Hyperglycemia and hypoglycemia may also occur. In one series, hyperglycemia was rare and

was associated only with episodes of peritonitis.²⁶ No episodes of hypoglycemia were reported.²⁶ There is no reason to believe that either disorder occurs more often with the intraperitoneal than with the subcutaneous route.

Dosage and Administration

Most studies of intraperitoneal insulin involve CAPD rather than automated peritoneal dialysis (PD) using a cycling machine overnight; therefore, recommendations for CAPD in most studies do not apply to cycler PD. The customary treatment of patients with diabetes and ESRD receiving CAPD is to add regular insulin to each dialysate bag. In general, doses are divided equally among the bags; however, some authors recommend adding a higher amount to bags with a higher concentration of dextrose.^{26, 28} This may be necessary not because the dextrose concentration affects insulin absorption, but because of an increased carbohydrate load.

The dose should be decreased when added to a bag used for an overnight dwell because of increased overall insulin absorption from the peritoneal cavity with a longer equilibrium time, and because of the tendency for reduced insulin requirements at night, both resulting in the danger of nocturnal hypoglycemia.²⁶ Administration of insulin is normally timed with respect to dialysate exchanges. Some authors recommended that exchanges during the day be timed to start 30 minutes before a meal to allow the peak insulin concentration to coincide approximately with the meal.²⁶

There is no basis for recommending a specific species of insulin for intraperitoneal injection. The species of regular insulin employed was reported in some of the studies; in most instances it was human insulin. The choice of species would be expected to have only a minimal influence on insulin's pharmacokinetics and pharmacodynamics. It should be made for intraperitoneal insulin with the same considerations as for subcutaneous administration.

When switching from the subcutaneous to intraperitoneal route, the difference in absorption should be considered. Up to 100% of subcutaneous insulin is absorbed, compared with 25–50% of intraperitoneal insulin.^{5, 14, 15} As in any patient starting CAPD, initially the dialysate may have to contain a high concentration of dextrose, and the increased carbohydrate load could be expected to necessitate a corresponding increase in the insulin dose. Taking these factors into consideration, the usually recommended starting dose is 2–3 times the subcutaneous dose in patients beginning intraperitoneal insulin at the time of starting CAPD.¹⁵ As when insulin is given subcutaneously, adjustments may be based on

fasting, preprandial, and postprandial blood glucose concentrations. Home blood glucose monitoring is required. For patients who are stabilized on CAPD before initiation of intraperitoneal insulin, the subcutaneous dose should have been adjusted to account for the CAPD dextrose load. Therefore, in these patients, the conversion factor from subcutaneous to intraperitoneal insulin may be less.

When patients receiving CAPD develop peritonitis it may be necessary to coadminister insulin with any one of several agents given intraperitoneally. Ampicillin, azlocillin, cephapirin, clindamycin, mezlocillin, piperacillin, and tobramycin retain greater than 90% activity at room temperature for 48 hours when added to dialysate solutions containing heparin and insulin.^{33, 34} Cefotaxime, nafcillin, and vancomycin are compatible with insulin at 24 hours; however, the stability of the insulin in these solutions was not studied. Nonetheless, coadministration may still be reasonable because the absorption of insulin can be monitored by blood glucose concentrations.

Conclusion

Administration of insulin in the peritoneal dialysate solution may be a viable option to subcutaneous insulin in patients with diabetes and ESRD undergoing CAPD. Possible advantages are convenience and avoidance of peripheral hyperinsulinemia. No trial performed to date has demonstrated a clinically significant difference in glycemic control between intraperitoneal and subcutaneous routes, or any benefit from an improved ratio of peripheral to portal insulin concentrations. Intraperitoneal administration has not been compared with intensive subcutaneous therapy.

A possible disadvantage of intraperitoneal insulin is the necessity of relatively large doses, which would increase the cost of therapy. Unless controlled studies document a clinical difference between the intraperitoneal and subcutaneous routes, the decision remains largely a matter of patient preference.

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