Safety of Oral Carnitine in Dialysis Patients

Is oral carnitine contraindicated in dialysis patients?

Levocarnitine is available in both an intravenous and oral formulation. In December 1999 the U.S. Food and Drug Administration (FDA) granted approval for the use of the intravenous form of levocarnitine (Carnitor) for "the prevention and treatment of carnitine deficiency in patients with end-stage renal disease who are undergoing dialysis." This approval was specific for the intravenous formulation, as the pharmacokinetic data supporting adequacy of replacement was specific to the parenteral form. Despite the fact that oral levocarnitine lacks FDA approval for the specific treatment of carnitine deficiency in end-stage renal disease (ESRD), nephrologists have frequently used oral levocarnitine for this purpose.

Oral levocarnitine differs from the intravenous form in terms of bioavailability (approximately 15%) and, consequently, achievable blood levels (1). In its 1994 review of 42 published studies in approximately 600 hemodialysis patients on the effects of levocarnitine supplementation in ESRD, the American Association of Kidney Patients Renal Dialysis Consensus Group concluded that there was a definite role for carnitine in the treatment of renal dialysis patients. The group elaborated the conditions for which carnitine should be used and further stated, "20 milligrams per kilogram of intravenous carnitine after each dialysis treatment should be the recommended dose and mode of therapy." With respect to lower doses and oral administration, the panel stated "the data are not sufficiently controlled…to be definitive" (2).

In addition to these differences in achievable levels and FDA-approved indications, specific safety issues have been raised relative to the use of oral levocarnitine and high doses for prolonged periods in the ESRD population. These safety concerns are the basis for the precaution added to the Carnitor package insert in July 2001. The precaution states, "Administration of high doses of the oral formulation of levocarnitine is not recommended in patients with severely compromised renal function or in ESRD patients on dialysis due to the fact that major metabolites formed following oral administration, trimethylamine (TMA) and trimethylamine- N-oxide (TMAO), will accumulate since they cannot be efficiently removed by the kidneys. This does not occur to the same extent following intravenous administration."

This precaution is based on the different metabolic fates of oral and intravenous carnitine. When administered orally, unabsorbed levocarnitine is substantially degraded by intestinal bacteria to two principal by-products, TMA (up to 49% of administered dose) and butyrobetaine (up to 45% of administered dose) (3). As the bacterial population of the uremic gut has been shown to exceed that of normal by up to 10^5-fold, these by-products would be expected to be particularly abundant in dialysis patients (4,5). Whereas butyrobetaine is eliminated in the feces, TMA is efficiently absorbed through the intestinal mucosa. Absorbed TMA is further metabolized in the liver to TMAO by a saturable flavin containing monooxygenase isoform 3 (FMO 3). In patients with normal renal function, this TMAO is eliminated by renal excretion. On the other hand, in patients with renal failure, TMAO is not normally eliminated. Despite the fact that TMAO is partially dialyzed out, the intermittent nature of hemodialysis would predict that ambient TMAO levels in dialysis patients would be higher than in patients with normal renal function. At higher plasma concentrations, TMAO can be converted back to TMA. Unfortunately TMA and other methylamines are potentially toxic for a number of reasons: 1) Both TMA and its breakdown product dimethylamine (DMA) may be teratogenic, inhibiting production of DNA, RNA, and protein (6). 2) If DMA is formed from a minor metabolic pathway of TMA, N-nitrosodimethylamine (a potent carcinogen) may also be produced (7). 3) In studies confined specifically to dialysis patients, increased plasma TMA and DMA correlate with lengthening of choice reaction time (CRT) indicating cognitive impairment (8). 4) DMA and TMA are responsible for the malodorous nature of uremic breath with consequent social implications (9).

By bypassing the gut, intravenous levocarnitine avoids degradation to any substantial degree of these methylamine by-products so that these toxicity considerations would not apply. The toxic effects of these by-products are assumed to be cumulative and dose dependent; hence the reason for the precaution in using oral carnitine in ESRD patients at high doses for prolonged periods.

Brian Schreiber
Neenah, WI

References

1. Brass E: Pharmacokinetic considerations for the therapeutic use of carnitine in hemodialysis patients *Clin Ther* 17:176–185, 1995
2. AAKP Carnitine Renal Dialysis Group: Role of L-carnitine in treating renal dialysis patients. *Dial Transplant* 23:177–181, 1994
3. Rebouche C, Chenard C: Metabolic fate of dietary carnitine in human adults: identification and quantification of urinary and fecal metabolites. *J Nutr* 121:539–546, 1991
4. Simenhoff ML: Bacterial population of the small intestine in uremia. *Nephron* 22:63–68, 1978
5. Simenhoff ML, Saukkonen J, Burke J, Wesson L, et al.: Amine metabolism and the small bowel in uremia. *Lancet* 2:818, 1976
6. Guest I, Varma DR: Developmental toxicity of methylamines in mice J. *Toxicol Environ Health* 32:319–330, 1991
7. Lijinsky W, Reuber MD: Carcinogenesis in rats by nitrosodimethylamine and other nitrosomethylalkylamines at low doses. *Cancer Lett* 22:83–88, 1984
8. Simenhoff ML, Ginn HE, Teschan PE: Toxicity of aliphatic amines in uremia. *Trans Am Soc Artif Intern Organs* 23:560–565, 1977
9. Simenhoff ML, Burke JF, Saukkonen JJ, Ordinario AT, Doty R: Biochemical profile of uremic breath. *N Engl J Med* 297:132–135, 1977

Alteplase Use for Clotted Catheters

How exactly is alteplase used and handled for dialysis catheter thrombosis?

Tissue plasminogen activator has been used to declot accesses in hemodialysis patients for almost 10 years. Prior to 1998 the thrombolytic agent of choice for thrombosed hemodialysis catheters was urokinase. In 1998 the U.S. Food and Drug Administration (FDA) prohibited the distribution of this agent because of an associated risk for infection. Since that time streptokinase and alteplase have been the only agents available. The allergenic nature of streptokinase prevents repeated use of this agent, therefore alteplase has become the agent of choice.

Alteplase has two major problems in comparison to urokinase—it is more expensive and is unstable. Alteplase retains maximum thrombolytic activity when stored for no more than 48 hours at 2 °C. The cost of alteplase in our institution is approximately $48.00 per 1 mg dose. Alteplase (Activase; Genentech) is prepared in the pharmacy in 1 ml aliquots in a concentration of 1 mg/ml from 50 mg alteplase vials and stored in a constant temperature freezer at minus 20 °C. The product is removed from the freezer immediately prior to use and is completely thawed within a few minutes prior to administration.

Reports in the literature have documented the use of alteplase in doses from 2 to 45 mg with dwell times varying from 30 minutes to 4 days. Successful restoration of catheter patency ranged from 67 to 87.5% (1–4). Haire et al. (5) conducted the first randomized double-blind study to compare the efficiency of alteplase 2 mg/ml to urokinase 10,000 U/2 ml in oncology patients. Catheter function was restored in 89% with alteplase and in 59% with urokinase.

We have just completed a retrospective study comparing alteplase with urokinase (6). Our protocol was 1 ml of alteplase at a concentration of 1 mg/ml or 1 ml of 5000 U/ml of urokinase instilled into each catheter port. The catheter lumen was then filled to total volume with normal saline. At 20-minute intervals, 0.2 ml of normal saline was added to each port. The thrombolytic agent was allowed to dwell in the catheter for a total of 60 minutes before being aspirated. Hemodialysis was then reattempted. In our experience 70% of the patients receiving alteplase achieved posttreatment blood flow rates greater than 300 cc/min compared to 35% in the urokinase group. We have experienced no adverse events during the use of alteplase.

Patients with a fibrin sheath surrounding the catheter do not usually respond to this treatment. When urokinase was available we had good results with high-dose infusions of urokinase during dialysis producing dissolution of fibrin sheaths. We have not utilized high-dose continuing infusions of alteplase primarily because of the expense. Our current practice is to use alteplase only in tunneled catheters. We have replaced thrombosed temporary catheters over a wire in order to avoid the delay required for the use of the thrombolytic agent and the expense of the agent.

Edwin J. Macon
Atlanta, GA

References

1. Ahmed A, Shapiro WB, Porush JG: The use of tissue plasminogen activator to declot arteriovenous access in hemodialysis patients. *Am J Kidney Dis* 21:38–43, 1993
2. Daeihaigh P, Jordan J, Chen GJ, Rocco M: Efficacy of tissue plasminogen activator administration of patency of hemodialysis access catheters. *Am J Kidney Dis* 36:75–79, 2000
3. Paulsen D, Reisoether A, Aasen M, Fauchald P: Use of tissue plasminogen activator for opening of clotted dialysis catheters. *Nephron* 64:468–470, 1993
4. Vlassopoulos D, Logothetis E, Arvanitis D, Noussias C, Magana P, Katopodis K, Hadjiconstantinou V: Local thrombolysis with recombinant tissue plasminogen activator for thrombosed vascular access in hemodialysis patients. *Clin Nephrol* 46:77–78, 1996
5. Haire WB, Atkinson JB, Stephens LC, Kotulak GD: Urokinase versus recombinant tissue plasminogen activator in thrombosed central venous catheters: a double-blinded, randomized trial. *Thromb Haemost* 72:543–547, 1994
6. Eyrich H, Walton T, Macon E, Howe A: Efficiency of alteplase versus urokinase in hemodialysis catheter thrombosis (submitted for publication)