Pharmacokinetics and Dialysability of Warfarin in End-Stage Renal Disease

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Dear Sir,

Warfarin is a widely used anticoagulant in the general population, but rarely in end-stage renal disease (ESRD) because of the bleeding tendency associated with uremia [1]. The drug's half-life ($t_{1/2}$) is 42 h in people with normal kidney function but 30 h with ESRD [2, 3]. This decrease has been attributed to decreased protein binding [2, 4, 5] by Bachmann et al. [2] in a study that involved 4 patients with creatinine clearances of 11, 16, 35, and 48 ml/min (mean 28). We are unaware of any determinations of the $t_{1/2}$ for warfarin in patients on hemodialysis, nor is there any current recommendation on the timing of daily doses of warfarin relative to hemodialysis, perhaps because of suggestions that it is not dialyzable. To establish a dosing schedule and determine the dialysability and pharmacokinetics of warfarin in ESRD, we studied a stable 44-year-old man with ESRD of unknown etiology on maintenance hemodialysis for 1 year, receiving warfarin to prevent recurrent clotting of his hemodialysis access. The patient was dialyzed for 4 h on a 135 sulphated cellulose acetate (SCE) dialyzer (Manufactured by Althin CD Medical Inc., Miami Lakes, Fla., USA) and lost 5 pounds (3.3% of his predialysis weight) during each treatment. The dialysate had a k^+ concentration of 2 mEq/l, $HC < 5/8$ 34 mEq/l, and a dialysate flow rate of 500 cmVmin; blood flow rate was 300 cmVmin. Plasma warfarin levels were measured before and after dialysis on two different occasions while the patient was on a maintenance dose of 10 mg daily. During a non-dialysis day, plasma warfarin levels were measured at intervals following an

oral dose of 10 mg. Neither warfarin nor its metabolites were detected in the urine, and the patient's prothrombin time remained in the desired therapeutic range. Warfarin measurements were done using high-pressure liquid chromatography.

There was a 31% drop in plasma warfarin from a mean $\pm$ SD of 1.95 ± 0.15 μ g/ml before to 1.35 ± 0.45 μ g/ml after dialysis (fig. 1). Figure 2 gives the concentration-time curve for warfarin in the plasma following a 10-mg oral dose. The distribution $t_{1/2}$ obtained using the equation $t_{1/2} = 0.69/k$ was 15 h.

Warfarin is a water-soluble anticoagulant that is metabolized in the liver. In ESRD, the pharmacokinetics of most drugs are altered even when their primary route of elimination is not renal [4, 5] due to changes in protein binding, volume of distribution and/or acid-

2.5 i

2.0-

$\alpha > 1.5$

1.0

0.5

Time In hours

Fig. 1. Plasma warfarin following a 10-mg oral dose.

Fig. 2. Effect of hemodialysis on plasma warfarin.

0.0

Predialysis Postdialysis

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base disturbance [4, 5]. We have demonstrated a clinically significant drop in serum warfarin following a 4-hour hemodialysis treatment using an SCE dialyzer. This leads us to suggest that the single daily dose in hemodialyzed ESRD patients receiving warfarin should be taken after their hemodialysis treatment. While this drop in plasma warfarin following hemodialysis was not statistically significant, most likely because of the limited data points, the distribution $t_{1/2}$ was 15 h, suggesting that a single daily dose remains appropriate.

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