Effect of Hemodialysis on the Metabolic Clearance of 5-Fluorouracil in a Patient With End-Stage Renal Failure

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Abstract: A 64-year-old man on chronic hemodialysis for end-stage renal disease developed peritoneal carcinomatosis, and palliative chemotherapy with fluorouracil was started. The drug was administered (325 mg/m^2 as IV bolus, at 2 PM) on 2 separate occasions, ie, 1 hour after dialysis and 2 days later, 49 hours after dialysis. The time course of the fluorouracil plasma concentration was determined, and the main pharmacokinetic parameters were calculated. The slope of the monoexponential decay of plasma concentration was significantly greater 1 hour (0.161 minutes^{-1}) than 49 hours after dialysis (0.127 minutes^{-1}), and plasma clearance was correspondingly higher (1.78 L/min versus 1.46 L/min). The volume of distribution did not change (11.1 L versus 11.5 L). Because fluorouracil is minimally excreted by the renal route (about 10% of the dose) and is almost entirely metabolized by dihydropyrimidine dehydrogenase (DPD), it is suggested that plasma factors that accumulate during the interdialytic period and are removed by dialysis may inhibit DPD activity and, consequently, fluorouracil metabolic clearance.

Key Words: fluorouracil, metabolism, dihydropyrimidine dehydrogenase, renal failure, hemodialysis

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Fluorouracil is currently used in combination with leucovorin and other chemotherapeutic drugs to treat various types of solid tumors. More than 80% of an IV dose is inactivated by dihydropyrimidine dehydrogenase (DPD), mainly in the liver but also in other tissues.[1] Fluorouracil plasma clearance varies greatly among patients, partly because of dose- and time-dependent kinetics[2] and partly as a result of genetic polymorphism of DPD.[3] Because only 10% of fluorouracil is eliminated by the kidney,[4] end-stage renal failure should not substantially alter fluorouracil kinetics. Nevertheless, considerable experimental and clinical evidence suggests that renal insufficiency may decrease liver drug metabolism by at least 2 mechanisms: enzyme inhibition by dialyzable circulating factors and reduced expression of specific cytochrome P450 isoforms.[5] At present, it is unknown whether DPD activity is reduced in end-stage renal failure and, if so, whether hemodialysis can reverse this situation. To clarify this question, we studied fluorouracil kinetics on the day of dialysis and 2 days after in a patient on chronic replacement renal therapy, who started fluorouracil-based chemotherapy for a gastrointestinal cancer.

PATIENT HISTORY AND METHODS

A 64-year-old man with end-stage renal disease (58 kg, 185 cm), who had been on standard bicarbonate-dialysis therapy (3 treatments per week) for 3.5 years, started palliative chemotherapeutic treatment with fluorouracil because of the onset of peritoneal carcinomatosis of gastrointestinal origin. The patient also had a diffuse atherosclerotic vascular disease involving renal, femoral, and coronary arteries. At the time of the study, he was taking erythropoietin (10,000 IU 3 times a week), iron gluconate (62.5 mg/wk, IM), calcitriol (0.5 mg after dialysis), omeprazole (10 mg PO, QD), vitamin B/niacin/folic acid complex (PO, BID), and carnitine (2 g PO, after dialysis). Dialytic treatments lasted 4 hours (from 9 AM to 1 PM) and were applied on Tuesday, Thursday, and Saturday. Dialysis parameters were as follows: blood flow 300 mL/min; ultrafiltration rate 0.65 L/h; membrane low-flux polysulfone, surface 1.8 m^2. The patient was informed about the aim and procedures of the study and gave his consent. The first fluorouracil dose (325 mg/m^2 = 600 mg IV in 2 minutes) was administered at 2 PM, ie, 1 hour after the end of dialysis (on Thursday). After a 4-day wash-out, the same dose was administered at 2 PM, ie, 2 days (49 hours) after the last hemodialysis. On both occasions, 2 mL blood samples were drawn from the contralateral arm vein, at baseline and at 3–4, 6–7.5, 10, 20, and 30 minutes after bolus administration. No severe adverse reactions occurred, and on the following day, the patient started the first cycle of fluorouracil-based chemotherapy. The drug was assayed in plasma by means of a previously described HPLC method.[6] The detection limit was 20 ng/mL, and no endogenous interfering peaks were present in blank plasma. Intraday and between-days coefficients of variation were 4.5% and 6.1%, respectively. A 1-compartment model was fitted to the time course of fluorouracil plasma concentrations, using the Prism 4 statistical package (GraphPad Software, San Diego, CA), which provides an estimate of the Y-intercept (C_o) and the slope (k), and of their 95% confidence intervals (Fig. 1). The

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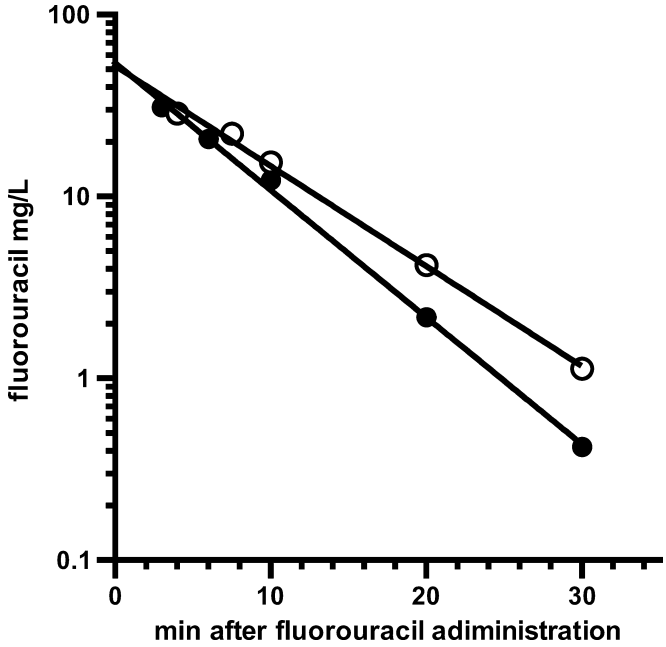

FIGURE 1. Time courses of fluorouracil plasma concentrations 1 hour (closed circles) and 49 hours (open circles) after hemodialysis.

following pharmacokinetic parameters were also calculated: the area under the curve ($AUC_{o-\infty}$) = C_o/k; plasma clearance (CL) = Dose/$AUC_{o-\infty}$; distribution volume (Vd) = Dose/C_o; plasma half-life ($T_{½}$) = 0.693/k. The Y-intercept and the slope were considered significantly different if their 95% confidence intervals did not overlap. Based on this criterion, the Y-intercepts of the two exponential equations did not differ significantly, whereas the slope was significantly greater (+27%), and the plasma half-life shorter (−21%), on the day of dialysis than 2 days after. Accordingly, total plasma clearance was also higher on the day of dialysis (+22%). Instead, the volume of distribution showed only a minimal, nonsignificant reduction (−3.5%), which was roughly equivalent to the change in body weight (−2.4%). Table 1 shows the values of fluorouracil pharmacokinetic parameters and the corresponding indices of renal function, measured on the 2 occasions. To exclude time-dependent kinetic changes, fluorouracil clearance was also calculated in 8 cancer patients (1 female and 7 male) aged between 56 and 84 years (body weight 57–96 kg), with normal renal function who received the drug as IV bolus for 5 consecutive days, according to the Mayo schedule. They underwent routine AUC monitoring on day 2 and gave their consent to repeat the sampling procedure 4 days later, on day 5 of the therapy cycle. Fluorouracil clearance did not significantly differ in the same patient between the 2 days (day 2, 1.39 ± 0.52 L/min; day 5, 1.36 ± 0.50 L/min; *t* test for paired data, $P = 0.46$).

DISCUSSION

On the whole, the pharmacokinetic parameters of fluorouracil were within the range reported for patients with normal renal function, treated with similar doses. Our results are in agreement with those of another case report on the pharmacokinetics of fluorouracil in chronic hemodialysis.[7] However, given the wide pharmacokinetic variability of the drug, these findings cannot prove that renal failure has no influence on fluorouracil disposition. In fact, we showed that fluorouracil plasma clearance measured 1 hour after hemodialysis was 22% higher than that measured 49 hours after it, indicating that circulating factors that accumulate in uremic plasma may inhibit fluorouracil metabolic clearance. This intraindividual difference cannot be explained by circadian variations in drug metabolism or dose-dependent kinetics because fluorouracil was administered at the same time of day and with the same dose schedule on the 2 occasions. Furthermore, in a control group of cancer patients being treated with fluorouracil according to the Mayo schedule, drug clearance did not change between day 2 and day 5 of the same cycle. Drug–drug interactions can also be excluded because the coadministered drugs did not change. On theoretical grounds, the clearance (CL) of highly metabolized drugs depends on liver blood flow (Q), drug unbound fraction in plasma (f_u), and intrinsic metabolic clearance (CL_{int}), according to the equation[8]:

$$CL = Q \times f_u \times CL_{int}/(Q + f_u \times CL_{int}).$$

TABLE 1. Pharmacokinetic Parameters of Fluorouracil as Well as Plasma Creatinine and Urea Measured 49 Hours and 1 Hour After Hemodialysis

	49 Hours After HD	1 Hour After HD	% Change
Y-intercept (mg/L)	52.2 (41.1–63.3)*	54.2 (43.2–65.2)*	+ 3.8
Slope (1/min)	0.127 (0.115–0.139)*	0.161 (0.149–0.173)*	+ 26.8
$T_{½}$ (min)	5.5 (5.0–6.0)*	4.3 (4.0–4.6)*	−21.4
AUC (mg × min/L)	411.3	336.8	−18.1
CL (L/min)	1.46	1.78	+ 21.9
Vd (L)	11.5	11.1	−3.5
Body weight (Kg)	58.0	56.6	−2.4
Plasma creatinine (mg/dL)	7.3	2.9	−60
Plasma urea (mg/dL)	130	41	−68

*95% confidence interval in parentheses.

An increase in f_u can hardly account for the observed CL increase because fluorouracil is negligibly bound to plasma proteins ($f_u \approx 0.9$),[5] and the postdialysis blood concentration should have decreased (not increased) the unbound fraction. Although the acute effect of dialysis on liver blood flow is unknown, cardiac preload and systemic output are reduced after dialysis,[9] so that an increase in liver blood flow is not justifiable from a hemodynamic point of view. Thus, the most probable explanation for the postdialysis fluorouracil CL increase appears to be an increase in CL_{int}. In keeping with this possibility, several experimental studies indicate that the blood or serum of rats with acute and chronic renal failure contains substances that can inhibit the activity, protein expression, and mRNA levels of various liver cytochromes P450.[10–14] Studies in patients with chronic renal failure confirm that nonrenal clearance of many drugs may be reduced to various extents (28%–92%)[5,15] and that dialytic treatment can normalize nonrenal clearance.[16] Various compounds have been suspected to be responsible for enzyme inhibition in chronic renal failure. Guevin et al[12] found that only the proteins in the 10- to 30-kDa fraction of uremic rat plasma can down-regulate the total cytochrome P450 activity in rat hepatocytes and proposed that increased circulating levels of PTH and/or cytokines may be involved.

The degree of postdialysis CL change in our patient is apparently small (+22%) and of little clinical importance. However, because fluorouracil is a drug with an intermediate liver extraction (0.22–0.45),[17] the relationship between its intrinsic metabolic clearance and plasma CL is not a line (as for low-extraction drugs) but a hyperbola.[8] As a consequence, the true increase in fluoruracil metabolism after dialysis should be greater than that measured through its plasma CL.

Nevertheless, in view of the wide variability of fluorouracil clearance even in subjects with normal renal function, this observation in a single case cannot be automatically extended to all patients with chronic renal failure without confirming the results in a larger population. Because patients requiring both fluorouracil treatment and hemodialysis at the same time are extremely infrequent, a more feasible approach could be to evaluate DPD activity in peripheral blood mononuclear cells in a large number of patients with normal and impaired renal function.

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