CAPILLARY BLOOD VERSUS ARTERIAL OR VENOUS BLOOD FOR TACROLIMUS MONITORING IN LIVER TRANSPLANTATION[1]

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Tacrolimus has been found to be useful in clinical solid organ transplantation. A very careful monitoring of the tacrolimus levels and dose adjustments are essential, at least in the immediate post-liver transplantation situation. However, quite often after liver transplantation, patients have limited venous access for daily monitoring of tacrolimus levels. When the blood is sampled from a multilumen central venous catheter, used also for intravenous administration of tacrolimus, falsely elevated concentrations of tacrolimus have been observed. The present study examines the concentration of tacrolimus in capillary blood samples obtained from finger stick and compares its concentrations in simultaneously drawn samples from arterial line, peripheral venous puncture, and multilumen centrally placed venous catheter from the port used for tacrolimus infusion and the port not used for tacrolimus infusion. Ten adult post-liver transplantation recipients were studied. Whole blood concentration of tacrolimus in capillary blood was comparable to that of arterial blood, as well as to that of peripheral venous blood samples (r^2=0.99; P=0.72). Concentrations of tacrolimus in venous blood drawn from the port of the multilumen catheter used for intravenous tacrolimus infusion were 3–23 times higher (P=0.0015), while the concentrations of venous blood drawn from the port not used for tacrolimus infusion were 1.7–4.5 times higher (P=0.016), as compared with arterial, capillary, or peripheral venous whole blood concentrations.

The benefits of tacrolimus (formerly FK506) are well recognized in solid organ transplantation (*1–4*). The pharmacokinetics of tacrolimus is widely variable between patients and elimination of the drug is affected by the functional status of the liver, as well as presence of various drugs (*5–9*). While high tacrolimus blood concentrations are associated with nephrotoxicity and neurotoxicity (*10*), persistently low blood concentrations may precipitate rejection of the transplanted organ. (*11*) Individualization of the dosing regimen of tacrolimus, to achieve the desired range of blood concentration, requires periodic monitoring of the blood concentrations of tacrolimus in transplant patients. In liver transplant patients, tacrolimus is usually administered intravenously during the immediate postoperative period and switched to oral doses once the bowel function returns to normal. During the postoperative period, tacrolimus is typically administered through one of the centrally placed multilumen venous catheters or by the peripheral venous lines. Blood samples for various purposes are taken from the arterial line. Once the arterial line is discontinued, venous blood is obtained through the multilumen central line or by peripheral venipuncture. If the central line is used for tacrolimus infusion, blood sampling from the same line can give falsely elevated tacrolimus concentrations due to significant adsorption of tacrolimus on to the wall of the tubing (*12*). Direct venipuncture may be necessary in such patients for proper estimation of tacrolimus concentrations. In patients with limited venous access, blood samples for various parameter estimates have been obtained from the capillary using the direct finger stick method. The objective of the present study is to compare the blood concentrations of tacrolimus obtained simultaneously from the capillary by finger stick, from the arterial lines, from the multiple lumen central venous catheter, and from the peripheral vein, in order to establish a reliable alternate method of blood sampling for monitoring tacrolimus concentrations.

Ten orthotopic liver transplant recipients (6 men and 4 women) were included in this study. Three of the patients (1, 3, and 5) were studied twice, for a total of 13 observations. The mean ± SD age of the patients was 54±11 years. Table 1 summarizes the patients' characteristics, the indications for liver transplantation, the study day after transplantation, the dose of tacrolimus, serum bilirubin concentration, and serum creatinine concentration in these patients. Informed consent was taken before the study.

Capillary blood (0.3 ml) was obtained by finger stick using a Unistick (Owen Mumford, Ltd., Oxford, UK). Simultaneously, 0.5-ml blood samples were obtained from a peripheral vein, an arterial line, the lumen through which tacrolimus was infused (A), and another lumen not used for tacrolimus infusion (B) in a Swan-Ganz (Baxter Healthcare Corp., Irvine, CA) or a 8.5-F quad lumen central venous catheter (Arrow International, Inc., Reading, PA). Tacrolimus infusion was discontinued for 5 min before the sample was obtained from port A. Whenever the blood was sampled from the arterial or venous lines, 5 ml of the sample were discarded before the actual sample was collected.

All blood samples were analyzed for tacrolimus concentration using the IM_x technique (Transplant Diagnostic IM_x System for tacrolimus, Abbot Laboratories Diagnostic Division, Abbott Park, IL) (*13, 14*). Thirteen capillary blood samples were compared with 13 simultaneously drawn arterial blood samples, 5 peripheral venous samples, 13 venous samples from the lumen through which tacrolimus was infused (A) and 13 venous samples from the lumen not used for tacrolimus infusion (B). Wilcoxon's signed rank test, a nonparametric test, was used to determine statistical significance at $P \leq 0.05$.

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TABLE 1. Patient characteristics

Patient	Age	Sex	Diagnosis	Post-op day	i.v. Tacrolimus (mg/day)	Bilirubin (mg/dl)	Creatinine (mg/dl)
1	54	F	Hep B+C	2	3	1.8	0.5
1b				2	3	1.1	0.7
2	44	M	Hep B+C	7	0.5	8.1	4
3	38	M	Wilson's	1	2	14.7	1.2
3b				2	2	15.7	1.1
4	47	M	Hep C	2	4[a]	2.9	0.7
5	43	M	PNCE	1	4	2.6	1
5b				3	3	2.2	0.8
6	66	M	PNCE	4	1	1.1	1.2
7	67	M	Cryptogenic	7	2	13.1	1.4
8	63	M	Cryptogenic	3	4	4.8	2
9	53	F	HCV-HCC	3	1	3.4	1.2
10	65	M	Hep C	6	1.5	29.5	2

[a] Tacrolimus discontinued 12 h before study.

As shown in Table 2, there was a good correlation between the arterial and the capillary blood concentrations of tacrolimus (r^2=0.99), capillary versus peripheral venous blood concentrations of tacrolimus (r^2=0.997), and arterial versus peripheral venous blood concentration of tacrolimus (r^2=0.997). There were no significant differences in the concentrations of tacrolimus in the arterial, capillary, or peripheral venous blood (P=0.72). On a scatter plot of the tacrolimus concentrations in the capillary versus arterial blood (Fig. 1), the slope was found to be close to the line of unity (slope = 1.11), with a mean difference of −0.39±1.91 and a 95% confidence interval of −1.56, 0.78.

Seven of 13 samples from the port not used for tacrolimus infusion (B) revealed tacrolimus concentrations that were 1.7–4.5 times higher than capillary/arterial blood samples (P=0.016). Concentrations of tacrolimus in blood sample obtained from tacrolimus infusion port A were significantly (3–23 times) higher as compared with capillary or arterial blood samples (P=0.0015). Neither hepatic dysfunction (serum bilirubin, 1.1–29.5 mg/dl) nor renal impairment (serum creatinine, 0.5–2.0 mg/dl) was found to have any influence

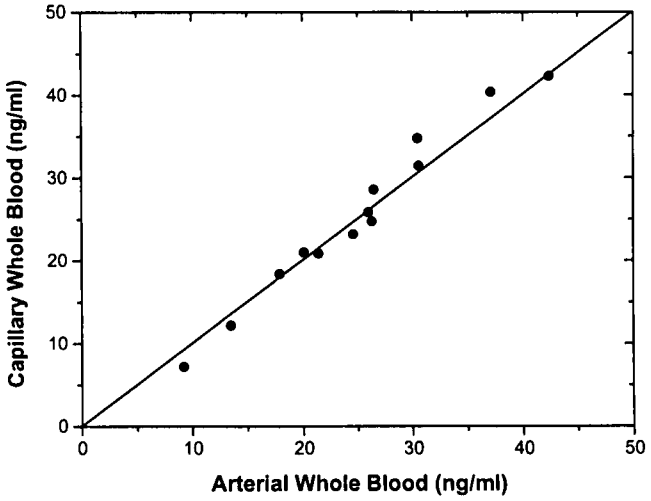

FIGURE 1. Scatter plot of tacrolimus concentration of capillary verses arterial blood. Solid line represents the line of unity. Mean difference = −0.39±1.91, 95% confidence interval = −1.56, 0.78, slope = 1.11.

TABLE 2. Whole blood tacrolimus level (ng/ml)

Patient	Tacrolimus infusion port A	Port not used for tacrolimus infusion (B)	Arterial blood[a]	Capillary blood[b]	Venous blood[c]	Central venous blood	
						Port A[d]	Port B[e]
1	Prox-infusion	Prox-injectate	21.4	20.9	21	>300	21.5
	Prox-infusion	Introducer-Swan	26.3	24.8	—	>300	119.5
2	Prox-injectate	Prox-infusion	13.5	12.2	12.2	175.5	28.2
3	Introducer-Swan	Prox-infusion[f]	20.1	21	21.1	62.7	45.5
	Introducer-Swan	Prox-injectate	30.5	34.8	30.5	298.5	33.2
4	Prox-injectate	Prox-infusion	26.5	28.6	—	83.4	26.4
5	Prox-injectate	Introducer-Swan	26.5	25.9	—	>600	99
	Prox-injectate	Prox-infusion	24.6	23.2	—	>300	99
6	Prox-injectate	Introducer-Swan	17.9	18.4	—	485	19.4
7	16-G distal@	18-G medial[g]	9.2	7.2	—	313	8.9
8	Introducer-Swan	Prox-injectate	37.1	40.4	38.7	446	40.3
9	Prox-injectate	Prox-infusion	42.4	42.3	—	>300	143
10	Prox-injectate	Introducer	30.6	31.5	—	462	52.6
Mean			25.08	25.48	24.70	>317.39	56.65

Note. P = values: a vs. b = 0.73; a vs. c = 0.72; b vs. c = 0.47; a vs. d = 0.016; a vs. e = 0.0015.

[f] Tacrolimus infusion changed from proximal infusion port 30 min before study.

[g] ARROW quadruple lumen central venous catheter.

when tacrolimus concentrations from various sites in the same patient were compared.

Measurement of chemicals in the arterial blood sample is normally considered the ideal practice because it represents the concentration of the chemical delivered to an organ. However, it is not very practical to measure chemicals in the arterial blood. Peripheral venous sampling is used for therapeutic monitoring of drugs. In patients with limited venous access, capillary blood may be the only option. However, capillary blood is normally contaminated with tissue fluids and may provide false concentration estimates of certain chemicals. In this study, the concentration of tacrolimus in the arterial blood sample was in good agreement with the concentration of tacrolimus measured in the blood obtained from peripheral vein and by the capillary method. This indicates that the capillary method is an acceptable method of obtaining blood samples for tacrolimus estimation. Since tacrolimus can be estimated in a small volume of blood (0.2 ml), this method of blood sampling is very useful in patients with limited venous access. Blood sampling from these 3 sites can be also be used interchangeably on different occasions. On the other hand, blood sampling from multiple lumen central venous catheters provides artifactually high estimates of tacrolimus concentrations. Samples obtained from the lumen used for infusion of tacrolimus provide values that are several times higher than the value obtained from capillary or arterial blood, due to contamination of the line by tacrolimus. Adsorption of tacrolimus onto the lumen of these tubes during infusion and release of tacrolimus into the blood withdrawn can account for such observations. In the majority of the cases (7/13), the concentration of tacrolimus in blood samples obtained from the lumen that was not used for tacrolimus infusion was also higher than the arterial blood concentrations of tacrolimus. This is possibly due to the high local concentration of tacrolimus in the blood at the site of sampling because of its proximity to the drug infusion site. It is also possible that this lumen might have been used earlier for tacrolimus infusion. It can be concluded that blood sampling from multiple lumen venous catheters is not reliable for measuring tacrolimus concentrations when the same catheters are also used for tacrolimus infusion. The capillary stick method is an acceptable alternative to peripheral venous blood sampling for measurement of tacrolimus blood concentrations.

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