Transpl Int (1997) 10: 409–410

LETTER TO THE EDITOR

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Comparison of old and new IMX assays for monitoring of tacrolimus levels

Received: 28 April 1997
Accepted: 13 May 1997

Sir: Tacrolimus (formerly known as FK 506) is a potent immunosuppressive agent for the prevention and treatment of allograft rejection in organ transplant recipients [2]. The dosing of tacrolimus is complicated by a narrow therapeutic range between insufficient immunosuppression and toxicity [1, 3] and a large inter- and intraindividual pharmacokinetic variability. For example, major individual dose adjustments are required when certain antiepileptic or antibiotic drugs are co-administered. Therefore, regular monitoring of tacrolimus blood levels is necessary to maintain effective treatment and keep unwanted side effects at a minimum.

When tacrolimus was introduced into clinical medicine, recommended target trough blood concentrations were 15–20 ng/ml; however, with growing experience, recommended target blood concentrations have declined to 5–10 ng/ml for most patients and they are even lower in some cases [1]. Several techniques are available to monitor tacrolimus blood concentrations. One frequently used is a monoclonal antibody-based microparticle enzyme immunoassay (MEIA) provided by Abbott (Chicago, Ill., USA). The tacrolimus MEIA ("Tacro I") was originally designed with the old target concentrations in mind. This has led to two major problems at current dosing regimens. Firstly, the precision of the method at concentrations of less than 10 ng/ml is poor. Secondly, the assay is defined only for concentrations of 5 ng/ml or more. Thus, for many patients, this assay yields relatively unreliable results.

Very recently, an improved version of the MEIA ("Tacro II") has been introduced. While this assay uses the same monoclonal antibody, the assay procedure has been altered in various ways to improve sensitivity (lower limit of detection 2 ng/ml) and precision. To evaluate this modified assay, we have compared the precision of both methods over a range of tacrolimus concentrations and have also compared apparent concentrations as determined by the two methods. All measurements were performed according to the manufacturer's instructions, and the laboratory successfully participated in the European Quality Assessment Scheme for tacrolimus monitoring organized by Dr. D. W. Holt (Analytical Unit, St. George's Hospital Medical School, London, England).

The interday coefficients of variations of the Tacro II assay for blood concentrations of 5, 11, and 21 ng/ml, as determined on 20 consecutive days, were 13.9 %, 10.5 %, and 11.2 %, respectively. To compare the Tacro I and Tacro II assays, intraday coefficients of variation were determined for both methods using a quintuplicate measurement of each sample. For this purpose, only blood samples with a mean concentration of at least 5 and 2 ng/ml were included for the Tacro I and Tacro II analysis, respectively. As expected, the intra-assay coefficient of variation was inversely correlated with the blood levels of tacrolimus for both methods, i.e., highest in the samples with the lowest blood levels (Fig. 1). In the range where both assays were tested (5–10 ng/ml), the coefficient of variation was considerably greater for the old than for the new assay (15.5 % ± 1.9 % vs 4.3 % ± 0.6 %; $n = 11$ each; $P < 0.0001$ in an unpaired, two-tailed t-test; Fig. 1).

The Tacro I assay has been validated against other monitoring techniques [1]. Therefore, we validated the Tacro II assay by comparing results obtained in parallel with the Tacro I and II tests. For this purpose, 143 consecutive kidney transplant patient samples were analyzed in duplicate with each method. Of these, only those 116 whose measurements were above 5 ng/ml in the Tacro I assay were included in the correlation analysis. Values in the Tacro II assay ranged between 3.9 and 30 ng/ml. Results from both assays were positively correlated with only minimal deviations from the line of identity [slope 0.839 ± 0.029 (95 % confidence interval 0.781–0.897), Y-intercept 1.607 ± 0.268, r^2 0.8795; $P < 0.0001$; Fig. 2]. A good correlation between the two meth-

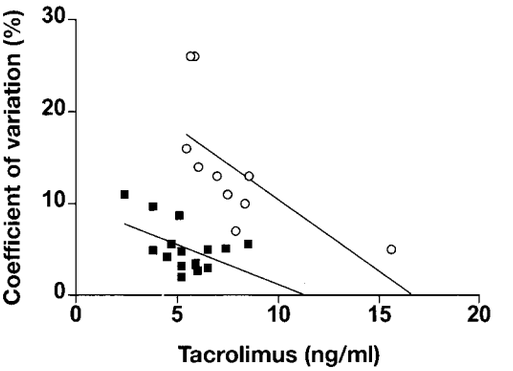

Fig. 1 Coefficients of variation as determined from quintuplicate measurements with the old ("Tacro I", *open circles*) and the improved ("Tacro II", *filled squares*) tacrolimus assay

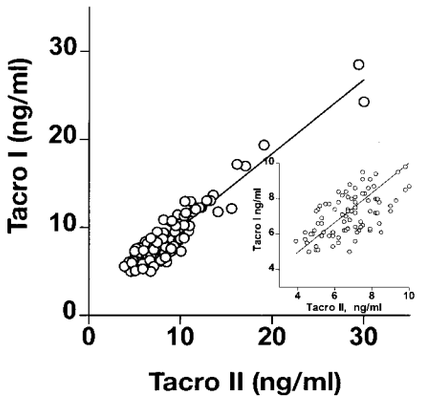

Fig. 2 Correlation between tacrolimus concentrations as determined in parallel by the old ("Tacro I", y-axis) and the improved ("Tacro II", x-axis) tacrolimus assay. Each data point is the mean of a duplicate determination with each method. The *insert* shows a magnification of the data with values of less than 10 ng/ml. Values with less than 5 ng/ml and less than 2 ng/ml in the Tacro I and Tacro II assay, respectively, were excluded from the analysis since the assays are not defined for that range. $n = 116$, $r^2 = 0.880$, $P < 0.0001$

ods was also seen in the clinically important range between 5 and 10 ng/ml (Fig. 2, insert).

Based on these results, we conclude that the Tacro II assay is not only more sensitive than its predecessor but also provides greater precision over the whole range of therapeutically relevant tacrolimus concentrations. Since both assays yield virtually identical estimates of tacrolimus blood concentrations, it does not appear necessary in clinical practice to introduce a correction factor when converting from the Tacro I to the Tacro II assay in the drug monitoring laboratory.

References

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