Minimal Sampling Strategy to Estimate the Terminal Elimination Rate Constant

Presenting Author: Elie Sarraf[1]
Co-Authors: Donald M. Mathews[1]

[1]University of Vermont College of Medicine, Burlington, Vermont

Introduction: Methadone is a long acting opioid with NMDA receptor antagonist properties which has been commonly used for both chronic pain and as a drug detoxification for opioid abuse. Methadone induction is a clinical challenge due to its long and variable half-life [1-4] thus requiring many days to achieve steady state. In a separate abstract we describe an optimal methadone induction strategy by identifying the terminal elimination rate constant (β) of the patient using a small initial dose followed by a dosing strategy using the accumulation index. We seek to determine the error of estimating β using a minimal sampling strategy that can be performed routinely on an outpatient basis and measure the impact of the error on this induction strategy.

Methods: Using Matlab (R2017b), we simulated the blood levels of 1,000,000 patients after a single test dose of methadone. The value of T½α and T½β were randomly generated using a uniform random distribution with values between 1.5 and 4.2 hours and 8.5 and 120 hours respectively. The blood levels were sampled after the test dose of methadone. 3%, 4%, 5% and 7% coefficient of variation error was added to the sampled values. β was calculated in one of two manners:

1) Using the two samples and direct computation:
$$\beta = \frac{\ln(C(t_1)) - \ln(C(t_2))}{t_2 - t_1}$$
With C(t) being the measured plasma concentration at time t.
This method was applied to measurements that were sampled at a) 24 and 48 hours, and b) 24 and 72 hours.
2) Three samples collected at 24, 48 and 120 hours were used to identify the parameters B and β in the equation $C_e(t) = Be^{-\beta t}$ such that it would minimize the following equation:
$$f(B,\beta) = \sum_i \left(\frac{C_e(t_i) - C(t_i)}{C_e(t_i)} \right)^2$$

Once the value of β was estimated, the optimal daily dosing strategy was applied to those simulated patients to determine the time for the methadone trough to be within 10% of the steady state trough (time to convergence). Also determined were the values of β that had a non-zero probability of having a 50% overshoot.

Results: Figure 1 shows the residual error plot between actual and the estimated values of β. Table 1 shows the mean and standard deviation of the residuals. The impact of the estimated β on the final time to convergence is shown in Figure 2. Table 2 shows the maximum T½β estimates that would ensure 0% probability of greater than 50% overshoot, while values above those listed in the table would have a progressively increasing risk of overshoot.

Discussion: As would be expected, one can improve the β estimates by increasing the number of samples collected, increasing the delay between samples and using a laboratory device that provides more precise measurements. Given that the vast majority of real patient T½β values of methadone are below 60 hours (beta = 0.011/hr) [1-4], one can effectively generate a minimal simple dosing strategy provided one has a well characterized laboratory device. This analysis will allow clinicians to have an appropriate margin of safety when dosing methadone through the optimal methadone induction strategy.

References

1. Nilsson MI et al. Acta Anaesthesiol Scand Suppl. 1982:74: 66-69
2. Meresaar U et al. Eur J Clin Pharmacol. 1981: 20(6): 473-478
3. Wolff K et al. Eur J Clin Pharmacol. 1993: 44(2): 189-194
4. de Vos JW et al. Eur J Clin Pharmacol. 1995: 48(5):361-6.

Figures and Tables

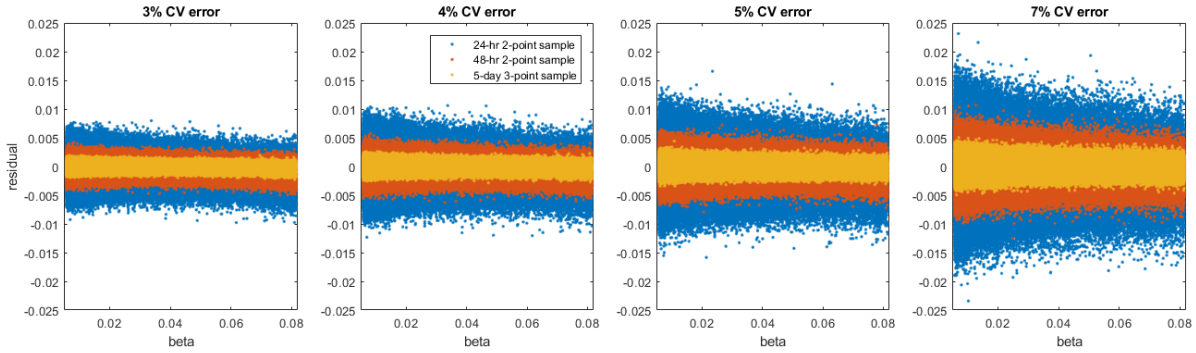

Figure 1: residual plot of β estimates

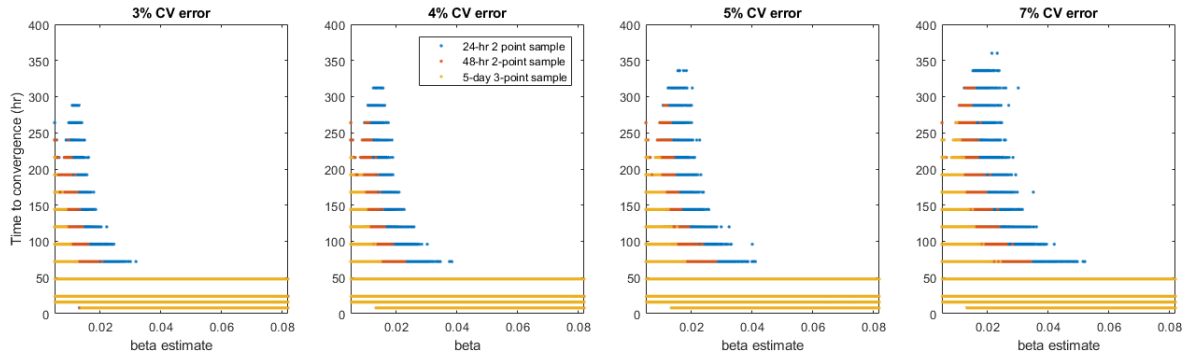

Figure 2: scatter of plot of time to convergence as a function of the estimated β

Beta residuals x 1000				
		Sampling method		
		24 hr	48 hr	3 points
%CV error	3%	0.34 +/- 1.82	0.17 +/- 0.91	0.06 +/- 0.43
	4%	0.34 +/- 2.40	0.17 +/- 1.20	0.06 +/- 0.57
	5%	0.35 +/- 2.99	0.18 +/- 1.49	0.05 +/- 0.72
	7%	0.34 +/- 4.18	0.18 +/- 2.09	0.04 +/- 1.00

Table 1: residual error of the β estimates. All values were multiplied by 1000

Critical estimated T1/2 β (hours)				
		Sampling method		
		24 hr	48 hr	3 points
%CV error	3%	56.66062	101.6738	
	4%	52.22409	82.94461	153.2405
	5%	36.35486	76.72882	143.378
	7%	31.3061	44.90001	105.2546

Table 2: Critical estimated T1/2 β values that would lead to 0% chance of 50% overshoot.