Elimination Clearance of Dexmedetomidine: Cross-examining What the Data Say

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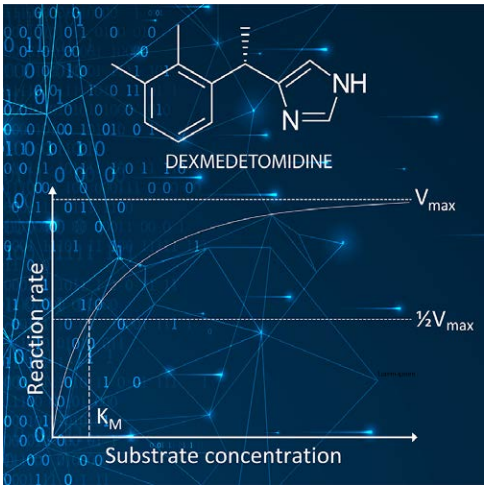
A phrase we often hear among pharmacometricians is "let the data speak." This is often good advice, but sometimes data are really bad at speaking, and letting them do so can create more questions than answers, particularly when the questions are complex.[1]

With pharmacokinetic modeling, stationarity is typically assumed (*i.e.*, volumes and clearances do not vary for the duration of the study). In this issue of Anesthesiology, Alvarez-Jimenez *et al.*[2] report data indicating that this assumption has most likely been violated for dexmedetomidine elimination clearance and suggest, in their title, that this finding has implications for dexmedetomidine dosing. We will therefore discuss three possible sources of this nonstationarity. As always, context is important, so for our considerations, the drug is assumed to be administered by intravenous infusion (dosing) either at a fixed rate or a variable rate (*e.g.*, target-controlled infusion). During infusion, plasma drug concentration will approach a steady state as determined by the ratio of dosing rate and elimination clearance. With stationary clearance, plasma concentrations are proportional to the dosing rate (*e.g.*, doubling the dosing doubles the concentrations). Currently, very few drugs can achieve regulatory approval if elimination clearance is not stationary because it requires clinicians to consider that doubling drug dosing may not simply double the plasma drug concentrations but rather increase them even more. Legacy drugs that have nonstationary elimination clearance include ethanol, phenytoin, and coumadin, and therapeutic drug monitoring is usually recommended for them.



"It is unlikely…that dexmedetomidine plasma concentrations will approach anywhere near the concentration reported to result in nonlinear pharmacokinetics."

The first and garden variety nonstationary elimination clearance (Cl_e) is the result of hepatic enzyme saturation.[3] This is easily understood from the Michaelis–Menten equation,

$$v = \frac{V_{MAX} \cdot C}{K_M + C} \quad (1)$$

where v is the rate of the enzymatic reaction; V_{MAX} is the maximum metabolic rate of the enzyme; K_M is the Michaelis–Menten constant, which is numerically equal to the drug concentration at which the rate of the enzymatic reaction is half of V_{MAX} and is inversely related to the affinity of the enzyme for the drug; and C is the drug concentration. Normally, therapeutic plasma drug concentrations (C_p) are much lower than K_M, so C_p has negligible effect on the denominator, and the rate of drug metabolism is linearly related to drug concentration, $(V_{MAX}/K_M) \cdot C_p$. In this case, the clearance (V_{MAX}/K_M) is stationary because it is independent of the concentration, and the rate of drug elimination ($Cl_e \cdot C_p$) increases proportionately with increasing concentration (*i.e.*, it is linear). In contrast, as drug concentration approaches and exceeds the K_M, the rate of metabolism nears and then becomes "saturated" at V_{MAX}, and as a result, at saturation the rate of drug elimination is constant and independent of concentration. In this "saturated" circumstance, the elimination rate is fixed at V_{MAX}, so by definition, elimination clearance is equal to V_{MAX}/C_p. Elimination clearance is nonstationary because clearance changes inversely with drug concentration and is nonlinear. Thus, as drug concentrations become near or well

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above K_M, clearance decreases, and plasma drug concentration increases disproportionately with increased dosing.

This is the modeling approach taken by Alvarez-Jimenez *et al.*[2] While their Michaelis–Menten approach nicely captures the nonlinearity of their data, it erroneously implies that the metabolic elimination of dexmedetomidine is saturable at clinically relevant concentrations. In contradistinction, clinically relevant dexmedetomidine concentrations[4] are much lower than the K_M values for CYP2A6 and the glucuronosyltransferases that metabolize dexmedetomidine, as shown from *in vitro* data. This makes enzyme saturation and nonstationary clearance theoretically unlikely.[4] In addition, no drug interactions have been reported for dexmedetomidine to date, suggesting that even if K_M or V_{MAX} is altered by other drugs, it does not affect its Cl_e. These facts speak against garden variety enzyme saturation being the cause of nonstationary dexmedetomidine clearance and nonlinear pharmacokinetics.

A deeper conversation with the data to understand what they are capable of saying may therefore be useful to more fully understand the relevance of the important findings of Alvarez-Jimenez *et al.*[2] The authors considered second and third sources of nonstationary clearance leading to the observed nonlinear pharmacokinetics.

A second possible source of apparent nonstationary clearance is the effect of incomplete intravascular mixing and, by extension, incomplete central compartment mixing that results from sampling arterial blood during an intravenous drug infusion. The principle laid out by Upton[5] and implemented in a model of arterial and venous ketamine concentrations[6] states that during an intravenous infusion, arterial drug concentration ($C_{arterial}$) is determined by

$$C_{arterial} = C_{mixed\ venous} + \frac{\text{infusion rate}}{\text{cardiac output}} \quad (2)$$

Thus, during an intravenous infusion, arterial drug concentration is the sum of the fully mixed and the incompletely mixed portions of the drug concentration, the latter of which is inversely proportional to cardiac output independent of other pharmacokinetic considerations. If arterial drug concentrations are modeled naively without separating the fully and incompletely mixed portions and if cardiac output is affected by drug concentrations, then elimination clearance would appear to be nonstationary.

Since multiple studies have demonstrated that dexmedetomidine decreases cardiac output,[4,7,8] this source of nonlinearity needs to be considered. Instead of incorporating their cardiac output data in a pharmacokinetic model according to Equation 2 and letting these data speak, Alvarez-Jimenez *et al.*[2] dealt with this potential confounding factor by omitting arterial dexmedetomidine concentrations during and immediately after dexmedetomidine infusion and then suggesting that incomplete intravascular mixing was not the reason for the observed nonlinear kinetics.

The third possible source of nonstationary clearance is an effect of dexmedetomidine on hepatic blood flow. This can be understood from Rowland's well stirred model of hepatic drug clearance, described by Equation 3,[3]

$$Cl_e = \frac{Q_H \cdot Cl_{int}}{Q_H + Cl_{int}} \quad (3)$$

where Q_H is hepatic blood flow, and Cl_{int} is the intrinsic clearance that is determined by the rate of hepatic metabolism. At one extreme in which Cl_{int} far exceeds Q_H, the equation states that Cl_e is equal to Q_H. At the other extreme, in which Cl_{int} is far less than Q_H, the equation states that Cl_e is equal to Cl_{int}. Dexmedetomidine has a high hepatic extraction ratio[4] and, thus, high Cl_{int}. Its clearance, therefore, would be influenced by changes in liver blood flow. Experimental evidence suggests that dexmedetomidine decreases hepatic blood flow.[9,10] α-Adrenergic agonists, including dexmedetomidine,[7] have been shown to reduce splanchnic blood flow.[11,12] Thus, increasing dexmedetomidine concentrations could lead to reduced hepatic blood flow and decreased (*i.e.*, nonstationary) dexmedetomidine clearance, producing the nonlinear pharmacokinetic behavior as reported by Alvarez-Jimenez *et al.*[2]

Why should we care whether the enzymes are saturated, cardiac output decreases, or hepatic blood flow is reduced as long as the equation that is invoked in the modeling process fits the data and can predict dexmedetomidine concentrations for target-controlled infusion rates? It matters greatly. From our discussion above, the most likely cause of the observed nonstationary clearance is an inverse relationship between hepatic blood flow (influencing Cl_e) and dexmedetomidine concentrations. Since many intravenously administered drugs used during anesthesia (*e.g.*, propofol, ketamine, fentanyl, sufentanil, lidocaine) also have very high Cl_{int}, any reduction in hepatic blood flow caused by dexmedetomidine would reduce their clearance as well. This nonstationarity could increase their clinical effects and possibly prolong emergence.

Another important fact is relevant to these observations; namely, Alvarez-Jimenez *et al.*[2] reported that the dexmedetomidine concentration producing a 50% reduction in clearance was 5.75 ng/ml. This concentration is well above dexmedetomidine concentrations producing desired clinical effects as predicted from simulations of 14 published clinical dosing regimens (range, 0.49 to 1.15 ng/ml),[4] as well as the dexmedetomidine concentration of 1.9 ng/ml that produces unarousable deep sedation.[7,13] It is unlikely, therefore, in clinical practice that dexmedetomidine plasma concentrations will approach anywhere near the concentration reported to result in nonlinear pharmacokinetics.

So, what are the data saying in this case? The data have clearly stated that if enough dexmedetomidine is administered to produce supraclinical plasma dexmedetomidine concentrations, its elimination clearance will be reduced. However, the data cannot offer an opinion as to whether the cause of nonstationary elimination clearance is

hepatic enzyme saturation, reduced cardiac output, or reduced hepatic blood flow caused by α_2 agonist effects in the splanchnic vasculature. Since the two latter causes could affect the pharmacokinetics of other high hepatic-extraction anesthetic drugs, when given repeatedly or by infusion, interrogating additional data is required.

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Competing Interests

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