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Metformin: A Case Study in the Meaning of Serum Concentrations

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A primary question for any drug is the value of its serum concentration. What is not commonly considered is the relationship between this value and the drug concentration at the physiological target site. In the case of metformin, the issue is in some ways simple: metformin is water soluble and has negligible binding to serum proteins. It is not converted to other compounds, but excreted unchanged by the kidney [1]. Yet, the volume of distribution is very high: above 500 l. This is because its serum concentration is low (micromolar) and yet the dosing is very high (up to nearly gram amounts). The precise volume of distribution value is complicated by the fact that serum levels do not reach a simple steady state but rather sharply descend with time. This has been described as "following a multiphasic pattern" [2].

The mechanism for its intracellular action remains unresolved, perhaps surprising for a drug that has been known for over 50 years. Yet, studies on cells *in vitro* require concentrations of millimolar rather than micromolar [3,4]. Our own proposal for the action of metformin (inhibition of AMP deaminase [4]) has been criticized partly on the basis of using millimolar concentrations rather than its serum concentration [5]. A simple rebuttal – that this is the concentration required to observe the established physiological effects, and that the same concentrations are used by other investigators with similar cells – does not address a deeper underlying concern: what really is the significance of the serum concentration?

There is a tacit assumption that the serum concentration of a drug, measured when it reaches steady state after dosing, is a good estimate of the effective concentration of drug for its target site. If the drug target is extracellular, and the drug has no unusual disposition (binding or metabolism), this would seem reasonable. However, when the target is intracellular, then the only way in which the serum concentration could match the intracellular concentration is if there is a near-equilibrium between serum and intracellular space. This is unlikely to be the case for many drugs. In the particular case of metformin, it clearly is not the case. The biguanide structure is far too water soluble to enter cells in significant amounts by diffusion. It is known that its transport in many cells is accomplished by one of the cationic amino acid transporters [2]. As these transporters involve exchange with sodium ions, they are routes of secondary active transport. Thus it can be expected that the extracellular concentration is lower than the intracellular one. While it is not known what concentrations are achieved by metformin intracellularly, it is known that some cells – including the known metformin targets liver and muscle – accumulate metformin several-fold above serum levels [1].

Like other drugs with an unknown target site, having an estimate of the active concentration for its target is valuable information. However, in the case of metformin, we are without even a good estimation of intracellular concentration. In general terms, it is prudent to recognize that serum drug concentrations are indices of drug action only in specific, qualified cases. For metformin in particular, this value is misleading.

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