Pharmacokinetics 101

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Basic pharmacokinetics (PK) knowledge and skills are essential in practicing therapeutics. Compared with physicians, pharmacists receive intense PK training through their professional education; therefore, they are far advanced in their capability of interpreting and assessing the pharmaceutical part of therapeutic management of patients. Some may argue that those of us in the medical profession do not need to have such PK skills. My position on this issue, however, is very clear: Physicians must have basic knowledge and skills in PK aspects of therapeutics. This will help us maximize the effectiveness of our therapeutic management of patients, which will no doubt help us gain the confidence of patients and their families. In the present article, my focus is on PK in children, particularly clearance (CL) and volume of distribution (Vd). In parallel, I will discuss basic PK concepts that can be applied to all age groups in everyday clinical practice.

PATIENT

Morphine is being given as a constant infusion to a 10-year-old boy to control severe pain. The dose and infusion rate are kept constant for approximately 8 h to assess his response. After 8 h, the infusion rate does not seem high enough to control his pain (despite a couple of breakthrough doses). A newly developed point-of-care device for morphine serum level was used to check his morphine level (note: no such device currently exists), which turned out to be very low despite a standard dose. What is going on?

WHY DOES IT TAKE FOUR HALF-LIVES TO REACH A STEADY STATE?

Everyone knows how long it takes to reach a steady state if a drug is given at a regular interval: four to five half-lives. Can you explain why? In a single dose, serum concentrations decline to the following levels:

- 50% of the peak level by one half-life ($t_{1/2}$),
- 25% by $2 \times t_{1/2}$,
- 12.5% by $3 \times t_{1/2}$,
- 6.25% by $4 \times t_{1/2}$, and
- 3.125% by $5 \times t_{1/2}$.

So, by $4 \times t_{1/2}$ to $5 \times t_{1/2}$, the serum levels are reduced by almost 94% to 97% of the peak level. In other words, the entire dose you gave is almost gone from the body by $4 \times t_{1/2}$ to $5 \times t_{1/2}$.

Assume that a dose is given repeatedly and regularly, and that serum levels during one dosing interval are averaged for the sake of discussion. The average serum level in the second dosing interval is (most likely) higher than that of the first dosing interval, and this trend will continue. Around $4 \times t_{1/2}$ to $5 \times t_{1/2}$ from dose 1, the first dose has disappeared from the serum. From that point on, the serum levels are a sum of the remaining dose 2 all the way to dose N. The same thing happens next in dose N+1 because dose 2 is now gone (ie, dose 3, 4, 5,..., N+1), and so on. As a result, after $4 \times t_{1/2}$ to $5 \times t_{1/2}$ from the first dose of the repeated dosing regimen, there is no substantial difference in the average serum concentrations from dose N to the next dose. This is a steady state. So, the boy described above will achieve a plateau level in approximately 8 h (morphine $t_{1/2} \times 4 = 2$ h $\times 4 =$ 8 h) if the infusion speed and dose remain the same, and if he has a morphine $t_{1/2}$ of a population average. This is why we will wait several hours before making a decision as to whether a dose increase is needed. Then, what defines the steady state serum level?

CL DEFINES SERUM DRUG LEVELS AT A STEADY STATE

CL of a drug is arguably the most important PK parameter (CL is usually total body CL, which is a sum of hepatic, renal and other tissue CL). 'Drug' CL is the same concept as 'creatinine' CL, which indicates how well the kidney (ie, glomerular filtration rate [GFR]) is functioning. Because endogenous creatinine production is relatively stable over time (similar to a steady state of drug therapy), decreased creatinine excretion due to a low GFR elevates the serum creatinine level. Similarly, if a drug is given regularly, CL defines serum drug concentrations at a steady state. CL tells us how well the patient eliminates the drug. For example, we reduce the dose/time of a kidney-excreted drug, such as digoxin, if the patient's GFR is decreased, so that the steady-state drug concentration in the serum does not elevate into a supratherapeutic toxic range. For drugs metabolized by the liver, it is (basically) the same, but whether CL is influenced by hepatic blood flow or the intrinsic liver metabolic capacity for the drug depends on each drug; therefore, dose adjustments in patients with liver dysfunction are not straightforward.

Drug CL per body weight is lower in neonates and young infants than in older children because renal function is immature and/or drug metabolizing enzymes remain to be developed in neonates and young infants. To maintain the same serum levels, neonates and young infants need lower doses/kg per time than older children. How rapidly CL/kg develops depends on the drug. However, preschool children tend to have higher CL/kg than adults (not always, but for many drugs). This is why their doses per body weight per time (eg, mg/kg/day) are the highest of all age groups. The reason for this increased CL/kg in preadolescent children is not entirely clear, but is at least partly due to a larger liver and kidney per body weight (1-3).

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These CL concepts are easy to grasp, but did you notice that we were able to explain average serum concentrations at a steady state without using the term 'volume of distribution'? Because the patient described above showed low steady-state morphine levels despite a standard dose/time, we can conclude that his CL/kg is somehow higher than usual. You may think that the Vd for this boy (L/kg) is larger than usual, but this is unlikely, as I explain below.

Vd: A CONFUSING AND OFTEN MISUNDERSTOOD PK PARAMETER

The importance of Vd is clear, but it is often misunderstood. When a 'glass of water' example is used to explain the PK concept, it is obvious that Vd (ie, water volume) defines a concentration of drug put into the glass; the bigger the volume, the lower the concentration. However, some people make mistakes by extrapolating this principle to steady-state serum concentrations of a drug. This 'glass of water' example does not have a time dimension. In other words, this only exemplifies the moment after the dose is administered. As discussed above, average steady-state levels are defined by CL and dose/time, but not by Vd. Vd determines how high the peak level would rise after each dose. Together with CL, it also determines $t_{1/2}$: the larger the Vd, the longer the $t_{1/2}$. In clinical settings, we rarely need to consider individual Vd differences. However, if a certain peak level needs to be achieved (gentamicin, for example), a higher dose per body weight is administered for patients with a larger Vd/kg such as in neonates (they have a larger water volume/kg than adults). Then, because their CL/kg is lower, they cannot eliminate gentamicin fast enough for the next dose. This is why a dose/kg of gentamicin in neonates is higher, but their dosing interval for gentamicin is longer than in other age groups. So, in the patient on morphine, the most likely explanation for the therapeutic failure is 'increased CL of morphine'. Here is some simple advice in everyday practice: Don't use Vd to explain individual differences in steady-state levels.

SUMMARY

CL is important for dose adjustment because steady-state serum levels depend on it at a given dose, and could be significantly different among individual patients. Vd is also an important concept, but its application in clinical settings is relatively limited. Health care professionals will benefit from having a basic understanding of the PK principles of therapeutics.

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