

Therapeutics Initiative

Better prescribing. Better health.

Simple clinical pharmacology can improve prescribing

Case vignette 1: For painful shingles (*H. zoster*), a 69 year old took pregabalin 300mg/d and immediate (IR) and slow release (SR) morphine (total 30mg/d). When he developed new "cognitive impairment," a neurologist recommended he reduce or stop both sedative drugs. Now taking pregabalin at 150mg/d and morphine at only 10mg/d (as IR), he has sweats and mild chills. His "cognitive impairment" is resolved, and thinking his new symptoms may be from opioid withdrawal, your patient telephones for advice. If this is withdrawal, he prefers to "get it over with." Will knowing the drug half-lives help you respond appropriately?

Understanding clinical pharmacology may be under-appreciated in health care. The explosion of new drug categories and curriculum changes have eroded many clinicians' knowledge of drugs, and no consensus exists on what is most important to learn.¹⁻³ Recent interviews with Canadian prescribers identified limited drug knowledge as one barrier to safe prescribing and deprescribing.⁴ Reliance on guidelines can camouflage "pharmacignorance" and even clinicians with specific pharmacological training do not always apply their knowledge effectively to medication reviews.⁵ Pharmacokinetic (PK) concepts may seem abstruse; but whether we think about them or not, they influence our daily clinical practice. This Letter explores PK principles that can help us prescribe efficiently and avoid common problems.

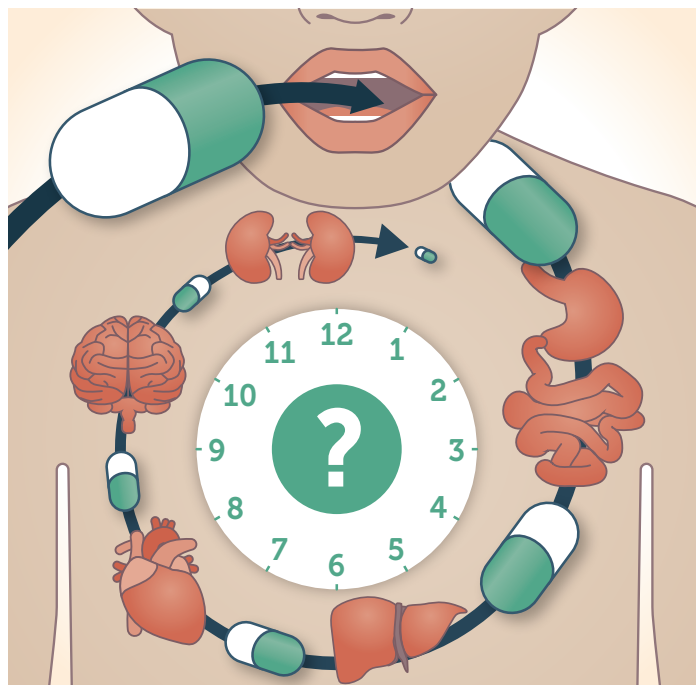
How can PK parameters help with prescribing?

Pharmacokinetics refers to how drugs enter the body, are distributed and metabolized, and how they finally leave. Drug distribution within the body can include "compartments" with different PK characteristics: blood, interstitial spaces, brain, liver, kidney, lungs, heart, muscle, fat, skin, prostate and eyes. Changes from infancy to old age, genetic or environmental factors, and medical conditions affecting absorption (celiac, short gut) or excretion (kidney or severe liver disease) are sometimes important. Non-lovers of mathematics may find PK intimidating,⁶ but the simpler concepts can be surprisingly helpful when applied to prescribing, timing of clinical re-assessments, and deprescribing.

Knowing the approximate time when a drug reaches its maximal concentration in blood (T_{max}) helps predict onset of effects for drugs that work rapidly (e.g. naproxen, most antibiotics). Knowing the average time for drug concentration to fall by half ($T_{1/2}$) may suggest a minimum duration for therapeutic trials. It also suggests how soon to expect any withdrawal symptoms after deprescribing. The online Table includes illustrative examples. Therapeutics Letter 134 showed that therapeutic trials of pain drugs are often longer than randomized trials suggest should be necessary.⁷

T_{max} predicts onset of effects

T_{max} is the time to reach peak concentration in blood after a drug is administered. In the Figure the blue arrow shows T_{max} after a dose of



a hypothetical drug. For oral drugs T_{max} can depend upon the fed or unfed state and delay in stomach emptying. Drugs given by intravenous (IV) bolus reach T_{max} almost instantaneously, and some inhaled drugs behave similarly (e.g. oxygen, nicotine, cannabis). Maximal absorption is also prompt after intramuscular or subcutaneous injections of opioids, naloxone, epinephrine or other drugs given for emergencies.

$T_{1/2}$ predicts time to accumulate or dissipate

Half-life ($T_{1/2}$) is the mean time for a drug's concentration to decrease by half after reaching its peak in blood (Figure). $T_{1/2}$ can vary substantially; but the mean can be useful to predict the duration of most drug effects. **For drugs given intravenously the distribution half-life ($T_{1/2d}$)** is important to anaesthesiologists and emergency personnel (not shown in Figure). Fat-soluble drugs like propofol, fentanyl, or midazolam distribute swiftly from blood into the brain, which receives 20% of resting cardiac output. But these drugs soon **redistribute** to a much larger mass of body fat outside the brain. Declining drug concentration in the brain determines the rapid offset of effects – even while most of the drug remains elsewhere in the body.

Elimination half-life ($T_{1/2elim}$) is more broadly relevant to clinical decisions. Usually shown as $T_{1/2}$, it predicts duration of effects for oral drugs, and for IV drugs after redistribution. The Figure shows how $T_{1/2}$ suggests when to expect "steady state" during repeated dosing, when drug elimination balances input. **Usually cited as 4 to 5 times the expected half-life, "steady state" is approached by 3 to 4 times $T_{1/2}$.**

Case vignette 1 - resolution: This man said he preferred to "get it over with" if his symptoms were from withdrawal. Given morphine's mean $T_{1/2}$ of 2 to 4 h, the worst should be over within 24 h. With normal kidneys, pregabalin's mean $T_{1/2}$ is 6 h, so he can stop pregabalin next. He stopped both, without problem. Had he missed either drug, he could have regained "steady state" within 1/2 to 1 day.



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Finding and using T_{max} and $T_{1/2}$ in practice

Case vignette 2: A patient says “That pill helped my pain fast, but I wish I didn’t have to wait so long to take another.” What if you were in her place?

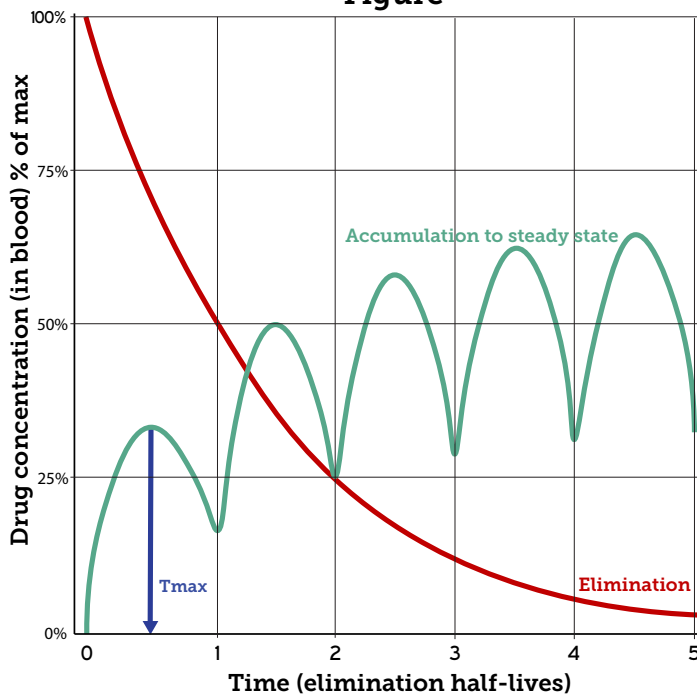
T_{max} and $T_{1/2}$ are usually reported as means from PK experiments in small groups. Sometimes the inter-individual range is important and depends (for $T_{1/2}$) on genetic polymorphisms (Table). PK values appear in the Clinical Pharmacology sections of online drug monographs, or can be found by a specific search: e.g., “cyclobenzaprine half-life” (mean 18 h). Finding inter-individual ranges may take more work. When a patient says a drug wears off faster or lasts much longer than expected, her individual $T_{1/2}$ may differ from the reported mean.

Case vignette 2 - resolution: “listen to the patient – she is telling you the kinetics.”⁸ If the drug has a rapid T_{max} but a short $T_{1/2}$ of 1 to 4 hours, consider more frequent dosing or a formulation that delays absorption.

Remembering drug elimination

Most drugs are cleared by liver metabolism and/or renal excretion. When proportional to blood concentration, this is termed “first order” kinetics. Once a drug is stopped the concentration should decline exponentially (Figure). $T_{1/2}$ suggests when concentration will be negligible — although inter-individual variability of $T_{1/2}$ and reduced kidney function or severe liver disease can surprise us (Table). Important exceptions include alcohol, phenytoin, or acetaminophen in toxic overdose. When their concentration saturates metabolic pathways, these are cleared at a fixed rate — “zero order” metabolism.

Figure



Vertical axis: drug concentration after each dose, as % of maximum attained, absolute values depend on dose, volume of distribution (V_d) and body mass. **Horizontal axis:** arbitrary units of $T_{1/2}$. **Blue arrow:** T_{max} . **Green line:** “steady state” is approached by 4-5 half-lives. **Red line:** “first order” exponential decline after final dose (metabolism not saturated, liver/kidney function constant).

Case vignette 3: A 73 year-old with estimated GFR of 12mL/min took gabapentin 300mg tid for painful diabetic neuropathy. By day 10 he felt “too sick to attend my appointment” but was called in and hospitalized. The video (online) shows how predictable pharmacokinetics affected his recovery from acute gabapentin toxicity.

Case vignette 4: A 68 year-old inadvertently took too much phenytoin after her dose per capsule changed. How long after stopping phenytoin will she recover? The video (online) shows how adverse drug effects relate to initial zero order pharmacokinetics.

In a clinical scenario when too much drug puts a patient in danger and the drug has a long $T_{1/2}$ or its elimination may be zero order, **stop the drug immediately**. Wait for the blood concentration to fall, and drug effects will wane. The Table (online) shows examples for which simple PK understanding is clinically helpful.

‘Long-acting’ formulations

When a rapidly absorbed drug is also eliminated quickly, extending T_{max} can prolong its effects. Oral controlled, extended, or slow release (CD/CR/ER/LA/SR/XR) formulations postpone absorption; they do not change $T_{1/2}$. Once absorption is complete (typically 12-24 h), drug concentration falls just as it would if the peak occurred earlier. For cancer pain, the smoother concentration profile was a major 1980’s breakthrough for morphine analgesia ($T_{1/2}$ 2 to 4 h). Competitors soon followed. For many people with non-cancer pain, predictable tolerance and pharmacologic dependence arising from continuous drug exposure brought significant and sometimes fatal consequences.

Some modified absorption formulations or prodrugs are developed to prolong or avoid patent protection (“evergreening”).⁹ A recent example is the prodrug lisdexamfetamine (Vyvanse™), which is metabolized to d-amphetamine.¹⁰ PK parameters nearly identical to d-amphetamine were demonstrated by academic pharmacologists.¹¹ Transdermal (patch) delivery systems and injectable depot formulations (e.g., antipsychotics, steroids, naltrexone) can also prolong the apparent $T_{1/2}$ but like drug metabolism polymorphisms, they are too complex to discuss in this Letter.

Conclusions

- Knowing T_{max} can suggest when to assess symptomatic effects of a drug (good or bad).
- Allowing 4 to 5 half-lives predicts steady state effects of drugs taken for symptoms. When a drug is stopped, expect effects to dissipate or potential withdrawal symptoms to emerge after a similar interval.
- Some half-lives reported as means have significant inter-individual ranges. Patients who report shorter or longer duration of effects than expected may have different elimination kinetics.
- “Steady state” seldom applies in sick people. Acute decline in kidney function or saturated liver metabolism can cause dangerous toxicity: e.g., K^+ , lithium, gabapentin, pregabalin, acetaminophen, phenytoin, alcohol.

For additional content including the Table, embedded patient videos and the complete list of references go to:

ti.ubc.ca/letter142