Use of Half-life information

In the practice of clinical medicine, the physician is greatly aided by the availability of agents which have the ability to alter unwanted processes and thereby assist her/him in helping the patient recover from an illness or, at least, lead a relatively normal life. The physician learns to account for the many variables and factors which make her/his use of medicines effective. Some of the factors such as the patient's age, life-style, income, intelligence (to follow instructions) and disease state are "patient factors" with which the physician has little control.

The "drug factors" include the drug's bioavailability and the processes of absorption, distribution, metabolism (biotransformation) and elimination. Collectively, these processes are known as the *pharmacokinetic* properties. These factors are somewhat under the control of the physician in that she/he chooses the drug, the dose, and the dose interval.

One of the Pharmacokinetic concepts which has proven to be of greatest help to the practitioner and which is essential for the research physician to know is that of the elimination *half-life* (**t½**). One of the main reasons that this is useful is that to use it for rational prescribing or in understanding the time course of adverse events does not require complicated mathematics.

Basically, the half-life of a drug is that time required for the body to eliminate or biotransform half of the amount present in the body at any given point in time. This, correctly, suggests that elimination (metabolism and excretion) are the rate limiting factors (i.e. slower) than the other pharmacokinetic variables (absorption and distribution). Thus, for most drugs, the time taken for absorption and distribution may be neglected in determining dosing requirements.

The drugs with which we associate and use the half-life concept are those which are cleared from the body (eliminated and/or biotransformed) by a fixed rate. This means that the amount eliminated is <u>proportional</u> to the amount available to be eliminated. Stated another way, the greater the drug concentration, the greater the amount cleared per unit time. Mathematically this is known as a *first order* process (would plot out as a straight line on semi-log paper). Most drugs are in this category.

This is in contrast to the *zero order* process where a <u>fixed amount</u> of the drug is eliminated per unit time. Thus, the amount cleared is independent of the amount to be cleared. Drugs such as ASA, ethanol and phenytoin are primary examples in this category. These drugs present quite a different problem to the physician. With these, the only way to speed the elimination process is to go to dialysis.

One way to visualize the *first order* process is the following:

Amount of drug in the body in units (ng, mg, gm)	Number of elapsed half-life's	Cumulated percent eliminated
100	0	0.0 %
50	1	50.0 %
25	2	75.0 %
12.5	3	87.5 %
6.25	4	93.75 %
3.13	5	96.88 %

From this tabulation, it can be seen that at the end of <u>one</u> **t½,** 50% of whatever was present is gone and at the end of <u>five</u> **t½**'s, 97% of the drug has been eliminated regardless of how much was around at the beginning. Thus, if the continued presence of the drug is important, one would repeat the dose at intervals less than 5 half-life's and usually less than one half-life.

An important use of half-life information is in chronic drug use where doses are repeated prior to the complete disappearance of the previous dose. Drug dosing in this manner guarantees accumulation meaning that the maximum concentration of the drug does not occur until the amount administered and the amount eliminated are equal. Knowing the time it will take to reach this maximum concentration plateau and the expected fluctuations in drug concentration between doses (and about that plateau) is of considerable utility to the physician bent on rationally using drugs.

The plateau concentration is reached when the dosage amount given (by any route) is equivalent to the amount of the drug leaving the body by whatever route it is eliminated. The time it takes to reach this "plateau" is related to the half-life of the drug by the following:

Percent of final plateau level achieved	Time in terms of the half-life of the drug
50.0 %	1
75.0 %	2
87.5 %	3
93.75 %	4
96.88 %	5

From the above, it can be seen that after five **t½**'s of a drug you will reach ≈ 97% of the final mean plateau concentration if the drug is given prior to its complete elimination (prior to 5 times the half life of the drug). Fluctuations about the mean plateau concentration will obviously depend upon the dosing interval - being greatest as you increase the interval in relation to the half-life of the drug and being smallest as you decrease the dosing interval. Thus, the smallest fluctuation would occur with an i.v. infusion. Please note that even with a

constant infusion it will still take 5 times the half-life of the drug to reach the maximum plateau concentration.

In clinical practice, the choice of the dosage interval usually represents a compromise between the desirability of minimizing the between dose variations of effectiveness and patient inconvenience (and poor compliance) from too frequent dosing. It is most likely easiest for patients to remember a once-a-day regime but this is not always possible with many drugs.

In clinical research, the half-life is needed and used to determine how long after the dosing of the test agent that one is required to take blood samples so that the area under the time course curve (AUC) represents the true time course of the drug.

The following demonstrate that both the time to plateau and the time for elimination are determined by the plasma half-life:

Agent/drug	**Plasma t½**	**Time to plateau or Time to elimination**
Lidocaine	13 minutes (α)	65 minutes
	1.7 hours (ß)	8.5 hours
penicillin G	56 minutes	4.5 hours
amoxicilin	1 hour	5 hours
indomethacin	1-2 hours	8 hours
cimetidine	2 hours	10 hours
gentimicin	2.5 hours	12 hours
theophylline	3-13 hours	15-60 hours
quinidine	6 hours	30 hours
tetracycline	9 hours	45 hours
oxazepam	5-10 hours	24-48 hours
lorazepam	10-20 hours	2-3 days
digoxin	33 hours	7 days
haloperidol	36 hours	7.5 days
diazepam	24-48 hours	5-10 days
flurazepam	48-90 hours	10-19 days
chlorthalidone	60 hours	12.5 days
phenobarbital	2-6 days	10-30 days
tricyclics	2-5 days	10-25 days
chlorpromazine	8-12 days	40-60 days
trimethadione	6-13 days	30-65 days

Note that the time to 97% of the plateau (considered the plateau) or steady state concentration or the time to 97% elimination (considered complete) is not only the same but is independent of both the dosage given and the frequency of the dosing. The dose and frequency of dosing affect only the height or magnitude of the plateau concentration.

In general, agents with very short **t½**'s will require an intravenous infusion to maintain the continued presence of the drug. Examples include lidocaine and dopamine. Other agents

with a short half-life are knowingly given at intervals longer than 5 times their plasma **t½** either because the continued presence of the drug is not required for receptor activity or because the effect of the drug outlasts the plasma concentration. The organic acid antibiotics fall into the former group. The later group is large and brings up the concept of an effect (efficaciousness) half-life.

Drugs whose effects or efficacy or actions outlast their plasma concentration form a very significant group and introduce the term "*efficacy half-life*". This is defined as that time it would take for a drug to lose half of it's effectiveness or efficacy. This is obviously more difficult to measure and less precise than a plasma concentration making it difficult to determine with accuracy. Non-the-less, the concept is valid.

What usually happens is that it is noticed that a dug with a relatively short half-life is still able to produce an effect long after it is supposedly eliminated (which would be 5 times the plasma half-life). It is presumed that the drug is acting intracellularly and either remains partly bound to the receptor long after most of the extracellular drug has been eliminated **or** the drug is a "hit-and -run" type which alters a receptor such that the effect remains long after the drug is gone. The reason it is important to always be on the lookout for this phenomenon is that it is far easier for patients to take a drug once or twice a day than three of four times a day. Agents of note where this concept is operational include the following:

Agent/drug	**Plasma t½**	**Acceptable dosing interval**
propranolol	3.3 hours	once or twice a day (for BP)
hydrochlorothiazide	3.5 hours	once a day
alpha-methyldopa	2 hours	once a day
hydrazine	4.5 hours	twice a day
prednisone	3.5 hours	once a day
colchicine	20 minutes	once a day
allopurinol (oxypurinol)	2 hours (18-30 hours)	once a day or longer

Agents which have half-life's longer than the usual dosing interval would be expected to accumulate and reach a plateau. Some agents have a half-life such that they would accumulate even if given once a week. They are clearly once-a-day medications. It has always been a puzzle that patients will appear taking medications such as diazepam (**t½** = 24-48 hours) t.i.d. or even q.i.d. or amitriptyline (**t½** = 2-5 days) t.i.d. Both of these agents would be expected to have the same effects given once-a-day. Using this same information, it is not surprising (the phenomena of tolerance)that flurazepam (**t½** = 48-90 hours) loses it's effectiveness as a sleeping pill with time.

Knowing the plasma half-life is of considerable assistance to the physician as it allows her/him to asses the response to therapy more precisely. Knowing, also, the factors affecting the half-life such as the patients age, hepatic function, or renal function, the discerning physician would more likely adjust the dose or dose interval in the elderly or those with hepatic or renal failure. Taking into account individual patient differences as well as the

efficaciousness of a drug will result in appropriate drug use which is rewarding indeed.