



Pharmacokinetics

How Drugs of Abuse are Handled in the Body

ISSUE 1



SureScreen Diagnostics Ltd
Cutting Edge Biotechnology

Pharmacokinetics is the study of how drugs are handled by the body. **Data for the common drugs of abuse** is of particular interest to physicians, nurses, drug workers and forensic scientists working in **drug abuse & harm minimisation**.

Having this information to hand can help drug testers and medical professionals make rapid, often life-saving decisions about whether drugs of abuse are involved, how much was taken, when they were taken and what effect, if any, they are having on physiological function and behaviour.

Several processes collectively determine how a drug is handled by the body, how much drug reaches its site of action, and how this changes over time.

These processes are **absorption, distribution & elimination**.

The **absorption** or entry of a drug into the body depends on its route of administration e.g. whether it is ingested, inhaled, snorted or injected.

The **distribution** of the drug around the body to its site of action depends on the drug concentration achieved, the permeability of the membranes in the body to the different drugs, and the rate of blood flow to the different organs.

The **elimination** of the drug from the body depends on its excretion by the kidney or its metabolism by the liver into a form that can be excreted.

All of these factors play a part in the drug's **half-life**



Absorption affects bioavailability - how quickly and how much of a drug reaches the brain. Factors that affect absorption (and therefore bioavailability) include its physical and chemical properties, and the physiologic characteristics of the person taking the drug. Physiologic characteristics that may affect the absorption of drugs taken by mouth include how long the stomach takes to empty, what the acidity (pH) of

the stomach is, and how quickly the drug is moved through the digestive tract.

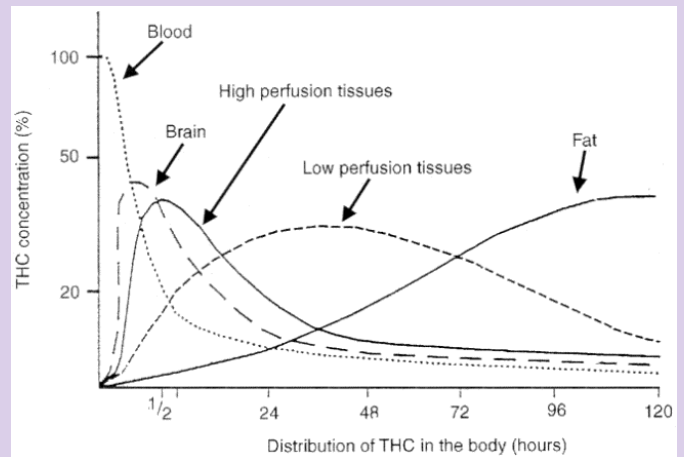
The drug product properties include the actual dose, and hence purity; and whether a powder, tablet, capsule or solution, and whether snorted, injected, smoked or taken orally. The action may be affected by whether the drug is cut, and with what. Pharmaceuticals often include the drug (active ingredient) and additives (inactive ingredients). For example, tablets are a mixture of drug and diluents, stabilizers, disintegrants (called excipients), and lubricants. The mixture is granulated and compressed into a tablet.

The type and amount of additives and the degree of compression affect how quickly the tablet disintegrates and the drug is absorbed. Drug manufacturers adjust these variables to optimise absorption. If a tablet releases the drug too quickly, the blood level of the drug may become too high, causing an excessive response. If the tablet does not release the drug quickly enough, much of the drug may be eliminated in the faeces without being

absorbed. Drug manufacturers formulate the tablet to release the drug at the desired speed.

Some drug products are specially formulated to release their active ingredients slowly or in repeated small amounts over time - usually for a period of 12 hours or more. This dosage form is called modified-release, controlled-release, sustained-release, or extended-release.

Food, other drugs, and digestive disorders can affect drug absorption and bioavailability. For example, high-fibre foods may bind with a drug and prevent it from being absorbed. Laxatives and diarrhoea, which speed up the passage of substances through the digestive tract, may reduce drug absorption. Surgical removal of parts of the digestive tract (such as the stomach or colon) may also affect drug absorption.



Cannabis distribution throughout the body

How long and how well a drug is stored can affect drug bioavailability. The drug in some pharmaceutical products deteriorates and becomes ineffective or harmful if stored improperly or kept too long. Some products must be stored in the refrigerator or in a cool, dry, or dark place.

Distribution of the drug can be rapid. Cocaine hits the brain in seven seconds when snorted. After a drug is absorbed into the bloodstream, it rapidly circulates through the body; the average circulation time of blood is 1 minute. As the blood recirculates, the drug moves from the bloodstream into the body tissue.

The half life of a drug can be a good index of its addiction potential.

Once absorbed, most drugs do not spread evenly throughout the body. Drugs that dissolve in water (water-soluble drugs) tend to stay within the blood and intercellular fluid. Drugs that dissolve in fat (such as benzodiazepines and cannabis) tend to concentrate in fatty tissues.

Other drugs may concentrate mainly in only one small part of the body because the tissues there have a special affinity for, and ability to retain, the drug.

Benzodiazepines are unusual in that most are not water soluble and require lipids (fats) to enter the bloodstream. Some, like diazepam reach peak blood concentration within one hour while others require several hours. Some, such as Chlorazepate and Prazepam act as pro-drugs, being rapidly broken down into the active drug Nordiazepam.

Drugs penetrate different tissues at different speeds, depending on the drug's ability to cross membranes. In general, fat-soluble drugs can cross cell membranes more quickly than water-soluble drugs can. Most illicit drugs (except notably benzos, crack and cannabis) are water soluble.

Distribution of a given drug may also vary from person to person. For instance, obese people may store large amounts of fat-soluble drugs, whereas very thin people may store relatively little. Older people, even when thin, may store large amounts of fat-soluble drugs because the proportion of body fat increases with age.

All drugs are **eliminated** from the body in a chemically altered (metabolised) form or by excretion. Most drugs, particularly water-soluble drugs and their metabolites, are eliminated largely by the kidneys in urine. The acidity of urine, which is affected by diet, drugs, and kidney disorders, can affect the rate at which the kidneys excrete some drugs.

Some drugs leave the bloodstream very slowly, because they bind tightly to proteins circulating in the blood, while others quickly leave the bloodstream and enter other tissues. Most molecules of some drugs may be bound to blood proteins. The protein-bound part is generally inactive. As unbound drug is distributed to tissues and its level in the bloodstream decreases, blood proteins gradually release the drug bound to them, so the bound drug in the bloodstream acts as a reservoir for the drug.

The kidneys' ability to excrete drugs also depends on urine flow, blood flow through the kidneys, and the condition of the kidneys. Kidney function can be impaired by many disorders (especially high blood pressure, diabetes, and recurring kidney infections), by exposure to high levels of toxic chemicals, and by age-related changes. As people age, kidney function decreases. The kidney of an 85-year-old person excretes drugs only about half as efficiently as that of a 35-year-old.

A urine test can be performed to measure the level of creatinine (a muscle waste product) in urine to estimate dilution factors because creatinine clearance rates are fairly constant in most individuals. SureScreen has a simple creatinine test for this.

A few drugs pass through the liver and are excreted unchanged in the bile. The bile then enters the digestive tract. From there, drugs are eliminated in faeces or reabsorbed into the bloodstream and thus recycled. Other drugs are converted to metabolites that are excreted in the bile. This route is slower if the liver is not functioning normally, but there is no simple way to assess liver function quantitatively for drug metabolism comparable to those for kidney function.

Some drugs are excreted in saliva, sweat, breast milk, and even exhaled air. Most are excreted in very small amounts. The excretion of drugs in breast milk is significant only because the drug may affect the breastfeeding infant. The drug also deposits in the infant's hair and can be detected long-term.

WHAT IS THE HALF LIFE OF A DRUG?

This is the time taken for the amount of drug in the body to decrease by 50%. If the half life is four hours then after four hours the dose is half, after 8 hours it is a quarter, after 12 hours it is an eighth, and so on.



WHY IS HALF LIFE SO IMPORTANT?

Knowing a drug's half life can be very helpful to the forensic chemist in evaluating evidence of drug abuse. Having a reliable half life for a particular drug of abuse can tell us how long the drug or its metabolites can be expected to last in the body under normal circumstances. Positive detection of a drug of abuse like cocaine with a short half life, for instance, can indicate ongoing abuse, whereas identification of those with longer half lives such as cannabis may suggest ongoing excretion of an earlier episode of drug abuse and the need for a more tolerant medical review.

Medical professionals also routinely rely on experience of drug half lives to prevent fatalities from drug overdosing because this information tells them how long a drug and its effects can be expected to last in the body. Methadone overdose, for instance, is treated with the opioid antagonist drug Naloxone which is commonly used to rouse a patient from an often life-threatening coma. But without taking into account methadone's long half-life, a patient could easily be given insufficient Naloxone and quickly lapse back into a coma once it is metabolised and the methadone continues to exert its effects.

Half life is also important to medical professionals in assessing the risks of one drug over another. For instance, whereas drugs like cocaine with a short half life are rapidly removed from the body and need to be repeatedly administered to maintain blood levels, drugs with longer half lives like some benzodiazepines can accumulate to potentially dangerous levels in the blood over time with a fixed daily dose and hence carry a greater risk of toxicity and overdosing. Unfortunately this risk is not lessened by the so-called "shorter" acting benzodiazepines like Flurazepam which, whilst possessing a shorter half life, are quickly metabolised into longer-acting end-products with half lives of several days.

ADDICTION POTENTIAL

The half life of a drug can also be a good index of its addiction potential. For instance physically addictive drugs such as heroin and morphine which have short half-lives are associated with rapid development of tolerance, dependence and addiction. Also the shorter the drug half life is, the greater also is the severity of the withdrawal symptoms but the shorter the time taken for their resolution.

One of the most addictive drugs, nicotine, has a very short half life below 2 hours. Craving for the next cigarette is said to start after about 20 minutes, and become extreme after an hour because of drug depletion. That is why smokers find it extremely difficult to cut back below about eight cigarettes a day. Cotinine, its metabolite, has a half life of 21 hours, so a smoker is detectable for several days based on cotinine, not nicotine.

Short-acting opioids like heroin and its metabolite morphine have a half life of 4-6 hours and need to be taken several times a day. They are characterised by the onset of severe withdrawal symptoms within 8-16 hours after the last dose, with peak withdrawal occurring between 36 and 72 hours and resolution of the acute withdrawal effects after 5-8 days. It is on this basis that longer-acting prescription opioids like methadone have been introduced with a half life of around 30 hours to tackle the crime-related drug withdrawal syndrome associated with heroin addiction. Unlike heroin or morphine, the onset of methadone withdrawal symptoms occurs much later typically between 2-3 days after last use, peaking at around 1-2 weeks and persisting for several months for complete resolution of symptoms. Heroin and methadone addictions therefore require totally different treatment regimes.

A long half-life is not always a disadvantage. Whilst the intermediate-acting class of benzodiazepine tranquilizers have a half-life of 10 hours or less (e.g. Oxazepam, Temazepam) and produce significant withdrawal symptoms 6 to 8 hours after decreasing blood levels, the longer-acting analogues with half lives of 30

Italians consume around fourteen billion espressos a year

hours or more (e.g. Diazepam, Clonazepam) possess a sort of “self-tapering” neuroadaptive effect which may moderate the withdrawal syndrome and may not precipitate milder symptoms for several days.

It is on the basis of its self-same long half life and this “self-tapering” effect that cannabis is thought to be relatively free of a withdrawal syndrome.

HALF LIVES OF SOME ANTIDEPRESSANTS

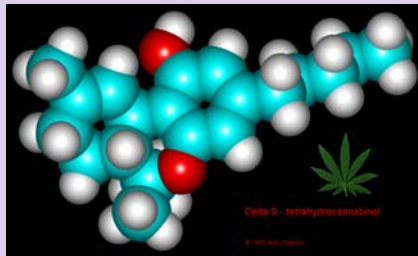
Brand	Drug	Half live (hrs)
Anafranil	Clomipramine	19-37
Cipramil	Citalopram	28-42
Edronax	Reboxetine	8
Efexor	Venlafaxine	5-11
Efenor XL	Venlafaxine	20-22
Faverin	Fluvoxamine	21
Lentizol	Amitriptyline	10-28
Lustral	Sertraline	22-33
Prothiaden	Dothiepin	19-33
Prozac	Fluoxetine	7-9 days
Seroxat	Paroxetine	21-26
Sinequan	Doxepin	28-52
Surmontil	Trimipramine	24
Tofranil	Imipramine	19
Triptafen	Phenothiazine	30
Zispin	Mirtazapine	20-40

The effects of cocaine quickly wear off because it has quite a short half life, but when taken with alcohol the euphoriant metabolite cocaethylene (ethylcocaine) is produced and this has a half life of 120 minutes which extends the effects experienced by the cocaine user. However, cocaethylene is more toxic.

WHAT FACTORS AFFECT DRUG HALF LIFE?

1. Clearance and volume of distribution

Drug half life is strongly dependent on two mathematical values: **clearance** which refers to the volume of blood effectively stripped of the drug through the liver and kidneys per minute, and **volume of distribution** which refers to the extent to which the drug is distributed into all the body's tissues, not just blood, but also its binding to other tissues which will affect how hard the body has to work to remove the drug.



Cannabis molecule showing organic 'head' and fat-soluble aliphatic 'tail'

On this basis a heavier person will require a greater dose for a similar effect but the drug will leave the body more slowly.

2. Disease, Age and Drug Interactions

Because these two values of clearance and volume of distribution can change with the effects of **disease, age and drug interactions** on the liver, the latter can also have a strong influence over a drug's half life. For instance, whereas the half life for caffeine is normally between 4 to 6 hours in healthy adults it is significantly lengthened in those with liver or kidney disease. In newborns with undeveloped liver enzyme systems and immature renal function, this figure can be prolonged from between 80 to 100 hours. Caffeine, like many dangerous drugs of abuse, is also subject to numerous drug interactions with oral contraceptive steroids, antihistamines like cimetidine (Tagamet) and antidepressants like fluvoxamine (Faverin, Luvox) which, by interfering with the liver's handling of the drug, decrease its rate of removal from the body and hence lengthen its half life significantly.

Incidentally, Italians consume fourteen billion espressos a year but generally limit their high-caffeine shot to the morning, revert-

ing to low-caffeine cappuccinos in the afternoon and wine in the evenings to avoid sleep problems that night.

3. Drug Dosages and Half Life

Drug half life is also dependent on the initial concentration of the drug achieved in the blood after a single dose. Normally by four to five half lives, the drug is essentially removed from the blood, assuming no additional drug is absorbed. But if multiple doses are taken, the drug that is removed is being constantly replaced and the blood concentration of drug will increase and this lengthens the half life. Ascertaining whether multiple doses of a drug is involved can be important in clinical decision making. However, whilst this rule is true for most drugs, there are exceptions. The half life of cocaine, for instance, which is around 60 minutes, appears to be fixed irrespective of the dose taken.

4. Drug Chemistry

The half life can also depend on whether the drug tends to dissolve in water or body fat. The more fat-soluble methamphetamine for instance has a longer half-life than its cousin d-amphetamine. Highly fat soluble drugs like delta-tetrahydrocannabinol (THC) found in cannabis release very slowly from the body's fat stores and can have a long half-life of several days. This needs to be taken into account when evaluating whether a positive urine test represents a new episode of drug use or just continued excretion of drug stores in the body. Urine concentrations can see-saw as the user exercises, which may result in a positive result after a few days of negative results, which might otherwise be thought to represent re-use while in rehabilitation. Daily testing thereafter would resolve this issue.

Half life can also depend on whether the drug is an acid or a base and the final pH of urine. If the drug in question is basic, for instance, then a more alkaline urine will prevent its ionisation to a charged state and reduce its solubility in water but this will increase its solubility in body fat thereby decreasing drug removal and increasing its final half life. The half life of the highly basic drug d-amphetamine, for instance, can be increased 7 hours for every unit increase in urine pH. It is for this reason that bicarbonate of soda is often taken with amphetamine to prolong its effect. But the opposite case is true also. Medical professionals routinely exploit this principle to shorten the half-life of the basic hallucinogen phencyclidine (PCP) in overdose scenarios by acidifying the urine in order to ionise the drug to a charged state and hold it in solution for rapid excretion.

CONCLUSIONS

Whether it is the mathematical values of clearance and volume of distribution or the physical effects of age, disease, drug interactions or drug chemistry, all of these influences on a particular drug's half life need to be taken into consideration by scientists and medical professionals in the field of drug testing, drug detoxification and medical emergency.

The elimination of drugs is complicated, and requires the expertise of a pharmacologist to evaluate fully. Even then, there is significant variation from one individual to another because there are so many factors involved. The half life of a drug, its method of use, and the pharmacokinetics of the body are inextricably linked to behaviour, and length of time taken to excrete the drug and its metabolites. This is complicated.

Nevertheless, knowing a drug's half life goes a long way towards understanding the addictive tendency of a drug and the length of time it takes to be eliminated from the limbic system that governs addiction.

Next issue: Retention times and drug cut off levels.

SureScreen Diagnostics Ltd, 1 Prime Parkway Derby DE1 3QB U.K. **Tel:** 0044 (0)1332 365318 **Fax:** 0044 (0)1332 292230 **Web:** www.surescreen.com **Email:** info@surescreen.com

Drug Name	Half Life Value(s)	Psychoactive Period
Heroin	<u>Intravenous</u> 3 min - 5 min <u>Inhaled</u> 4.6 min	2 h
Morphine	<u>Intravenous</u> 43 min, 2.2 – 2.5 h, 5.9 – 9.2 h	1 - 2 h
Methadone	<u>Ingested</u> 24 - 36 h, 30 h, 35 h	4 h
Cocaine	<u>Snorted</u> 60 min	5 - 90 min
	<u>Intravenous</u> 31 - 82 min	
Amphetamine	<u>Ingested</u> 4.2 - 6.8 h, 10 h, 11 - 13 h, 15 h, 15.3 h, 20 h, 30 h	2 - 8 h
Methamphetamine	<u>Ingested</u> 10 h <u>Smoked</u> 11.1 h <u>Injected</u> 12 h 12.2 h	6 - 24 h
Cannabis	<u>Smoked</u> 1.5 h, 2.3 h, 19 - 20 h, 28 h, 20 - 30 h, 2 - 3 days, 3 - 4 days	2 - 3 h
PCP	<u>Ingested</u> 7 - 16 h, 27 h <u>Intravenous</u> 16 h	4 - 6 h
LSD	<u>Ingested</u> 3 h	12 h
Mescaline	<u>Ingested</u> 6 h	12 h
MDMA	<u>Ingested</u> 7.7 - 8.6 h, 8 h, 8 - 9 h	4 - 6 h
MDA	<u>Ingested</u> 16 - 25 h, 16 - 28 h, 25 h	4 h
Ketamine	<u>Intravenous</u> 1.3 h, 2 h, 2.5 h, 4.9h	1 - 3 h
Ephedrine	<u>Ingested</u> 3 h, 3 - 6 h	1 - 4 h
GHB	<u>Ingested</u> 22 - 28 min, 30 min, 40 min, 53 min	3 - 4 h
Benzodiazepines	<u>Ingested</u>	
Short-acting	3 h	
Flurazepam	1 h	
Intermediate-acting	6 - 24 h	
Oxazepam	8 h	
Temazepam	8 h	
Lorazepam	12 h	
Chlordiazepoxide	12 h	
Long-acting	>24 h	
Nitrazepam	28 h	
Diazepam	32 h	
Clonazepam	50 h	
Barbiturates	<u>Ingested</u>	
Short-acting	24 h	
Intermediate-acting	48 h	
Long-acting	48 - 120 h	
Phenobarbitone	24 - 96 h 80 - 100 h	
Inhaled Fluorocarbons	1.5 h	

Please note the range of half-life values in the table above reflect different sources of reference. References and source material for this Technical Bulletin are also shown at www.surescreen.com

SureScreen Diagnostics is one of Europe's leaders in in-vitro diagnostic testing, including drug tests, pregnancy, disease and lifestyle tests.

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