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BACK-TRACKING CALCULATIONS

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Introduction

What is Backtracking?

Backtracking calculations ("back-calculations") are most commonly used to estimate previous concentrations of drugs, including alcohol (ethanol), in a biological fluid such as blood. Typically, a drug concentration is measured in a blood specimen taken some time after a critical event and it becomes necessary to establish what the concentration would have been at that earlier time. One example might be the estimation of blood alcohol concentration (BAC) at the time of a road traffic accident based on the analysis of a blood or breath specimen from the driver obtained some hours after the accident. It is clearly important to know if the driver was above the prescribed alcohol limit at the time of the accident. Another common example is the estimation of the maximum acetaminophen (paracetamol) concentration that might have been achieved in an overdose patient based on a blood sample taken on admission at the emergency room: the high-point concentration is critical in determining patient treatment and outcome.

The starting point for these calculations is the concentration of the drug in a sample of the biological fluid taken at a given time after the critical event. This is often measured in a forensic toxicology or clinical biochemistry laboratory but, with the advent of increasingly sophisticated and accurate on-site instruments, alternatives now include the police station and will potentially in future include the roadside or ambulance.

Backtracking calculations may also be used in completely different contexts within forensic medicine, for example, the estimation of the postmortem interval based on body temperature, but this article will be restricted to applications involving drugs, used here in its widest interpretation to include alcohol and other substances.

Pharmacokinetics and Pharmacodynamics

Back-calculation requires knowledge of the pharmacology of the relevant substance, particularly with respect to its pharmacokinetics, which is concerned with how the body handles the substance, i.e., the question: what does the body do to the substance? Pharmacokinetics relates to the rate of elimination of substances from the body and is critical for backward extrapolation. In contrast, the pharmacodynamics of the substance is more concerned with its effects, i.e., the question: what does the substance do to the body? Often these two questions are tied together when interpreting a forensic case, when an attempt is made to estimate a drug concentration in blood and relate it to its effects on the individual concerned.

Absorption, Distribution, Metabolism, and Elimination of Drugs

It is often easiest to consider drug concentrations versus time in a pictorial/graphical way and some common terminology is used to describe the different parts of the concentration-versus-time curve (Figure 1).

After administration, the concentration of drug in blood rises to a maximum (C_{max}) during the absorption phase and begins to decline in the distribution and elimination phase, following an exponential curve.

Concentration-versus-time Curves and Backtracking Calculations

The shape of the concentration-versus-time curve during the elimination phase is the basis of all backtracking calculations. Clearly, if the details of the curve are known, it will be possible to predict drug concentrations at any point on the curve. However, calculations are often restricted to the elimination phase unless details of dose and time of administration are known.

Some information is needed to allow the curve to be defined and difficulties arise if insufficient information is available. Typically, all that is known is the concentration of the drug of interest measured in a

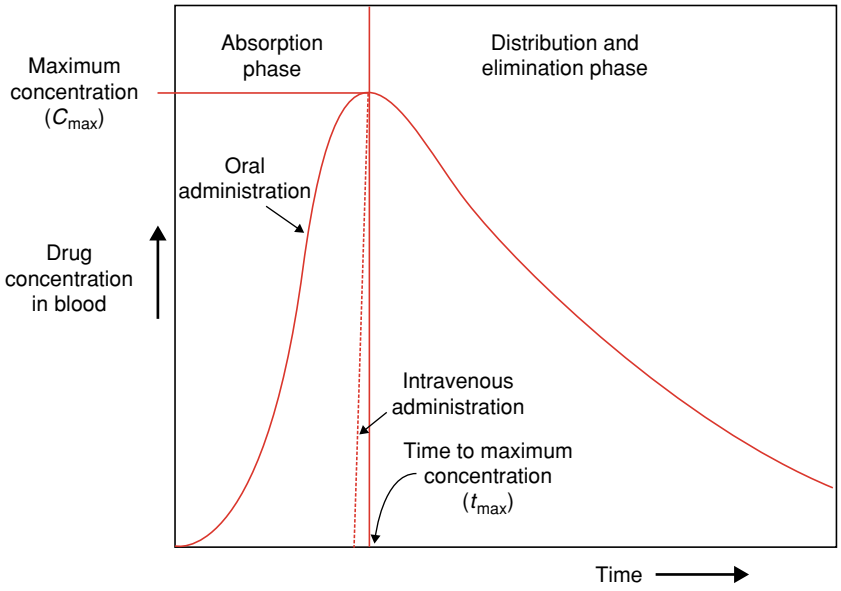

Figure 1 General graph showing concentration of drug in blood versus time after administration.

blood specimen taken at some stage after administration. To this must be added, usually from the literature, information on the peak blood levels obtained after administration of a known amount of the drug and the rate(s) of elimination of the drug. Additional factors need to be taken into account, for example, the weight of the subject, his/her build (tall, short, fat, thin), age, and experience/habituation to the drug. For most parameters of this type there is an average value for the population in general and an associated range of values encompassing the different values found in individual subjects. If the information is available in the literature, the population values used should relate to a population matched to the characteristics of the subject. As an example, the average rate of elimination of alcohol in a population of regular consumers of alcohol is higher than in a group of nondrinkers.

The shape of the curve in the elimination phase can adopt a variety of forms, depending on the dose of substance taken and its distribution and metabolism. For most drugs, the rate of elimination depends on the concentration of drug present – a constant proportion of the drug is eliminated in a given time interval and the curve is exponential. However, for a few drugs given in high doses, including alcohol and aspirin, a constant amount of drug is eliminated per unit of time and the curve is effectively linear. Alcohol will be considered separately below, then other drugs.

Alcohol

A typical concentration-versus-time curve for alcohol is given in Figure 2 Alcohol is unique as a drug

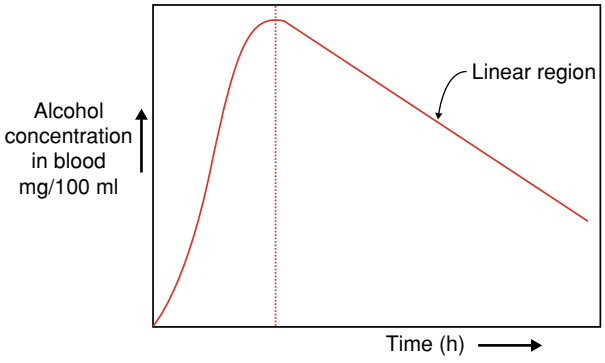

Figure 2 Concentration-versus-time curve for alcohol in blood.

because of the large doses that are administered (Table 1). No other drugs are administered in such large amounts. As a result, the concentration of alcohol in blood can be much higher than that obtained for any other drug and it saturates the metabolic capability of the liver (the main metabolic organ).

Units of concentration and dose of alcohol Concentrations of alcohol in beverages are given in terms of percentage alcohol by volume (vol%), which may be given on the bottle or packaging. Representative values are given in Table 1. When performing calculations it is advisable to establish the exact concentration of alcohol in the beverage consumed by the subject. The weight of alcohol in a measure of a beverage (equivalent to the "dose" of alcohol) can be obtained by multiplying the volume of alcohol it contains by the density of alcohol (0.791 at 20 °C).

Table 1 Representative alcohol concentrations in common beverages

Beverage	*Alcohol (%vol)*	*Common measures (cl)*	*Weight of alcohol at 20°C (g)*
Beer	3–6	Pint 56.8	15.7 (3.5% vol)
Strong beer	5–9	Pint 56.8	15.7 (3.5% vol)
		Bottle 33	10.4 (4%vol, 33 cl)
		Can 44	23.5 (9%vol, 33 cl)
Table wine	10–13	Bottle 75	71
		Glass 12.5	11.9
		Large glass 25	23.7
			(all based on 12%vol)
Fortified wines (sherry, port)	15–20	Bottle 75	104
		Glass 2.5	3.5
			(all based on 17.5%vol)
Spirits	35–40	Bottle 75	237
		''Single'' 2.5	7.9
		''Double'' 5	15.8
			(all based on 40%vol)

For example, 125 ml of wine (12 vol%) contains $125 \times 0.12 \times 0.791$ g alcohol at 20 °C, i.e., 11.9 g alcohol.

Other units of relevance are those used to describe alcohol in biofluids – blood, urine, and breath. For blood and urine, the units most often used are milligrams per 100 milliliters (mg%) or grams per 100 milliliters (g%). The latter is obtained by dividing the former by 1000. For example:

$$\text{Legal limit for driving in the UK is } 80\,\text{mg\%} = 0.08\,\text{g\%}$$

Breath alcohol concentrations are much lower and are expressed as micrograms per 100 millilitres of breath (μg%). In other jurisdictions, for example the USA, the units are grams per 2100 liters of breath, because USA traffic legislation is based on a blood:breath ratio of 2100:1.

It is usually convenient to convert alcohol concentrations in breath or urine to the equivalent blood concentration, using the ratios specified by the prescribed limits in the relevant jurisdiction. After the calculations are carried out, the breath or urine concentrations can be obtained by reversing the conversion process.

Pharmacokinetics of Alcohol

Administration of alcohol is almost always by the oral route. It is absorbed from all parts of the alimentary tract but mostly enters the circulation from the small intestine. If the stomach is empty, the absorption can be rapid, within 30 min or less, but the presence of food can delay absorption for several hours. For the purpose of calculations, a period of 1 h after the last drink can be allowed for complete absorption of alcohol.

Ethanol is considered to be uniformly and rapidly distributed throughout the body water. The relative concentrations of alcohol in biological fluids or tissues therefore depend on their water contents.

Alcohol is also distributed into breath according to the partition ratio between blood and air in the lungs. The partition ratio used in UK legislation is blood:breath = 2300:1 and the prescribed limit for alcohol in breath when driving is 35 μg of alcohol per 100 ml of breath (note the different units: milligrams of alcohol in blood and micrograms in breath).

For the purposes of backtracking calculations, the elimination part of the blood alcohol curve is considered to be linear as long as the BAC is above 20 mg%, indicating that the rate of elimination is independent of the alcohol concentration ("zero-order" or "saturation" kinetics). When the alcohol concentration falls below 20 mg% the liver is no longer saturated and an exponential curve is followed. Many studies have been carried out in different populations to establish the average and range of elimination rates during the linear part of the curve. The average rate often used in backtracking calculations is 15 mg alcohol per 100 ml blood per hour (15 mg% h^{-1}). The range of elimination rates varies widely: 9–29 mg% h^{-1}. It has also been established that regular drinkers often have a higher elimination rate, averaging 18–20 mg% h^{-1}. An average elimination rate of 18 mg% h^{-1} is recommended by many workers in this field as the basis of backtracking calculations.

Calculations The simplest backtracking calculations relate to the linear portion of the blood alcohol curve (Figure 3). The starting point is usually a blood (or breath or urine) alcohol concentration in a specimen obtained at a known time. The aim of the calculation is to estimate the blood (or breath equivalent)

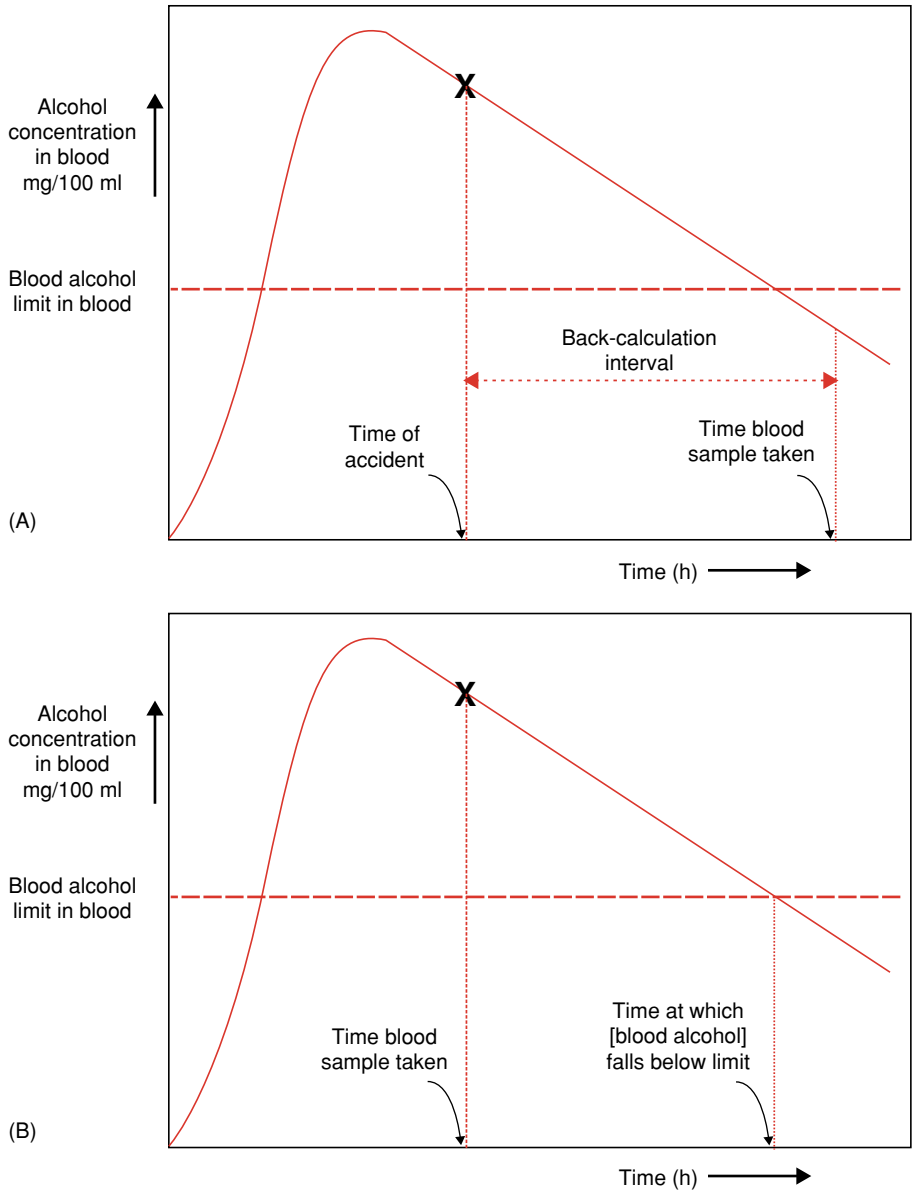

Figure 3 (A) Back-calculation; (B) no likelihood of driving.

concentration at an earlier time than when the specimen was obtained (back-calculation). Road traffic legislation in the UK permits this to be carried out for specimens obtained up to 18 h after an incident such as a road accident. A similar calculation can be used to determine when the blood (or equivalent) alcohol concentration would fall below the limit prescribed in the relevant jurisdiction. This is one of the two statutory defenses created within UK legislation – no likelihood of driving whilst unfit to drive through drink or drugs.

A more complex calculation is often requested as a result of postaccident consumption of alcohol – the other statutory defense allowed within the UK legislation. It concerns a defendant who consumes alcohol after being involved in a road traffic incident, typically a road accident, and whose blood or breath alcohol is subsequently found to be above the prescribed limit. The defense seeks to establish that, at the time of the accident, the defendant's alcohol concentration was below the limit. It is important to recognize that calculations are based on the information supplied by the defendant, which may be incorrect either intentionally or unintentionally. The fact that a set of calculations supports a defendant's version of events does not mean that it is true.

Back-calculation Certain assumptions are made in this type of calculation and should be stated in a report prepared for court purposes:

- It is assumed that the BAC has been falling continuously and linearly during the time interval between the incident and obtaining the specimen from the defendant.
- It is assumed that no alcohol was consumed during this interval.

The back-calculation interval is the time between the incident/accident and the time at which the blood or other specimen was taken (Figure 3A). This is multiplied by the average rate of alcohol elimination to obtain the amount by which the BAC has fallen during the interval. The BAC at the time of the incident is then obtained by adding this value to the BAC measured in the specimen. A range of values can be calculated using the range of elimination rates given above.

This type of calculation is, arguably, acceptable over a short time interval of a few hours, but is likely to be inaccurate over a long period such as that permitted under UK legislation (18 h).

For example, a blood specimen was obtained from the defendant 4 h after a fatal road accident. The BAC was 60 mg%. Over a 4-h period the BAC would have fallen by $4 \times 18 = 72$ mg%, on average (range is 36–116 mg%, based on elimination rates of 9 and 29 mg% h^{-1}). The defendant's BAC at the time of the accident would have been 132 mg% (range 96–176 mg%).

Time to fall below prescribed limit Assumptions made in this calculation are:

- It is assumed that the defendant was in the elimination phase when the BAC was measured and that it would have continued to fall linearly until it fell below the prescribed limit.
- It is assumed that no additional alcohol would be consumed during this interval.

The difference between the measured BAC in the blood specimen and the prescribed limit for driving is obtained by subtraction. The clearance time (in hours) required for a decrease in BAC of this magnitude to occur is calculated by dividing this difference by the average elimination rate. The time of day when the defendant would have been entitled to drive can then be obtained by adding the clearance time to the time when the blood specimen was obtained. A range of times can be calculated using the range of elimination rates given above.

For example, a defendant was found sleeping in his car at 11.30 P.M. and his breath alcohol concentration was subsequently measured at midnight. This gave a reading of 55 μg of alcohol per 100 ml of breath. His defense is that he did not intend to drive until 8 A.M. the following morning.

In this example, the breath alcohol concentration can be converted into the equivalent blood concentration, using the blood:breath ratio incorporated into the legislation. In the UK this factor is 2300:1. Alternatively, the average elimination rates for blood can be converted into the equivalent values for breath.

The defendant's breath alcohol concentration needs to fall to 35 μg of alcohol per 100 ml of breath before he would be entitled to drive. This represents a fall of 20 μg of alcohol per 100 ml of breath. The equivalent fall in blood concentration can be obtained by multiplying by 2.3 (since the units for breath are 1000 times smaller than for blood), i.e., $20 \times 2.3 = 46$ mg per 100 ml blood.

Using the average clearance rate of 18 mg% h^{-1}, it would take $2\frac{1}{2}$ h for the defendant's BAC to fall by 46 mg%. The range of times obtained by using the fastest and slowest elimination rates is 1.6 h (1 h 36 min) to 5 h. Even with the slowest rate of elimination the defendant would have been below the prescribed limit at 8 A.M. the following morning.

Postaccident consumption of alcohol The defendant needs to provide the information listed in Table 2. This information can usually be obtained through the solicitor for the defense.

Table 2 Information required for postaccident drinking defense

- Details of alcohol consumption for the 24 h preceding the road traffic incident, i.e., the quantities and types of beverages and the time periods over which they were consumed. In many cases, the defendant has consumed alcohol before driving and being involved in the traffic incident. The aim is to establish that this would not have resulted in an alcohol concentration above the limit. It is also important to ensure that there is no residual alcohol from the previous day. The quantities of alcohol consumed by the defendant are often estimates made some time after the event. If the alcohol was consumed in a bar then bar measures are reasonably reliable with respect to volume. If the alcohol was consumed at home or elsewhere the defendant should be asked to mark on the original bottle or glass (if possible) how much was used
- The time of the traffic incident
- Details of postaccident consumption of alcohol (quantity, type, time period)
- Details of police involvement and subsequent breath or blood sample obtained. The defendant's recollection of the timescale may be inaccurate but police officers make a detailed and accurate note of their movements. Similarly, breath alcohol analysis instruments or attending physicians record the time of sample collection
- The result of the breath or blood analysis
- The defendant's height and weight at the time of the incident

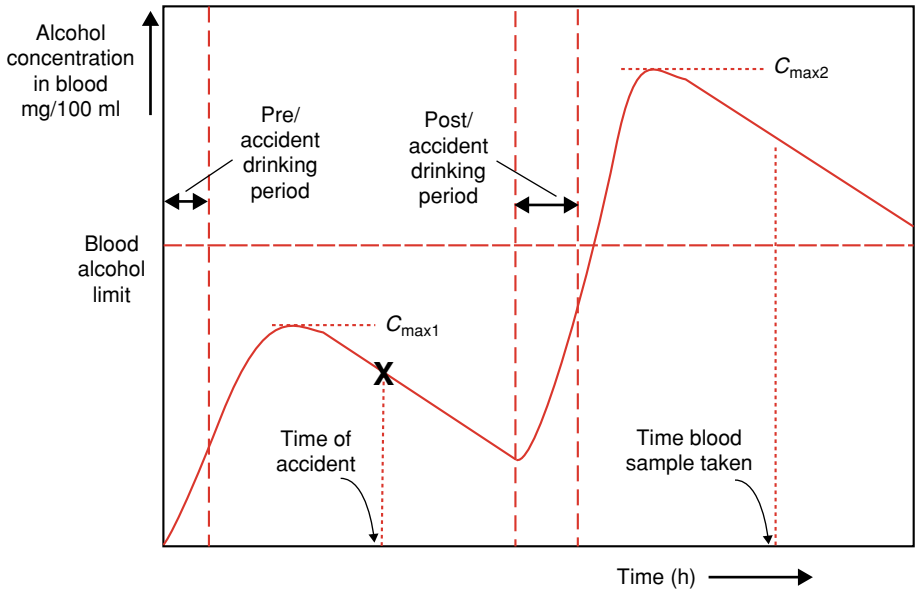

Figure 4 Blood alcohol-versus-time curve for a postincident drinking scenario.

The concentration-versus-time curve for this scenario is shown in Figure 4. The calculation breaks down into two parts corresponding to pre- and post-accident consumption of alcohol. Calculations shown below deal with BACs. Interconversion of breath and blood concentrations can be carried out using the blood:breath ratio accepted in the relevant jurisdiction.

Complete definition of the curve requires the information listed in Table 2 on quantities and times of alcohol consumed. It is necessary to estimate C_{max1} and C_{max2}, i.e., to relate the BAC to the alcohol consumed.

Calculation of maximum alcohol concentration (C_{max}) after consumption of alcohol The number of grams of alcohol contained in the drink(s) consumed is calculated as described earlier. This alcohol is assumed to be completely and rapidly absorbed and evenly distributed throughout body water before any significant elimination has occurred.

The value of C_{max} can be obtained if the total volume of body water and the fraction of blood that is composed of water are known – this is relatively constant at 0.8 times the blood volume. The problem is now to estimate the total amount of water in the body. Several ways of doing this have been published in the literature (Table 3).

Perhaps the best known of these was published by Widmark in 1936. The factor r in Table 3 is now usually called the "Widmark factor." Men and women, on average, have slightly different body compositions and Widmark's empirical values of r for men and women are 0.68 and 0.55, respectively.

Watson and coworkers in 1980 derived formulae for estimating total body water from anthropometric measurements (height, weight, and age) in men and women.

More recently, Forrest published in 1986 what might be considered the most reliable approach, based on the body mass index. The total body water can be calculated from the body's fat-free mass as the water content of fat-free tissue has been shown to be 724 g kg^{-1} on average (standard deviation 34 g kg^{-1}). Body fat, in turn, can be calculated using the body mass index.

A rule-of-thumb method for C_{max} was derived by Smith and Oliver based on in-house measurements (personal communication). Each drink containing 9 g of alcohol consumed by a 70-kg person increases the BAC by 20 mg%. The range on C_{max} is ±20%, which allows for differences in body composition. The C_{max} value is adjusted proportionately for body weight but no distinction is made between men and women.

Allowance for alcohol eliminated due to metabolism C_{max} is calculated on the assumption that alcohol is consumed and absorbed over a short time period, during which there is no significant loss of alcohol by metabolism. In reality, absorption may not be rapid and an allowance may be made for the absorption time – 1 h is reasonable for complete absorption of alcohol. C_{max} would therefore occur approximately 1 h after the last drink was consumed. In addition, more than one drink is often consumed and the period of consumption may well be a number of hours. In this situation, C_{max} is estimated as usual

Table 3 Methods of estimating maximum alcohol concentration (C_{max})

Author	*Equations*
Widmark	$a = c \times p \times r$ where: a = amount of alcohol consumed (g) c = blood alcohol concentration ($g\,l^{-1}$) p = the weight of the subject (kg) r = the ratio of water content of the whole body to that in blood i.e., r = (total body water/body weight) ÷ 0.8
Watson and coworkers	Total body water (men) = 2.45 + (0.107 × height) + (0.336 × weight) − (0.0952 × age) Total body water (women) = 2.10 + (0.107 × height) + (0.247 × weight) where total body water is in liters height is in meters weight is in kilograms
Forrest	Total body water = 0.724 × (body weight − body fat) where total body water is in kilograms (approximates to liters) body weight is in kilograms body fat is in kilograms and Fat as a percentage body weight (men) = 1.340 × body mass index − 12.469 Fat as a percentage body weight (women) = 1.371 × body mass index − 3.467 and body mass index = (weight in kg) ÷ (height in meters)^2
Smith and Oliver (personal communication)	C_{max} in blood = 20 × (weight alcohol consumed/9) × (70/body weight)

but is then adjusted downwards to take account of metabolism during the consumption period. For example, if several drinks were consumed over 3 h, the C_{max} value would be adjusted by subtracting 3 × the elimination rate (average and range). An alternative approach advocated by some practitioners is based on the fact that metabolism begins as alcohol enters the blood circulation, i.e., immediately after drinking commences, so no allowance is made for the absorption time.

For example, a defendant's statement indicates that he went to his local bar and consumed four single measures of whisky (25 ml per measure, 40 vol%) and one pint of beer (3.5 vol%) between 8 and 10 P.M. He left the bar and later drove his car. He was involved in a road accident at midnight, in which his car skidded and ended up in a ditch. His car was badly damaged but no one was injured. He wandered away from the scene in a state of shock, arriving home at 12.15 A.M. He then consumed a further quantity of whisky to calm his nerves. The volume of whisky consumed was estimated from the glass used by the defendant as 150 ml. The police arrived at the defendant's house at 1 A.M. and subsequently a blood specimen was obtained at 2 A.M., which was found to contain 100 mg% alcohol, which is above the UK statutory limit of 80 mg%. The defendant's weight at the time was 11 stone (70 kg) and his height is 5 ft 8 in. (1.72 m). The defense wishes to show that the defendant's BAC was below the limit at the time of the accident and that his postaccident drinking explains the alcohol found in his blood specimen.

This will be worked through using the method proposed by Forrest and also using the rule-of-thumb method of Smith and Oliver. For both calculations the quantities of alcohol consumed before and after the accident were:

- Alcohol consumed before driving:
  4 × 25 ml = 100 ml whisky = 31.6 g alcohol
  1 pint beer = 568 ml (3.5 vol%) = 15.7 g alcohol
  Total = 47.3 g alcohol
- Alcohol consumed after the accident:
  150 ml whisky = 47.5 g alcohol

Method of Forrest

- The defendant's body mass index (BMI)
  = (weight in kg) ÷ (height in m)^2
  = 70 × 1.72^2
  = 23.7
- Fat as a percentage of body weight
  = 1.340 × body mass index − 12.469
  = 19.3%
- Weight of body fat = 70 × 0.193 = 13.5 kg
- Total body water
  = 0.724 × (body weight − body fat)
  = 0.724 × (70 − 13.5)
  = 40.9 kg (= 40.9 l)

95% confidence interval based on ±2 standard deviations is ± 3.8 l
That is, 37.1–44.7 l

- Widmark factor r
  = total body water ÷ (total body weight × 0.8)
  = 40.9 ÷ (70 × 0.8)
  = 0.73
  Range = 0.66–0.80
- Using the Widmark equation ($a = c \times p \times r$):
  $47.3 = C_{max} \times 70 \times 0.73$
  $C_{max} = 0.926\ g\ l^{-1}$ blood = 93 mg%
  (rounded to nearest whole number)
  Range = $0.845-1.02\ g\ l^{-1}$
  blood = 84.5–102 mg%
  C_{max} will be obtained 1 h after the last drink, i.e., at 11 P.M.
- Adjusting C_{max} for metabolism between 9 and 11 P.M.:
  Average rate of elimination
  = 18 mg% h^{-1} (range 9–29 mg% h^{-1})
  Loss of alcohol from 9 to 11 P.M.
  = 2 × 18 = 36 mg% (range 18–58 mg%)
  Adjusted C_{max} = 57 mg%
  The range on this figure takes into account range on C_{max} and range in elimination rates:
  Maximum range
  = (84.5–58) to (102–18) = 26.5–84 mg%
- At the time of the accident (midnight):
  Additional loss of alcohol by metabolism from 11 P.M. to midnight is 18 mg% on average (range 9–29).
  Net BAC = 39 mg% (range 0–75 mg%).
- Postaccident consumption of 150 ml whisky (47.5 g alcohol) between 12.15 and 1 A.M. would result in C_{max2} at about 2 A.M., when the blood specimen was obtained. Using the Widmark equation C_{max2} is 93 mg%. This value needs to be adjusted to allow for residual alcohol from the drinks consumed earlier and for metabolism between 12.10 and 2 A.M. Note that the defendant's blood alcohol never reaches zero at any time (referring to the average rate of metabolism) so metabolism continues without interruption. However, a fast metabolizer would achieve a zero BAC shortly after midnight.
  Residual blood alcohol from preaccident consumption is 39 mg% (range 0–75 mg%) at midnight.
  Blood alcohol increase from postaccident drinking is 93 mg% (range 85–103 mg%).
  Total is 132 mg% (range 85–178 mg%).
  C_{max2} is adjusted to take into account metabolism from midnight to 2 A.M. equivalent to 36 mg% (range 18–29* mg%) (asterisk represents fast metabolizers who would have achieved a zero blood alcohol shortly after midnight so a metabolism period of 1 h is used).
  Net result for C_{max2}
  = 96 mg% on average (range 56–160 mg%).
- The alcohol concentration in the defendant's blood specimen was 100 mg%, which is in reasonable agreement with the average calculated value.

Method of Smith and Oliver (personal communication)

- Preaccident consumption of 47.3 g alcohol would give a BAC of 20 × 47.3/9 mg% on average = 105 mg% (range on this is ±20%, i.e., 84–126 mg%). Adjusting C_{max1} for metabolism between 9 and 12 P.M. (an allowance of 1 h is made for the alcohol to be absorbed initially so the metabolism time begins at 9 P.M.):
  Average rate of metabolism gives a decrease of
  3 × 18 = 54 mg%.
  Range: slow metabolism gives a decrease of 3 × 9 = 27 mg%; fast metabolism gives a decrease of 3 × 29 = 87 mg%.
  Net BAC at the time of the accident:
  Average: 105 − 54 = 51 mg%
  Maximum range is obtained by subtracting maximum and minimum decrease due to metabolism from the lower and upper end of the range on C_{max1}:
  Low end of range: 84 − 87 = 0 mg%.
  Top end of range: 126 − 27 = 99 mg%.
- On average, the defendant would have been below the limit at the time of the accident. However, note that the range is wide and extends above the limit. Values at the extremities of the range are theoretically possible but are unlikely to occur.
- Calculation of the BAC at 2 A.M. is based on the total alcohol consumed before and after the accident and the total metabolic time:
  Total alcohol consumed = 47.3 + 47.5 = 94.8 g.
  This gives a C_{max} value of 20 × 94.8/9 = 211 mg%
  (range ± 20% = 169 − 253 mg%).
  Total metabolism time = 9 P.M. − 2 A.M. = 5 h.
  This gives a decrease in BAC = 5 × 18 = 90 mg%.
  Range due to metabolism is : low end
  = 5 × 9 = 45 mg%; top end = 4 × 29 = 116 mg%*
  where asterisk represents metabolism period of only 4 h because the BAC would have been zero between midnight and 1 A.M. approximately.
  Net BAC at 2 A.M.:
  Average: 211 − 90 = 121 mg%,
  range: low end = 169 − 145 = 24 mg%;
  top end = 253 − 45 = 208 mg%.
- The average calculated value is 121 mg%, which is somewhat higher than the alcohol concentration measured in the blood specimen. However, the range is very wide and it allows the defense to argue that the defendant's postaccident drinking would account for the blood test result.

Drugs Other than Alcohol

The curve shown in Figure 1 applies to most drugs taken orally in a single dose. Obviously, administration of more than one dose would result in a more complex curve with multiple peaks and the following discussion is restricted to the part of the curve after the peak, i.e., the elimination phase.

The elimination phase is a sigmoidal, S-shaped curve, which can be represented mathematically by an exponential equation of the form:

$$C_t = C_0 e^{-kt} \qquad [1]$$

where C_t is the drug concentration at time t; C_0 is the theoretical drug concentration, which would be obtained if the drug had been administered at time t_0 and distributed immediately around the blood in circulation; and k is the elimination rate constant.

In practice, the elimination curve is more complex, and the equation contains two or more exponential terms rather than one, as in eqn [1]. These might be interpreted as the distribution (alpha) and excretion (beta) phases of the curve (Figure 5). Many data points are needed to define a multiexponential curve and backtracking calculations are necessarily restricted to the simpler single-exponential model. This, in turn, usually restricts the calculations to the terminal beta phase.

Eqn [1] is usually transformed to the following, which is easier to work with as it is the equation of a straight line (Figure 6):

$$\log_{10} C_t = \log_{10} C_0 - kt/2.3 \qquad [2]$$

An additional equation, the derivation of which is shown in all pharmacokinetic texts, relates the elimination rate constant to the half-life of the drug in plasma. This is the time it takes for the drug concentration to fall to half of its original value and it is available for most drugs in reference textbooks.

$$t_{1/2} = 0.693/k \qquad [3]$$

where $t_{1/2}$ is the plasma half-life and k is the elimination rate constant.

It is therefore possible to obtain k for most drugs using eqn [3] and as a result it is possible to solve eqn [2] to obtain drug concentrations at times prior to when the biological specimen was obtained. This is best illustrated with some typical examples.

Acetaminophen (paracetamol) The patient, Mrs Y, has been admitted to hospital after taking an overdose of acetaminophen tablets. This occurred at about 5–6 P.M. and it is now 10 P.M. The attending physician takes a blood sample from the patient and sends it to the laboratory for acetaminophen measurement. The result from the lab is 50 mg acetaminophen per liter of plasma.

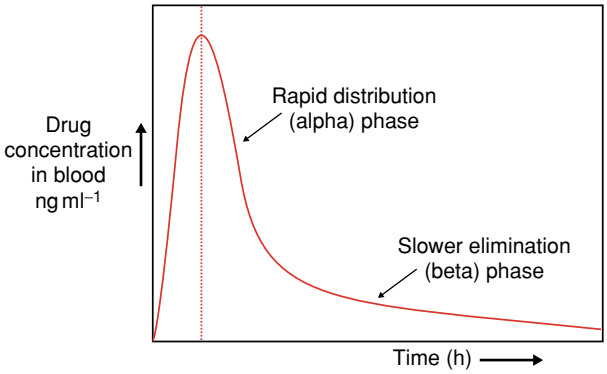

Figure 5 The elimination curve for most drugs contains at least two phases.

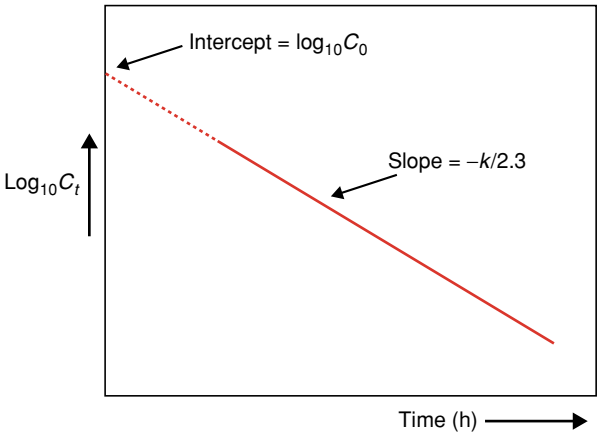

Figure 6 Semilogarithmic plot of elimination curve.

The course of treatment of an acetaminophen overdose depends on the amount of drug consumed and what the plasma concentration of the drug was at its highest. A threshold applies: if the peak concentration was below 150 mg l^{-1} plasma, then no intervention is necessary other than general support. However, if it was above this threshold, then severe liver damage is likely to occur and therapeutic intervention is indicated. This would entail the administration of a drug such as acetylcysteine, which protects the liver from damage caused by acetaminophen. It is therefore necessary to carry out a backtracking calculation to estimate the acetaminophen concentration in the patient's blood 4 h before admission to hospital. (In practice, standard graphs have been prepared and are used instead of calculations.)

Data required: the plasma half-life of acetaminophen is 2 ± 0.4 h.

The easiest way of doing this backtracking calculation is to divide the time elapsed by the half-life to get

the number of half-lives which have passed since the peak drug concentration. In this example, the elapsed time is from 6 to 10 P.M., i.e., 4 h. The half-life is 2 h, therefore approximately two half-lives have passed since the drug concentration was at its highest and in each of these the concentration decreased by 50%. The concentration at 10 P.M. was $50\,\mathrm{mg\,l^{-1}}$. Two hours earlier (one half-life) it would have been twice this value, i.e., $2 \times 50 = 100\,\mathrm{mg\,l^{-1}}$ and 2 h before that it would have been $2 \times 100 = 200\,\mathrm{mg\,l^{-1}}$. This puts the patient above the threshold for therapeutic intervention.

Diamorphine (heroin) The deceased, Mr X, had a history of drug abuse. On the evening before his death, he was drinking in a bar with friends and purchased heroin before leaving. From statements obtained by the police, he injected the heroin intravenously shortly before midnight and lapsed into a semicoma. He was put to bed and his friends watched over him for about 2 h before they went to bed. His girlfriend looked in on him at 3 A.M. when she heard him snoring. Unable to sleep, she again looked in on him at 4 A.M. and found him unresponsive and not breathing. The paramedic team that arrived shortly thereafter found no trace of life and he was pronounced dead on arrival at the local hospital at 4.30 A.M. At autopsy, he was found to have significant pulmonary edema and congestion. A sample of blood taken at the autopsy had a blood morphine concentration of $0.15\,\mathrm{mg\,l^{-1}}$ of blood.

Data required: the half-life or morphine after administration of diamorphine (heroin) is 2.5 h.

When diamorphine is injected, it rapidly breaks down into morphine, which is measured in blood. The literature records many studies of heroin-related deaths in which the concentration of morphine is low and is not significantly above the therapeutic range. In this example, a blood concentration of morphine equal to $0.15\,\mathrm{mg\,l^{-1}}$ is about 50% higher than the usual therapeutically effective concentration range in patients who are not regularly treated with the drug (up to about $0.1\,\mathrm{mg\,l^{-1}}$) and does not indicate an obvious overdose concentration. However, during the period after intravenous injection, the blood concentration will decrease and the peak concentration can be estimated using the known half-life. The elapsed time is about 4 h between drug administration and death.

From eqn [3]:

$$t_{1/2} = 0.693/k$$

In this example, $t_{1/2} = 2.5$ h; therefore $k = 0.693/t_{1/2} = 0.28$.

From eqn [2]:

$$\log_{10} C_t = \log_{10} C_0 - kt/2.3$$

In this example, $C_t = 0.15\,\mathrm{mg\,l^{-1}}$, $t = 4$ h, and $k = 0.28$.

$$\log_{10} 0.15 = \log_{10} C_0 - (0.28 \times 4/2.3)$$

therefore $\log_{10} C_0 = -0.82 + 0.49 = -0.33$ and $C_0 = 0.47\,\mathrm{mg\,l^{-1}}$.

The peak concentration is well above the therapeutic range and incurs a significant risk of opiate overdose.

See Also

Autopsy, Findings: Drug Deaths; Postmortem Drug Measurements, Interpretation of; Postmortem Drug Sampling and Redistribution; **Pharmacology of Legal and Illicit Drugs**; **Road Traffic, Determination of Fitness To Drive:** Sobriety Tests and Drug Recognition; **Substance Misuse:** Substitution Drugs; Miscellaneous Drugs

Further Reading

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