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Pharmacokinetic Considerations in Clinical Toxicology

Clinical Applications

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Abstract

Pharmacokinetic and pharmacodynamic principles should be regarded in the assessment and proper management of patients exposed to a poison. Clinicians must apply these principles to make rational clinical decisions regarding the significance of the poisoning (risk assessment) and to formulate an appropriate management plan. However, pharmacokinetic processes and parameters may be changed in the patient with acute poisoning. This may result from saturation of the capacity of a number of physiological processes due to the high dose, or the toxic effects of the poison may change these processes directly. For example, absorption kinetics may be altered because of increased gastrointestinal transit time (e.g. cholinergic receptor antagonists) or saturable absorption (e.g. methotrexate). Saturation of protein binding may increase the volume of distribution and thereby increase the elimination half-life (e.g. salicylates). Alteration of the acid-base balance (poison-induced or iatrogenic) may also increase or decrease the distribution of a poison. Saturation of metabolism at high doses can prolong toxicity (e.g. phenytoin) or lead to other routes of metabolism that lead to increased toxicity (e.g. paracetamol [acetaminophen]). Excretion may be reduced by saturation of active transporters or decreased renal blood flow.

A better understanding of pharmacokinetic principles should improve the clinical care of patients. It should lead to more accurate interpretation of blood concentrations or biomarkers (e.g. ECG intervals or acetylcholinesterase activity) and how these relate to the time course for that poison, and better prediction of prognosis. This in turn, indicates the appropriate duration of observation and the requirement for some specific treatments. Many specific poisoning treatments aim to favourably alter the pharmacokinetics of the poison. These include activated charcoal, whole bowel irrigation, extracorporeal elimination, chelating agents, antitoxins and urinary alkalinisation. The evidence supporting them, their indications and limitations can only be understood using pharmacokinetic principles. These principles also underpin the appropriate choice within the flexible dosage regimen for many antidotes. In particular, naloxone, flumazenil, methylene blue, atropine and pralidoxime all use variable doses and have an elimination half-life that is much shorter than many (but not all) of the poisons treated by these agents. A firm grounding in pharmacokinetics/toxicokinetics should be regarded as a core competency for all professionals involved in clinical care or undertaking research in clinical toxicology.

1. Introduction

An understanding of pharmacokinetic and pharmacodynamic principles is essential for optimal assessment and management of patients exposed to a poison. Such principles enable pharmacokinetic data to be applied in clinical decision-making related to that poison. Rapid risk assessment and decisions about gastrointestinal decontamination, elimination enhancement, use of agents that modify drug distribution, and the optimal duration of antidote therapy all require a sound working knowledge of clinical pharmacokinetic principles and how pharmacokinetics can be substantially changed with overdose (toxicokinetics[1]).

1.1 Principles of Exposure

Blood or urine concentrations have a role in quantification of systemic exposure and prediction of clinical outcomes for a number of poisons. A detectable concentration of a poison merely confirms some exposure. In many poisonings, there is a fairly poor correlation between the reported exposure/dose and the concentrations obtained and a much better correlation between the concentration data and the severity of clinical toxicity. In these cases, the concentration is a practical estimate of the bioavailable dose. However, interpretation of these concentrations and their limitations is only possible by considering the pharmacokinetics in overdose of the poison and the range of possible times since

1 Pharmacokinetics and toxicokinetics both describe the time course of a xenobiotic in a biological system. How they differ is poorly described, although commonly the term 'pharmacokinetics' is used for agents intended for therapeutic use, while the term 'toxicokinetics' refers to nontherapeutic exposures to agents such as household, industrial or agricultural chemicals. The term 'toxicokinetics' has also been used to describe changes in pharmacokinetics following supratherapeutic exposures to pharmaceuticals, but often the two terms are used interchangeably. Further, since the pharmacodynamic endpoint of concern is toxicity, the terms 'toxicodynamics' and 'toxicokinetics' appear more appropriate. This review discusses kinetic issues irrespective of the intended use and dose of the xenobiotic, and so the terms 'poison' and 'toxicokinetic' are used preferentially unless referring to the kinetics of pharmaceuticals.

exposure.[1] For an exposure of a poison to be significant, the poison must be absorbed and distributed in a sufficient amount to the site where it causes clinical toxicity.

1.2 Hazard and Risk Assessment

To estimate the potential for toxicity, a clinical risk assessment should be conducted in all patients with acute poisoning. This requires a balanced consideration of the type of poison (hazard assessment), the reported amount and route of exposure, the time since the exposure, clinical features, patient factors and available medical facilities.[2]

It is not possible to interpret clinical information without appreciating the kinetics of the poison. Similarly, this is required for understanding when interventions that alter the toxicokinetics (absorption, distribution or elimination) are warranted, and also their limitations.

For many poisons, the pharmacokinetic/toxicokinetic data that are available are limited to low-dose or therapeutic exposures and case reports. The pharmacokinetics in overdose of many agents can be altered dramatically after an acute exposure due to either the dose (dose-dependent kinetics) or the clinical effects of the poison affecting organ function (table I). This causes the concentrations to change in a disproportionate manner, which is known as nonlinear kinetics. Therefore, these toxicokinetic considerations may substantially alter the risk from particular exposures and the efficacy of potential treatments.

The purpose of this article is to review toxicokinetic principles in acute overdose and to highlight how consideration of these may assist in the clinical management of patients.

2. Changes in Pharmacokinetics in Clinical Toxicology (Toxicokinetics)

When serial blood samples are obtained following an acute exposure, a standard concentration-time profile, often referred to as a Bateman curve, is formed (figure 1). The shape of this curve varies between poisons and is determined primarily by the rate and extent of four physiological processes: absorption, distribution, metabolism and excretion (ADME). For most substances used in therapeutic doses, the rate constants ($time^{-1}$) of these processes are apparently independent of the dose or concentration. For example, doubling of the dose is assumed to result in doubling of the exposure. When ADME are independent of changes in dose, this is referred to as first-order kinetics, and all processes can be quantified using rate constants (e.g. the absorption rate constant [k_a] and elimination rate constant [k_e]). However, this independence is only within a certain exposure range. The fundamental principles of mass-action imply that nearly all ADME processes for all substances will eventually be altered with increasing concentrations. Processes utilising specific proteins (enzymes and active transporters) are always capacity limited, and saturation will be readily noted with increasing dose. This will then manifest with a corresponding alteration in the plasma concentration-time profile. (The measured concentration of a poison in a blood sample can be a whole-blood, plasma or serum concentration. Plasma concentrations will be used in this review as they are most frequently measured. The actual concentration may be quite different with each method, but the principles outlined should apply to all). Dose-dependent saturation of absorption is probably protective in overdose, whereas saturation of clearance will increase the potential for toxicity.

2.1 Absorption

2.1.1 General Principles

Absorption describes the passage of a poison from outside the body through a biological barrier into the blood, where it becomes systemically available. A poison must be absorbed to cause systemic toxicity, and so any procedure that reduces absorp-

Table I. Factors influencing toxicokinetics in acute poisoning[3-11]

Poison	Patient	Pathophysiology
Absorption		
Exposure route of exposure dose/concentration acute, acute-on-chronic, chronic Physical form solid (immediate release, controlled release, seed), chewed or swallowed liquid Physicochemical properties pKa solubility	Age Total absorptive surface area, nutritional status, pre-existing diseases Saturability of transport proteins due to limited capacity (e.g. pharmacogenetic) or interfering substances Gastrointestinal milieu: food, enzymes, bacterial flora, pH Gastrointestinal motility Enterohepatic recirculation	Anticholinergic effects due to the poison or a co-ingestant (slows gut motility) Gastric irritation (increased gut motility) Hypotension or hypothermia causing hypoperfusion to the gut (prolonged and erratic absorption) Hypoxaemia
Distribution		
Dose/concentration Physicochemical properties pKa solubility	Age Nutritional status Pre-existing diseases[a], hypoalbuminaemia (increases V_d), uraemia (increases V_d) Saturability of transport proteins due to limited capacity (e.g. pharmacogenetic) or interfering substances Saturation of plasma protein binding due to limited binding capacity of the protein or interfering substances (increases V_d)	Disturbances in acid-base balance with alterations in protein and tissue binding Hypotension or hypothermia causing hypoperfusion to nontoxic compartments (e.g. adipose tissue), decreasing V_d
Elimination (metabolism and excretion)		
Dose/concentration Physicochemical properties pKa solubility	Age Nutritional status Pre-existing diseases[a] Changes in free concentration due to saturation of protein binding Altered function of metabolising enzymes (activating or deactivating) or transport proteins such as P-gp or OATP Induction or inhibition by concomitant poisons (including cigarettes) Genetic influences	Hypotension or hypothermia causing hypoperfusion to eliminating organs, e.g. liver and kidney (perfusion-limited metabolism) Saturation of metabolising enzymes (capacity-limited metabolism) Dose-dependent metabolic pathways, including co-substrate depletion Enzyme dysfunction due to hypoxaemia or metabolic dysequilibrium

a In particular, hepatic or renal dysfunction.

OATP = organic anion-transporting polypeptide; **P-gp** = P-glycoprotein (ABCB1); **pKa** = acid dissociation constant; **V_d** = volume of distribution.

tion is often assumed to be beneficial. However, an estimate of the extent of the reduction is required to determine if the benefit outweighs the risk of the procedure. With the exception of toxic gases/vapours, oral exposures are more often associated with systemic toxicity than inhalation, dermal or ocular exposures. The determinants of oral absorption kinetics are the rate of delivery and passage through the intestine, the extent of absorption from the lumen (incorporating dissolution, intestinal permeability and specific transporters) and first-pass metabolism (see section 2.3.5).

2.1.2 Changes in Gastrointestinal Transit Time

Most absorption occurs from the small intestine, which has a mean transit time of 3.3 hours.[12] Gastrointestinal absorption kinetics can also be altered by the clinical effects of the poison or the antidote (e.g. atropine), such as vomiting, diarrhoea, pylorospasm or ileus.[3,13-23] This can contribute to delayed or prolonged absorption and may secondarily influence the bioavailability of drugs with substantial

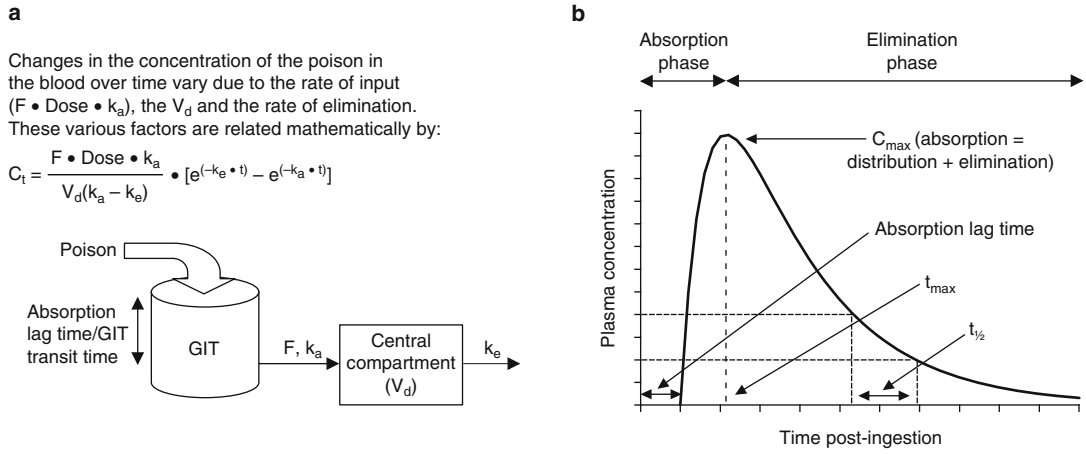

Fig. 1. Oral ingestion of a poison with single-compartment kinetics. (**a**) Schematic representation of a single-compartment model with oral exposure. (**b**) Concentration-time curve post-ingestion of a poison with single-compartment pharmacokinetics. If there is a true elimination phase, the curve during this time should be straight in a semi-logarithmic graph. The elimination rate constant (k_e) [see sections 2.3, 2.4 and 3.5] can be estimated in the elimination phase using the formula $\ln C_t = \ln C_0 - k_e \bullet t$, where C_0 is the initial concentration and C_t is the subsequent concentration after a known time (t). The half life ($t_{½}$) is determined by $t_{½} = 0.693/k_e$. Alternatively, the formula $t_{½} = 0.693 \bullet V_d/CL$ can be used when these variables are known and there are no dose-dependent changes in kinetics. In clinical toxicology, it is difficult to exclude the effect of ongoing absorption and distribution,[4] and so the $t_{½}$ is often expressed as the 'apparent plasma half-life' (see section 3.5). **CL** = apparent total body clearance; **C_{max}** = maximum observed concentration; **F** = bioavailability (see sections 2.3.5 and 3.1); **GIT** = gastrointestinal tract; **k_a** = absorption rate constant (see section 2.1.4); **t_{max}** = time to reach C_{max}; **V_d** = volume of distribution (see section 3.3).

first-pass metabolism. Marked reductions in gut motility are seen with overdose of carbamazepine, cholinergic receptor antagonists (anticholinergics), opioids and calcium channel antagonists. Hypotension and hypothermia reduce perfusion of the gastrointestinal tract, which impairs function (e.g. barbiturates). Inotropes or vasopressors may improve gut perfusion in such cases, but paradoxically also enhance absorption and potentially exacerbate clinical toxicity.

2.1.3 Influence of Formulation, including Pharmacobezoar Formation

Substances must be dissolved to be absorbed from the gut, and so absorption is more rapid for poisons in solution than for solid dosage forms. When multiple controlled-release tablets are ingested, the absorption phase may be even further prolonged and also erratic because the tablets aggregate into a mass (termed a pharmacobezoar), which unpredictably disintegrates and reforms. This has been noted with theophylline, diltiazem and carbamazepine. Pharmacobezoars are often characterised by delayed (or multiple) peaks and a prolonged time when plasma concentrations are close to the maximum concentration (C_{max}).[24] Similar absorption kinetics can be noted following ingestion of plant products due to the toxin being encased in a cellulose matrix; for example, partially chewed seeds.[13]

2.1.4 Rate of Absorption

Absorption is more rapid and complete for substances that readily penetrate cell membranes, notably small and nonionised molecules.[25] In general, absorption is more rapid than elimination and is complete within 1–2 hours of ingestion. Elimination occurs throughout this phase, and once elimination starts to exceed absorption, the C_{max} has been reached. The time when this occurs is known as the t_{max} (figure 1). The t_{max} may be significantly delayed in overdose when there is prolonged absorption. For example, this has been observed with tricy-

clic antidepressants,[4] phenytoin,[26] valproic acid,[27] moclobemide,[28] 4-chloro-2-methyl phenoxyacetic acid (MCPA)[29] and iron.[30] Possible contributing mechanisms are poor solubility (e.g. phenytoin[26] and aspirin [acetylsalicylic acid], although absorption of aspirin is also limited by gastric emptying[31]) or a saturable specific absorption mechanism (see section 2.1.5). However, the mechanism by which the rate of absorption is reduced is often poorly understood.

Some interventions may also alter absorption kinetics. Oral alkali coadministration increases the rate of absorption of aspirin due to improved tablet disintegration and passage to the duodenum without changing bioavailability (notwithstanding, dissolved aspirin is more readily absorbed in the stomach at an acidic pH).[31] Administration of activated charcoal may slow the rate of absorption because poisons are reversibly bound, although volunteer studies with pharmaceuticals usually demonstrate that charcoal simply decreases the amount of poison absorbed.[32-34]

Where the rate of absorption from the gut is slower than elimination, absorption kinetics will have the most influence on the observed plasma concentration-time profile. This is known as 'flip-flop' or 'absorption-dependent' toxicokinetics.[24] Flip-flop kinetics are most often observed with controlled-release medications and dermal exposures. However, they have been observed with injection of depot preparations and even with attempted intravenous administration when there has been significant extravasation. The apparent absorption/elimination half-life in such cases represents the sum effect of both processes.

2.1.5 Saturable Absorption

Some substances are actively absorbed via a specific transporter. Examples include iron,[30] gabapentin,[35,36] carotenoids,[37] ascorbic acid,[38] calcitriol[39] and methotrexate.[40-42] Because these processes are saturable, in overdose there is a relatively much smaller increase in the plasma concentration (and risk) than might be expected with the dose. However, the proportion of the dose absorbed may increase if there is reduced gut motility (due to more opportunity for absorption) or if multiple overdoses are taken over a long period. Apparently, saturable absorption has been seen for some other substances where there is no known specific transporter (e.g. yellow oleander [*Thevetia peruviana*][13] and lithium[43]). It is plausible that direct toxic effects on the gastrointestinal cells by some poisons may nonspecifically reduce absorption.

2.1.6 Dermal Absorption

The skin is designed to be a barrier, and few poisons penetrate the skin to a significant degree. Dermal absorption can be predicted using the physicochemical properties of the poison, its concentration, the duration of exposure and the health of the skin.[44] In general, even if a poison can penetrate the skin, it is incompletely absorbed and the t_{max} is delayed compared with the t_{max} noted with oral exposures. For example, the t_{max} for a major metabolite of the organophosphorus pesticide chlorpyrifos is 6 hours for an oral exposure compared with 24 hours for a dermal exposure. Despite being applied to the skin for 12 hours, less than 3% of the dose was recovered in the urine following a dermal application compared with 70% following the same dose administered orally.[45]

2.1.7 Clinical Applications

Estimates of the k_a are used when considering the likely efficacy of interventions to decrease absorption (e.g. activated charcoal). Therefore, a significant reduction in the bioavailable dose would not be expected for most liquid poisons and pharmaceuticals after 1 hour, whereas for controlled-release formulations, reduced absorption might be possible despite a delay of >24 hours. The therapeutic or observed t_{max} may be misleading in these circumstances with respect to whether absorption can be reduced. Poisons with slow absorption and relative-

ly rapid elimination may still have a substantial amount remaining for absorption after the peak concentration has been reached (see 'flip-flop kinetics' in section 2.1.4).

The absorption profile is also one factor used when predicting the likely time course of the onset of clinical toxicity following an acute exposure. In general, there is a rough correlation between the C_{max} and the occurrence of clinical toxicity, although there are important exceptions (see section 5.3).

There is a small risk of secondary poisoning of healthcare workers who treat patients with anticholinesterase nerve-agent poisoning, although previous experience suggests that this is limited.[46] Some people have assumed that this risk also applies to pesticide poisoning even though the factors required for significant dermal absorption (see section 2.1.6) are not fulfilled in the latter case. This is supported by the lack of documented cases of cholinesterase inhibition in this situation.[47,48]

2.2 Distribution

Most poisons are not confined to the blood and require some time to be distributed more widely. After a poison is absorbed, there are often relatively high concentrations in the blood before its distribution to other tissues. Toxicity may either closely reflect blood concentrations (e.g. cardiac ion channel-blocking drugs) or concentrations elsewhere (e.g. sedative drugs). Therefore, changes in the systemic distribution of a poison can increase or decrease toxicity.

2.2.1 General Principles

Distribution of a poison from the central circulation to peripheral tissues occurs concurrently with absorption and elimination, and this period is referred to as the disposition phase. The concept of pharmacokinetic compartments is a useful approach for understanding disposition kinetics, as shown in figure 2. Here, the blood is the central compartment and the tissues to which the poison is distributed are the peripheral compartments. Typically a poison is distributed faster than it is eliminated, which produces a concentration-time curve with a multi-phasic profile. As the number of compartments increases, the number of phases during elimination also increases. Figure 2 shows the concentration-time curve following oral administration of a poison with two-compartment kinetics and the corresponding biphasic elimination curve. This profile is observed for most poisonings.

Compartments are tissues that are functionally (rather than anatomically) discrete. This is based primarily on the differing rates and extent of tissue perfusion, the permeability of the tissue's cell membrane and partitioning of the drug between the tissues and the central compartment (blood).[51] The extent to which a molecule is distributed from the central compartment is determined largely by lipophilicity and molecular weight.[52,53] Because small lipid-soluble molecules diffuse rapidly across cell membranes, their rate of distribution is determined by perfusion (flow-limited); in contrast, distribution of larger or polar molecules is diffusion-limited.[5,52] For some poisons, the rate of distribution into multiple anatomically discrete regions (adipose, skeletal muscle, interstitial fluid, etc.) is so rapid that the toxicokinetic profile may be considered single-compartment (figure 1).

Because the rate of distribution differs between such compartments, this will be reflected in the time course and risk factors for clinical toxicity. The specific time course of toxicity depends on the rate of distribution to and from the 'toxic effect' compartment. If the 'toxic effect' compartment is in close equilibrium with the plasma (the central compartment), then the onset and duration of toxicity will relate to absorption and clearance, respectively. Where the 'toxic effect' compartment is located peripherally, the onset and recovery relate to the

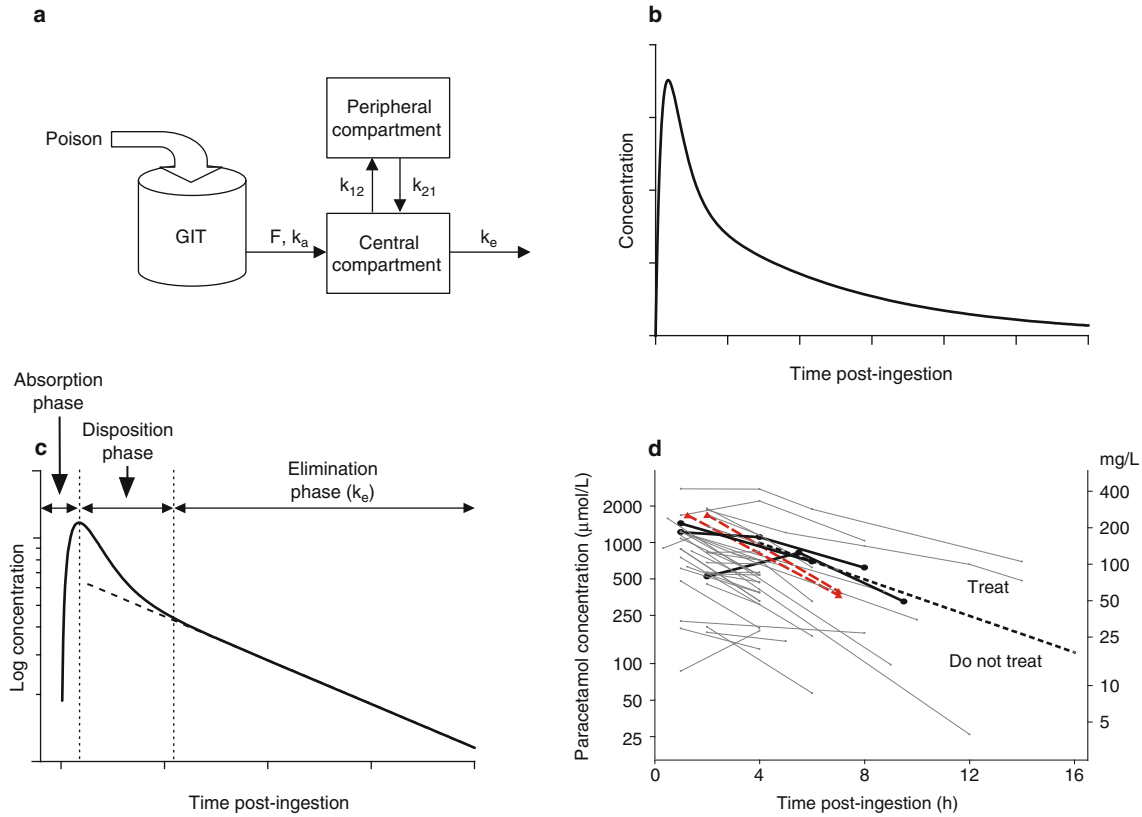

Fig. 2. Multicompartment kinetics following oral ingestion. (**a**) Simplified two-compartment kinetic model with oral administration. The mathematical formula that describes the rate of change in the concentration with time in this relatively simple model is particularly more complex than that in figure 1a, and so it has been omitted. An increase in the number of compartments greatly increases the complexity of the model and the associated formulae. (**b**) Concentration-time curve corresponding to the model in (a), showing a biphasic decrease in the plasma concentration (standard cartesian plot). Note that it is difficult to differentiate between this biphasic graph and a monophasic graph (figure 1b) with this plot. (**c**) Semi-logarithmic plot of the same data shown in (b). Note that a biphasic decrease is now readily apparent. The plot is divided into three phases and the dominant process is indicated. However, it should be noted that in reality there are probably other coexistent processes (during the absorption phase both distribution and elimination occur; similarly, the disposition phase represents both distribution and elimination). The elimination half-life is determined as in figure 1a in the elimination phase. (**d**) Changes in paracetamol (acetaminophen) concentrations within the first 4 hours post-ingestion. Note that on re-testing at 4 hours, the potential for risk (based on extrapolation of the current treatment line [thick black dashed line][49] to earlier times) had changed for some patients. Three patients (thick black solid lines) required treatment with *N*-acetylcysteine while two patients (thick red dashed lines) did not. It is interesting to note the differing apparent elimination half-lives between patients; some alternated between the 'treat' and 'do not treat' areas, the clinical significance of which is not known. Data obtained from Buckley et al.[50] **F** = bioavailability (see sections 2.3.5 and 3.1); **GIT** = gastrointestinal tract; $\mathbf{k_a}$ = absorption rate constant (see section 2.1.4); $\mathbf{k_e}$ = elimination rate constant (metabolism and/or excretion; see sections 2.3, 2.4 and 3.5); $\mathbf{k_{xy}}$ = distribution rate constant from compartment *x* to *y* (see section 2.2).

rates of distribution from and redistribution to the central compartment, respectively.

Lithium

Lithium is a small molecule that is distributed widely in the extracellular fluid (similarly to sodium), with significant toxicity being mediated primarily in the CNS.[4,43,54] The rate of distribution of lithium from the central compartment (plasma) to interstitial fluids plus clearance is more rapid than distribution to the brain.[55] Therefore, despite high initial plasma concentrations in acute poisonings, if

renal function and hydration are normal, lithium concentrations fall to nontoxic levels by distribution into other body tissues and renal excretion before equilibration can occur with the CNS.[54] Therefore, the central neuronal concentrations are rarely elevated to a significant extent. In chronic poisoning, however, blood concentrations are high for an extended duration, allowing much more lithium to penetrate the CNS.[43] This explains clinical experiences that acute overdoses of lithium rarely cause significant CNS toxicity and also the prolonged duration of CNS toxicity with lithium even after concentrations in the plasma have fallen.[54]

Tricyclic Antidepressants

Tricyclic antidepressants are an important cause of mortality from self-poisoning.[56,57] Tricyclic antidepressants induce multisystem toxicity, but severe cardiovascular toxicity due to inhibition of cardiac sodium channels is an important mechanism of toxicity.[56] Induction of alkalinaemia with sodium bicarbonate or hyperventilation is a recommended treatment for severe toxicity, although the mechanism of action is poorly defined.[58,59] It is theorised that alkalaemia reduces the free concentration of the drug either by increasing the distribution of these lipophilic weak bases from the central (toxic) compartment to one that is nontoxic, or by increasing protein binding.[60,61] The net effect of these mechanisms is a decrease in the concentration in equilibrium with cardiac sodium channels; unfortunately, data confirming this apparent mechanism are sparse. Alkalaemia also appears to increase protein binding to α_1-acid glycoprotein, to which it usually binds,[62] but also to albumin, due in part to changes in the conformation of this protein with increasing pH.[63] Other animal studies and clinical reports of severe tricyclic antidepressant poisoning have reported prompt clinical improvement, particularly narrowing of the QRS duration on ECG, with use of sodium bicarbonate.[58,59] This may also reflect increased distribution of the drug given that the QRS duration roughly correlates with the concentration of the tricyclic antidepressant;[64,65] more mechanistic data would be useful in these and other studies. However, there is much debate regarding the relative effect of the sodium component and other effects of pH on sodium channels and nerve function on these outcomes.[59]

2.2.2 Transport Proteins

There are a number of transport proteins that contribute to systemic distribution (as well as absorption and clearance) of some poisons, in particular P-glycoprotein (P-gp; ABCB1) and organic anion-transporting polypeptides (OATPs). There are genetic polymorphisms affecting the activity of these proteins, which probably contribute to interindividual differences in toxicokinetics. There are also a number of clinically relevant drug interactions reported, indicating that their capacity is both saturable and modified by environmental factors.[6] For poisons transported by these proteins, this implies that both the rate and the extent of distribution may be altered in overdose.

2.2.3 Blood pH

Distribution kinetics may be influenced by the blood pH. This is particularly noted in weak acids with a low acid dissociation constant (pKa), such as aspirin (3.5) and chlorophenoxy herbicides (2.8–3.3), where the proportion of the poison that is nonionised (not charged) increases with acidaemia. This form more readily crosses cellular membranes, distributing from the central to the peripheral compartment(s).[66-68]

The clinical manifestations of a poison may induce subsequent changes in its own distribution kinetics. For example, aspirin and chlorophenoxy herbicides both induce an initial respiratory alkalosis but subsequently cause metabolic acidosis by uncoupling of oxidative phosphorylation. The acidosis in turn increases intracellular concentrations of the poison and hence the degree of uncoupling as

well as other manifestations of clinical toxicity. In these cases, treatment is directed to correcting the pH.[29,69] Conversely, hypotension or hypothermia due to drugs such as barbiturates may reduce organ perfusion and reduce distribution to nontoxic compartments such as adipose tissue (table I).

2.2.4 Protein Binding

Generally, only a poison that is unbound to plasma proteins ('free') can be distributed beyond the central compartment, and so protein binding is an important consideration in distribution kinetics.[124,125] Further, since only the free concentration of a poison can exert a toxic effect, binding to plasma proteins or tissues leaves the poison functionally inactive. But as the plasma concentration of a poison increases, the binding capacity of plasma proteins can become saturated, an effect that is compounded by low protein states. The resulting increased ratio of free **:** bound poison increases the proportion that is available for distribution from the central compartment, and this increases the volume of distribution (V_d, see section 3.3). The effect on the V_d is limited if endogenous clearance is relatively rapid and not capacity-limited, due to the prompt removal of unbound poison. Where clearance cannot compensate for saturation of protein binding, the increased ratio of free **:** bound poison will persist and the V_d can increase. Because the elimination half-life is proportional to the V_d (see section 3.5), an increase in concentration beyond that where protein binding is saturated produces a biphasic convex semi-logarithmic concentration-time curve (similar to that seen with saturated elimination, as discussed later).[7,126] This has been noted to occur with salicylates such as aspirin[31] and chlorophenoxy herbicides,[122] and these principles are demonstrated in the case of chlorophenoxy herbicides in figure 3.

2.2.5 Clinical Applications

Risk Assessment During the Distribution (And Absorption) Phases

Plasma concentrations change rapidly and unpredictably during the absorption and distribution phases (figure 2), and so it is not possible to estimate the bioavailable dose from the measured concentrations during this time. Many nomograms (e.g. those for paracetamol [acetaminophen] and paraquat) estimate the dose from the plasma concentrations obtained and thus usually suggest that concentrations should not be measured within 4 hours (figure 2d).[49,121] In the case of paracetamol, the t_{max} is noted 60–90 minutes post-ingestion, but it was decided to use a prediction line from 4 hours post-ingestion to account for changes in gastric emptying from the co-formulant propoxyphene.[49] Similarly, digoxin has a distribution phase of >6 hours following oral administration (3 hours for intravenous administration) and so concentrations should be determined after this time for a proper estimate of systemic exposure.[136,137] There is also an additional delay to the onset of clinical effects, which is attributed to slow receptor binding.[138]

Movement from the 'Toxic Effect' Compartment

Distribution of a poison from the site of toxicity (the 'toxic effect' compartment, generally known as the biophase) to one that is nontoxic (a 'depot compartment', e.g. adipose tissue, tissue binding, or even the central compartment for some poisons) can decrease clinical toxicity. Reduction of the concentration of a poison in the 'toxic effect' compartment is the basis for many treatments that involve altering the blood pH. Alkalinisation is commonly used in the treatment of significant poisoning with weak bases such as tricyclic antidepressants[59] and weak acids such as aspirin[69] or chlorophenoxy herbicides.[29,139] For weak bases, the volume (and rate) of distribution is increased with alkalinisation (the free plasma concentration decreases), whereas the converse is true of the weak acids.[66-68] However, the

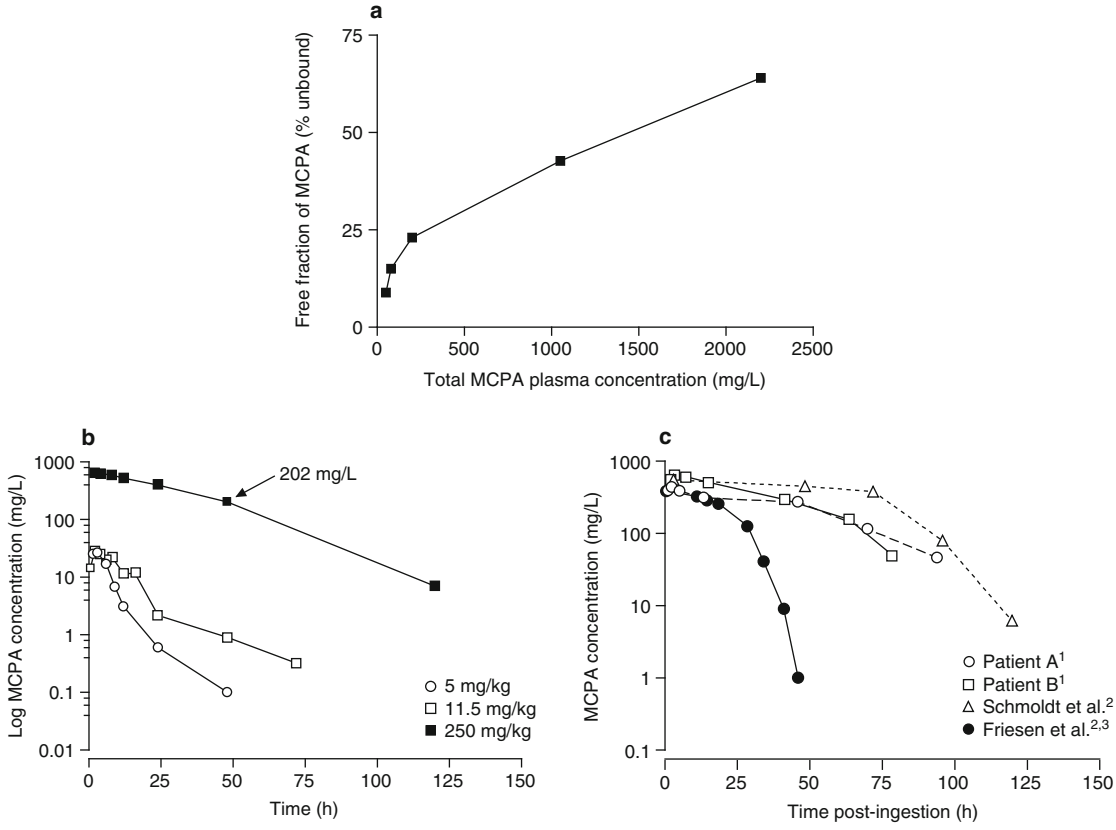

Fig. 3. Toxicokinetics of the chlorophenoxy herbicide 4-chloro-2-methyl phenoxyacetic acid (MCPA) in acute exposures, demonstrating saturation of protein binding. (**a**) Saturation of protein binding of MCPA in rats *in vitro*. There is an increase in the free concentration of MCPA as the total concentration increases.[127-130] This is due to saturation of protein binding, which occurs when the total MCPA concentration is ~250 mg/L. Plasma concentrations exceeding this concentration where there is saturation of protein binding are readily observed in patients presenting with acute intentional self-poisoning.[29] (**b**) Semi-logarithmic concentration-time profiles following a single dose of MCPA in rats. A convex biphasic elimination curve is noted in animals administered high-dose MCPA (250 mg/kg)[127] compared with lower doses (5 mg/kg[131] and 11.5 mg/kg[132]). The concentration of the inflection roughly correlates with the point where there is saturation of protein binding (a). The prolonged initial phase probably also suggests saturation of elimination because otherwise elimination would be expected to increase. (**c**) Acute chlorophenoxy herbicide exposures in humans, demonstrating a biphasic convex elimination curve. **1** = Patients treated with supportive care, including intravenous fluids, but not urinary alkalinisation or forced diuresis.[133] **2** = Patients described in the literature who were treated with urinary alkalinisation ± diuresis.[134,135] In these cases (and others in the literature), there was a decrease in the apparent elimination half-life at approximately the time when urinary alkalinisation was commenced. It was concluded by the investigators in these cases that urinary alkalinisation was an effective means of enhanced elimination; however, the probable contribution of saturated protein binding to the profile was not considered. Because the change in urinary clearance of the chlorophenoxy herbicide in these patients was not widely assessed (e.g. the amount of chlorophenoxy herbicide in the urine), the true effect of urinary alkalinisation for enhanced elimination is not known.[122] **3** = Time of poisoning unknown.

'toxic effect' compartment of these drugs is also the opposite. Alkalinisation reduces cardiac toxicity from tricyclic antidepressants because it increases distribution from the central compartment where tricyclic antidepressants bind to cardiac ion channels and other receptors. Alkalinisation appears to reduce the toxicity of weak acids such as salicylates by reducing distribution to the peripheral 'toxic effect' compartment – the CNS and intracellular mitochondria.[4,66-68] The rapid effect of Fab antitoxins

and chelating drugs is due not to enhanced elimination from the body, but to redistribution and reduced free concentrations (table II).[70]

Impact of Distribution on Elimination

Treatments to enhance elimination only remove poison from the blood. The effect of these treatments on overall (systemic) elimination, or elimination from the 'toxic effect' compartment, is often determined by the rate and extent of distribution. In some cases, systemic elimination is entirely dependent on the rate of redistribution back from the peripheral compartments. For example, lithium is slowly redistributed from the 'toxic effect' compartment (the CNS) back to the central compartment.[55] Haemodialysis rapidly decreases the lithium concentration in plasma, but CNS concentrations may remain toxic for many days.[43] Similarly, with methotrexate, much of the drug remains in the intracellular space and is slowly redistributed to the plasma, and so enhanced elimination methods are unlikely to significantly increase systemic clearance.[140] Haemodialysis for paraquat poisoning in dogs increases elimination and reduces lethality if commenced during the distribution phase but is ineffective after a few hours when paraquat has been distributed into lung tissue.[141] The V_d is generally large for organophosphorus pesticides, although it varies between individual compounds, which may influence the clearance achieved with extracorporeal techniques.[142]

2.3 Metabolism

2.3.1 General Principles

The liver is not the only organ involved in metabolism, but it is the main one, and so this article focuses on hepatic metabolism; similar principles apply to all metabolism. Common hepatic metabolic pathways include those of the cytochrome P450 (CYP) system (phase I reactions, particularly oxidation, reduction and de-esterification)[143] and conjugation (phase II reactions) with glutathione or glucuronic acid or sulphate. These phase II reactions increase polarity and/or molecular weight, which has the general effect of decreasing the V_d and/or increasing elimination of the poison. While phase I reactions are generally detoxification reactions, some compounds are activated by metabolism to a compound that may be more active than the parent. In this context, these parent compounds are called pro-poisons, and examples include paracetamol,[49] codeine,[144] 1-4 butanediol,[145] organophosphorothioate pesticides,[146] dapsone (figure 4)[113,147] and propanil.[148-150] Other bioactivation reactions incompletely convert one poison to another, with the potential to induce different clinical effects, for example aspirin,[31] propanil,[149,151] thioridazine,[152] ethylene glycol,[153] methanol[111] and pethidine (meperidine).[154,155]

2.3.2 Capacity-Limited Metabolism

Enzymatic metabolism of poisons may be saturable in a dose-dependent manner, which is known as capacity-limited metabolism. The relationship between the poison's concentration and enzyme activity is described by Michaelis-Menten kinetics (figure 5). When the substrate's concentration is less than the Michaelis-Menten constant (Km), then metabolism is approximately first order (the rate of metabolism is proportional to the concentration). With further increases in concentration, there is a progressive decrease in the rate of the increase in metabolism until the enzyme is saturated. At this point, metabolism is maximal and elimination is regarded as zero order or concentration independent. Capacity-limited metabolism is not observed at therapeutic concentrations of most drugs.[5] In overdose, capacity-limited metabolism would be expected to prolong elimination, which increases exposure, and well described examples of this include alcohol (ethanol), phenytoin, theophylline and aspirin. Following a single 3g oral dose of aspirin, two of the five routes of clearance are saturated (and there is also

Table II. Toxicokinetic interventions used in clinical toxicology

Intervention	Mechanism[70]	Poisons for which it has been used	Adverse effects
Forced emesis, e.g. ipecac-induced,[71] soap-water,[72] large volume of fluid[73]	Decreased bioavailability by decreasing the amount of a poison absorbed from the gastrointestinal tract (most effective for poisons that are slowly absorbed from the gut)	Nonspecific Generally considered for use with poisons that are not expected to decrease the level of consciousness	Prolonged vomiting, electrolyte abnormalities, aspiration
Gastric lavage[74]		Nonspecific May be more useful in liquid ingestions	Electrolyte abnormalities, aspiration
Activated charcoal 1–2 g/kg orally as a single dose		Nonspecific Poisons are reversibly adsorbed to charcoal in the gastrointestinal tract Consider the poison's affinity for charcoal, which depends on its size, charge and potentially other co-ingestants Efficacy is decreased if the dose is inadequate[32,33] Efficacy is decreased when administered more than 1h post-ingestion[33,75]	Nausea, vomiting, transient abdominal pain and aspiration (rare) Coadministration with orally administered antidotes may reduce their efficacy[76]
Fullers earth[77,78]		Paraquat	
Whole bowel irrigation (~2 L/h orally of an isotonic solution such as polyethylene glycol until the rectal effluent is clear)[79]		Nonspecific Consider with large ingestions of controlled-release formulations[24] or poisons where there are limited options for gastrointestinal decontamination, such as iron	Mild electrolyte and acid-base abnormalities
Competitive inhibition of absorption from gastrointestinal tract		Oral folic or folinic acid (leucovorin) for methotrexate (this is a theoretical interaction given that saturable absorption has been observed with increasing oral doses of both methotrexate[40-42] and folinic acid)[80] It should be noted that these agents also alter the distribution of methotrexate, which may interfere with clinical studies assessing this interaction[81]	
Chelation in gastrointestinal tract		Calcium for fluoride, resonium for potassium and lithium	

Continued next page

Table II. Contd

Intervention	Mechanism[70]	Poisons for which it has been used	Adverse effects
Urinary alkalinisation, target urine pH >7.5[82-84]	Enhanced elimination of the unchanged poison (most effective for poisons with single-compartment kinetics or multicompartment kinetics with fast redistribution to the central compartment, slow endogenous clearance (<4 mL/min/kg) and a small V_d (<1 L/kg) Note that nonspecific treatments may also increase clearance of an antidote, thus requiring dose adjustment	Nonspecific Most effective if: weakly acidic (pKa 3.5–7.4) significant renal excretion	Electrolyte abnormalities, hypercarbia, vasoconstriction
Multiple-dose activated charcoal, e.g. 1 g/kg orally every 4 hours[85,86]		Nonspecific Most effective if: enterohepatic circulation prolonged absorption (e.g. controlled-release products) poorly bound to plasma proteins	Transient constipation or occasional bowel obstruction, vomiting, aspiration
Haemodialysis[87-89] a		Nonspecific Most effective if: molecular weight <500Da water soluble poorly bound to plasma proteins	Procedural complications,[b] electrolyte abnormalities
Haemoperfusion[87-89,97] a		Nonspecific Most effective if: adsorbed by activated charcoal[c] poorly bound to plasma proteins	Procedural complications,[b] thrombocytopenia, leukopenia, hypocalcaemia[d]
Haemofiltration[88,89] a		Nonspecific Most effective if: molecular weight usually <40 000Da poorly bound to plasma proteins	Procedural complications,[b] electrolyte abnormalities
Molecular adsorbents recirculating system[99]		Nonspecific Most useful for drugs with significant protein binding Efficacy is inversely proportional to protein binding and depends somewhat on the membrane permeability and affinity for charcoal of the poison, and may not exceed the individual effect of these treatments[100,101]	Procedural complications,[b] electrolyte abnormalities
Plasmapheresis (similar principles apply to blood exchange transfusions)[88,102]		Nonspecific Consider if lipophilic and highly protein-bound	Procedural complications,[b] electrolyte abnormalities, transfusion-associated reactions

Continued next page

Table II. Contd

Intervention	Mechanism[70]	Poisons for which it has been used	Adverse effects
Chelating agents		Desferrioxamine for iron Hydroxocobalamin for cyanide Succimer for lead, arsenic and mercury	Also chelates similar metals in the body, e.g. calcium, iron, copper, etc.
Antibodies, e.g. Fab fragments[103]		Plant poisons;[104] in particular, *Thevetia* and *Digitalis* cardenolides[105] Pharmaceuticals[103,106] Snake envenomation[107] Spider envenomation[108]	Acute hypersensitivity Incidence and severity varies depending on the purity of the product and individual sensitivity Immune-complex reactions, particularly with large doses
Oxygen[109]		Carbon monoxide	
Forced diuresis[82]		Nonspecific Most effective if significant renal excretion	Fluid overload with pulmonary oedema, electrolyte abnormalities[110]
Inhibition of alcohol dehydrogenase, e.g. alcohol (ethanol) or fomepizole (4-methylprazole)	Decreased metabolic bioactivation to a toxic product	Toxic alcohols[111,112]	Dysphoria from alcohol
Inhibition of cytochrome P450, e.g. cimetidine		Dapsone,[113-117] paracetamol (acetaminophen)[118]	Drug-drug interactions
Glutathione donators, e.g. *N*-acetylcysteine, methionine	Increased metabolic deactivation	Paracetamol,[119,120] paraquat[121]	Anaphylactoid reactions
Thiosulfate		Cyanide	
Chelating agents and antibodies	Redistribution from the 'toxic effect' compartment	(As above)	
Alkalinisation, e.g. sodium bicarbonate or hyperventilation		Tricyclic antidepressants,[59] salicylates, chlorophenoxy herbicides[122]	Electrolyte abnormalities, hypercarbia, vasoconstriction
Methaemoglobin-inducing agents such as 4-dimethylaminophenol		Cyanide[123]	Tissue hypoxia (dose-related)

a Clearance is influenced by the flow rate[90] and blood pressure.[89,91] In general, if a compound is adsorbed by charcoal, clearance is higher by haemoperfusion than by haemodialysis,[89] although recently high-flux haemodialysis for carbamazepine has generated clearances that compared favourably with haemoperfusion.[92-94]

b Complications include damage to vessels from attempted cannulation,[95] and hypotension, blood loss, haematomas, air embolism and metabolic disequilibrium such as electrolyte changes may be noted with these techniques.[89] Electrolyte changes are less likely with haemoperfusion.[87] Initial clinical improvement may be followed by deterioration with a rebound in plasma drug concentrations with haemoperfusion and high-flux haemodialysis/haemofiltration,[89,91,96] which may be avoided with continuous techniques.[90]

c The cartridge becomes saturated with the poison after a certain period of use, noted when the concentration difference between the inlet and outlet decreases, at which point a replacement cartridge is required.[87]

d Decreased with coated charcoal cartridges.[95,98] The platelet count usually decreases by 30–50% after each 4- to 8h haemoperfusion treatment.[89]

pKa = acid dissociation constant; $\mathbf{V_d}$ = volume of distribution.

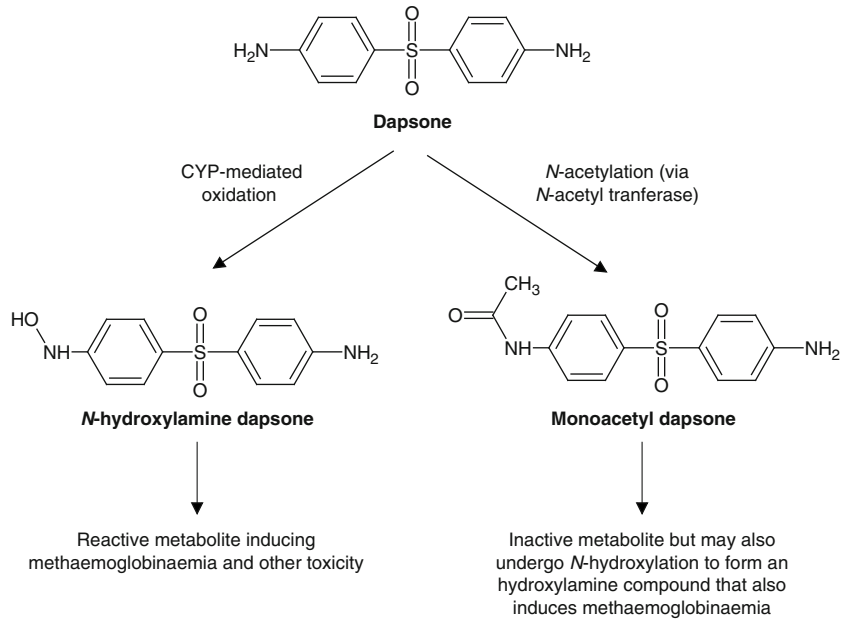

Fig. 4. Metabolism of dapsone *in vivo*. The rate of these competing metabolic reactions varies between individuals[156-160] and, from experience with therapeutic dosing of dapsone, patients in whom there is rapid hydroxylation and slow acetylation appear to be more susceptible to toxicity.[156] Inhibition of multiple cytochrome P450 (CYP) enzymes using cimetidine appears to decrease toxicity in animals[113,114] and with therapeutic use of dapsone,[116,117] presumably due to decreased production of the *N*-hydroxylamine metabolite. Treatment with cimetidine also decreases clearance so that plasma concentrations are elevated,[115-117] which does not lead to other markers of toxicity.

saturation of protein binding).[161] In humans, the Km of alcohol dehydrogenase metabolism of alcohol is approximately 2.71 mmol/L (≈0.01% alcohol in whole blood) although there are two isoforms, which differ in their affinity. Ethanol clearance will increase nonlinearly with concentrations beyond these, approaching a maximum rate (V_{max}) of 7–8g (or less than one standard drink) per hour.[5,7]

The Michaelis-Menten curve depicts changes in enzymatic activity with the dose and is shown in figure 5a. The implications of such nonlinear kinetics are demonstrated in figures 5b and 5c, using the example of phenytoin. Note that in figure 5b, a biphasic convex curve is produced with large exposures due to reduced clearance at correspondingly high concentrations.

Metabolic clearance of theophylline is noted to be partially saturated at therapeutic doses,[162,163] and it has nonlinear clearance. Clearance is greatly reduced in overdose, which presumably relates to complete saturation of CYP1A2. A biphasic convex curve has also been noted following acute theophylline poisoning because of the initial saturation of metabolic clearance, similar to phenytoin in figure 5b.[7,164,165] Interestingly, saturable clearance was not noted in earlier volunteer studies (therapeutic dosing) that utilised plasma concentrations because of an initial increase in renal clearance secondary to xanthine-induced diuresis.[162,163,166] This highlights the importance of measuring the change in clearance in multiple organ systems when exploring dose-dependent pharmacokinetics.

Altered metabolic clearances have also been noted for other poisons in overdose, although the mechanism is not well described. However, most poisons

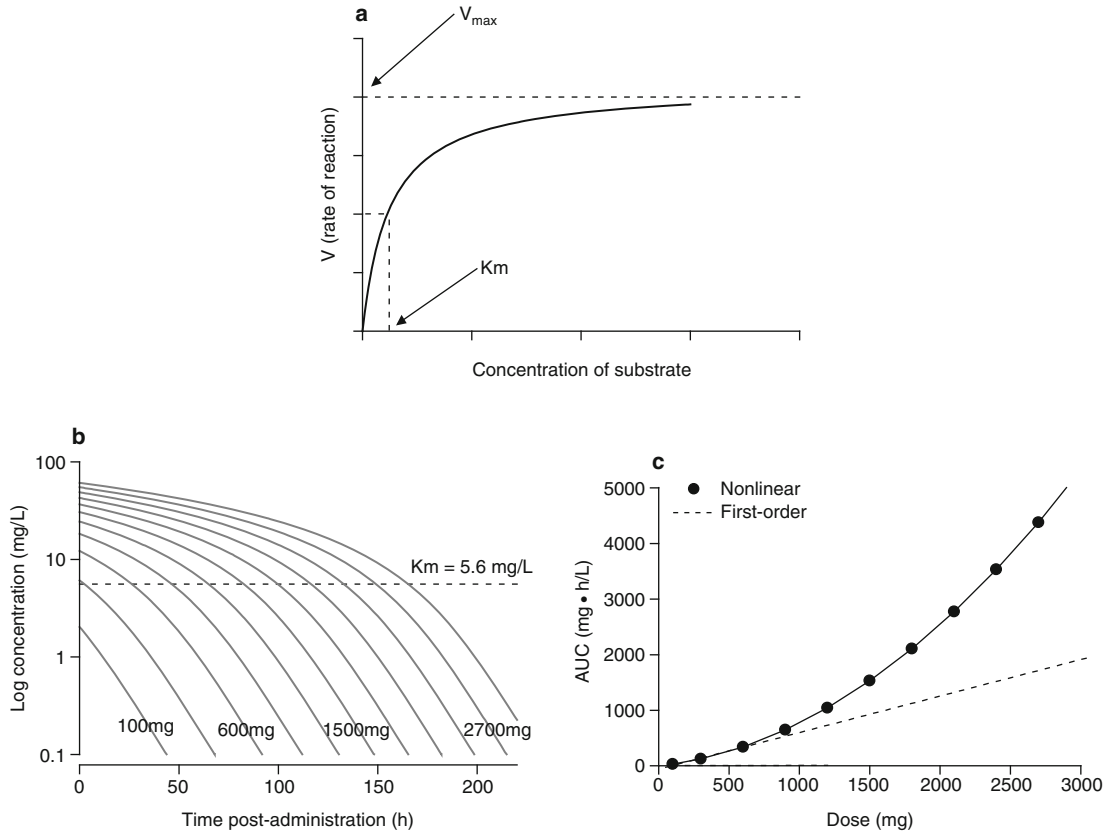

Fig. 5. Nonlinear elimination due to saturable enzymes. (**a**) Changes in the rate of reaction that is saturable: Michaelis-Menten kinetics. The Michaelis-Menten curve shows how the rate of an enzymatic function (e.g. oxidation by the cytochrome P450 system or active excretion by P-glycoprotein) is relative to the concentration of the poison. It is described by the formula $V = (V_{max} \bullet C_p)/(Km + C_p)$, where V_{max} is the maximum rate of the reaction, Km (Michaelis-Menten constant) is the concentration at which the reaction proceeds at half of the V_{max}, and C_p is the concentration of the poison. When $C_p < Km$, the reaction is approximately first-order and clearance (CL) by that mechanism can be calculated by $CL = V_{max}/Km$. When $C_p > Km$, the capacity of the process approaches saturation such that clearance becomes nonlinear until it reaches the V_{max}, and this is known as zero-order kinetics. The best-studied examples of drugs displaying saturable metabolism are phenytoin, alcohol (ethanol) and conjugation of aspirin. The effect of saturable elimination of phenytoin is shown in (b). (**b**) Effect of the dose on the observed concentration-time profile in a poison with saturable elimination: the example of phenytoin. These data were simulated on the basis of intravenous administration of phenytoin in a 70kg patient using the Michaelis-Menten values: V_{max} = 20.4 mg/h, Km = 5.6 mg/L and V_d = 0.693 L/kg, which was assumed to be fixed at this dose range.[7] Note that the initial elimination phase is nonlinear for doses of >300mg until the concentration is approximately less than the Km, when linear (parallel decay curves) are noted. (**c**) Effect of the dose on the area under the concentration-time curve (AUC) in poisons with linear or nonlinear pharmacokinetics. Note a disproportionate increase in the AUC as the dose increases, which is representative of nonlinear elimination; data obtained from phenytoin simulations in (b) and a proportional increase in the AUC with the dose, which is representative of first-order elimination.

have not been studied in sufficient depth to categorise when and to what extent this occurs.

It is worth noting that not all poisons with low hepatic extraction have capacity-limited metabolism and zero-order kinetics. For many of these substances, diffusion of the drug or co-substrate (e.g. oxygen) to the enzyme appears to be the rate-limiting factor.[167] If diffusion of the poison is the only rate-limiting factor, then increasing concentrations should lead to a linear increase in elimination.

2.3.3 Perfusion-Limited Metabolism

When the metabolic capacity of the liver for a poison is not limited, a high proportion of the amount delivered is extracted. In these cases, the factor with the greatest influence on systemic clearance is the amount of blood flow to the liver, which is known as perfusion-limited metabolism. In such cases, systemic clearance varies with organ perfusion, and this depends on the cardiac output and blood pressure.

Poison-induced hypotension and hypothermia may impair the clearance of a poison with perfusion-limited metabolism and prolong toxicity (table I). For example, large ingestions of propranolol, diltiazem and many barbiturates produce marked hypotension and are thereby expected to impair their own clearance. Close attention to resuscitation and supportive care measures that improve blood pressure can improve clearance (if the metabolic pathway is not already capacity limited), which may, therefore, facilitate recovery. Where severe hypotension due to cardiovascular toxicity is refractory to pharmacological interventions, external mechanical assistance may improve perfusion of end organs and hence clearance of the poison.[58] This is supported in animal studies of severe poisoning with lignocaine (lidocaine), pentobarbital, verapamil and tricyclic antidepressants.[58,168] Successful use of mechanical cardiac bypass in the management of severe acute poisoning has been reported for a number of poisons exerting cardiovascular toxicity.[168-171]

2.3.4 Dose-Dependent Metabolic Pathways, including Co-Substrate Depletion

The proportion of a dose that is metabolised, and the pathway by which this occurs, can change as the dose increases. This may relate to changes in protein binding where there is an increase in the free concentration or changes in enzymatic capacity. Paracetamol conjugation pathways appear to become saturated with high doses so that the elimination half-life is prolonged and an increasing proportion of the drug is metabolised by CYP enzymes to the toxic metabolite *N*-acetyl-p-benzoquinoneimine (NAPQI).[5,49,172] The relative importance of renal elimination for salicylates is increased in overdose because the metabolic conjugation pathways for salicylates are readily saturated at supratherapeutic doses.[161] Methanol is metabolised to formaldehyde and formic acid; further metabolism of these toxic products in overdose is capacity limited, which is further limited by a deficit of the co-substrate folic acid.[173-175]

2.3.5 First-Pass Metabolism

Bioavailability refers to the proportion of a dose that reaches the systemic circulation, and in the case of oral ingestion it is limited by first-pass metabolism.[8] Thus the bioavailability of drugs that are extensively extracted is low, and their doses are increased in therapeutic use to account for this. For some drugs, such as naloxone, first-pass metabolism is so extensive that it precludes oral administration.[176]

Despite the high capacity of these enzymes, in overdose the extremely high concentration in the portal blood circulation during the absorption phase can saturate the first-pass metabolism. This leads to a much greater than expected increase in the bioavailable dose.[8] For example, the bioavailability of verapamil is usually <30% because of high hepatic extraction, but this increases at higher doses due to saturation of hepatic microsomes.[177] For example, at steady state the bioavailability of verapamil was noted to increase >2-fold as the dose administered to volunteers increased, with a correspondingly disproportionate increase in the plasma concentrations.[178] Other examples of saturation of first-pass metabolism include diltiazem,[179] propranolol[180,181] and sertindole.[182]

2.3.6 Clinical Applications

An appreciation of the magnitude of dose-dependent changes in metabolism would be useful in the process of risk assessment. Unfortunately, however, there are few specific data to quantify these relationships. The hazards of large doses of oral chlormethiazole in patients with alcoholic cirrhosis is an example of the potential magnitude of such changes and its clinical significance.[183] The bioavailability of even normal doses increases 10-fold in patients with cirrhosis compared with healthy volunteers due to a reduction in the very high first-pass effect.[184] Such changes probably contribute to the steep dose-toxicity relationship of many poisons with very high first-pass metabolism, including propranolol, calcium channel antagonists, tricyclic antidepressants, quinidine, ergotamine and propoxyphene.[8]

Enhanced elimination of a poison by enzyme induction may be theoretically useful; however, it is generally not possible to induce metabolism within a useful timeframe for acute poisoning, since most mechanisms of induction require a minimum of 24–48 hours to take effect. However, for poisons with toxic metabolites, it may be therapeutic to block particular pathways of metabolism. The most widely used example of this approach is the treatment of methanol or ethylene glycol poisoning where blocking of alcohol dehydrogenase by alcohol or fomepizole reduces toxic metabolite production.[111,153]

Similarly, serendipitous paracetamol and alcohol co-ingestion appears to reduce production of NAPQI.[185-187] Animal studies suggest that such strategies might be more widely applicable. For example, cimetidine reduces methylparathion toxicity,[188] cimetidine pre-treatment prevents paracetamol hepatotoxicity[118] and dapsone-induced methaemoglobinaemia (figure 4),[113,114] and fomepizole decreases toxicity from 1,4-butanediol.[145] Translation of these outcomes into routine clinical use has the substantial limitation that patients must present and be treated prior to most of the poison being metabolised to toxic metabolites.

Variability in the activity of A-esterases may influence outcomes in patients exposed to organophosphorus pesticides.[189,190] For example, genetic polymorphisms of paraoxonase (PON1)[190] or inhibition of carboxylesterase by trace contamination with isomalathion[191,192] are both associated with increased toxicity. Similarly, induction by chronic alcohol use may increase toxicity from paracetamol,[49,185] as may polymorphisms inducing a deficiency in the enzyme uridine diphosphate glucuronosyltransferase.[193,194] In the case of theophylline, there are substantial interindividual differences in clearance, but this relates more to variations in the enzymatic Km than to the V_{max}.[162] In the case of the latter, it is likely that interindividual variations in clearance will be more obvious at therapeutic doses than post-overdose.

2.4 Excretion

2.4.1 General Principles

Excretion refers to the removal of a poison or metabolite from the body. It usually occurs via the biliary or renal system, although respiratory clearance may be significant for some poisons, such as phosphine. Excretion is usually, but not always, irreversible. Enterohepatic recirculation refers to the process by which a poison (or its conjugated metabolite) is excreted via the biliary tree and then reabsorbed. In some cases, this requires bacteria to cleave the conjugate. This may lead to prolonged and variable elimination of the poison, with a decrease in the apparent clearance.[22]

For the sake of simplicity, this article focuses on renal excretion, but similar dose-related principles affect biliary and other modes of excretion. A poison is renally excreted by either passive filtration in the glomerulus or active secretion at the proximal tubule. There may also be both active and passive reabsorption from the tubule, and active reabsorp-

tion is rarely saturable (e.g. riboflavin[195]). Passive reabsorption may vary with the filtrate pH and flow rate, and manipulation of these has been used to enhance elimination in poisoning. Clearance may be reduced where there is poison-induced hypotension or hypothermia due to reduced renal blood flow (table I) or direct renal toxicity.

2.4.2 Elimination and Plasma Protein Binding

Clearance by filtration is a function of glomerular blood flow and the free concentration of the poison. Increases in the proportion of unbound poison may occur due to saturation of protein binding or a change in the pH. This increases clearance by filtration because more is available to diffuse across the glomerular membrane. An increase in the free plasma concentration may also increase the elimination by secretion (depending on the affinity of the transporter) but only if it is not saturated. The effect of changes in protein binding on overall elimination depends on the individual poison, especially the V_d and endogenous clearance.[125]

2.4.3 Saturation of Active Transport

Active secretion at the proximal tubule is less dependent on free concentrations, but these efflux transporters may be saturable at high doses, which would reduce clearance and prolong the elimination half-life.[5,196,197] P-gp and OATP are two specific transporters that mediate excretion of poisons and are saturable, leading to nonlinear kinetics.[198-200] Nonlinear dose-dependent renal clearance of chlorophenoxy herbicides has been noted in animal studies and has been attributed to differing activities of the OATP.[131,201,202]

2.4.4 Time-Dependent Excretion

If a poison causes toxicity to an organ mediating its excretion, then clearance may decrease progressively over time. Elimination kinetics are therefore nonlinear with an elimination half-life that increases over time. This phenomenon explains why nomograms developed to predict death after acute paraquat poisoning[121] consistently show prediction lines that are nonlinear in a semi-logarithmic plot (although all points on each line presumably reflect the same estimated bioavailable dose). Similar observations have been made in dogs poisoned with paraquat.[141]

2.4.5 Clinical Applications

Measures designed to enhance renal elimination by manipulating urine pH have been trialled for a number of poisons.[82] The ideal candidate is a weak acid with a pKa of 3–5 that is predominantly renally eliminated. Alkalinisation of the urine (usually with intravenous bicarbonate to give a pH of tubular urine >7.5) increases the proportion of poison in the urinary filtrate present as the dissociated anion.[9] Because passive reabsorption from the distal tubule is reduced for charged molecules ('ion trapping'), the net effect of alkalinisation is increased renal excretion of the poison. Acidification can achieve the same results for weak bases; however, because urine is more commonly acidic, it is unlikely to have a marked effect on clearance. Moreover, acidaemia is usually best avoided in overdoses of weak bases due to unfavourable effects on distribution, making rapid acidification of the urine difficult to achieve (see also section 5.5.4).

2.5 Individual Variability in Toxicokinetics

The toxicokinetics of a poison can vary widely between patients independently of the dose- and poison-induced changes discussed earlier. Variability may be due to environmental or inherited differences in populations. For example, genotypic variation of *MDR1* has been linked to differences in the pharmacokinetics of digoxin in some studies,[199,200] which may influence the efficacy of multiple-dose activated charcoal (MDAC) in acute cardenolide poisoning. Phenotypic variants of OATP may also influence the pharmacokinetic profile of digoxin and other poisons.[198] Most poisons have not been studied in sufficient depth to identify the clinical

importance of these pharmacogenetic variations in humans and, in any case, a full coverage of these is beyond the scope of this review. However, this complex interacting variability must be kept in mind when interpreting data from small or uncontrolled studies.

3. Quantifying Kinetics in Clinical Toxicology

To describe the contribution of the above physiological processes to the concentration-time profile of a substance, a number of kinetic parameters are commonly used. These processes can then be quantified and mathematical models can be applied for the accurate prediction of subsequent *in vivo* observations, including the effect of a particular intervention.[124]

However, most pharmacokinetic techniques used to derive these parameters require an accurate estimate of the dose and time of ingestion and frequent sampling, but in overdose such data are rarely complete or accurate. Some of the mathematical techniques also assume first-order kinetics, which may not necessarily be valid. It is common to simply apply the kinetic parameters derived from pharmacokinetic studies at therapeutic doses; however, this also makes assumptions that there are no dose-dependent or toxicity-induced changes in kinetics. Alternative methods to estimate these parameters are therefore desirable to achieve a greater understanding of the toxicokinetics.

3.1 Bioavailability

This is the proportion of a dose that reaches the systemic circulation after administration. For oral doses, this is the amount that is absorbed and not metabolised on the first pass through the small intestine and liver.[8] Oral bioavailability may change with increasing dosage because of alteration of normal gut physiology (table I) or saturable absorption kinetics or first-pass metabolism (see sections 2.1.4, 2.1.5 and 2.3.5).[8] When there are dose-dependent changes in bioavailability, there is a nonlinear relationship between the area under the concentration-time curve (AUC) and the dose (e.g. phenytoin, figure 5c) although this is not the only cause of this observation (e.g. changes in protein binding; see section 2.2.4).

Bioavailability is usually determined by comparing the AUC (see section 3.2) for an oral exposure with the AUC for the same dose administered intravenously. Alternatively, bioavailability can also be estimated using radioisotope-labelled compounds, amongst other approaches.[8]

3.2 Area under the Concentration-Time Curve

The AUC is a measure of systemic exposure to a poison. It is calculated from the concentration-time curve generated from serial blood samples obtained post-administration. The AUC is most commonly determined using the trapezoidal method. For accurate estimates, frequent samples are required during the disposition phase. It can be used to calculate the dose, bioavailability and clearance, if other factors are known, using the following relationship: AUC = Dose • F/CL, where CL is total body clearance. However, it follows that there is an implicit assumption that clearance is not dose-dependent – an assumption that cannot be justified in many poisonings.

3.3 Volume of Distribution

The V_d is an apparent volume that reflects the extent to which a poison is distributed to various tissues and the extent to which it binds to proteins and tissues. The more extensively a poison is distributed from the central compartment (see section 2.2), the larger the V_d. It may be estimated directly from the concentration-time curve when the bioavailable dose is known.[52] However, as discussed earlier, this is usually not possible, and so it can also be estimat-

ed from the measured elimination half-life and clearance (see section 3.5).

This is an important parameter to consider for a number of interventions in clinical toxicology. A V_d of >1 L/kg bodyweight is usually considered large because this indicates that only a small proportion of the total dose (<5–10%) is in the plasma. In this situation, treatments such as haemodialysis that enhance the elimination of a poison from the blood compartment will have poor efficacy.

The rate of enhanced clearance and the rate of redistribution from the 'toxic effect' compartment to the central compartment will also influence the effect of these treatments. While the V_d can rarely be directly measured in the overdose setting, it is largely influenced by simple physicochemical characteristics and therefore has the advantage of being the parameter most accurately predicted from its chemical characteristics and animal studies. But there are a number of poisons that saturate protein binding, which can, in turn, influence drug distribution and toxicity, and that is less readily estimated empirically.

3.4 Clearance

Clearance is a measure of the volume of blood cleared of poison over time (e.g. mL/min). For a poison that is removed by a single organ, clearance cannot exceed the blood flow to that particular organ. Total body clearance can be estimated using the bioavailable dose and AUC ($CL = F \bullet Dose/AUC$) or from the elimination half-life ($t_{1/2}$) and V_d ($CL = 0.693 \bullet V_d/t_{1/2}$), which has limited application in clinical toxicology, as discussed in section 3.3. Clearance will also vary with dosage when pharmacokinetics are nonlinear (see section 2.3.2).

Clearance by particular routes can be measured directly; in particular, renal clearance can be determined from plasma and urine concentrations and urine volume. Similar calculations can be used to estimate clearance by extracorporeal elimination methods such as haemodialysis (see section 5.5). This is important for determining the extent to which a poison is cleared by this route and the potential for an intervention to increase the systemic clearance to a significant extent.

3.5 Apparent Elimination Half-Life

As long as first-order elimination kinetics prevail, this describes the time required for the plasma concentration to decrease by half. It is commonly reported in clinical toxicology because it can be determined without knowing the dose and can be calculated directly from the semi-logarithmic concentration-time curve beyond the point where absorption and distribution are assumed to be complete (figures 1 and 2). The elimination half-life varies proportionally with the V_d and inversely with clearance as follows: $t_{1/2} = 0.693 \bullet V_d/CL$.

The apparent elimination half-life is commonly used to infer changes in clearance, e.g. the clearance is assumed to have doubled due to an intervention because the elimination half-life has halved. However, this simple inverse relationship assumes that there is no change in the V_d and also that absorption and distribution are complete. It is often not clear if disposition is ongoing when blood samples are obtained, and so this 'apparent elimination half-life' may be highly misleading.[203,204] Dose-dependent changes in distribution (table I) may also have a major impact on the concentration-time profile observed in patients with acute poisoning (see section 2.2.4 and figures 3 and 5). Unless the toxicokinetics in overdose are well described for a given poison, it is unwise to attribute changes in the elimination half-life to a particular intervention or a change in elimination.

All of these caveats apply to a greater extent when sampling is limited, calling for results to be interpreted conservatively. The frequency of blood sampling is often limited in clinical studies to analysis of blood taken for other reasons. The observed

half-life might cover both the distribution and elimination phases.[4,205] It helps to plot the log of the concentration against time. If distribution is complete and clearance is not dose-dependent, then the concentration should fall with a constant slope. At least three data points, and preferably four or five, are required to determine this (allowing for laboratory measurement error). Where this is observed, this is likely to represent the true elimination half-life. These may be useful to roughly estimate the duration of the absorption and distribution phases (figure 2b).

The onset and duration of pharmacological action often correlate poorly with the elimination half-life,[51,124] for in many cases the pharmacodynamics depend on distribution kinetics rather than clearance.[51] These principles are discussed in section 2.2.1 and are exemplified by highlighting the difference in the pharmacokinetic-pharmacodynamic relationship between lithium and tricyclic antidepressants. Therefore, reported elimination half-lives cannot be used routinely for determining the duration of observation.

3.6 Problems with Estimation of Toxicokinetic Parameters in Poisoning

In phase I drug development studies, the pharmacokinetics of most drugs for therapeutic doses are described accurately, typically using frequent sampling in volunteers. As discussed in section 2, there are many reasons to believe that pharmacokinetics may be altered in poisoning. However, poisoned patients present acutely unwell, and both the dose and time of ingestion will usually be inaccurate estimates. Even if a reasonable estimate of the amount ingested is possible, there may be a change in bioavailability due to vomiting, dose-dependent absorption or saturable first-pass metabolism, or from treatments such as activated charcoal or atropine (table I). All of these factors complicate the estimation of pharmacokinetic parameters from the concentration-time profiles obtained in poisoned patients.

The half-life is the only parameter that can be accurately determined from blood concentrations without knowing the bioavailable dose. However, this 'apparent half-life' may represent absorption, distribution and/or elimination. Research using advanced methods of pharmacokinetic-dynamic modelling are one method of estimating parameters despite the missing data (e.g. citalopram).[206] Another is to measure the amount of a poison and/or metabolite in the urine post-ingestion to determine the dose (e.g. acute parathion [organophosphorus] poisoning).[14] A similar approach could conceivably be applied to amounts removed by haemodialysis and other extracorporeal elimination techniques. An estimate could be made from changes in the elimination half-life during the procedure of the ratio of the endogenous clearance to the procedure clearance, which could be directly measured.

4. Importance of Pharmacokinetic Principles When Quantifying Exposure

4.1 Impact of Assay Nonspecificity

The laboratory process for developing an analytical assay that will quantify the concentration of a particular poison is well described.[207] An additional consideration is the specificity of the assay for the target compound given the potential for cross-reacting substances such as metabolites or endogenous compounds in biological specimens. This has been noted to be a particular problem in studies using immunoassays where there was uncertainty regarding the actual species measured.[13,31,82,208] Cross-reactivity with metabolites can be a particular problem since they are generally more polar than the parent compound and so their V_d is expected to be smaller, and therefore the plasma concentration is relatively high. This may show increasing 'concentrations' of the poison as the patient is recover-

ing.[208] The 'concentration' of digoxin cross-reacting substances in cases of poisoning with the seeds of yellow oleander shows multiple and delayed peak concentrations. However, as these were measured with an immunoassay that cross-reacts with a range of compounds, the peaks may conceivably represent absorption or metabolism of other compounds.[13] The lack of specificity of digoxin assays is also demonstrated when anti-digoxin Fab antitoxin is administered to patients with digoxin toxicity. The measured digoxin concentration using most immunoassays will show a dramatic increase, as it also measures the inactivated digoxin bound to Fab. This digoxin-Fab complex will have the pharmacokinetic parameters of the larger Fab fragment. The free concentration of digoxin (after ultrafiltration of the sample) will usually be undetectable at this time.[103,137]

Appropriate assay selection requires prior consideration of the compound that mediates toxicity. If a compound is bioactivated, then usually the active product should be estimated. It is only worthwhile to measure the parent compound if its concentration is proportional to the active metabolite and the degree of toxicity.

For some nontherapeutic products, the active compound for its intended use may not be the most clinically important poison in the formulation. This is commonly seen with pesticides that have low mammalian toxicity but are formulated with various solvents and surfactants. For example, toxicity from glyphosate-based herbicides is mostly attributed to the surfactant.[209] Similarly, a very poor correlation was shown between clinical features and concentrations of the chlorophenoxy herbicide MCPA. One possible explanation is that MCPA is also not the principal toxic component of this herbicide and there is marked variability in unmeasured co-formulants such as surfactants or phenolic impurities between different proprietary brands.[29]

4.2 Risk Assessment from Plasma Concentrations

4.2.1 Mechanism and Dynamics of Toxicity

Toxicokinetic data can only be useful when clinical toxicity results from systemic exposure. There is little point in estimating systemic exposure for poisons with predominantly local effects from direct contact (e.g. oesophageal ulceration from ingestion of alkali). For similar reasons, the pharmacodynamics of the relationship between the concentration and the effect must also be considered. Where the toxic effect is due to a specific interaction with an ion channel or enzyme, consider whether binding is competitive or noncompetitive, reversible or irreversible. For example, toxicity from irreversible monoamine oxidase inhibitors should correlate best with peak concentrations, but later concentrations would be expected to be less helpful. The likely dose-response relationship in toxic concentrations is also important. The cardiovascular toxicity from overdose of ACE inhibitors, α_1- or selective β_1-adrenergic receptor antagonists is usually not much worse than that seen with the first therapeutic dose. This presumably indicates that inhibition is maximal at relatively low concentrations. In contrast, agents that affect ion channels, such as sodium channel antagonists (tricyclic antidepressants, local anaesthetics and propoxyphene) have relatively low binding in therapeutic doses and a steep dose-response curve.[57] The degree of adaptation or tolerance that is possible and the time course in which it occurs are also important for many poisons. For example, tolerance develops rapidly in benzodiazepine-induced sedation; however, there appears to be little tolerance of the cardiac effects of sodium channel antagonists.

Dose-response relationships for agents that cause toxicity by nonpharmacological mechanisms are usually simpler and do not have a ceiling. For example, there is no physiological limit to the amount of

free radical damage or uncoupling of oxidative phosphorylation that can occur (short of death). It remains important to consider the time course of the organ damage from these toxic effects, which often progresses over many days or weeks, depending on the exposure.

4.2.2 The Kinetic-Dynamic Relationship

The aim of studying pharmacokinetics should be to better describe and understand the complex relationship between changes in blood concentrations and clinical outcomes – the kinetic-dynamic relationship. This allows more clinical information to be obtained from any plasma concentration.[1,124] There are many poisons for which there appears to be a poor correlation between the measured blood concentration and outcomes.[210] In some cases, this is known to relate to specific mechanisms: formation of active or toxic metabolites (e.g. organophosphorus pesticides[211] or paracetamol[212]), physiological adaptations (e.g. glycogenolysis for sulfonylurea poisoning[213,214]), or slow distribution and receptor binding (e.g. digoxin[138]), or distribution kinetics to the 'toxic effect' compartment (e.g. salicylates[4]). In the case of poisons inducing irreversible damage such as ionising radiation and mutagens, the degree of toxicity is determined by both the concentration and the duration of the exposure, and therefore relates to the AUC. These observations may differ with chronic or subacute dosing due to development of steady-state conditions, for example after 1 week of treatment with high doses of aspirin, the free concentration correlates with the occurrence of ototoxicity in healthy volunteers.[215] In each example given above, it is possible to some extent to interpret blood concentrations if these factors are kept in mind and samples are appropriately timed. In some cases, kinetic-dynamic data support the conclusion that in the clinical setting it is more practical and rational to directly measure another biomarker, e.g. acetylcholinesterase activity, coagulation, ECGs or blood glucose concentrations.

4.2.3 Importance of Physiological Compartments to the Kinetic-Dynamic Relationship

It is generally only practical to measure the concentration of a poison in plasma, whole blood or urine. Most poisons will be distributed from a central compartment to various peripheral compartments. As concentrations fall in the central compartment, there is redistribution back from the peripheral compartments (see also section 2.2). The rate of change in the concentration within each compartment may vary depending on the dose (table I). The kinetic-dynamic relationship will be simple if the poison exerts its toxicity in the central compartment or one in close equilibration, such as sedation from meprobamate or phenobarbital (phenobarbitone),[216] seizures and cardiotoxicity from theophylline[217,218] or neuromuscular blockade by suxamethonium chloride.[219] In contrast, it is more complicated if toxicity is induced by a metabolite or in a peripheral compartment.[220] In the latter case, there will be a time lag before the onset of toxicity as the poison is distributed to that compartment. The duration of the lag time to peak effects is a function of the perfusion of the 'toxic effect' compartment and the rate of transfer (figure 2). An example of this phenomenon is the marked discordance between blood concentrations and clinical toxicity noted with lithium poisoning.[43,54,221,222]

Similarly, when redistribution to the central compartment is slow, a decrease in the plasma concentration due to endogenous clearance or enhanced elimination (see section 5.5) may overestimate the change in the total body burden of the poison or the change in the concentration in the 'toxic effect' compartment. Therefore, severe clinical toxicity from a poison may persist even though the plasma concentration has decreased markedly (or is undetectable). Other examples of poisons with clear evidence that toxicity relates to concentrations in a peripheral 'toxic effect' compartment rather than plasma concentrations include paraquat, salicylates, methotrexate and iron. This is demonstrated using

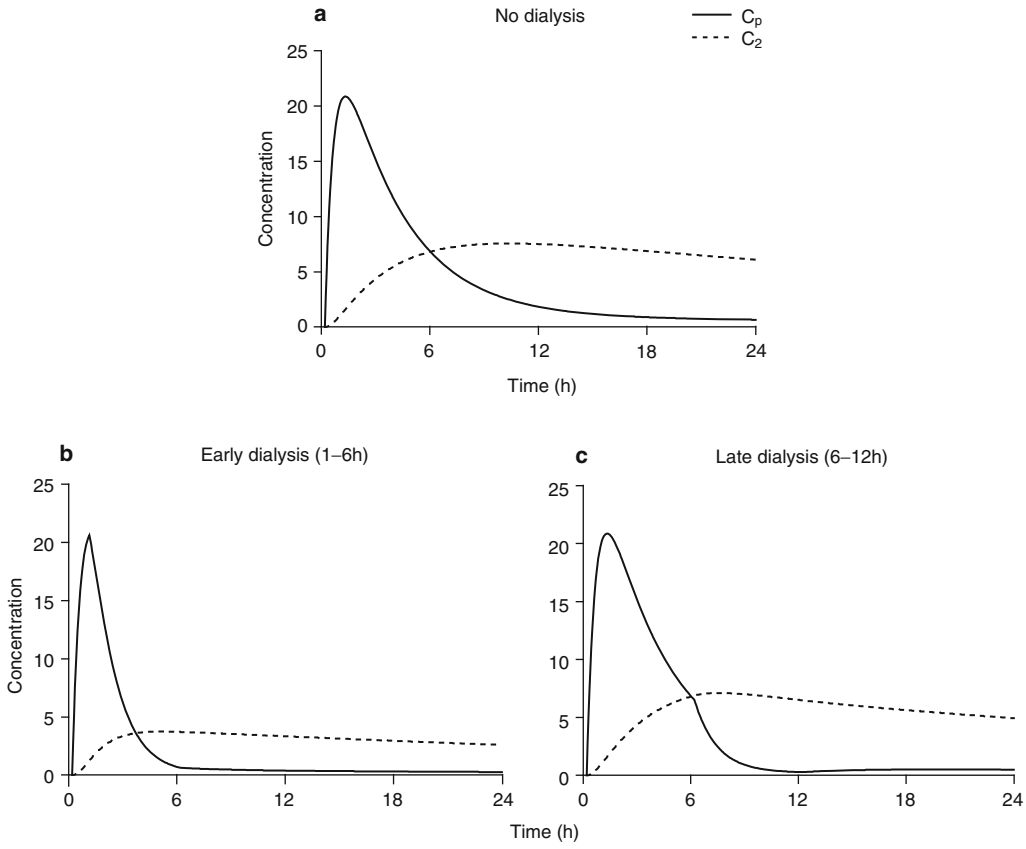

Fig. 6. Simulated concentration-time curves showing the effect of haemodialysis on the distribution and elimination of a poison. The importance of the disposition phase on the overall effect of a 6-hour haemodialysis treatment at different points during the time course is shown. This simulation was conducted using a two-compartment model using parameters similar to those noted for paraquat.[141] During haemodialysis, elimination was 2.5-fold greater than endogenous plasma elimination. (**a**) Note that the disposition phase persists for >24 hours and that dialysis will only decrease the concentration in the peripheral compartment (C_2) to a significant extent if commenced within 1 hour of ingestion. When the time to initiation of dialysis is delayed (**c**) there is a small rebound in the plasma concentration of the poison (C_p) after dialysis is ceased. This does not occur with early initiation of dialysis (**b**) because of the lower concentration in the peripheral compartment (C_2).

simulations of the effect of haemodialysis at various timepoints post-ingestion on paraquat concentrations (figure 6).

4.2.4 Role of Plasma Concentrations in Guiding Treatment

The purpose of risk assessment is to tailor management to the individual; for example, to make decisions about whether a patient requires admission for observation, if an antidote should be administered or if an enhanced elimination technique should be commenced. Later risk assessments may indicate when treatments should be ceased. From a practical perspective, it will be clinically useful only if the concentration can be rapidly measured and easily interpreted.

For optimal interpretation of a plasma concentration, the time since ingestion must be roughly known,[223] the kinetic-dynamic relationship understood and the influence of coexistent medical conditions (table I) considered. Early estimates of poison

concentration are used to assess risk for a number of poisons. The examples are not restricted to those with simple kinetic-dynamic relationships. On the contrary, it is often for those poisons with quite complex relationships and delayed toxicity that concentrations have proved most useful, as these are often agents for which risk prediction is difficult without investigations.

Thus, for example, in the case of paracetamol and paraquat, nomograms have been developed for use in acute poisoning that allow clinical outcomes to be predicted with a high degree of accuracy from a single plasma concentration at a known time post-ingestion (for paracetamol, see figure 2d). Yet toxicity due to paracetamol is due almost entirely to an unmeasured toxic metabolite that causes delayed toxicity. Many deaths from paraquat are due to active uptake and accumulation in the lung and toxic effects that persist despite a marked decrease in the plasma concentration.[78,141] Similarly, methotrexate, iron and salicylate concentrations may also have prognostic significance. In contrast, tricyclic antidepressants appear to rapidly cause dose-dependent cardiac toxicity in overdose, which is very closely related to concentrations in the central compartment. However, practical considerations mean that direct measurement of cardiac effects using the ECG is quicker, easier and more accurate.[224]

5. Importance of Toxicokinetic Principles in the Treatment of Poisonings

5.1 General Considerations

The most frequently used interventions in patients with acute poisoning are those that aim to alter ADME processes (table II). Knowledge of the expected toxicokinetic time course of a poison is often used to determine if treatments such as gastrointestinal decontamination, antidotes or enhanced elimination are warranted. The aim of many interventions is to decrease the effective concentration of a poison in its 'toxic effect' compartment.

In the case of toxic alcohol poisoning, for example with methanol and glycols, a number of toxicokinetic interventions are routinely used. Metabolism of toxic metabolites is inhibited with alcohol or fomepizole, and elimination of both the alcohol and the metabolites is enhanced with haemodialysis.[111,153] The rationale for their use is the well described kinetic relationship; the evidence being largely based on measured alterations in poison kinetics-dynamics with each treatment. The criteria for both initiation and cessation relate to poison concentrations (or an approximation using the osmolar gap) and investigations indicating the presence of toxic metabolites, particularly acidosis.

There have been no randomised controlled trials (RCTs) of these interventions for toxic alcohols,[225] nor for most other interventions used in poisoning.[226] Clinicians frequently need to rely on (and therefore interpret) causal evidence – i.e. evidence related to the mechanism of the intervention rather than clinical outcomes. Consensus statements and systematic reviews conducted to review the evidence supporting most of these treatments have found few good-quality RCTs and none that support routine use of any of these interventions.[32,71,74,79,82,85,226] Decisions about the expected efficacy of these interventions must be individualised and depend on interpretation of toxicokinetic data on the poison in the context of the clinical presentation of the patient (tables I and II).

5.2 Gastrointestinal Decontamination

Table II lists a number of potential treatments for gastrointestinal decontamination, the most common being single-dose activated charcoal (SDAC). If absorption is rapid, then any type of gastrointestinal decontamination is unlikely to be beneficial. The t_{max} serves as a guide to when further absorption is likely to be insignificant. Decontamination com-

menced after this is unlikely to have much benefit except for medications that form pharmacobezoars (see section 2.1.3). The t_{max} is consistently within 1–2 hours for most poisons, the exceptions being slow-release poisons and drugs causing marked slowing of gastrointestinal transit (table I).[32] Clinical benefits from routine use of SDAC in poisoned patients have not been demonstrated.[32] A recent RCT showed no difference in the length of stay or other patient outcomes with routine administration of SDAC in patients with acute pharmaceutical poisoning.[227] Data from the interim review of a large RCT in patients with predominantly pesticide and plant (yellow oleander) poisoning also did not report clinical benefits from SDAC, although the final analysis is awaited.[228]

Clinical studies suggesting benefit from SDAC are restricted to a handful of pharmacokinetic or kinetic-dynamic studies. A subgroup of patients with yellow oleander poisoning who were recruited to the large RCT[228] suggested that SDAC was beneficial compared with no activated charcoal.[13] SDAC also appeared to reduce the frequency of QT prolongation in citalopram overdose.[229]

5.3 Duration of Initial Clinical Observation

There is often a poor relationship between both maximum concentrations and the onset of symptoms, and the elimination half-life and offset of symptoms. The time course of toxicity correlates more closely with distribution kinetics (see section 2.2); in addition, there may be pharmacodynamic considerations (see section 4.2.2). From clinical experience, it is known that most patients who present with a significant poison exposure should be monitored for a minimum of 6 hours to allow sufficient time for the onset of symptoms. If they are asymptomatic at 6 hours post-ingestion, they may be medically cleared because this is usually sufficient time for the onset of cardiovascular or CNS toxicity by agents interacting with membrane-based receptors or ion channels.

However, there are important exceptions to this generalisation where there will be a delay in the onset of toxicity, including:

- controlled-release formulations or unrefined plant products due to the prolonged absorption phase and potential for flip-flop kinetics (see section 2.1.2). Patients ingesting these poisons should be observed for a minimum of 12–24 hours even when gastrointestinal decontamination has been apparently effective;[13,24]
- poisons that are bioactivated to a more toxic metabolite (e.g. paracetamol). The onset of poisoning for these poisons will relate to the production and toxicity of the metabolite (e.g. NAPQI). Other examples include organophosphorothioates, methanol, ethylene glycol and 1,4-butanediol;
- poisons whose primary mechanism of toxicity is by causing cellular organelle dysfunction. This includes mechanisms such as DNA alkylation, antimetabolites, oxidative stress or uncoupling of oxidative phosphorylation. Examples include paraquat, chlorophenoxy herbicides, phosphine, aspirin, dinitrophenol, colchicine, chemotherapeutic agents, copper and iron. The delay in these cases relates to distribution kinetics, the onset of individual cellular dysfunction and the more delayed cumulative effects on vital organ physiology;
- poisons that may cause prolonged interference with normal physiology, so that the determinant of the onset and duration of toxicity is the time course and the limitations of the compensation mechanism. For example, sulfonylurea oral antihyperglycaemic agents stimulate insulin release from the pancreas, which may continue for many days. While early hypoglycaemia may be noted, there is homeostatic compensation due to glycogenolysis, and ingested food will also coun-

teract the insulin. Hypoglycemia will only occur when carbohydrate intake is stopped and reserves are insufficient.[213,214] Coumarin anticoagulants (warfarin, brodifacoum and bromadiolone) are another example. The onset of coagulopathy and bleeding is always delayed as it depends on the elimination of coagulation factors that have already been produced.[230] Similar principles have been suggested for the time to recovery of coagulopathy post-administration of antivenom for Australian brown snake (*Pseudonaja spp.*) envenomation.[231]

5.4 Dosing of Antidotes

An antidote alters the dynamics or kinetics of a poison. The need for antidotes is usually based on clinical features and/or estimates of the prognosis without treatment (natural history). Some antidotes have standard empirical regimens, and others are titrated to a clinical endpoint. Effective use of many antidotes also requires careful consideration of the toxicokinetics of the poison, the antidote and how they interact. Some antidotes alter the toxicokinetics of the poison through various mechanisms (table II). The window of opportunity for the intervention is dependent on the toxicokinetics of the poison. In some cases this may be altered; for example, when there is ingestion of a poison (or treatment with drugs such as atropine) that prolongs gastrointestinal transit (table I).

If a poison's plasma concentration correlates closely with its clinical effects, the apparent elimination half-life may guide the dosing regimen of an antidote. Acute poisoning with dapsone may induce severe toxicity and death due to methaemoglobinaemia, which induces cellular hypoxia. Dapsone has a long elimination half-life, which correlates with the time course of methaemoglobin production (figure 7a).[232,233] Bolus doses of methylene blue are effective at reversing dapsone-induced methaemoglobinaemia, but the response is nonsustained and requires repeated doses.[147,234] The long plasma elimination half-life of dapsone means that methaemoglobinaemia recurs as methylene blue is rapidly cleared from the central compartment (figure 7b).[147,235] Dosing of the antidote methylene blue by intermittent bolus doses is the standard recommendation,[236,237] which does not appear rational for the treatment of a long-acting poison such as dapsone, and also propanil.[238] Instead, administration of methylene blue as an initial bolus and maintenance infusion is more likely to be effective, as shown with dapsone.[147,239,240]

Titrated infusion regimens of antidotes are commonly used in clinical toxicology, including naloxone for opioids,[243] flumazenil for benzodiazepines[244-246] and atropine and oximes for acute organophosphorus poisoning.[247] There are marked differences in the elimination half-life of the poisons in each of these classes, and the antidotes have a relatively short elimination half-life compared with many of the poisons. Initial loading doses of the antidote are usually titrated against the clinical effect. The starting dose of maintenance infusions is designed to maintain the concentration achieved with the bolus and, therefore, this is based on the pharmacokinetics of the antidote. For example, naloxone and flumazenil both have elimination half-lives of ≈1 hour, and so it is common to use a maintenance infusion rate of half the effective bolus dose per hour. Actually, to maintain the same concentration, the rate should be 0.693 of the effective bolus dose for an agent with an elimination half-life of 1 hour (data on naloxone in acute opioid poisoning support this[248]), but in practice the rule works reasonably well. The anticipated rate of reduction of the maintenance dose and the overall duration of the infusion will be guided to a large extent by the elimination half-life of the poison. Thus, in the case of acute opioid poisoning, prolonged infusions are usually required for methadone overdoses, whereas

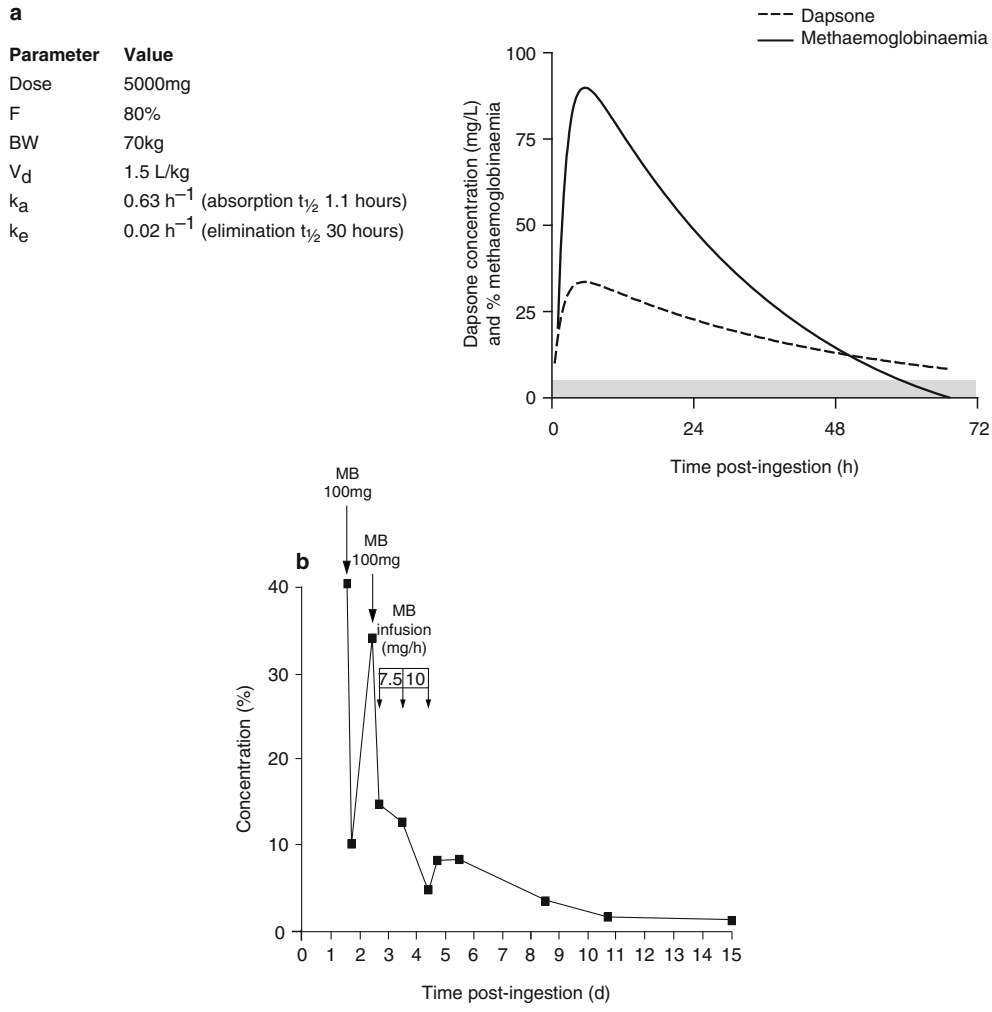

Fig. 7. Toxicokinetics of dapsone *in vivo*. (**a**) Simulated concentration-time profile of post-ingestion dapsone 5g and the corresponding methaemoglobinaemia (%) in a patient not treated with the short-acting antidote methylene blue (MB). This profile was approximated using a single-compartment model (figure 1a) and pharmacokinetic parameters obtained from data in healthy volunteers.[157] It is noted that dapsone may be subject to dose-dependent kinetics with an elimination $t_{1/2}$ of ~90 hours in overdose,[241,242] which will prolong the duration of methaemoglobinaemia. Methaemoglobinaemia was calculated using a formula determined by regression analysis of clinical data in a case series of 274 patients with acute dapsone ingestion,[232] as follows: methaemoglobinaemia = ([dapsone] – 12.9256 + 0.0682 • t)/0.234, where [dapsone] = dapsone concentration (mg/L) and t = time post-ingestion (hours). It is observed that methaemoglobinaemia spontaneously steadily resolves because of intracellular biochemical processes that reduce methaemoglobin to haemoglobin. Initially, methaemoglobinaemia declines at a rate that is approximately parallel to the concentration of dapsone, but later it resolves more rapidly. This rapid spontaneous resolution is due to the endogenous reducing mechanisms no longer being overpowered by the high concentration of the *N*-hydroxylamine metabolite (figure 4). [Note: it is not known whether the relationship described by the above formula has been validated and what the limitations of its application are. In particular, the peak methaemoglobinaemia is predicted to be 90% in this simulation, which is likely to be fatal. The therapeutic concentration is indicated as the shaded area. Nevertheless, it demonstrates useful principles that are observed clinically.] (**b**) Nonsustained reversal of methaemoglobinaemia in a patient with acute dapsone poisoning treated with MB.[147] The decreasing requirement for MB with time is likely to relate to endogenous clearance of dapsone, but lack of toxicokinetic data limits the conclusions that may be drawn. A similar response to intermittent bolus doses of MB has been noted by others previously.[234] **BW** = bodyweight; **F** = bioavailability; k_a = absorption rate constant; k_e = elimination rate constant; $t_{1/2}$ = half-life; V_d = volume of distribution.

no infusion may be required for most heroin overdoses.

5.5 Enhanced Elimination

5.5.1 General Principles

The main aim of enhanced elimination techniques is to increase the clearance of the poison from the body, and a number of treatments have been used in clinical toxicology[249] (table II). MDAC,[85] urinary alkalinisation and/or diuresis[250] and extracorporeal elimination (e.g. haemoperfusion or haemodialysis)[87] are the most common.

When endogenous elimination is rapid, there is unlikely to be a significant gain from enhanced elimination. However, where there is dysfunction of the organ that is responsible for clearance of the poison, these techniques may have a role. For example, if there is renal dysfunction, haemodialysis may be useful in acute poisoning with lithium.[43,54]

The normal route of excretion is obviously important when considering urinary alkalinisation. However, other generalisations based on the normal route of clearance of the substance cannot be easily made for other modes of enhanced elimination. High or low renal clearance in therapeutic doses does not indicate whether clearance will be correspondingly high or low for haemodialysis following an acute poisoning. Haemodialysis is a passive process and its efficacy relates to protein binding and the physicochemical properties of the poison, whereas renal clearance is also influenced by active processes involving secretion and reabsorption.

Similarly, some might assume that high hepatic or biliary clearance is predictive of enhanced elimination with MDAC. However, MDAC enhances the elimination of digoxin;[251-255] for example, in one study the mean digoxin clearance increased by 47% in healthy volunteers given therapeutic doses of intravenous digoxin and oral MDAC compared with healthy volunteers given intravenous digoxin alone.[251] Digoxin is predominantly renally cleared, and so this effect is probably related to active transport of digoxin into bile and from small intestinal cells. In the absence of charcoal, most digoxin would simply be reabsorbed. The extent to which different poisons undergo active transport in the gut is known for only a few substances, and thus pharmacokinetic data from studies in therapeutic use may be unhelpful for predicting the effect of treatments such as MDAC.

5.5.2 Distribution Kinetics

The central compartment (circulation) is the only compartment that is accessible to all of these treatments. The efficiency of a particular treatment for removing a poison from the body depends on the physicochemical properties of that poison (table II), the proportion of the poison in the central compartment and the rate of redistribution from peripheral compartments (figure 2). If a small proportion of the poison is in the central compartment (see section 3.3) and the rate of redistribution from peripheral compartments is slow relative to clearance with enhanced elimination, measures to increase plasma clearance will not lead to a similar increase in whole body clearance (figure 6).

Further, if the rate of redistribution is slow compared with clearance from the central compartment with enhanced elimination, once the intervention is ceased, redistribution will continue until there is equilibrium across the compartments. This may be observed as a 'rebound' in the plasma concentration, as noted in figure 6, where there is a slight increase in the concentration once haemodialysis is ceased. The extent to which this occurs and the time course is related to the rate of redistribution but cannot be predicted from the size of the V_d.

Any treatment for enhanced elimination will be most effective if commenced during the absorption and disposition phase, as this is the time when the most poison is present in the plasma. If the treatment is efficient and commenced promptly, it can decrease the amount of poison that is distributed into

peripheral compartments. This is particularly relevant for poisons that cause toxicity in peripheral compartments, such as paraquat, baclofen, phosphine, colchicine, amatoxin and iron. For example, rapid initiation of haemoperfusion within 2 hours post-exposure was noted to be effective in paraquat-poisoned dogs but was largely ineffective if commenced beyond that time.[141]

Enhanced elimination techniques are not likely to substantially increase the systemic clearance of poisons that are rapidly distributed to large peripheral compartments (and therefore have a large V_d [>>1 L/kg]; see section 3.3). Similarly, poisons with a high degree of protein binding are unlikely to be more rapidly cleared by treatments for enhanced elimination, as only the unbound fraction is able to be cleared. The molecular adsorbents recirculating system (MARS) and haemoperfusion are reported to be more effective for poisons with extensive protein binding than haemodialysis, although their relative benefit is not well defined.[88,100]

However, dose-dependent kinetics should be considered when evaluating these interventions. For example, a large ingestion of aspirin or chlorophenoxy herbicide saturates protein binding, which substantially increases the free concentration and will increase clearance with urinary alkalinisation or haemodialysis. However, there is also an increase in the V_d, and so the overall effect on elimination is unclear and may actually change with time.

Despite the mentioned limitations, haemodialysis or haemoperfusion may (or perhaps should) be trialled if maximal supportive care is unable to maintain acceptable physiological function in certain circumstances.[88] If there is a large V_d but the 'toxic effect' compartment is in close equilibration with the central compartment, then these techniques may temporarily decrease the concentration of poison in the 'toxic effect' compartment despite having little effect on the total body poison load. This might also facilitate elimination by other endogenous mechanisms. Theoretically, reducing free poison concentrations in blood returning to the heart might improve the blood pressure which, in turn, increases endogenous renal or hepatic clearance and distribution of the poison, even if the effect of the intervention on elimination is not in itself significant. For example, case reports of clinical improvement during treatment with haemoperfusion or MARS in acute tricyclic antidepressant poisoning have been reported.[100,256] Such arguments have been made in favour of using these techniques in patients with severe shock with barbiturate or tricyclic antidepressant poisoning despite what appear to be unfavourable toxicokinetic characteristics for these techniques (large V_d and high protein binding). Mechanical cardiac support devices (if available) are another alternative[168] and likely to be a more reliable means of achieving this effect.

5.5.3 Multiple-Dose Activated Charcoal

MDAC can potentially alter the toxicokinetics of a poison by decreasing absorption and increasing elimination. MDAC enhances elimination by one of two possible mechanisms: interruption of enterohepatic recirculation[22] (see section 2.4.1) or augmentation of enterocapillary exsorption, sometimes referred to as gastrointestinal dialysis. This term suggests that poison in the splanchnic circulation is available for diffusion across the gut wall back into the lumen by a passive process. It is also likely that many drugs are actively transported across the gut by transport proteins such as P-gp and OATP. In any case, the technique requires sufficient activated charcoal in the lumen such that the drug in the lumen will be bound and create a concentration gradient that promotes clearance from the circulation. The efficacy of MDAC for enhanced elimination is determined by multiple factors including splanchnic blood flow (1100 mL/min/70kg), the capacity for active and passive transport of the poison, the gut transit time and the concentration gradient across the gastrointestinal membrane.

The most common clinical situation in which MDAC is used is following ingestion of a controlled-release product. In this case, the aim is also to prevent absorption, and serial quantification of plasma concentrations will often be used to determine the effectiveness of treatments with MDAC.[24] For example, in carbamazepine or theophylline poisoning, MDAC is promptly initiated, and blood samples are obtained every 2 hours until plasma concentrations are noted to be consistently declining. Even when MDAC is ceased, serial blood samples and clinical monitoring are continued for some time because of the possibility of further absorption or clinical toxicity due to the presence of a pharmacobezoar. Due to the ongoing absorption, it is not possible to directly estimate the effect purely from elimination in this situation. Therefore high-quality evidence supporting this intervention is difficult to obtain.

A comprehensive review of studies found increased rates of elimination with MDAC for a large number of substances in healthy volunteers. This included amitriptyline, carbamazepine, dapsone, dextropropoxyphene, digitoxin, digoxin, disopyramide, nadolol, phenobarbital, phenylbutazone, phenytoin, piroxicam, quinine, sotalol and theophylline. No effect was found with other substances such as astemizole, chlorpropamide, doxepin, imipramine, valproic acid, tobramycin and vancomycin.[85] At the time of the previously mentioned review, there were no large RCTs, but since that time there have been two that compared MDAC with a single dose of charcoal. The first studied yellow oleander and found a marked benefit in clinical outcomes but had no toxicokinetic analysis to support the intervention.[257] The second has been completed and found no clinical benefits at the final interim analysis.[228] It also found no difference in the elimination half-life between SDAC and MDAC in a subgroup with yellow oleander poisoning.[105] Small case series or case reports have not conflicted with the healthy volunteer studies but did not provide further evidence of the extent of enhanced elimination or clinical effectiveness.[85]

5.5.4 Forced Diuresis, Urinary Alkalinisation or Urinary Acidification

The extent to which weak acids and bases are passively reabsorbed from the renal tubule will depend on the flow and pH of the filtrate. Treatments that modify these factors aim to decrease the amount of the poison that is passively reabsorbed, thereby increasing clearance. It is important to maintain a good urine output, but forced diuresis is rarely employed because it has the potential for complications, including fluid overload and pulmonary oedema. For weak acids, increasing the pH of the filtrate from the usual urine pH of 5–6 to >7.5 will greatly increase the proportion of weak acid that is ionised. As only the nonionised form is significantly absorbed, this decreases reabsorption and is known as 'ion trapping'. Similarly, urinary acidification can increase clearance by ion trapping of weak bases, although the potential effect of this appears less.[82-84]

In studies of healthy volunteers receiving these treatments, the clearance of a range of weak acids has been enhanced. These weak acids include salicylates, chlorophenoxy herbicides, diflunisal, methotrexate and phenobarbital.[82,83] There have been no RCTs, with the exception of salicylates[258] and phenobarbital,[259] and there appear to be only limited clinical data to support such treatments.[82] For salicylates, a 10-fold increase in the amount excreted in urine and a 3-fold reduction in the apparent elimination half-life were observed with urinary alkalinisation.[258] Similarly, large effects on enhanced clearance would be expected with chlorophenoxy herbicide poisoning, but the dose-dependent kinetics make interpretations of the existing clinical evidence difficult.[122]

Systemic alkalinisation or acidification may occur in the process of inducing changes in the urinary

pH. Systemic alkalinisation reduces the distribution of weak acids[66-68] and therefore should increase the rate of elimination. As both salicylates and chlorophenoxy herbicides mediate toxicity in peripheral compartments (mitochondria), this would also be expected to reduce toxicity. The most important weak bases from a toxicological perspective are generally cardiotoxic, and alkalinisation is in fact more likely to be used to increase plasma protein binding, increase the rate of distribution from the central compartment and decrease the cardiac ion-channel binding (see section 2.5.2).

5.5.5 Extracorporeal Elimination

Extracorporeal treatments are applied outside the body to enhance clearance. This includes haemodialysis, haemofiltration and charcoal haemoperfusion.

Haemodialysis and haemofiltration are forms of renal replacement therapy (RRT) developed for use in patients with renal insufficiency. They are widely available in intensive care units and are administered by various regimens, which were initially developed to maximise the clearance of urea rather than other solutes.[260] Haemoperfusion is performed rarely now, as it has a number of potential serious adverse effects and clearance that declines with time, and the cartridges are often unavailable.[261,262] In any case, the same toxicokinetic principles apply to this modality.

There have been no RCTs of these interventions in poisoning. There is more information on the extent to which these treatments will remove drugs from the body when used for RRT.[263] The efficiency of these treatments in removing a poison (and also antidotes) from the body depends largely on the principles of distribution kinetics, as outlined in section 5.5.2 and exemplified in figure 6. In addition, the actual clearance is a function of the blood flow through the device and the extraction ratio. Extraction of poison from the blood flowing through the device is determined by plasma protein binding, the surface area and permeability of the membrane, and the concentration gradient across the membrane. The concentration gradient is influenced by the flow rate of both the blood and effluent (counter-current). High-flux RRT is an imprecise term but refers to regimens with high blood flow and high effluent flow rates performed with machines with improved membrane characteristics. These are, therefore, always the preferred interventions for elimination enhancement (although other regimens may be adequate for standard RRT).

Haemodialysis is most commonly used with poisoning due to toxic alcohols, salicylate, valproic acid and lithium. In many cases, there is an additional justification for their use beyond enhancing elimination of a poison. For example, haemodialysis will treat the complications of poisoning, including metabolic acidosis from toxic alcohols[111,153] or salicylates,[69] hyperammonaemia with valproic acid intoxication[27] and renal failure from lithium poisoning.[43,54]

It has been suggested that haemoperfusion is preferable for meprobamate, carbamazepine or theophylline poisonings. However, clearances with high-flux haemodialysis regimens may approach those obtained by haemoperfusion and can be maintained for longer (the lifetime of a haemoperfusion cartridge is ~4 hours). Clearance is additive when the treatments are combined. For example, both haemodialysis and MDAC increase clearance of theophylline and carbamazepine.

For a number of the poisons listed, distribution kinetics appear to limit effectiveness despite apparently useful improvements in clearance. For example, despite excellent clearance of lithium from the plasma, there is limited evidence supporting faster resolution of CNS toxicity.[43,221] RRT also appears to increase plasma clearance of valproic acid in overdose[27,264,265] (saturation of protein binding is also observed with valproic acid[266-268]), but the effect on elimination from the intracellular 'toxic

effect' compartments and clinical outcomes are not well defined. The majority of exposures also result in mild toxicity, making it even harder to determine when the benefits outweigh the risks of this intervention.[269]

6. Conclusions

Large RCTs of most of the expensive and specialised interventions to enhance elimination are unlikely. In any case, the clinical and toxicokinetic effect will vary for each poison and even the extent of the overdose in some cases. Therefore, extensions of the indications for toxicokinetic interventions are likely to rely on careful clinical studies in small numbers of patients. Creating a much greater awareness of toxicokinetic principles amongst clinicians treating poisoning may improve their risk assessment and management. Equally important, it may mean that there is better collection and documentation of pivotal toxicokinetic data in the clinical literature underpinning the expert recommendations for these decisions.

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