Pr. BAUD

Méthodes critiques d'évaluation des antidotes

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Groupe de travail : F.J. Baud, S.W. Borron, C. Bismuth

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Modifying toxicokinetics with antidotes

F.J. Baud*, S.W. Borron, C. Bismuth

Réanimation Toxicologique, Hôpital Fernand Widal, Université Paris VII, 200, rue du Faubourg Saint-Denis, 75010 Paris, France

Abstract

Five approaches may be described through which antidotes can modify toxicokinetics: (1) Decreased bioavailability of the toxins; (2) Cellular redistribution of the toxin in the organism; (3) Promotion of elimination in an unchanged form; (4) Slowing of metabolic activation pathways; (5) Acceleration of metabolic deactivation pathways. However, the ability to modify toxicokinetics with a new treatment, while demonstrating an understanding of the mechanism of action, must never be construed to be, in and of itself, the goal of therapy. The ultimate evaluation of an antidote modifying toxicokinetics is strictly clinical.

Keywords: Antidote; Toxicokinetics; Toxicodynamics; 4-Methylpyrazole; *N*-acetylcysteine; *Digitalis*

1. Introduction

Toxic substances act principally by three mechanisms: physical (e.g. foam from shampoo), chemical (e.g. acid burns), or biological (e.g. *Digitalis*). In some cases (e.g. hydrofluoric acid) the mechanisms of toxicity are multiple. However, the vast majority of poisonings result from a biological mechanism. For toxicants which act by this third mechanism, the poison must be absorbed, distributed and must reach a critical concentration at the cellular target (toxicokinetics). Such a critical concentration results in cellular modifications, reversible or irreversible, which may ultimately be translated into signs and symptoms of clinical illness (toxicodynamics). The classic treatment paradigm in clinical toxicology includes: (1) Supportive treatment; (2) Prevention of absorption of toxic compounds; (3) Enhancement of their elimination; (4) Specific treatments, including antidotes. However, this description of general principles of treatment of poisoning does not take into account the importance of this duality of toxicokinetics and toxicodynamics, encountered in the majority of poisonings.

In all dictionaries throughout the world, antidotes are defined as 'a remedy to counteract the effects of a poison'. However, such a global definition does not help us, as physicians, to know what should be beneficial for our patients. Thus, we recently proposed a more conservative definition of antidotes [1] which we have now expanded: 'An antidote is a drug whose mechanisms of action have been determined, which is able to modify either the toxicokinetics or the toxicodynamics of the poison and whose administration to the poisoned patient reliably induces a significant benefit.' As such it appears that many drugs with unproven efficacy (Fuller's earth in

* Corresponding author.

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paraquat poisoning) in human poisoning or unknown mechanism (diazepam in chloroquine poisoning) should not presently be referred to as 'antidotes'. Such a restrictive definition should help to distinguish between drugs which are merely adjunctive therapy from those which are true antidotes.

Many classifications of antidotes have been proposed, none completely satisfactory [2]. Antidotes may be classified as a function of their mechanism of action into eight categories which cover the toxicodynamic and toxicokinetic aspects of intoxications (Table 1). Toxicokinetic treatment includes those antidotes that decrease the concentration of the toxic compound at the level of the cellular target. Toxicodynamic treatment involves antidotes which modify clinical symptomatology without affecting the concentration of the toxic compound at the level of the cellular target. In general, toxicodynamic treatment may dramatically improve immediately life-threatening symptoms but is devoid of effect on the duration of the poisoning. It should be noted that most supportive treatments work on a toxicodynamic basis. Toxicokinetic treatment such as gut decontamination, on the other hand, tends to either prevent or decrease the duration of the intoxication, but may not have any immediate effect on clinical symptoms. There are notable exceptions to these generalities. *Digitalis* antibodies which are a toxicokinetic therapy provide almost immediate clinical improvement while decreasing free *Digitalis* tissue concentration. In contrast, both ethanol and 4-methylpyrazole actually prolong the duration of exposure to the native toxin (ethylene glycol and methanol) but decrease the exposure to toxic metabolites (glycolate and formate). On the other hand, among acute poisonings causing life-threatening cardiovascular collapse, which has been shown to impair the elimination of toxins [3], it stands to reason that toxicodynamic treatments which improve hemodynamic status and tissue perfusion in the liver and kidney may be expected to decrease the duration of intoxication.

Decreasing the amount of toxin in the body should, in theory, improve the patient's condition. However, there are a number of factors which impede such a simple relationship (Fig. 1). The actual immediate clinical benefit of reduction of body burden of a toxin is dependent on (1) the amount of toxin present in the body in excess of that required to produce a toxic effect, (2) the slope of toxicity, (3) the ratio of the amount of toxin removed to the dose required to

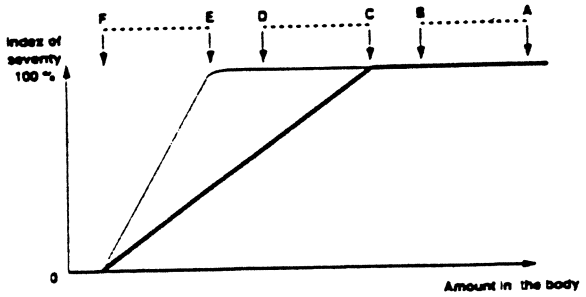

Fig. 1. Relationship between the clinical severity of the poisoning and the amount of toxin in the body in two types of intoxication, one with a gentle slope of toxicity (1) and the other with a steep one (2). The clinical effect of the removal of a fixed amount of toxin depends on the ratio of the amount of toxin removed to the dose required to produce a toxic effect.

Table 1
Classification of antidotes and chelators

Treatment	Effect
Toxicokinetic treatment	1 Decreased bioavailability of the toxins
	2 Cellular redistribution of the toxin in the organism
	3 Promotion of elimination in an unchanged form
	4 Slowing of metabolic activation pathways
	5 Acceleration of metabolic deactivation pathways
Toxicodynamic treatment	6 Competitive or non-competitive displacement of the toxin from its binding site
	7 Bypass of the binding of the toxin to the receptor
	8 Correction of peripheral effects of the toxins (including supportive treatments)

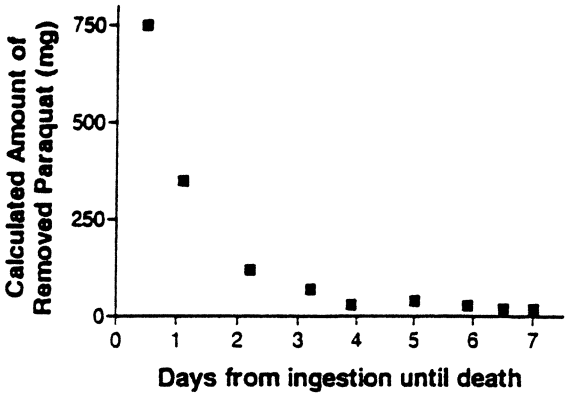

Fig. 2. Efficacy of hemoperfusion/hemodialysis and time to death in nine paraquat poisoning patients. The greater the amount of paraquat removed, the faster the patient succumbed. From Bismuth [20] with permission.

produce a toxic effect, (4) the delay in onset of treatment. These factors appear critical for toxins inducing irreversible lesions. Fig. 2 shows that in cases of acute paraquat poisoning treated by extracorporeal methods the greater the quantity of paraquat removed the more rapidly the patient died. We interpret this seeming paradox as follows: the total amount of toxin removed has no clinical significance per se. In this case, increased removal of toxin is consistent with a body burden far in excess of the amount required to produce death. Thus, we conclude that modifying toxicokinetics with a new treatment, while demonstrating an understanding of the mechanism of action, must never be construed to be, in and of itself, the goal of therapy.

Thus, it is necessary that we examine in further detail what constitutes a 'significant benefit' in antidotal therapy. It is necessary but not sufficient that an antidote improves the toxicokinetics and/or toxicodynamics in poisoning. To consider an antidote effective in human beings requires that the course of illness and the outcome are favorably modified. Significant benefits may be realized not only in improved prognosis but also as decreased duration or cost of hospitalization or decreased requirements for invasive procedures. Very few antidotes have been investigated in this light (Table 2). In fact, the evaluation of antidotes in humans has been constrained by numerous factors. First of all, for a number of potentially lethal toxins, there are an insignificant number of patients encountered in any one treatment center to permit an assessment of efficacy on a prospective basis. In addition, increasing administrative and legal hurdles limit testing of new antidotes and even old ones. It must be taken into account that many acute intoxications induce rapid onset of severe symptoms requiring emergency treatment. In this particular clinical setting, the early administration of toxicokinetic antidotes is of utmost importance if they are to be effective. Requirements for informed consent, frequently impossible in the poisoned patient, may need to be waived.

Five approaches may be described through which antidotes can modify toxicokinetics: (1) Decreasing the bioavailability of the poison; (2) Enhanced elimination of unchanged poison

Table 2
Attempt at classification of toxicokinetic antidotes according to the derived benefit in human poisoning

Derived benefit	Proven efficacy	Possible efficacy
Life-saving	*N*-Acetylcysteine	Chelating agents
	Fab fragments	Cyanide antidotes
	Oxygen	Methylene blue
	Desferoxamine	
Decreased duration of hospitalization	?	Oxygen
		Activated charcoal (?)
		Digitalis Fab fragments (?)
Decreased cost of hospitalization	?	?
Decreased requirements for invasive procedures	Activated charcoal	Whole bowel irrigation
	4-Methylpyrazole	
	DMSA	

through natural means; (3) Slowing of metabolic activation; (4) Accelerating an inactivating metabolism; (5) Promoting an extracellular redistribution of toxicant.

2. Decreasing the bioavailability of the poison

Gastric lavage should no longer be considered as a routine management procedure in poisoned patients, as it has a very limited application. Currently, gastrointestinal decontamination is accomplished by a pharmacological intervention (Table 3).

A single dose of activated charcoal appears capable of preventing the absorption of many toxic compounds, providing that both the delay between drug ingestion and charcoal administration is short and the ratio of the dose of activated charcoal to the ingested dose of the toxicant is nearly 10:1. Furthermore, repeated doses of activated charcoal may increase the endogenous clearance of many toxic compounds through 'gastrointestinal dialysis' [4]. However, the actual clinical benefit of single and repeated doses of activated charcoal for many poisonings remains to be determined. Due to its safety, repeated doses of activated charcoal should be recommended in various intoxications [5] such as phenobarbital, theophylline (in which case, repeated doses of activated charcoal should be considered as viable alternative to hemoperfusion), phenytoin, carbamazepine, and salicylates (Table 3). One randomized clinical study compared the effect of repeated doses of activated charcoal to a single dose in phenobarbital poisoning. The half-life of phenobarbital in plasma was significantly shortened while the duration of intubation did not differ [6].

3. Enhanced elimination of unchanged poison through natural means

3.1. Chelating agents for heavy metals (Table 4)

One of the earliest chelating agents was dimercaprol (BAL). Recently, two other related drugs have been introduced, dimercaptosuccinic acid (DMSA) and dimercaptopropane sulfonic acid (DMPS) that possess the same dithiol

Table 3
Decreasing the bioavailability of the poison

Antidotes	Toxicants
Activated charcoal	'All' but toxic alcohols, caustics, iron, lithium[a]
Whole bowel irrigation	Body-packers, iron, theophylline[b], verapamil[b], lead, zinc sulfate
Prussian blue	Thallium, cesium
Calcium salts	Fluoride
Magnesium sulfate	Barium (soluble forms)

[a] Also increase the elimination of digitoxin, phenobarbital, carbamazepine, phenylbutazone, dapsone, methotrexate, nadolol, theophylline, salicylate, cyclosporine E, propoxyphene, amitriptyline, and nortriptyline.
[b] Sustained-release preparations.

Table 4
Chelating agents used in human poisonings

Chelating agents	Toxicants
Disodium calcium ethylenediamine tetracetate (EDTA Na_2Ca)	Lead, zinc, cadmium (highly controversial)
Diethylenetriamine pentacetate (DTPA)	Plutonium, americium
Dimercaptopropanol (BAL)	Arsenic (inorganic and organic [lewisite]), mercury salts, lead[a]
Dimercaptopropanesulfonic acid (DMPS)	Arsenic, lead, mercury (organic and inorganic)
Dimercaptosuccinic acid (DMSA)	Lead, organic and inorganic mercury, arsenic
Penicillamine	Copper overload, lead, arsenic, mercury
Desferoxamine	Iron, aluminium

[a] In addition to EDTA $CaNa_2$.

chelating group, while the whole molecules are more hydrophilic [2,7]. Unlike dimercaprol, these two recent drugs can be used orally and have a better therapeutic index than BAL. A considerable amount of work has been carried out on reaction of the chelating agents with metals, and it is possible to predict the efficacy of particular chelating agents in particular metal poisonings on the basis of the affinity constant of the metal and chelator. It should be noted that the precise mechanisms of action by which the chelating agents work are not fully understood. It seems likely that the beneficial action of the chelating agents is probably a combination of effects, detoxification by complexation, mobilization, and elimination. Thus, the affinity constant cannot be the sole property that determines the efficiency of a particular chelating agent for a particular metal. Indeed, the properties of an ideal chelating agent have been defined by Yokel and Kostenbauder [8] and should include a high affinity for the metal of interest, be sufficiently water-soluble to take by mouth, and be sufficiently lipid-soluble to distribute to sites of accumulation of the metal. Thus, Marrs and Bateman [2] concluded that if this were generally the case, partition studies would clearly improve the predictive value of in vitro studies of the chelating agents.

3.2. Oxygen works in carbon monoxide poisoning by two mechanisms

A high partial pressure of oxygen displaces carbon monoxide from the iron of hemoglobin, myoglobin and various enzymes in a competitive manner. Simultaneously, a high partial pressure of oxygen increases the pulmonary elimination of carbon monoxide. It should be outlined that it is unusual for antagonistic antidotes to modify the kinetics of the toxicant. The relative importance of these two mechanisms in the treatment of human poisoning is not known. In our day-to-day experience, many carbon monoxide poisonings found unconscious awaken within a few minutes while breathing pure oxygen. This rapid improvement seems incompatible with what is known about the elimination half-life of carboxyhemoglobin. It must be emphasized that in comparison with what is known of the kinetics of other drugs, the knowledge of the kinetics of carbon monoxide is very limited.

4. Slowing of metabolic activation

The toxicity of both methanol and ethylene glycol (EG) results from their metabolism to more toxic metabolites by liver alcohol dehydrogenase: formate (methanol), glycolate and oxalate (ethylene glycol) [9]. The conventional treatment of these life-threatening poisonings includes gastric decontamination, massive amounts of sodium bicarbonate, blockade of the metabolism of toxic alcohols by ethanol, and hemodialysis. However, the indications for the respective parts of this treatment regimen remain a matter of debate, as ethanol treatment may be inefficient when doses used are too low or result in side-effects when administered in excess. 4-Methylpyrazole (4-MP) is a very potent inhibitor of alcohol dehydrogenase (ADH) activity in various species, including humans. 4-MP has a profound inhibitory effect on the oxidation of both methanol and EG in monkeys and dogs, respectively [10].

Because 4-MP is an inhibitor of ADH rather than a competitive substrate like ethanol, it has been suggested as having greater value than ethanol in treating EG poisoning. 4-MP has other therapeutic advantages over ethanol: it does not exert CNS depressant activity and it has a longer duration of action than ethanol because of slower elimination. Studies in animals and healthy volunteers have shown that repeated doses of 4-MP are safe, in contrast with its parent compound pyrazole. Recently, 4-MP treatment has been tried in a limited number of acute human ethylene glycol poisonings admitted early after ingestion. 4-MP was found to be both efficient and safe. Both intravenous and oral regimens of 4-MP, dosed every 12 h until plasma EG became undetectable, were able to block the metabolism of EG, avoiding the requirement for hemodialysis in patients with high plasma EG levels and normal renal function [11]. Normal renal function allows the elimination of unchanged EG. 4-MP appears to be a very promis-

ing antidote allowing a less invasive treatment of early-admitted EG poisoning.

To our knowledge, the efficiency of 4-MP in acute human methanol poisoning has not been assessed. There is a large body of knowledge supporting the use of 4-MP in methanol poisoning. However, some differences between EG and methanol poisonings preclude drawing any inference from the efficiency of 4-MP in EG poisoning. Indeed, in patients with normal renal function, the renal clearance of EG is in the range of 20–40 ml/min with an elimination half-life of about 12 h. In contrast, unchanged methanol is eliminated very slowly, mainly by the renal route, its renal clearance being about 1–2 ml/min, corresponding to a plasma half-life of about 40–50 h. Thus, theoretically, blocking methanol metabolism with an inhibitor requires consideration of hemodialysis as the safety of repeated doses of 4-MP has only been demonstrated to 96 h, and more prolonged treatment has not been assessed.

4-MP has also been shown to be useful in treating disulfiram-like reactions. These manifestations result from the ingestion of ethanol in a patient having a blockade of aldehyde dehydrogenase by disulfiram or related compounds, thus allowing the accumulation of acetaldehyde, the toxic metabolite. Disulfiram reactions can induce life-threatening poisoning due to the accumulation of acetaldehyde in blood. The conventional treatment of this occasional poisoning includes supportive treatment and at times β-blocking agents in case of vasoplegic shock. 4-MP was shown to block acetaldehyde accumulation and reverse the toxic manifestations in an animal model of disulfiram reactions. Similarly, a single intravenous 7 mg/kg dose of 4-MP reversed the signs and symptoms in a patient suffering from disulfiram reaction [12].

5. Accelerating an inactivating metabolism

N-Acetylcysteine (NAC) is a life-saving antidote in paracetamol poisoning. Clinical studies suggest that, depending on the delay between ingestion and treatment, several mechanisms of action may come into play. It is fascinating to note that the antidote in the early phase does not impede the production of the toxic metabolite *N*-acetyl-*para*-benzoquinonimine (NRPQI), but rather scavenges the toxic radical as it is produced. However, the mechanisms of action of *N*-acetylcysteine are quite complex, involving several metabolic pathways. Indeed, NAC enhances synthesis of glutathione and production of sulfate. Furthermore, it encourages the reduction of NAPQI to paracetamol [13]. This latter mechanism of action would be associated with an increase in the elimination half-life of paracetamol, which has been reported in severe poisoning but only in the setting of severe hepatic damage.

Thiosulfate is the cosubstrate of rhodanese, the hepatic enzyme, which transforms the cyanide ion to thiocyanate by incorporation of an atom of sulfur. Thiosulfate is a remarkably effective antidote in intoxications by compounds which slowly liberate cyanide such as sodium nitroprussate. In our experience it seems also beneficial during the acute phase of aliphatic nitrile poisonings in combination with hydroxocobalamin. We believe that hydroxocobalamin is the drug of choice to treat the acute manifestations of aliphatic nitrile poisonings and should be administered rapidly, while sodium thiosulfate has a more prolonged benefit and should be administered as a continuous infusion in the prevention of recurrent cyanide poisoning. As in the case of NAC, sodium thiosulfate does not inhibit hepatic production of the toxic metabolite (in this case cyanide) but provides for its rapid elimination.

6. Promoting an extracellular redistribution of toxicant

Among the antidotes acting by induction of an extracellular redistribution of the toxicant are the immunotoxicotherapeutic agents and several antidotes to cyanide, namely hydroxocobalamin and the methemoglobin-forming agents.

The last two decades have seen a rise in importance of immunotoxicotherapy. Two recent improvements in immunotherapy are representative: *Digitalis* and colchicine poisonings. The

development of *Digitalis* Fab fragments represented a major improvement in immunotherapy, greatly improving its safety in comparison with antivenoms. Fab fragments work by inducing (1) extracellular redistribution, (2) sequestration of the toxin in the extracellular space, and (3) renal elimination of a small molecular weight antibody-toxin complex. This therapeutic approach is limited by the ratio of the mass of the antidote to that of the poison. The practice of immunotoxicotherapy with *Digitalis* Fab has been to reverse the poisoning in an equimolar fashion. With drugs such as *Digitalis* which are toxic in minute amounts such an approach is feasible, but expensive. Our experience in *Digitalis* poisoning suggests that partial neutralization can effectively convert a fatal intoxication to a non life-threatening one. These preliminary results must be confirmed. The management of *Digitalis* intoxication continues to rely on supportive care of the patient, and early gastrointestinal decontamination. Due to their cost, *Digitalis*-specific Fab antibody fragments are recommended only in severe poisonings unresponsive to conventional treatment. However, in spite of the current availability of digoxin-specific Fab fragments, severely poisoned patients still die. Recently, in one large series of cardiac glycoside poisoning the analysis of the causes of death revealed that the main obstacles to the success of Fab fragments were pacing-induced arrhythmias and delayed or insufficient administration of Fab [14]. Indeed, the iatrogenic accidents of cardiac pacing were frequent (14/39) and often fatal (5/39). In contrast, immunotherapy was not associated with any serious side-effects (0/28) and was safer than pacing. Thus, cardiac pacing appears of limited value and even harmful in the treatment of acute *Digitalis* poisoning. These results suggest that Fab fragments should be first-line therapy during acute *Digitalis* intoxication. Fab treatment should be recommended in patients exhibiting either severe ventricular arrhythmias or poor prognostic factors. Poor prognostic factors of acute *Digitalis* poisoning include: (a) advanced age, (b) heart disease, (c) male sex, (d) high degree atrioventricular block or bradycardia refractory to atropine, and (e) hyperkalemia. In our experience, early treatment with *Digitalis* Fab fragments, while expensive, tends to decrease the duration of hospitalization in a critical care unit, offsetting the cost of the antidote (14).

Digitalis Fab fragments demonstrated that immunotoxicotherapy may be very effective against membrane-level toxins. The recent development of colchicine-specific Fab fragments has revealed the exciting proposition that immunologic fragments which remain in the extracellular space can reverse the effect of intracellular toxin [15]. The reversal of colchicine toxicity, at least in the case of delayed treatment, has not been global, however. While there is dramatic improvement in cardiovascular function, the effect on the hematopoietic system persists.

As was previously mentioned with regard to digoxin, partial neutralization presents numerous advantages in immunotoxicotherapy, due to the limited availability and high cost of the antibody products. This concept of partial neutralization has been further exploited in the form of colchicine-specific Fab fragments. As animal experiments demonstrated efficacy of partial neutralization of colchicine [16], the first human intoxication was treated with a substoichiometric dose of colchicine-specific Fab fragments [15].

Cyanide poisoning, more frequent than previously suspected [17], remains life-threatening. Supportive treatment in association with oxygen has been reported effective in acute cyanide poisoning. It should be noted that all presently available cyanide antidotes except for oxygen work on a toxicokinetic basis, specifically by the reduction of free cyanide at the tissue level. The efficacy of these other antidotes has not been unequivocally proven in man. Hydroxocobalamin and methemoglobin-forming agents act in proximity to the sites of injury, principally the brain and heart. Thiosulfate on the other hand provides a substrate for hepatic metabolism thus acting at a distance from the target organ. The transformation of hydroxocobalamin to cyanocobalamin has been demonstrated in vivo in acute cyanide poisoning [18]. This transformation is rapid and strictly related to the concentration of blood cyanide up to 1 mg/l. It appears to be

well tolerated in man even in the complex setting of smoke inhalation [19]. The administration of hydroxocobalamin is associated with a rapid and constant improvement in systolic blood pressure alleviating the need for catecholamine support. Whether it provides additional benefits remains to be seen.

7. Non-specific modulation of the toxicokinetics

All drugs that improve the hemodynamic status may also improve the perfusion of the gastrointestinal tract, liver and kidney. Thus, depending on the amount of toxin remaining in the gut, the net result may be either worsening of the clinical status due to increased absorption or improvement by promoting elimination of the toxicants.

8. Conclusion

Many possibilities exist to modify the toxicokinetics of a toxicant by specific antidotes. However, an efficient antidote is merely the translation of what we know of the pathophysiology of the poisoning. The introduction of a new antidote is the prize awarded for the molecular approach to the treatment of acute poisoning. The antidotal approach to the toxicokinetic treatment of human poisoning is less invasive and more easily administered than conventional supportive therapy, but requires more sophisticated reasoning. The ability to modify toxicokinetics with a new treatment, while demonstrating an understanding of the mechanism of action, must never be construed to be, in and of itself, the goal of therapy. The ultimate evaluation of an antidote modifying toxicokinetics is strictly clinical. Further clinical assessment of toxicokinetic treatments on a more stringent scientific basis using prospective methods must be promoted.

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