Measuring toxin concentrations in poisoning and improving care

Nick Bateman

Edinburgh

Basic Concepts

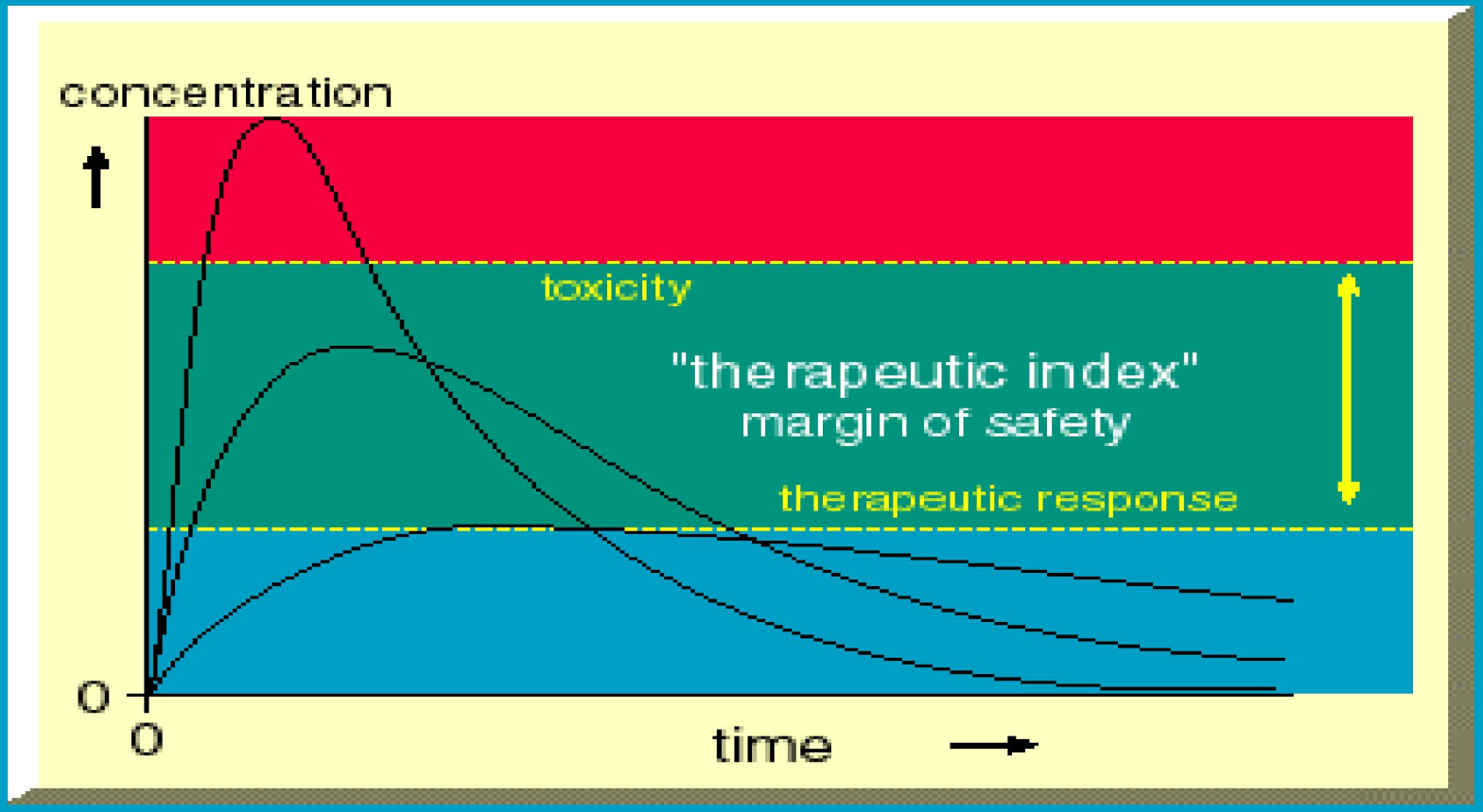
1. Toxins cause effects at receptors
2. Effect usually proportional to concentration
3. Speed of onset (absorption) may effect dynamics of response
4. Xenobiotics are generally fat soluble (some notable exceptions)
5. Metabolism makes them water soluble

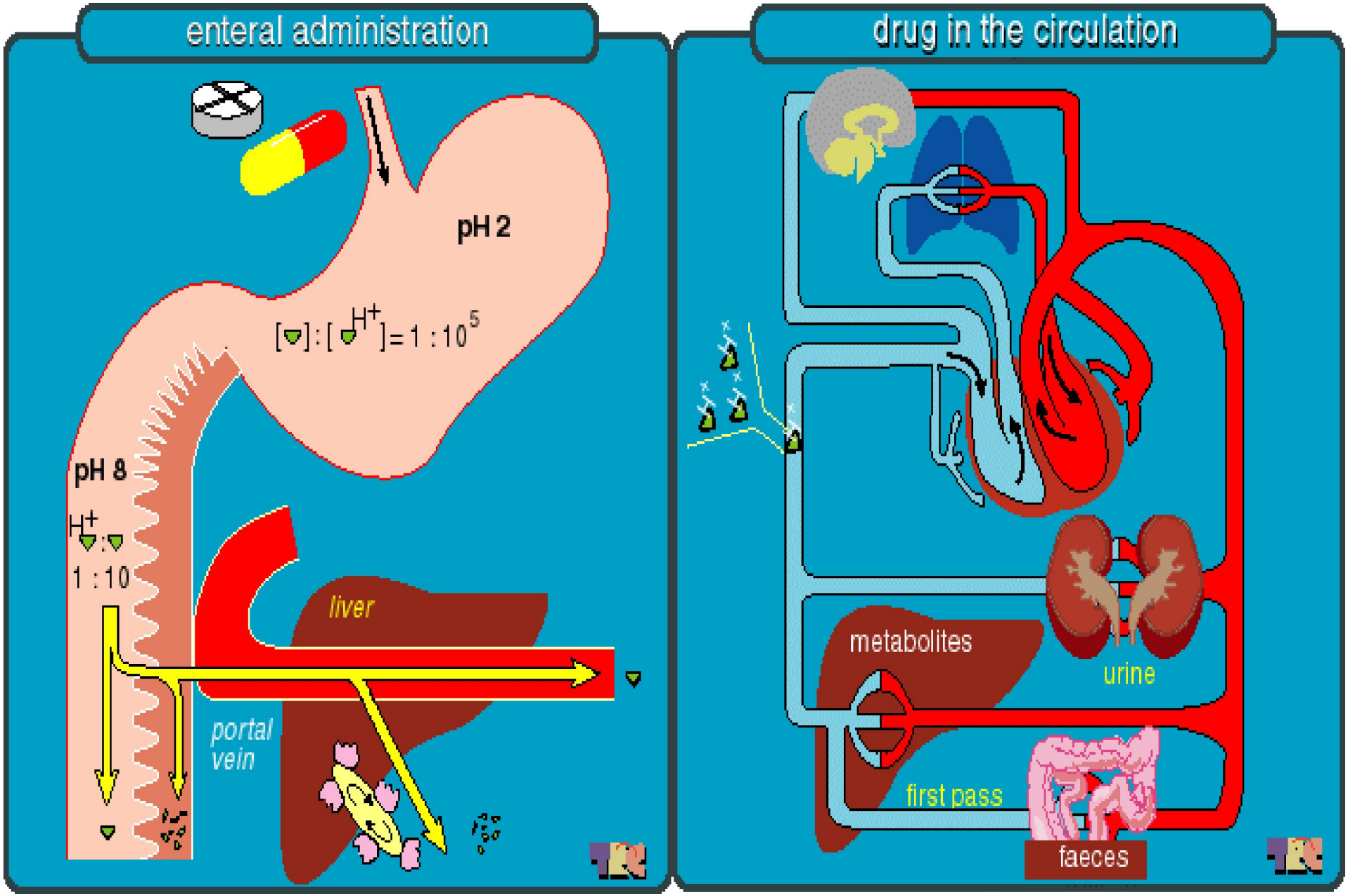
Why measure concentration in clinical practice?

There is a relationship between concentration and effect:-

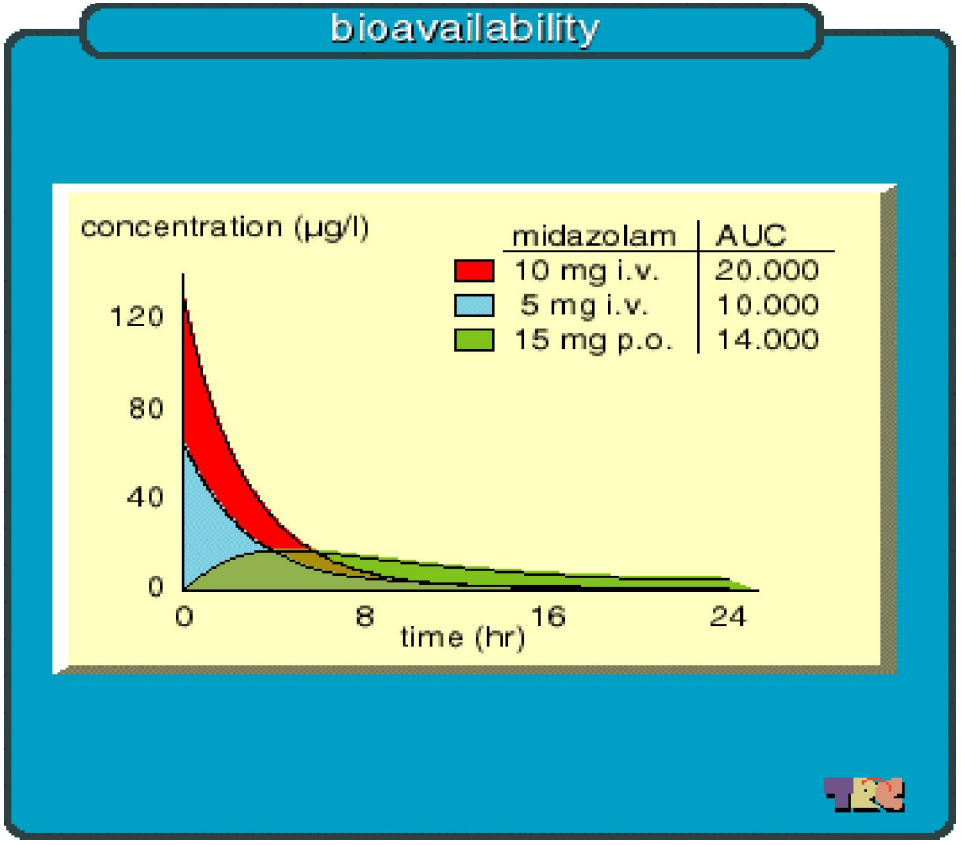
1. **To predict patient outcome**
2. **To decide treatment modality**
3. **To monitor effect of treatment**

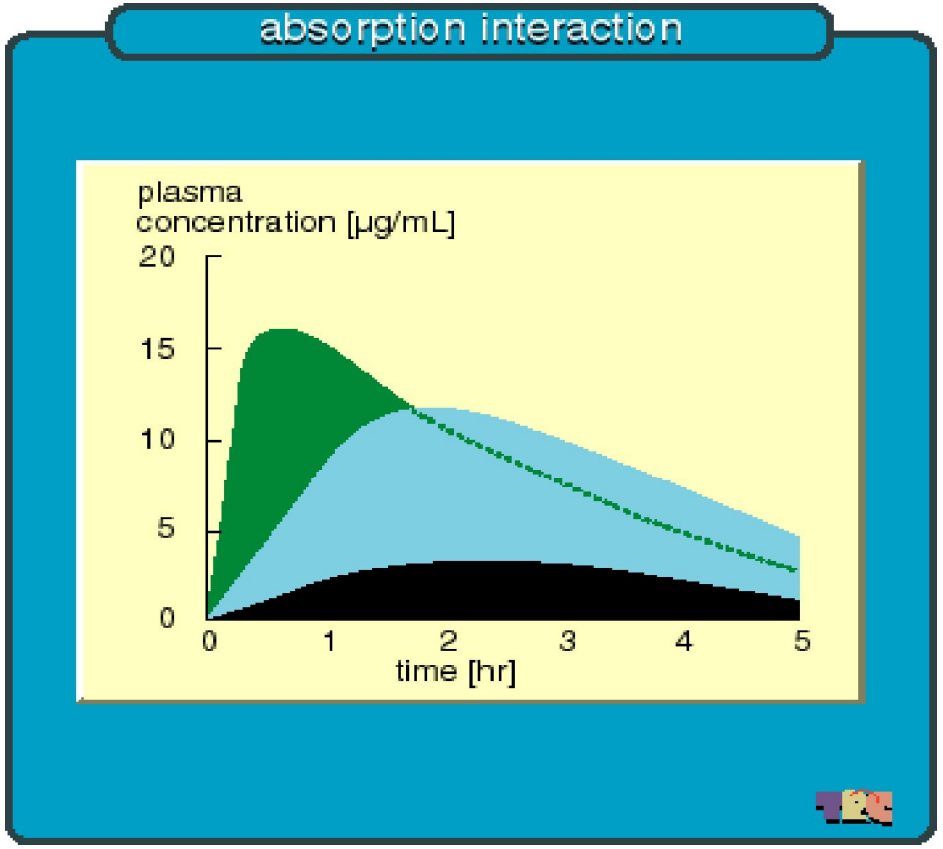
therapeutic index




enteral administration
pH 2
[▽]:[H+]=1:10^5
pH 8
H+:▽
1:10
liver
portal vein
drug in the circulation
metabolites
urine
first pass
faeces

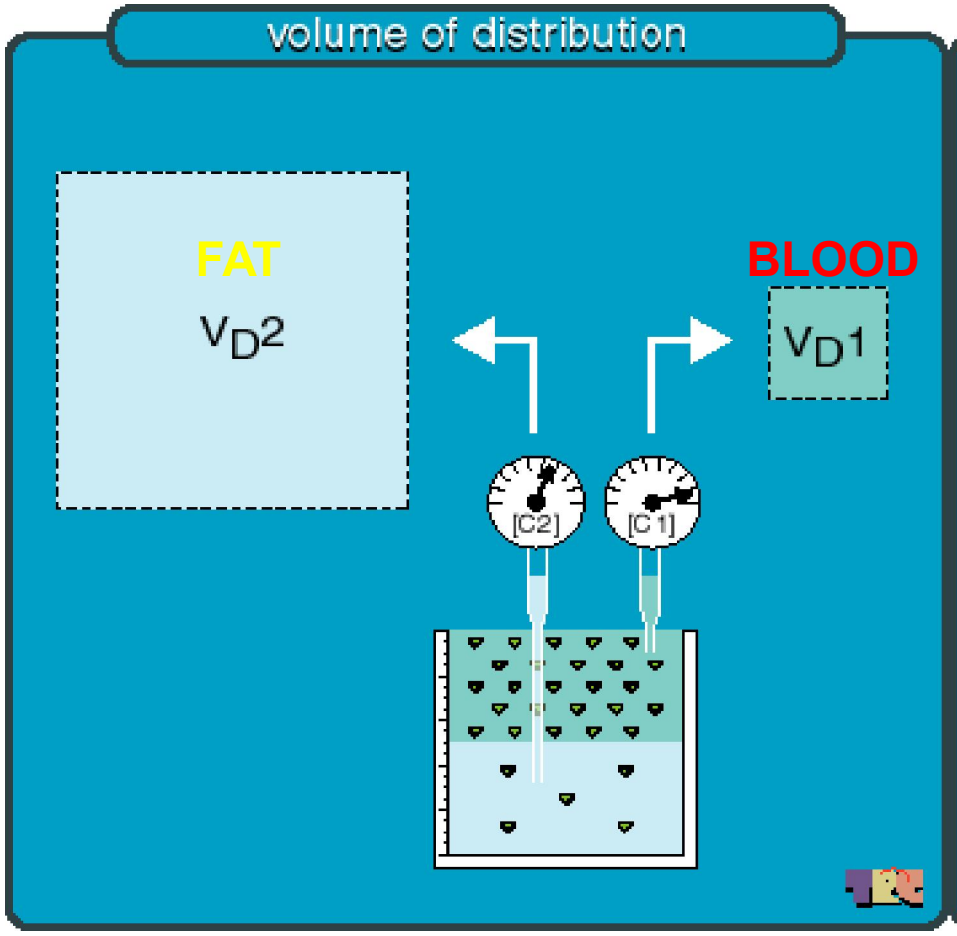
Basic Concepts:
1. Bioavailability

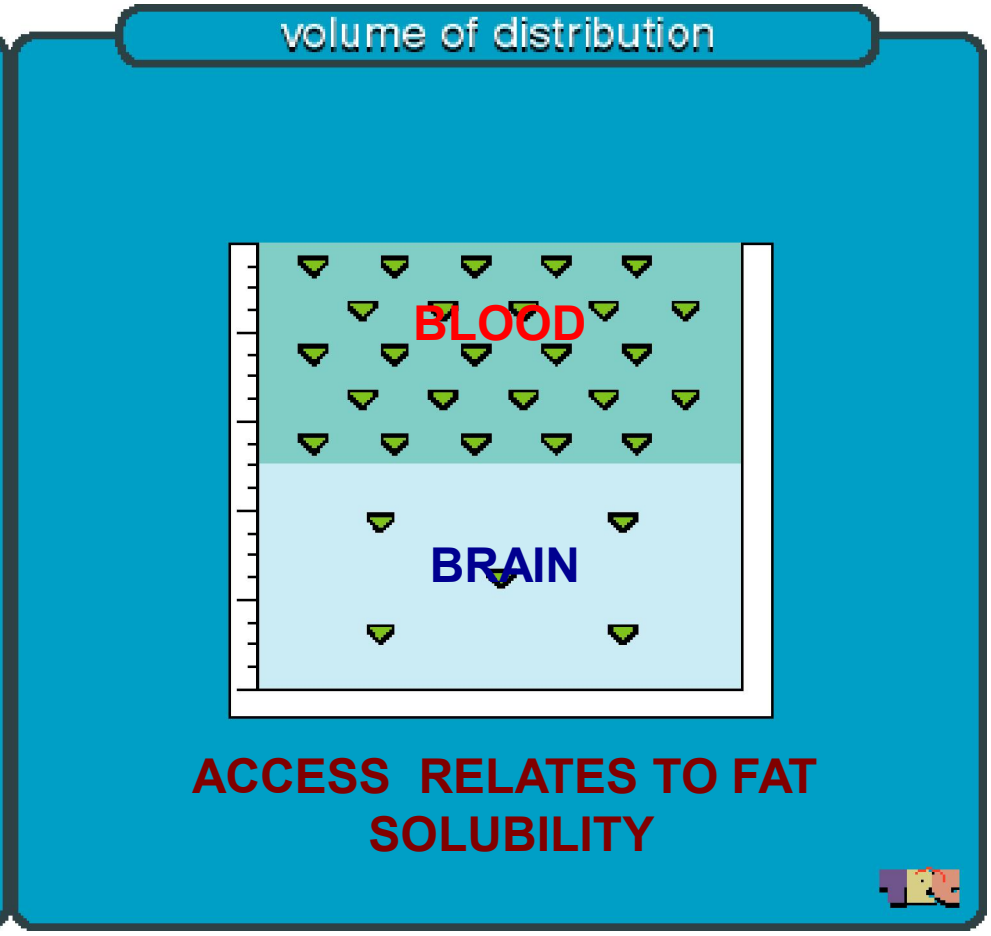




Effect of *metoclopramide* or *activated charcoal* on drug absorption

Basic Concepts: 2. Volume of distribution and blood-brain barrier





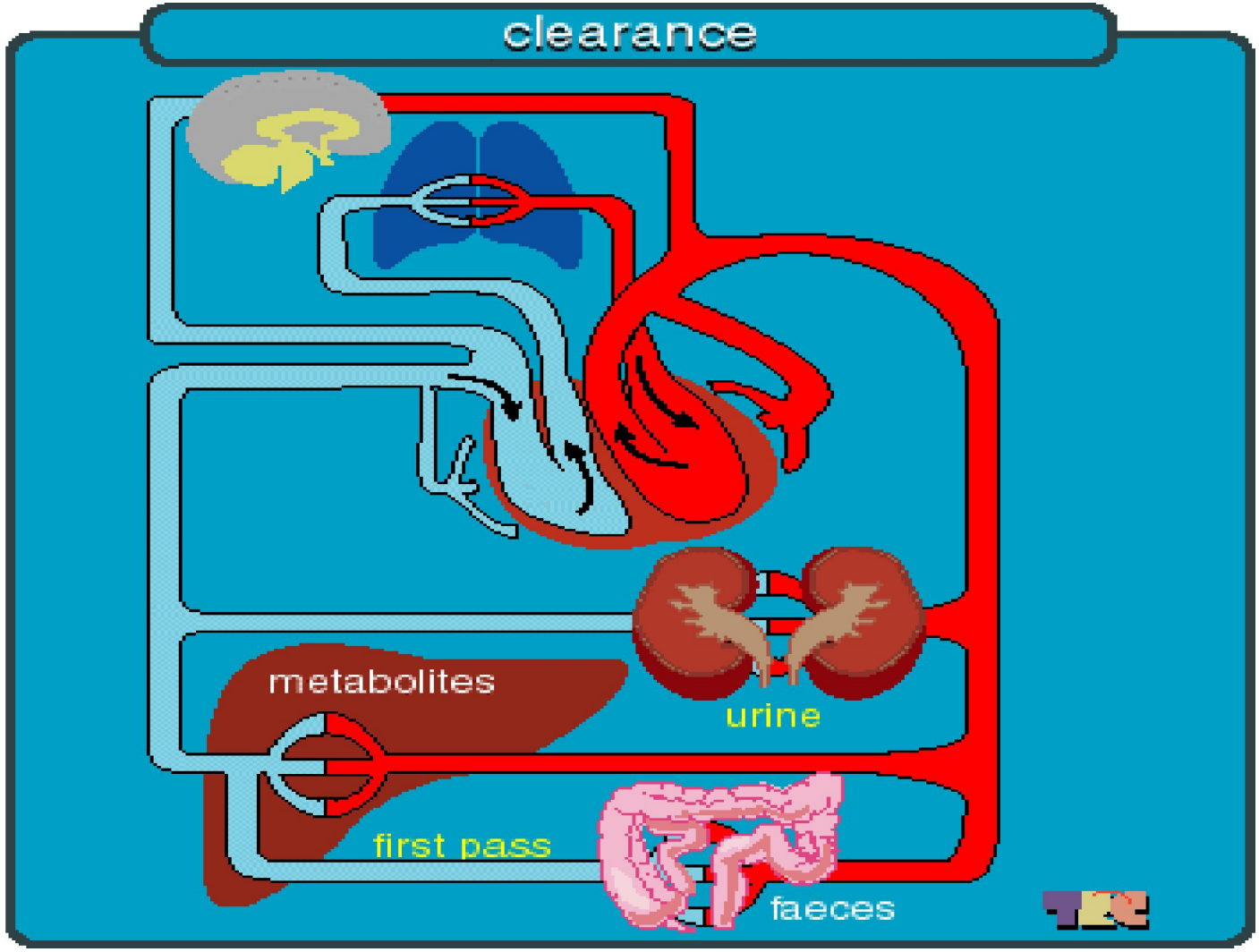
Volumes of distribution

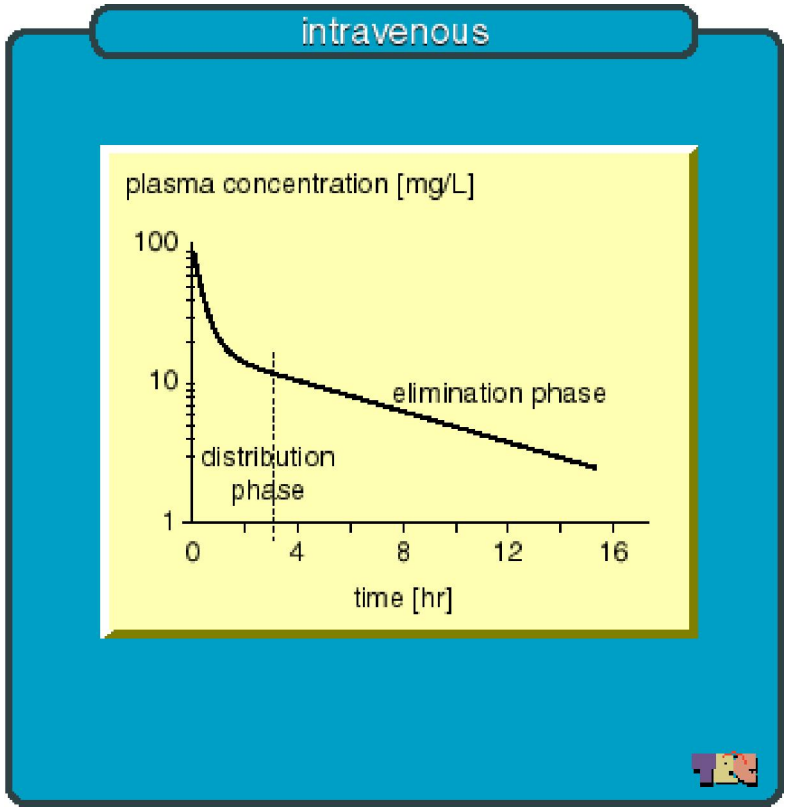
- **Aspirin** **0.15 L/kg**
  (physiological pH)
- **Paracetamol** **0.8-1 L/kg**

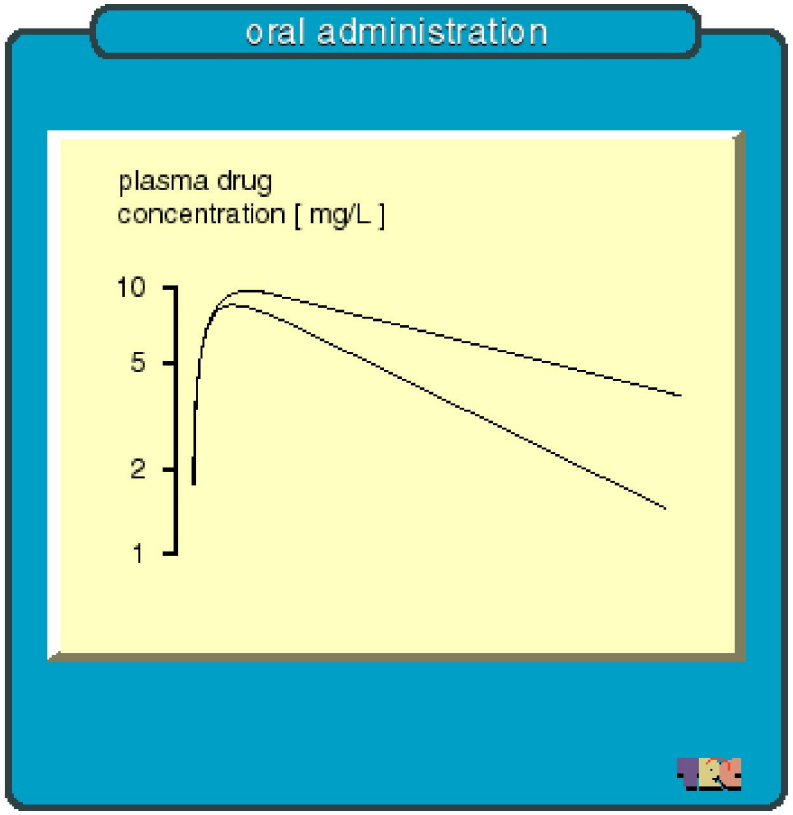
- **Propranolol** **4 L/kg**

- **Tricyclic antidepressants** **20 L/kg**

Basic concepts: 3. Clearance and Half-life







1st order elimination

Zero order kinetics-
Saturation

Basic Concepts

4. Protein binding

- Only free plasma concentrations of drugs are active
- Only free plasma concentrations are immediately available to cross membranes
- Binding varies from 0 (ethanol) to >95% (phenytoin)

Basic Concepts

5. Induction and inhibition

Enzyme Inducers

REQUIRE PROTEIN SYNTHESIS

Rifampicin
Phenytoin
Carbamazepine
Phenobarbitone
St John’s Wort
Chronic ethanol

Enzyme Inhibitors

WORK IMMEDIATELY BY DIRECT INTERACTION WITH ENZYME

CYP 450

Cimetidine

Ciprofloxacin

Erythromicin

Ethanol

Fluconazole

Competitive Enzyme Inhibitors

WORK IMMEDIATELY BY DIRECT INTERACTION WITH ENZYME

Eg Alcohol dehydrogenase

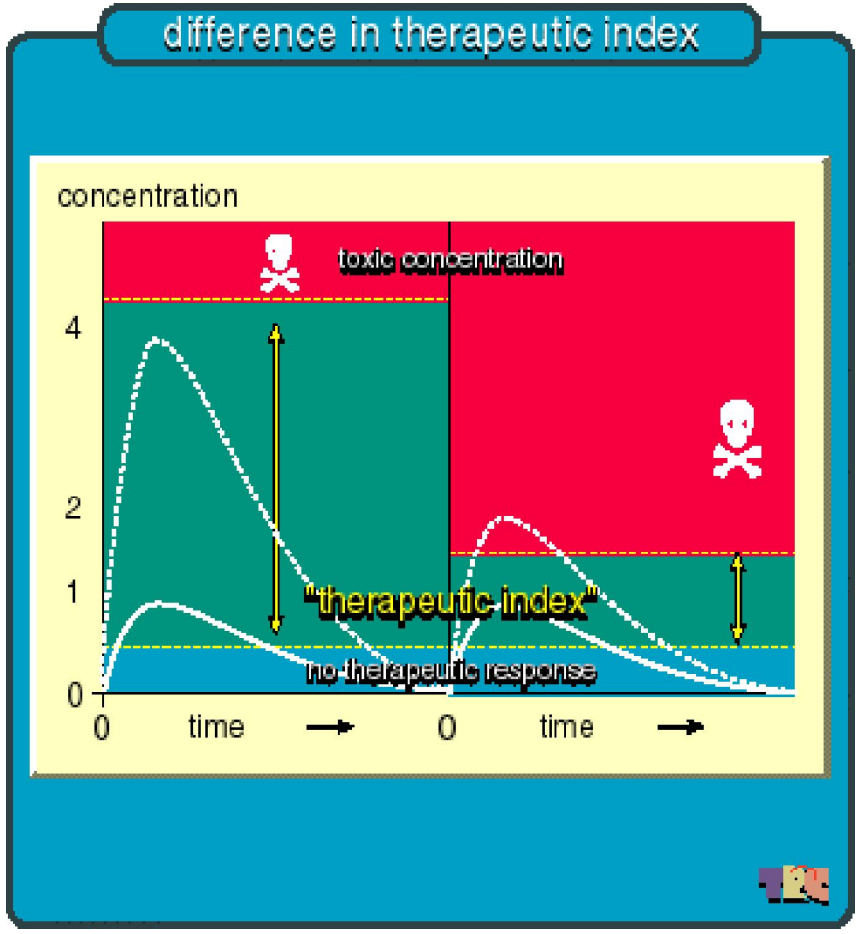
Ethanol or fomepizole in methanol and glycol poisoning

Measuring blood concentrations

1. To identify need for treatment
2. To exclude need for treatment
3. To determine when to stop treatment

Only where it makes a difference to treatment choice

eg Not for opioids or TCAs



Group 1: assays that should be available on a 24-h basis in all acute hospitals

- Carboxyhaemoglobin
- Digoxin
- Ethanol
- Iron
- Lithium
- Methaemoglobin
- Paracetamol
- (Paraquat (qualitative urine test) ??)
- Salicylate
- Theophylline
- Valproate

Results should normally be available within a maximum of 2 h of presentation (or sooner if possible) unless otherwise stated. Their use is summarized in Table 3 in Appendix 1.

Review Article

The Association for Clinical Biochemistry & Laboratory Medicine

Annals of Clinical Biochemistry
2014, Vol. 51(3) 312–325

DOI: 10.1177/0004563213519754
acb.sagepub.com
SAGE

Guidelines for laboratory analyses for poisoned patients in the United Kingdom

JP Thompson[1], ID Watson[2], HKR Thanacoody[3], S Morley[4], SHL Thomas[3], M Eddleston[5], JA Vale[6], DN Bateman[5] and CV Krishna[1]

Have to make a difference in clinical care

Plasma paracetamol Half life and toxicity

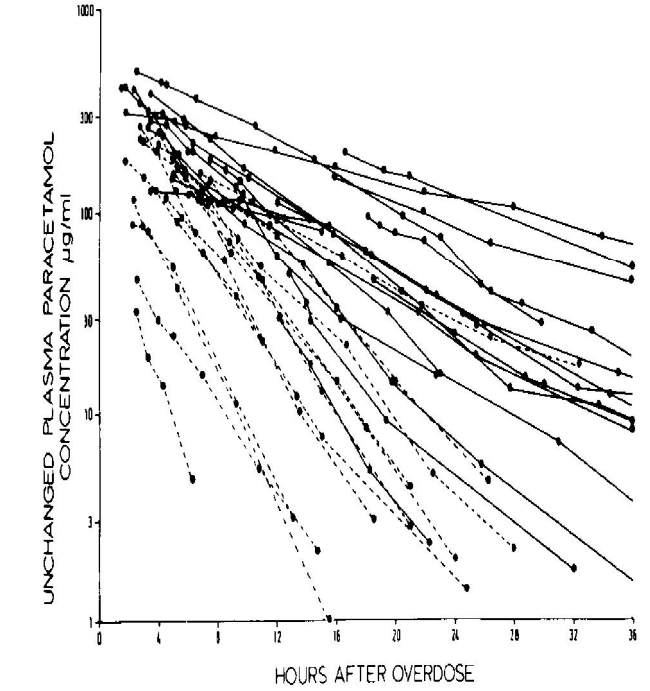
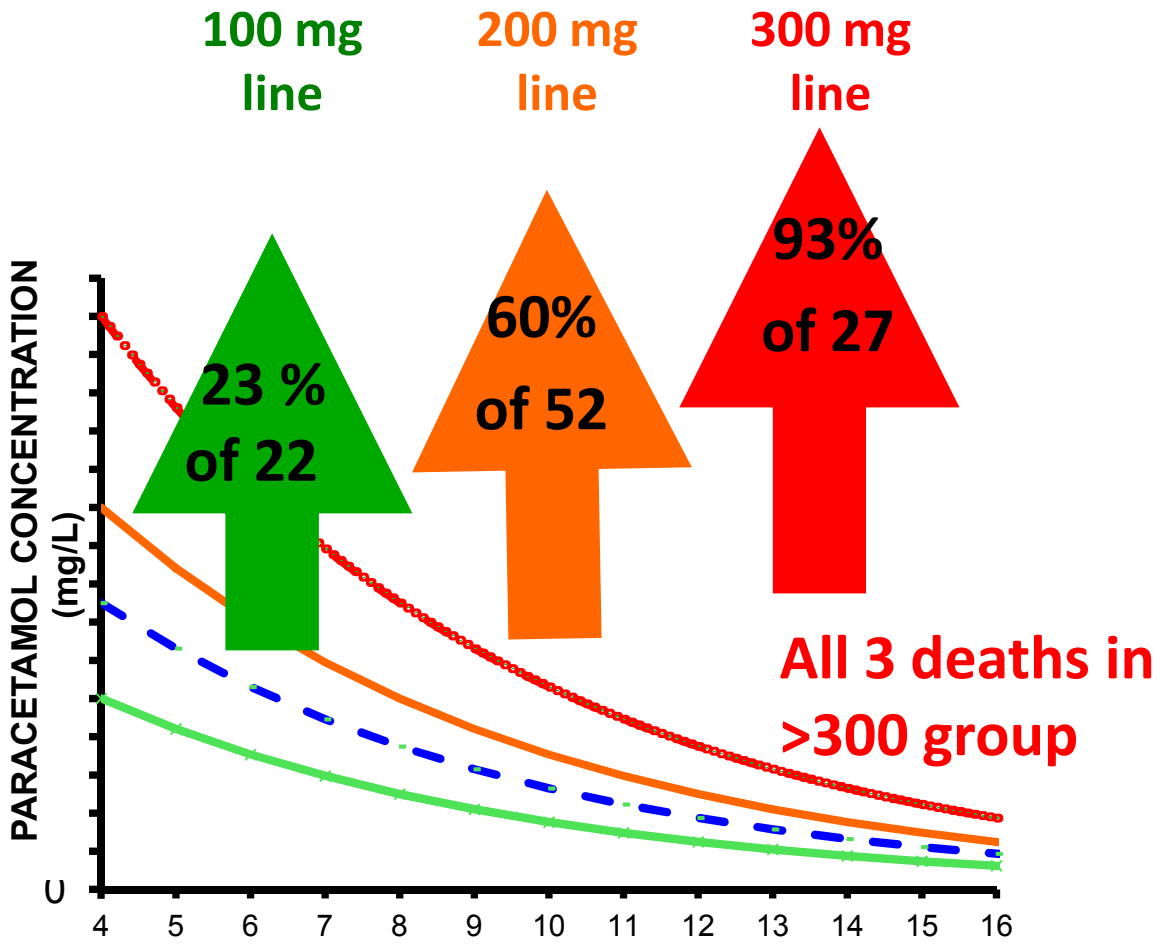


Figure 7.4 Plasma concentrations of paracetamol in 30 patients with and without liver damage following overdosage (redrawn from Prescott *et al.*, 1971).

Prescott et al Lancet 1972

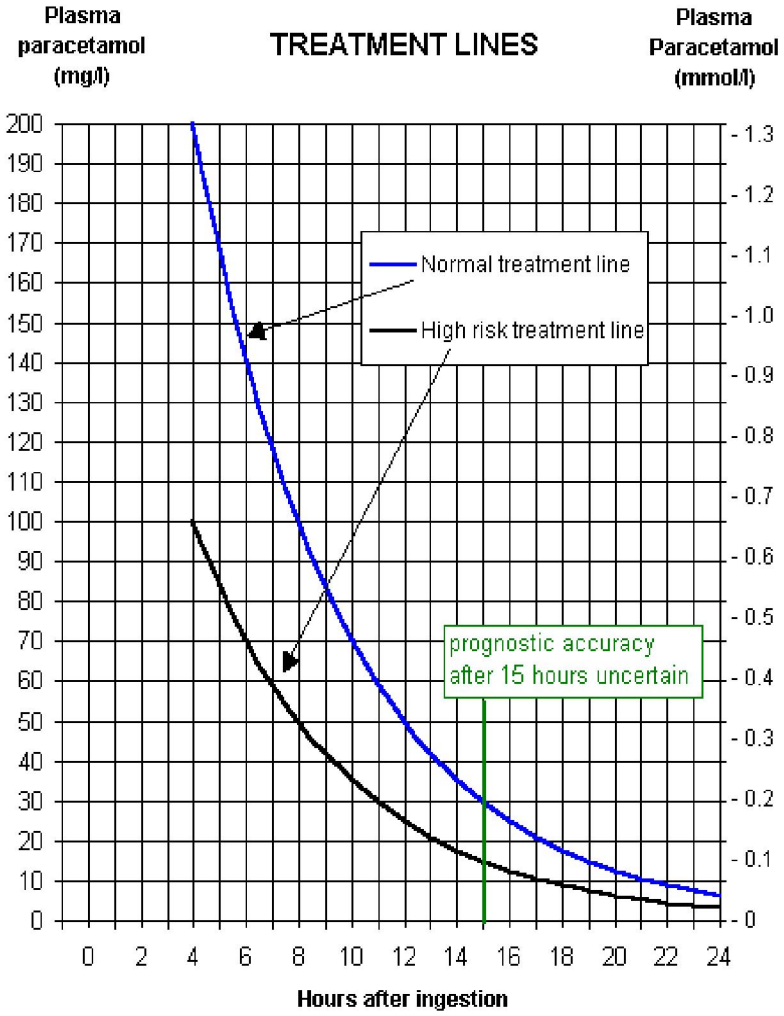
Risk of ALT > 1000 without treatment at 100, 200 and 300 mg/L "Risk lines"



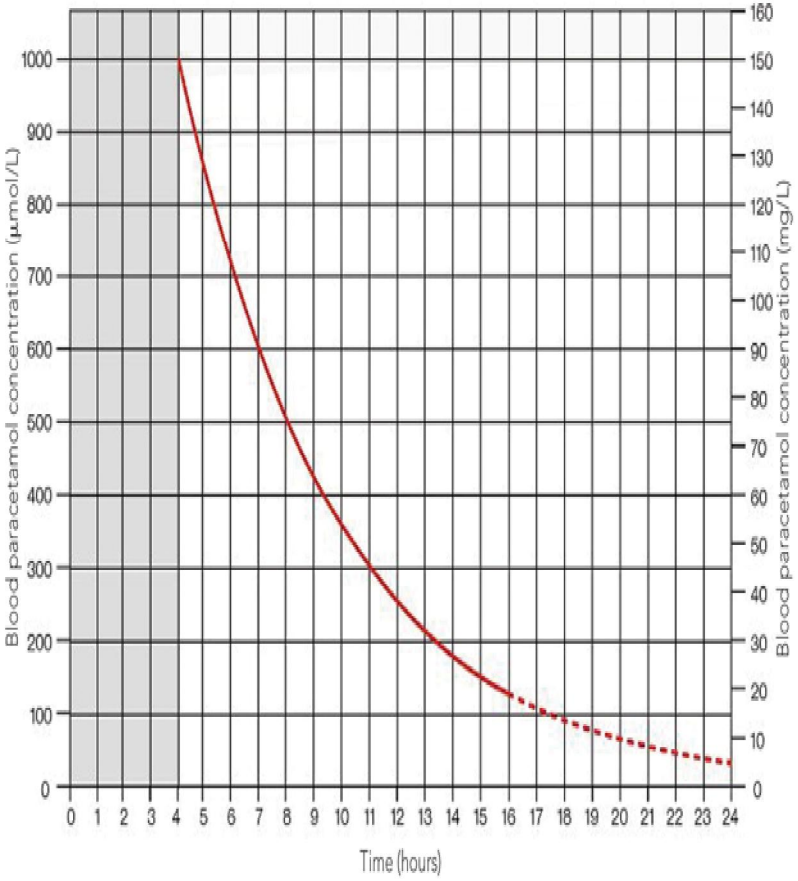
Prescott LF, Health Bulletin 1978, 204-212

Which approach to risk assessment?

UK 1995-2012



USA since 1970s
(NZ and Australia since 2008)



Salicylate
Concentration-effect relationship

- **Mild toxicity - peak plasma salicylate concn. less than 300 mg/L (< 2.2 mmol/L).**
- **Moderate toxicity - 300-700 mg/L (2.2-5.1 mmol/L).**
- **Severe toxicity - over 700 mg/L (5.1 mmol/L).**
- **Very severe toxicity – over 900 mg/L (6.4 mmol/L)**

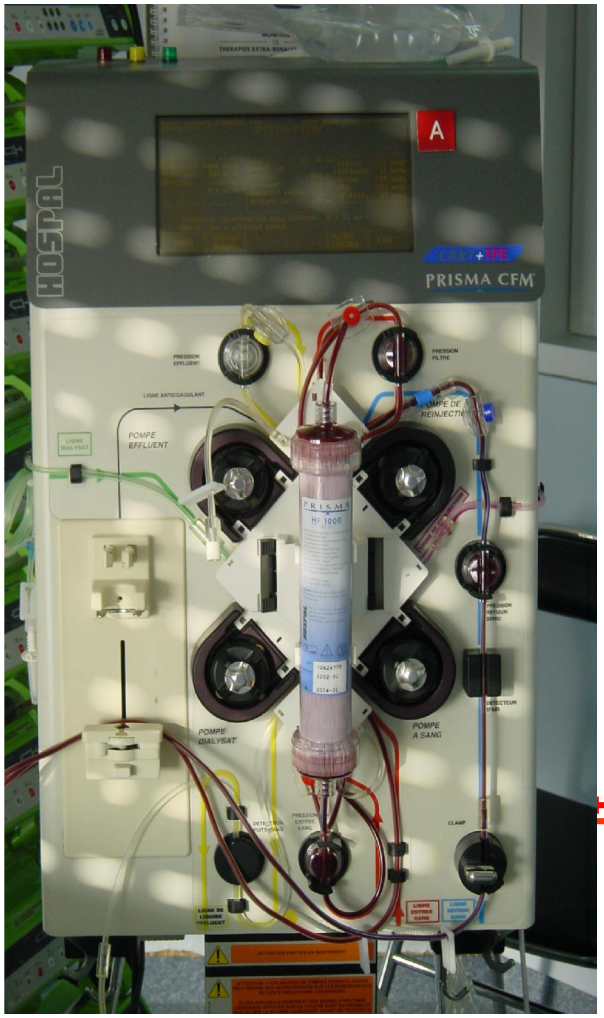
TOXCITY DEPENDANT ON DISTRIBUTION INTO BRAIN:

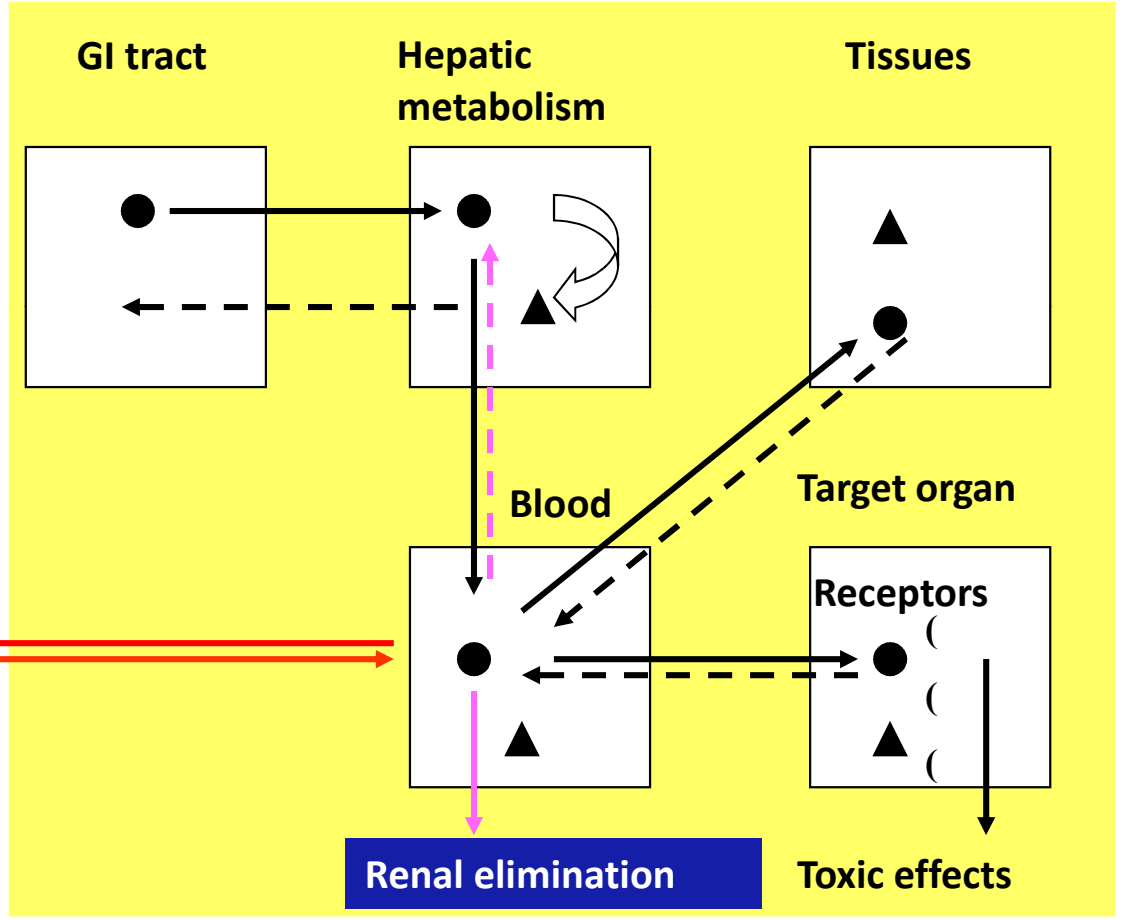
ACIDOSIS CAUSES CHANGE IN VD WITH BRAIN ACCESS

Discuss assay with clinical toxicologist

- Arsenic
- Carbamazepine
- Cholinesterase (plasma and erythrocyte)
- Cyanide
- Ethylene glycol
- Lead
- Mercury
- Methanol
- Methotrexate
- Paraquat (quantitative plasma assay)
- Phenobarbital
- Phenytoin
- Thallium
- Thyroxine
- Toxicology screen*

The kinetic approach to treatment





First use of haemodialysis in aspirin poisoning,1957

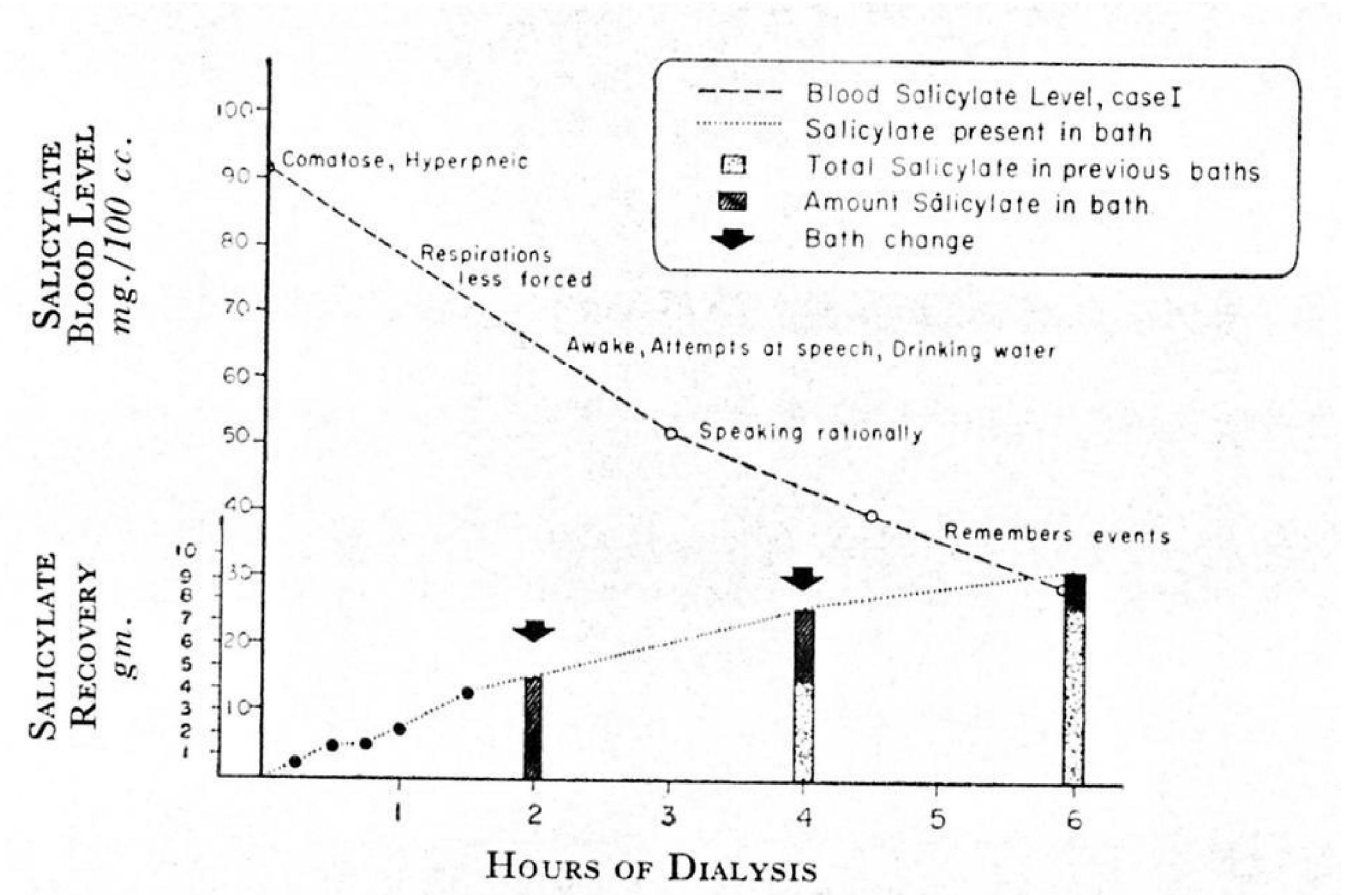


FIGURE 1. *Clinical Dialysis of Salicylate (Case 1).*

TABLE I

CURRENTLY KNOWN DIALYZABLE POISONS

Barbiturates*
- Barbital
- Phenobarbital
- Amobarbital
- Pentobarbital
- Butabarbital
- Secobarbital
- Cyclobarbital

Other Sedatives and Tranquilizers
- Glutethimide*
- Diphenylhydantoin
- Primidone
- Meprobamate
- Ethchlorvynol*
- Ethinamate
- Methypyrlon
- Imipramine
- Amitriptyline
- Phenelzine
- Tranylcypromine
- Pargyline
- Heroin
- Gallamine Triethiodide
- Paraldehyde
- Chloral Hydrate

Analgesics
- Acetysalicylic Acid*
- Methylsalicylate*
- Acetophenetidin
- Dextropropoxyphene

Halides
- Bromide*
- Chloride*
- Iodide
- Fluoride

Metals
- Strontium
- Calcium*
- Iron
- Lead
- Mercury
- Arsenic
- Sodium*
- Potassium*
- Magnesium*

Alcohols
- Ethanol*
- Methanol*
- Ethylene Glycol

Antibiotics
- Streptomycin
- Kanamycin
- Neomycin
- Vancomycin
- Penicillin
- Ampicillin
- Sulfonamides
- Cephalin
- Cephaloridine
- Chloramphenicol
- Tetracycline
- Nitrofurantoin
- Polymyxin
- Isoniazid
- Cycloserine

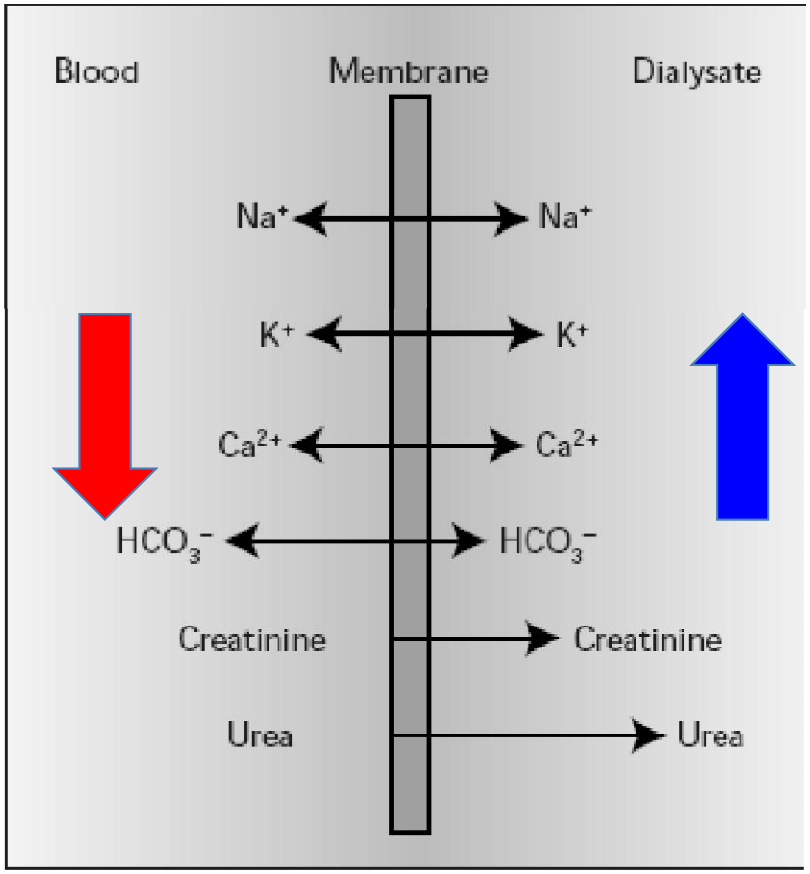
Endogenous Toxins
- Ammonia
- Uric Acid*
- Tritium*
- Bilirubin
- Lactic Acid
- Schizophrenia
- Myasthenia Gravis
- Porphyria
- Cystine
- Endotoxin

Miscellaneous Substances
- Thiocyanate*
- Aniline
- Sodium Chlorate
- Potassium Chlorate
- Eucalyptus Oil
- Boric Acid
- Potassium Dichromate
- Chromic Acid
- Digoxin
- Dextroamphetamine
- Sodium Citrate
- Dinitro-ortho-cresol
- Amanita Phalloides
- Carbon Tetrachloride
- Ergotamine
- Cyclophosphamide
- 5-Fluorouracil
- Methotrexate

* Kinetics of dialysis thoroughly studied and/or clinical experience extensive.

Maher JF and Schreiner GE.
Trans Amer Soc Artific Int Organs
1967;13:369-93.

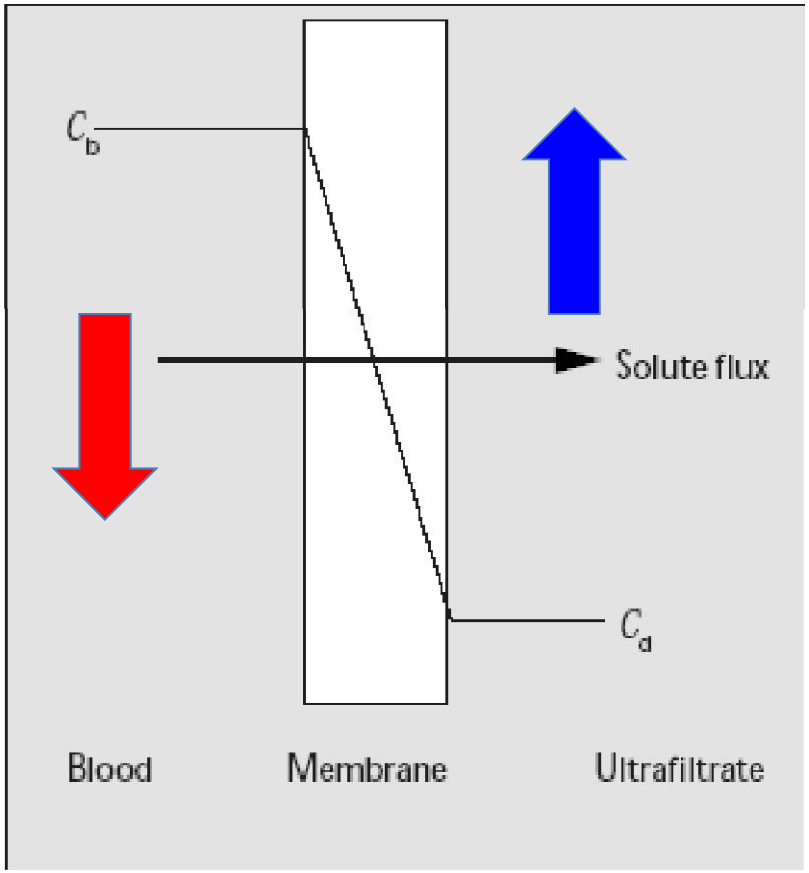
Dialysis



- **dialysis is the process of separating elements in a solution by diffusion across a semi-permeable membrane, down a concentration gradient**

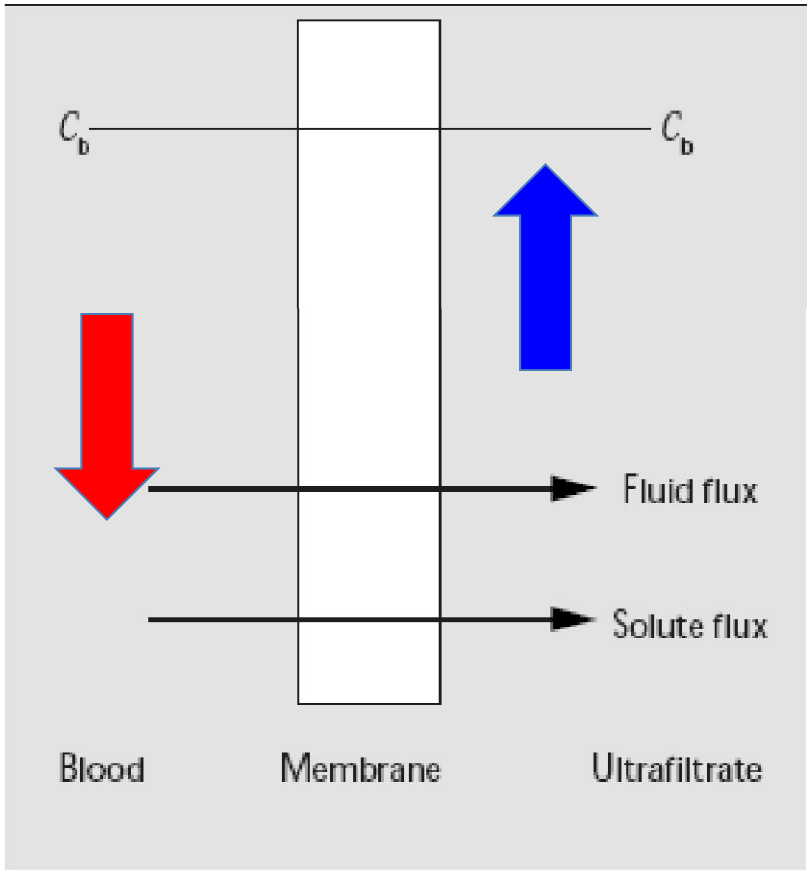
- **this is the principal process for removing small molecules and for repletion of the bicarbonate deficit of metabolic acidosis**

Haemodialysis (HD) in poisoning



- molecules small enough to pass through the dialysis membrane diffuse down a concentration gradient, from a higher plasma concentration (C_b) to a lower dialysate concentration (C_d)

Haemofiltration (HF)



- **haemofiltration achieves molecular clearance by convective transport (the solvent drag effect) through the membrane, with pore dimensions exceeding those in conventional dialysis treatment, by removing plasma water and toxin.**

The kinetic approach

- **The amount of drug removed depends on**

  → **plasma concentration**

  → **clearance achieved by the procedure**

  → **duration of the procedure**

Techniques:

Haemodialysis, Haemofiltration, Haemoperfusion, Peritoneal dialysis, Albumen dialysis, Exchange Transfusion, Plasma exchange?

Which agents?

Which techniques?

Which assessments?

The kinetic approach: criteria of efficacy ?

- **Plasma concentatrtion before v after the procedure**
- **T½ (during procedure) *vs* spontaneous T½**
- **Technique clearance *vs estimated* total clearance**
- **Amount recovered *vs estimated* intrinsic elimination (renal, hepatic metabolism)**

TABLE 1. Pharmacokinetic properties of a poison to assess its potential for extracorporeal therapy removal

	HD	HF	HP	Albumin dialysis	PD	ET	TPE
Mechanism of removal	Diffusion	Convection	Adsorption	Diffusion/Convection	Diffusion	Separation	Centrifugation/ Separation/ Convection
MW cut-off	Low-flux: 1000 Da High-flux: 11,000 Da	40 000 Da with exceptions	5000–10,000 Da	MARS/SPAD: 60,000 Da, Prometheus: ≈100,000 Da	<500 Da	No restriction	1,300,000 Da
Protein binding	<80% with exceptions	<80% with exceptions	<90%	Likely high	Likely low	No restriction	No restriction
V_D	Low V_D, (<1–2 l/kg), with exceptions					Requires very low V_D	

HD: hemodialysis, HF: hemofiltration, HP: hemoperfusion, PD: peritoneal dialysis, ET: exchange transfusion, TPE: therapeutic plasma exchange, MW: molecular weight, MARS: molecular adsorbent recirculating system, SPAD: single pass albumin dialysis, V_D: volume of distribution.

GHANNOUM, M., et al. 2014. A Stepwise Approach for the Management of Poisoning with Extracorporeal Treatments. *Seminars in Dialysis, 27, 362-370.*

TABLE 2. Maximal clearance with any extracorporeal treatment.

ECTR	Conditions	Maximal clearance
Peritoneal dialysis	2L exchange every hour, 50% equilibration of dialysate compared to plasma	16 ml/minute
TPE	A Q_B = 140 ml/minute and a plasma removal rate 50 ml/minute	50 ml/minute
Intermittent HD/HF/HP	A Q_B = 400 ml/minute, hematocrit = 40%, extraction ratio = 100%	240 ml/minute
CRRT	A Q_B = 180 ml/minute, high volume CRRT (effluent flow = 45 ml/hour/kg), weight = 70 kg	52 ml/minute
Exchange transfusion	1L whole blood exchanged/hour, hematocrit = 40%	10 ml/minute

HD: hemodialysis, HF: hemofiltration, HP: hemoperfusion, CRRT: continuous renal replacement therapy, ECTR: extracorporeal treatment.

GHANNOUM, M., et al. 2014. A Stepwise Approach for the Management of Poisoning with Extracorporeal Treatments. *Seminars in Dialysis, 27, 362-370.*

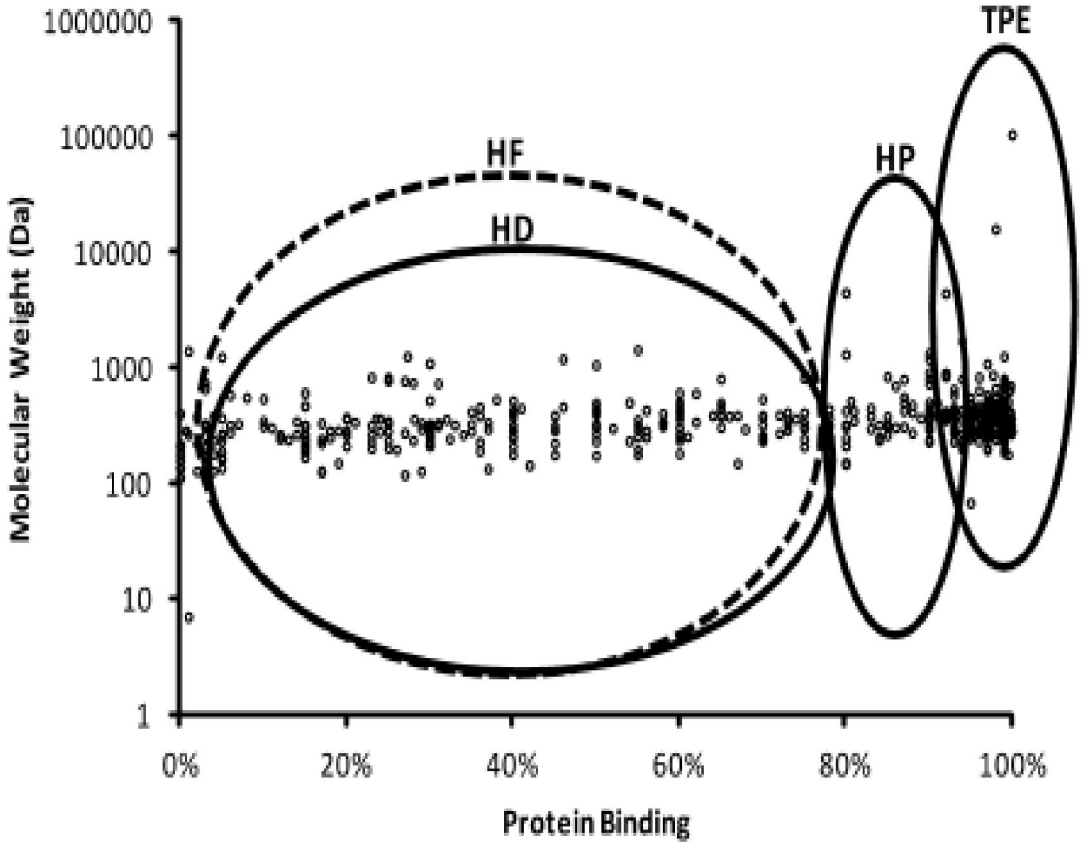


FIG. 1. Relationship between a drug's or poison's molecular weight and protein binding characteristics and the method of extracorporeal clearance that is anticipated to maximize clearance. Circles indicate for which poisons a specific ECTR is most useful. HD: Hemodialysis, HP: Hemoperfusion, HF: Hemofiltration, TPE: Therapeutic plasma exchange.

GHANNOUM, M., et al. 2014. A Stepwise Approach for the Management of Poisoning with Extracorporeal Treatments. *Seminars in Dialysis, 27, 362-370.*

Evaluation of elimination techniques

- **Efficacy**
  - **Does the technique increase the elimination of a given poison ?**
- **Clinical Effectiveness**
  - **Does the technique work in patients ?**
- **Efficiency**
  - **Does the technique compare favourably with other alternatives in terms of consequences (morbidity, mortality, adverse effects…) and costs ?**

The kinetic approach : pitfalls

- **Dose estimate**
- **Role of continued absorption**
- **Decrease of plasma concentration may reflect clearance, absorption OR distribution**

The kinetic approach : pitfalls

- **Over-estimation of procedure clearance**

- **Failure to assess procedure clearance *vs* Total clearance**

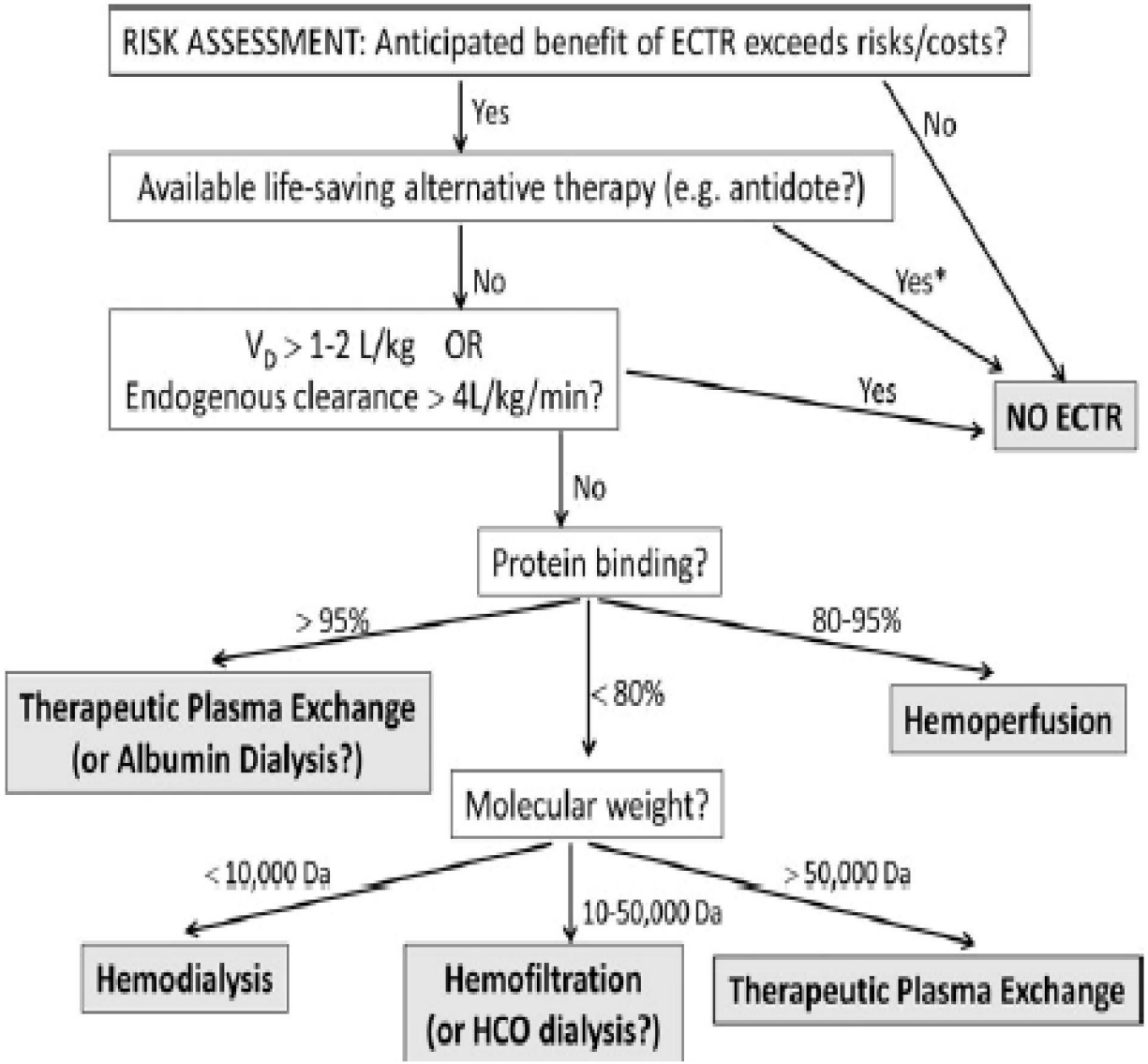


FIG. 2. Stepwise approach for the initiation of extracorporeal techniques for enhanced elimination in a poisoned patients. HCO HD: High cut-off hemodialysis, V_D: Volume of distribution, ECTR: extracorporeal treatment. *In some cases where an antidote is available it may also be appropriate to administer ECTR.

Lithium

Renal excretion
Pumped by Na^+/K^+ pumps in distal tubule
Accumulates in renal impairment

CAUSES: Renal, Thyroid and CNS toxicity

Lithium and HD: criteria

Clinical

* coma, convulsions, respiratory failure
* underlying disease favouring complications
* acute/chronic or chronic poisoning (severity increased)

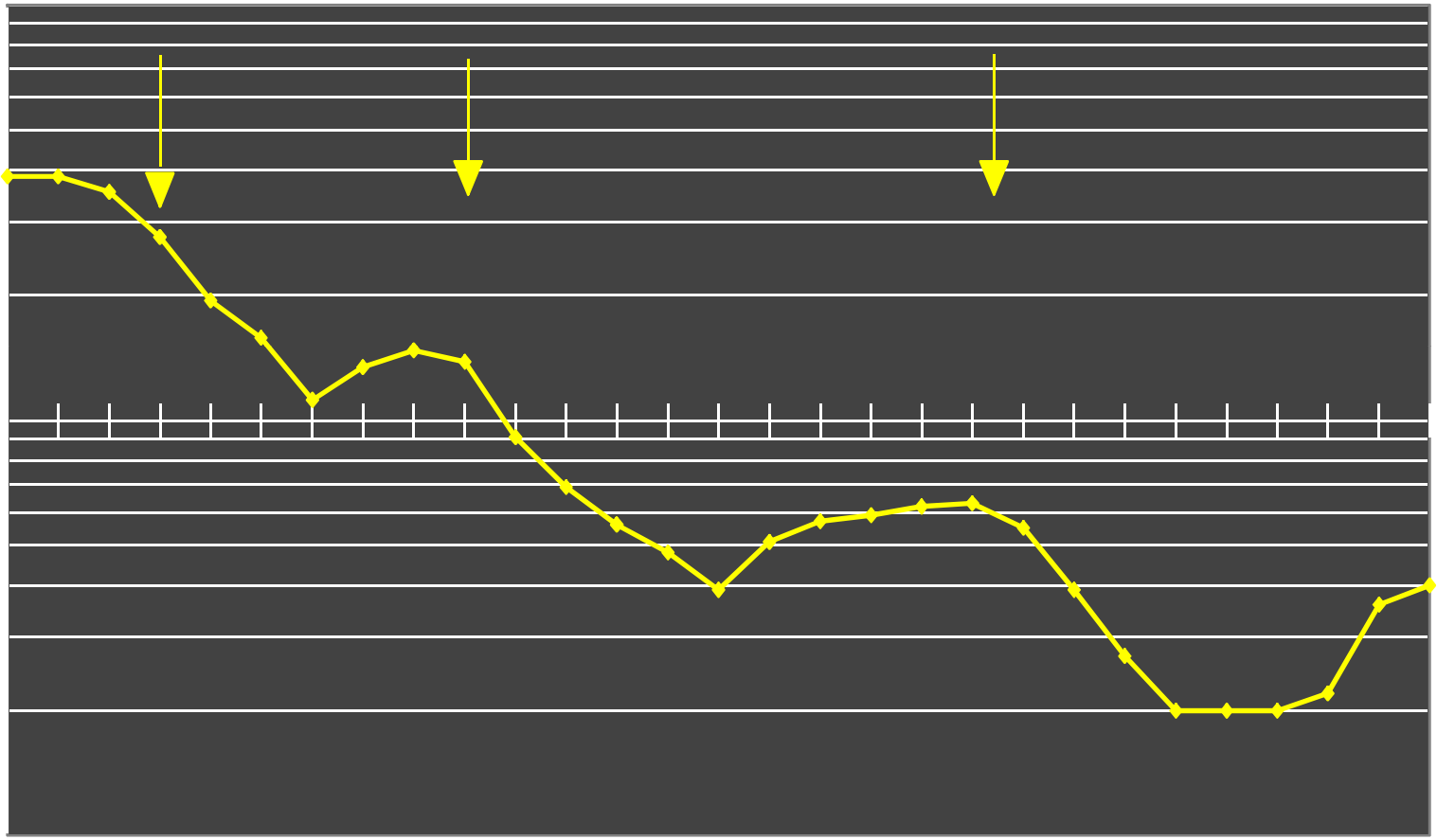
- **Kinetic**

* decreased renal elimination
* increased Li concentration and half-life
* Li increasing with cellular diffusion

expected amount of Li removed by 6-H HD > amount eliminated in urine over 24 H

- Jaeger et al. Clin Toxicol 1993;31:429-47.

Lithium poisoning treated by HD



Variations of lithium T1/2

	acute	acute on chronic	chronic
Dyson et al 1987	11.8	20.9 +/- 1.3	32.2 +/- 3.3
Jaeger et al 1993	11.8 +/- 3.3	16.25 +/- 10.4	30.0 +/- 14.3
Ferron et al 1995		25.1 +/- 4.3	49.6 +/- 15.1

Lithium poisoning treated by HD

HD	Li (mmol/l)		T ½ (h)	Cl HD (ml/min)	Li eliminated (mmol)	
	Before	After			HD	Urine
1 H 7-13	2.76	1.12	4.75	85.9	56.0	1.11
2 H 15-25	1.38	0.39	5.75	84.8	36.2	0.37
3 H 38-46	0.55	<0.2	5.40	75.8	11.6	0.30

CJASN ePress. Published on January 12, 2015 as doi: 10.2215/CJN.10021014

Extracorporeal Treatment for Lithium Poisoning: Systematic Review and Recommendations from the EXTRIP Workgroup

Brian S. Decker, David S. Goldfarb, Paul I. Dargan, Marjorie Friesen, Sophie Gosselin, Robert S. Hoffman, Valéry Lavergne, Thomas D. Nolin, and Marc Ghannoum, on behalf of the EXTRIP Workgroup

Table 5. Aggregate clearances obtained in the reported patients

Method of Removal	Clearance (mL/min)	
	Mean	Range
Endogenous	10.6	1.5–39.6 (n=53)
Peritoneal dialysis	10.9	9–14 (n=5)
Hemodialysis	106.9	40–180 (n=39)
Continuous RRT	43.1	19–64 (n=19)

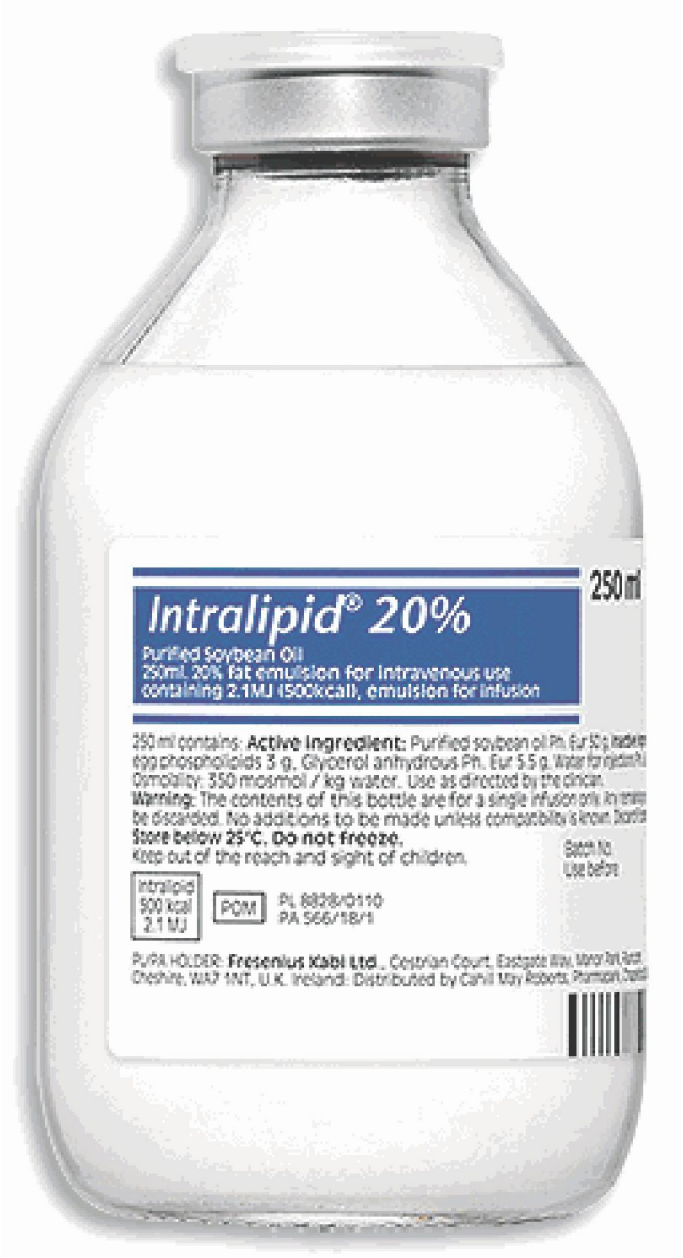
Conclusions (1)

- **High-performance HD seems to be more effective in the elimination of poisons - shorter time of procedure.**

- **HD delivers a more rapid elimination of toxin and a correction of associated acid-base and electrolyte disorders than continuous renal replacement therapy.**

Conclusions (2)

- **Continuous techniques are more widely used in the intensive care unit, mainly due to better haemodynamic tolerance.**
- **Continuous techniques achieve clearances close to normal renal clearance.**
- **Continuous techniques should be considered in patients who are haemodymically unstable.**


Intralipid® 20%
Purified Soybean Oil
250ml. 20% fat emulsion for intravenous use
containing 2.1MJ (500kcal), emulsion for infusion
250 ml
Intralipid
500 kcal
2.1 MJ
POM
PL 8828/0110
PA 566/18/1

Do you believe intralipid works?

A. Yes
B. No
C. Depends
D. Don’t know

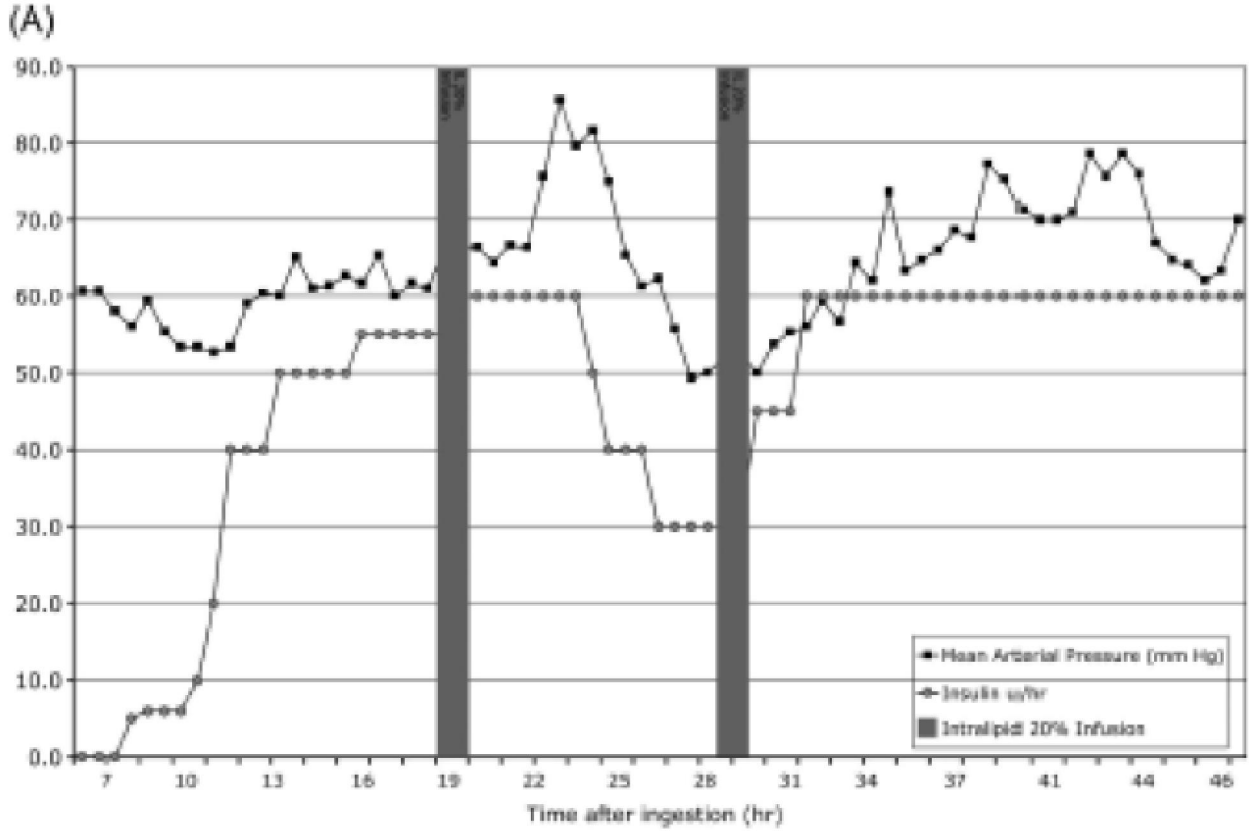
Intralipid

SHORT REPORT

Serum verapamil concentrations before and after Intralipid® therapy during treatment of an overdose

DEBORAH FRENCH[1], PATIL ARMENIAN[2], WEIMING RUAN[2], ALICIA WONG[2], KENNETH DRASNER[3], KENT R. OLSON[2], and ALAN H.B. WU[2]

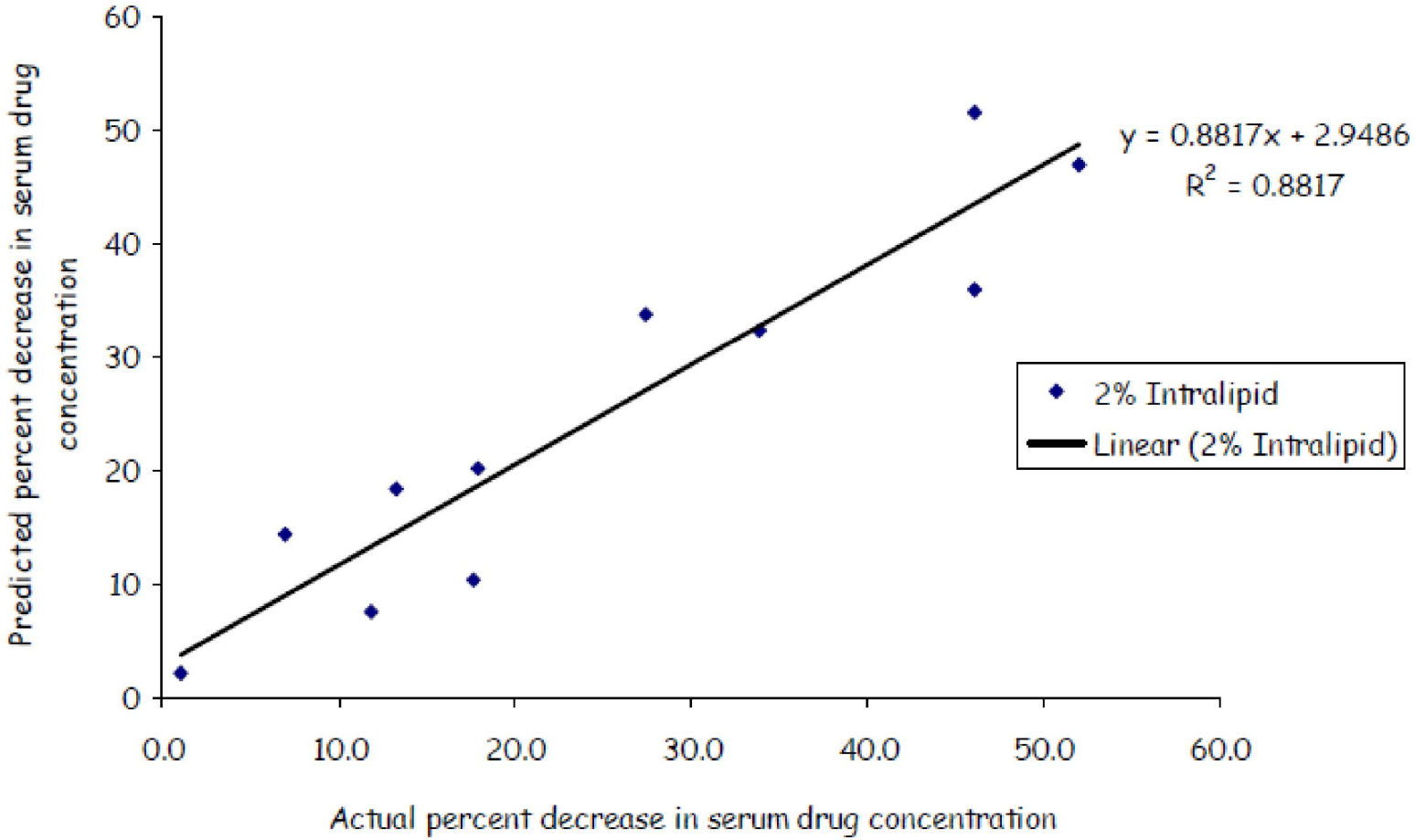
[1]*Department of Laboratory Medicine, University of California San Francisco, San Francisco 94107, USA*



Water-octanol partition constants, % decrease in serum drug concentration with 2% lipid and % CV

(French et al Clin Tox 2011)

Drug	Partition	% reduction	% CV
Lamotrigine	1.4	1	24
Mepivacaine	1.9	12	7
Quetiapine	2.1	13	3
Zolpidem	2.5	18	7
Ropivacaine	2.9	7	9
Haloperidol	3.2	27	3
Bupivacaine	3.4	18	4
Verapamil	3.8	34	5
Sertraline	4.8	46	4
Amitryptiline	5	52	7


Predicted percent decrease in serum drug concentration
Actual percent decrease in serum drug concentration
y = 0.8817x + 2.9486
R2 = 0.8817
2% Intralipid
Linear (2% Intralipid)
0
10
20
30
40
50
60
0.0
10.0
20.0
30.0
40.0
50.0
60.0

? The Science

Hypotheses:

1 Lipid sink

2 Action on sodium channel

3 Action on mitochondria

J. Med. Toxicol.
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TOXICOLOGY INVESTIGATION

Lipid Rescue 911: Are Poison Centers Recommending Intravenous Fat Emulsion Therapy for Severe Poisoning?

Michael R. Christian · Erin M. Pallasch · Michael Wahl · Mark B. Mycyk

45 US PCC Directors: All felt intralipid had a role

In cardiac arrest: “always” or “often” in
Bupivicaine (43/45) Verapamil (36/45)
Amitriptylline (31/45)

In shock: “always” or “often”
Bupivicaine (40/45) Verapamil (28/45)
Amitriptylline (25/45)

Clinical Toxicology 48: 26; 2010

Jamaty et al.

- **IFE should be used in local anaesthetic toxicity at the onset of neurological or cardiovascular symptoms.**

- **Reasonable to administer it in any other haemodynamically significant intoxication from fat soluble drugs *after* general supportive measures and recognized antidotes have been attempted unsuccessfully.**

- **No optimal regimen has been established,**

  SUGGEST IFE 1.5 m L/kg bolus then 0.25–0.5 mL/kg/min for 30–60 min.2,20,22,36,39–41,44

- **The bolus could be repeated in case of cardiac arrest. Titrating the infusion rate to the clinical response and repeating IFE administration at the onset of any recurrent deterioration appear reasonable.**

Intralipid

TOXBASE .org

UK NPIS 0844 892 0111
Ireland NPIC (01) 809 2566
mail@toxbase.org

10. If cardiotoxicity is unresponsive to the above consider the use of a lipid emulsion.

    In adults and children:

    1.5 mL/kg of 20% Intralipid as an intravenous bolus followed by 0.25 – 0.5 mL/kg/min for 30 - 60 minutes (Jamaty et al, 2010) to an initial maximum of 500 mL.

    The bolus could be repeated 1-2 times for persistent cardiovascular collapse or asystole.

    The infusion rate should be titrated against clinical response.

    Discuss with your local poisons information service: in the UK NPIS 0844 892 0111, in Ireland NPIC (01) 809 2566.

    Click here for details you may be required to give when telephoning NPIS.

    It is thought lipid may reduce free concentrations of active drug and therefore improve myocardial function, although other mechanisms are also postulated.

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METHODOLOGY

Methodology for AACT evidence-based recommendations on the use of intravenous lipid emulsion therapy in poisoning

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Intravenous lipid emulsion (ILE) therapy is a novel treatment that was discovered in the last decade. Despite unclear understanding of its mechanisms of action, numerous and diverse publications attested to its clinical use. However, current evidence supporting its use is unclear and recommendations are inconsistent. To assist clinicians in decision-making, the American Academy of Clinical Toxicology created a workgroup composed of international experts from various clinical specialties, which includes representatives of major clinical toxicology associations. Rigorous methodology using the Appraisal of Guidelines for Research and Evaluation or AGREE II instrument

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Summary:

- **Dialysis efficacy depends on equipment clearance. High flow rates are therefore likely to be more effective.**
- **Patient cardiovascular stability is key to successful dialysis.**
- **Kinetic factors of the toxin are key to suitability of dialysis and *perhaps* intralipid.**
- **Patient outcome is the key measure of success.**

Final Message

- **Evaluate efficacy on kinetic and dynamic criteria**
- **Report inefficacy as well as success**
- **Evidence based medicine**

  Role of the clinical toxicology societies position statements – guidelines

REMEMBER

“A scientific paper is a mythical reconstruction of what happened.”

Professor Ian Purchase

Fraud, Error and Gamesmanship in Clinical Toxicology
The British Toxicological Society
Paton Prize lecture, 2004

Thankyou

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