How effective is chelation? contrasts in iron and digoxin poisoning

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Chelation

- **Chemical chelating agents**

  chemical that bind metal ions and other toxic groups

  e.g. desferrioxamine for iron,

  cobalt edetate for cyanide

- **Antibodies**

  directed against a specific molecule, or against venoms (often in a more complex mixture)

  e.g. Fab antibodies for digoxin

  viper antivenin

Basic principles: 1

- **The toxin is active in and/or mostly dwelling within the blood compartment**
- **The toxin is bound to a non toxic molecule, and made inactive**
- **This binding generally is based on mass action**

  1 molecule of toxin is neutralised by 1 or more molecules of chelating agent in a fixed proportion
- **Thus generally for efficacy**

  moles of chelating agent ~= moles of toxin

Basic principles: 2

- **Ideally need to know the quantity of toxin to calculate the quantity of antidote needed and administer to neutralise**

BUT

- **In practice toxin quantity may not be clear**

So biomarkers of toxin effect may assist dosing decisions

Case example

A 17 year old female ingests her mother's cardiac medication after a domestic argument about her unplanned pregnancy.

Ingestion of spironolactone, digoxin and furosemide.
Patient presents to hospital 5 hours later, complaining of nausea.

15 weeks pregnant, has vomited in the ambulance
normal observations with a pulse rate of 75 /m and normal blood pressure.

ECG shows sinus rhythm and no obvious abnormality.

An urgent set of bloods are sent and these show
normal electrolytes,
serum digoxin of 7 ng/ml (normal therapeutic 1.5-2 ng/ml).

Question

- **Would you give Dig Fab??**
- **If so – how much??**

Case example

A 21 year old female ingests her mother's cardiac medication after a domestic argument about her unplanned pregnancy.

Ingestion of spironolactone, digoxin and furosemide.
Patient presents to hospital 5 hours later, complaining of nausea.

15 weeks pregnant, has vomited in the ambulance
normal observations with a pulse rate of 75 /m and normal blood pressure.

ECG shows sinus rhythm and no obvious abnormality.

An urgent set of bloods are sent and these show
normal electrolytes,
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Clinical presentations of digoxin toxicity

- toxicity during chronic therapy
- excessive loading dose
- single excess ingestion with heart disease
- single excess ingestion without heart disease

- accidental ingestion in a child

Clinical features of digoxin toxicity

- **GI: nausea, vomiting and diarrhoea**
- **METABOLIC: hyperkalaemia (Na/K ATPase blockade)**
- **CARDIAC: bradycardia and heart block, ventricular arrhythmias**
- **CNS: psychosis and seizures**

Efficacy

Time course of :

total serum digoxin (○ – ○)

Free serum digoxin (● ●)

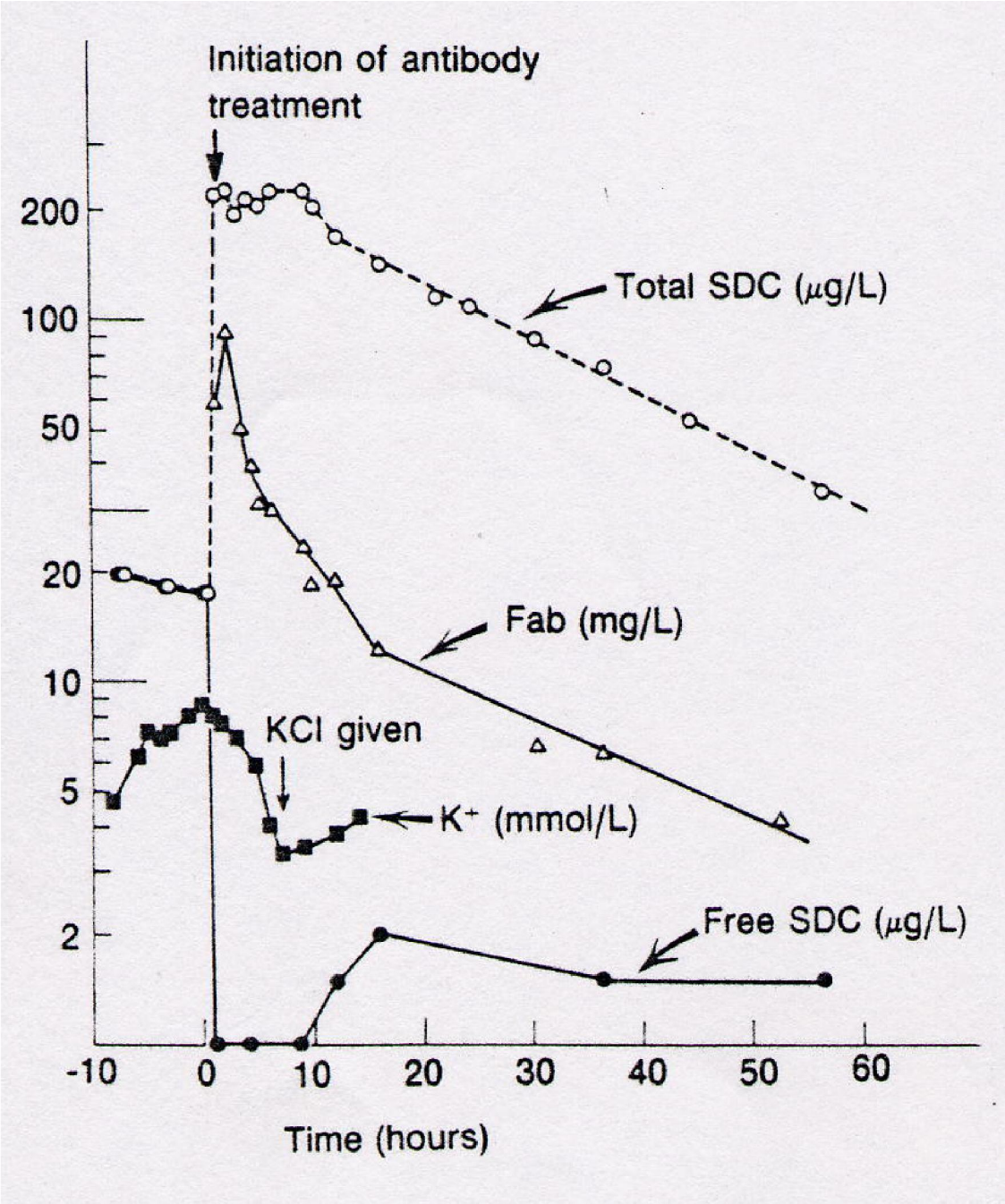
Fab fragments (△ △)

Serum potassium (■ ■)

After iv administration of DA

in a 39-year-old man

with severe digoxin poisoning.



Smith TW et al. Reversal of advanced digoxin intoxication with Fab fragments of digoxin-specific antibodies. N E J Med 1976;294:797-800.

Requirements for effective use

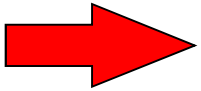
Understanding of toxicokinetics of toxin and kinetics of antidote

Dose calculation of antidote dose to neutralise toxin

Safety of antidote

Digoxin antibodies.
Binding capacity of Fab fragments

- **Digibind^{R} : 40 mg → 0.62 mg digoxin**
- **Digifab^{R} : 40 mg → 0.62 mg digoxin**
- **Digidot^{R} : 80 mg → 1 mg digoxin**



equimolar dose = Digibind^{R} and Digifab^{R}

: BL (mg) x 65

digidot^{R} : BL (mg) x 80

Digoxin antibodies: when ?

- life-threatening features
- hyperkalemia
- severe poisoning: HR < 50/mn

- patients at risk: elderly, underlying cardiac disease, mixed poisoning (cardiotropic drugs)

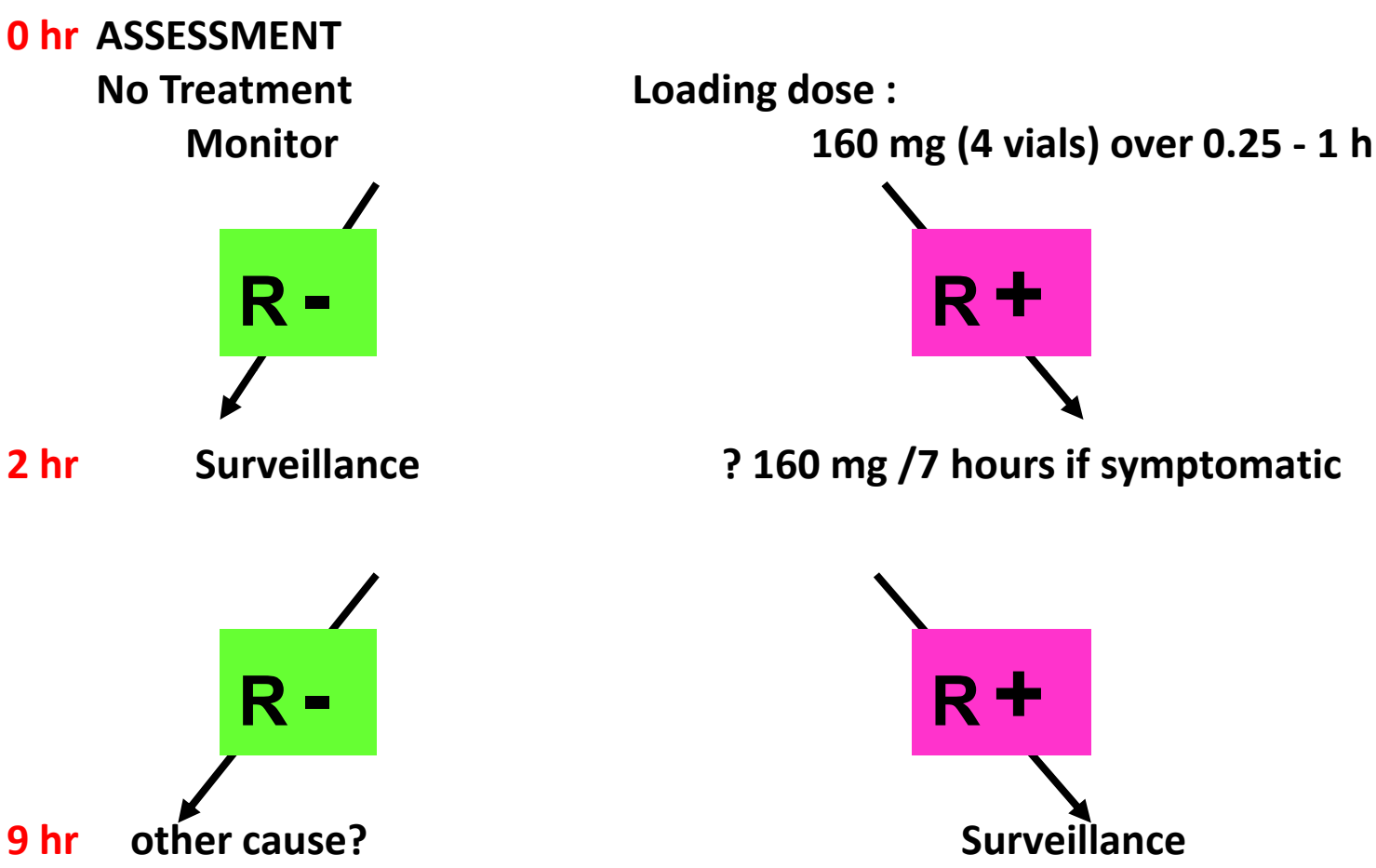
Digoxin antibodies. How much ?

Optimal dose MAY NOT BE equimolar dose

AIM to achieve neutralization of sufficient body-load (BL) of digoxin or digitoxin to stop toxic effect

Avoid waste of Fab by too rapid infusion

Proposed strategy of digoxin Fab administration: Digibind^{R} ; Digifab^{R}



Further doses as clinically indicated

Dynamics of the Digoxin-Fab complex

Dissociation of digoxin from the antibody or tissue redistribution, may lead to rebound of free digoxin and recurrence of toxic features.

Continue cardiac monitoring 24 hours after treatment (and longer in cases of severe renal failure).

Digoxin antibodies: how much ?

- **pragmatic strategy based on the clinical response**
- **don’t use the Fab too quickly**
- ***treat the patient and not the serum level***

Pitfalls of body-load calculation

Variations :

- **the kinetic-dynamic relationship (acute, acute/chronic, chronic poisoning)**
- **age**
- **underlying cardiac disease**
- **electrolyte disturbances (K^+)**
- **associated cardiotropic drugs**

Iron content of Tablets

Iron Content of Salts

Iron Salt	Tablet Size	Elemental Iron Content
Ferrous fumarate	200 mg	65 mg
Ferrous gluconate	300 mg	35 mg
Ferrous succinate	100 mg	35 mg
Ferrous sulphate	300 mg	60 mg
Ferrous sulphate (dried)	200 mg	65 mg

How does iron cause toxicity??

“Cellular dysfunction and death”

“Exact mechanism is unknown”

Features in severe cases are metabolic (lactic) acidosis, coma and multi-organ failure: all presumably due to intracellular toxicity

Westlin: Clin Paeds 1966

144 no coma or “shock” no deaths

28 coma or “shock” 3 deaths

46 conc > 5mg/L: 17 coma +/ shock
29 asymptomatic

Difficult to find a pattern as cases not uniformly collected

Chyka and Butler:

Am J Emerg Med 1993

TABLE 2. Relationship of Serum Iron Concentrations Above and Below 500 µg/dL and the Presence of Various Clinical or Laboratory Variables

Variable and Serum Iron (µg/dL)	No. of Patients: Variable Present	No. of Patients: Variable Absent	Predictive Value Positive	Predictive Value Negative	Odds Ratio	95% Confidence Interval	
Coma*							
≤500	1	83	0.67	0.93	27.67	4.55	168.38
>500	2	6					
Radiopacities							
≤500	24	46	0.17	0.96	4.79	0.97	23.70
>500	5	2					
WBC >15,000 mm³							
≤500	15	54	0.21	0.93	3.60	0.85	15.19
>500	4	4					
Anion gap >15							
≤500	21	41	0.19	0.93	3.25	0.74	14.25
>500	5	3					
Glucose >150 µg/dL							
≤500	14	45	0.12	0.90	1.29	0.22	7.44
>500	2	5					
Vomiting							
≤500	56	28	0.08	0.90	0.83	0.18	3.77
>500	5	3					
Diarrhea							
≤500	37	47	0.08	0.90	0.76	0.17	3.41
>500	3	5					

Abbreviation: WBC, white blood cell count.

* $P = .02$; all others not significant at $P < .05$.

Chyka and Butler: Pharmacother 1996

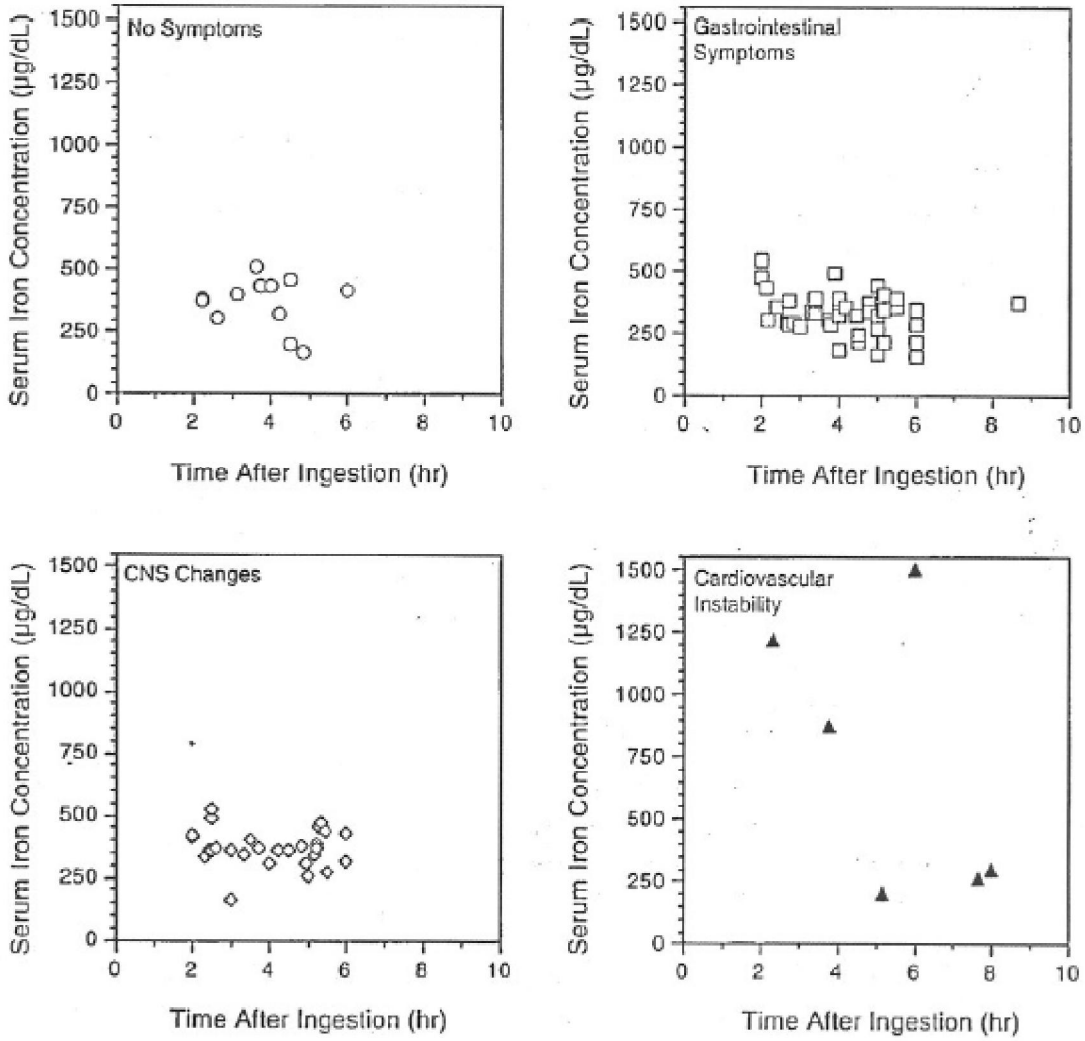


Figure 1. Serum iron concentrations after time of ingestion for patients categorized as no symptoms (○), gastrointestinal symptoms (□), CNS changes (◊), or cardiovascular instability (Δ).

Iron poisoning (TOXBASE)

- Ingested dose elemental iron (mg/kg body weight) and features seen

DOSE INGESTED

- Less than 20 mg/kg Mild features,
- More than 20mg/kg Features likely
- 150 – 300 mg/kg Severe - possibly fatal
- US textbooks suggest >60mg/kg potentially fatal

Concentrations in Iron poisoning (TOXBASE)

- **3 mg/L (55 micromol/L) mild toxicity**
- **3-5 mg/L (55-90 micromol/L) moderate toxicity**
- **> 5 mg/L (90 micromol/L) *potentially* severe toxicity**

Iron poisoning

- **PROBLEM**
- **> 5 mg/L (90 micromol/L) marker of "severe toxicity" is often found during acute ingestion phase prior to distribution**
- **Many such patients subsequently have a fall in concentration and seem fine**
- **If you treat these patients they get better anyway, ? biasing efficacy reports**

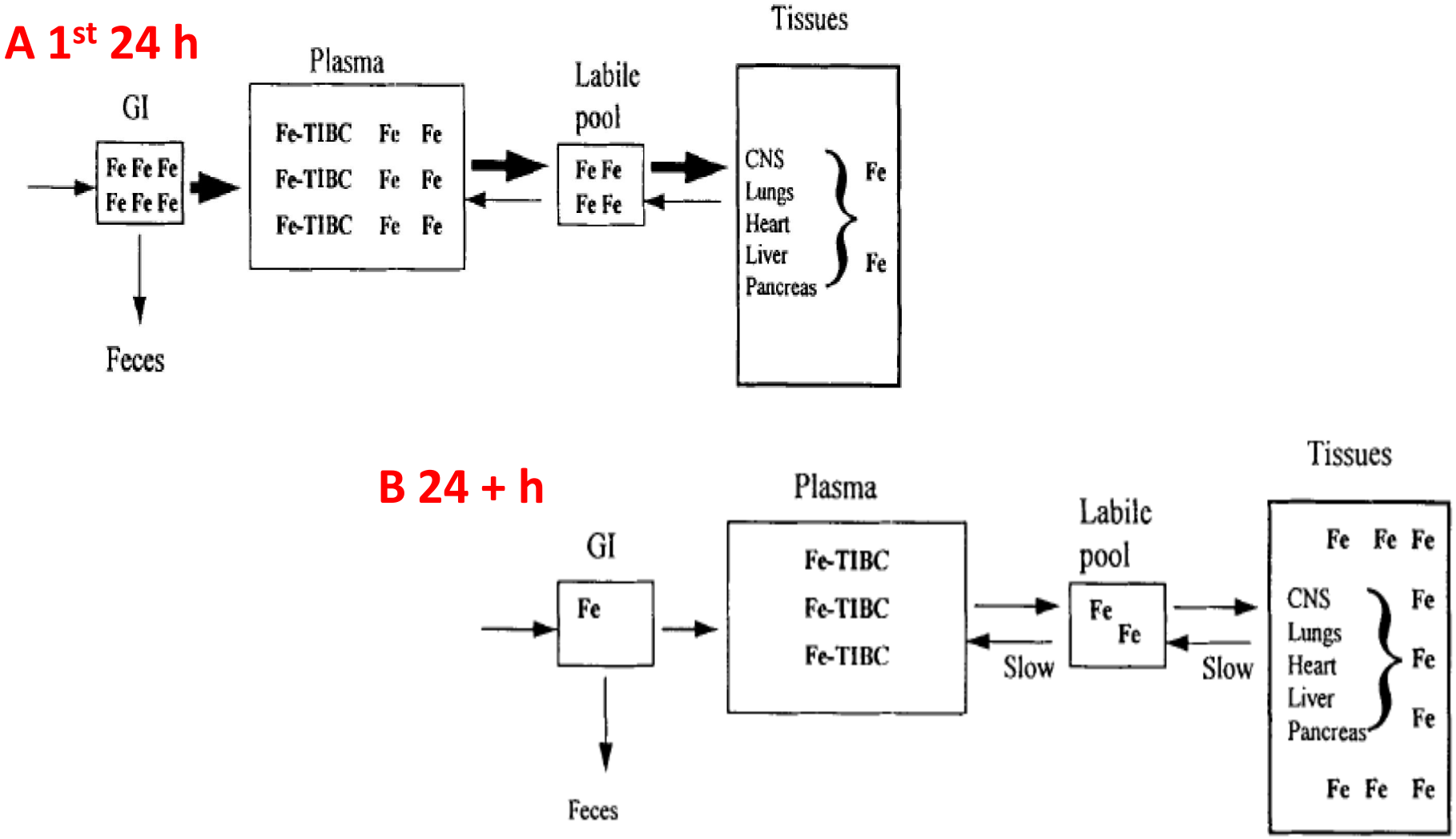
HOW MUCH IRON IS PRESENT?

- **Amount = Concn x VD**

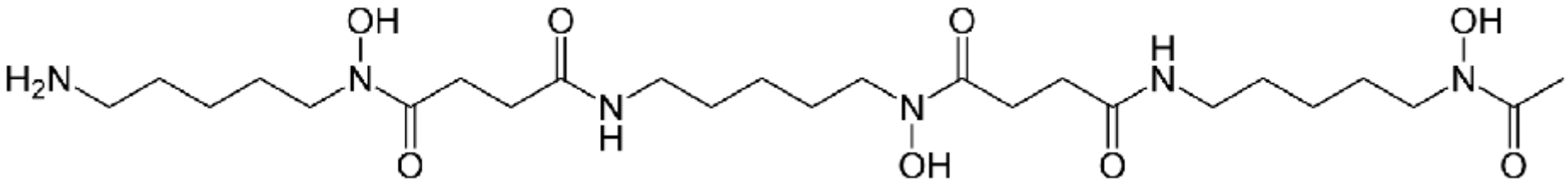
- **What is the correct volume to use for VD?**
- **Plasma, (~ 5L) , or Total Body Water (~ 40L)**

- **WHY IS THIS IMPORTANT??**

Iron distribution in OD:
A 1st 24 hours. B 24+ hours



Desferrioxamine



- Binds iron in molar equivalent amounts
- 560.7 DFO gm/mol
- 100 mg binds ~ 8.5 mg Fe

Desferrioxamine

Volume of distribution 0.6- 1.3 L/kg

Several metabolites (one ? Toxic)

T1/2 in Thalassaemia ~3hr

<u>Ferrioxamine VD 0.2 L/kg</u>
(renal excretion active and passive)

How Much Elemental Iron is Toxic??
Iron in a 50kg patient

TOXBASE

150 – 300 mg/kg

Severe – possibly fatal toxic dose/kg x wt:

150 x 50 = 7,500 mg = >100 tablets $FeSO_4$

US Texts >60mg /kg possibly fatal

60 x 50 = 3,000 mg = 50 Tablets $FeSO_4$

Desferrioxamine and Iron

100 mg of DFO binds ~8.5 mg elemental iron

“Maximum dose” of desferrioxamine is 90 mg/kg

Thus in a 50 kg patient

90mg/kg DFO (4500 mg) binds ~380 mg elemental iron

REMEMBER Toxic elemental iron dose is 3,500-7000 mg

Desferrioxamine and Iron

PROBLEM

Once DFO given iron levels cannot be easily interpreted

Iron levels are not well studied in early phases of OD (often go up then down)

What do we need?

better assessment of DOSE response to Iron and DFO

? A NOMOGRAM

DESFERRIOXAMINE TOXICITY
Is it a real problem??

- Hypotension: Whitten's first studies in 1965 and 66.

  800 and 1500 mg DFO over 15 minutes in 3 children. 2 hypotensive, 1 fitted. All survived.
- Pulmonary toxicity: ARDS reported in 4 adults receiving prolonged (days) 15 mg/kg/hr doses (Tenenbein et al 1992) for iron poisoning.

  Also reported in higher dose DFO in thalasaemia
- Ocular toxicity: All in chronic iron overload with "high dose" DFO
- Yersinnia and mucormycosis infection: in long term management
- Studies in dogs lead to empiric max rate of 15mg/kg/hr

Desferrioxamine and Iron in a 50kg patient

- Is it logical binding so little Iron is likely to work?
- Shouldn't chelator dose and iron dose be used together ?
- Complicated by changes in bioavailability of iron in poisoning

Survival After a Severe Iron Poisoning Treated with Intermittent Infusions of Deferoxamine

Clinical Toxicology, 33(1), 61–66 (1995)

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University of Nebraska Medical Center; The Poison Center Children's Hospital**, Omaha, Nebraska; The Winnipeg Children's Hospital and the University of Manitoba, The Manitoba Poison Control Centre, Canada****

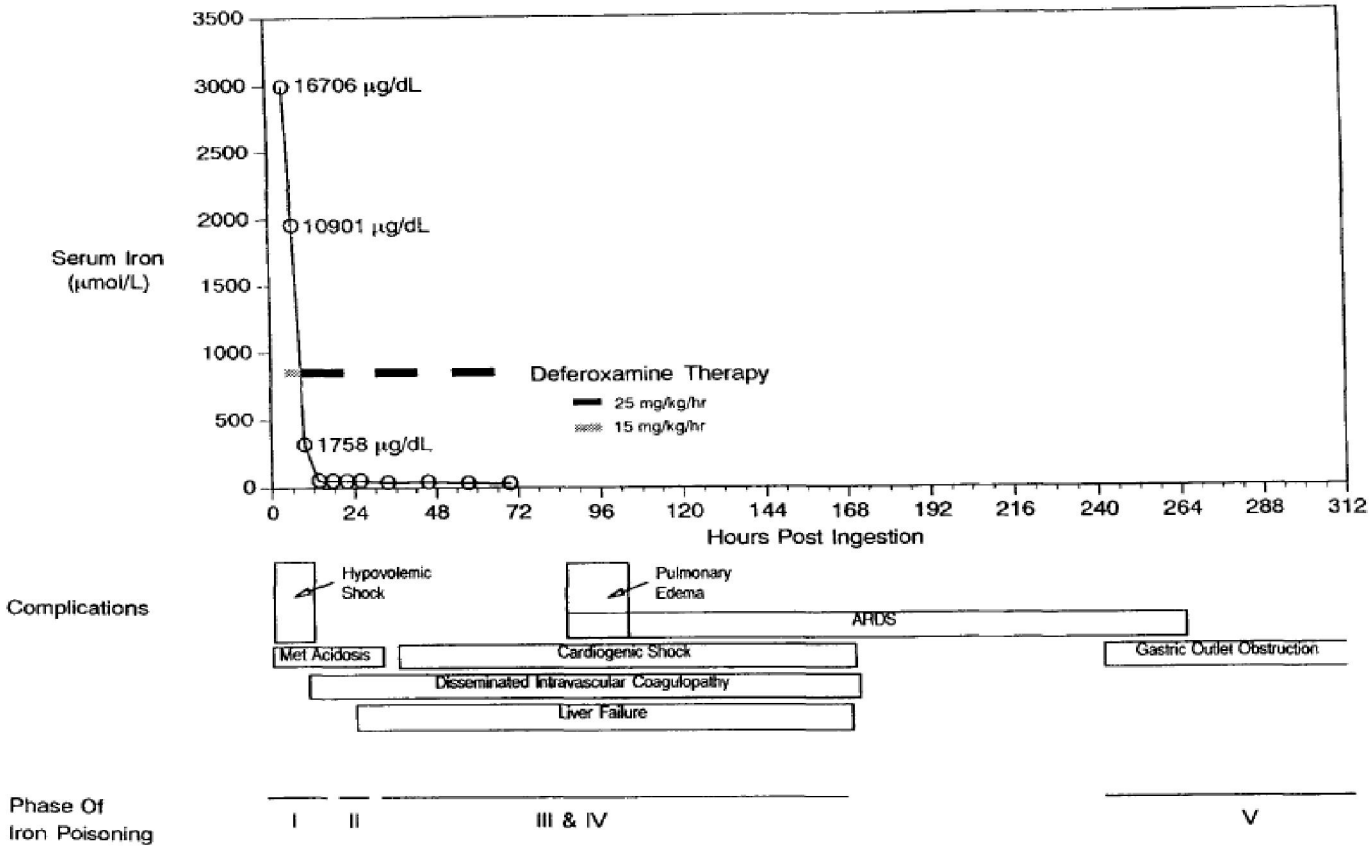

Figure 1 A summary of our patient's clinical course.

Take-Home messages:- 1

Digoxin FAB is effective, but should be reserved for patients who are suffering severe effects of digoxin

(eg bradycardia, hyperkalaemia and life-threatening arrythmias)

In most patients full neutralisation is unnecessary, and dose of Fab can be titrated

Take-Home messages:- 2

The evidence base for efficacy of

chelation of Iron in ACUTE OD is not good

Optimum time for delivery BEFORE 1st 24 –36 hr

BUT treatment assessment early is difficult in all except very severe cases

Doses of desferrioxamine should ideally be better calculated to match the body burden of the toxin

Conclusion

- Chelating agents are effective in some poisonings
- The theory is simple
- Digoxin shows a good approach
- Iron shows the problems of metal chelation
- There are few (if any) examples where there is uncontroversial evidence of a chelator's clinical efficacy in metal poisoning

Thankyou

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