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 \( \sim \) 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.

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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.

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\textsuperscript{R} : 40 mg $\rightarrow$ 0.62 mg digoxin
- Digifab\textsuperscript{R} : 40 mg $\rightarrow$ 0.62 mg digoxin
- Digidot\textsuperscript{R} : 80 mg $\rightarrow$ 1 mg digoxin

equimolar dose = Digibind\textsuperscript{R} and Digifab\textsuperscript{R} \\
: BL (mg) x 65

- Digidot\textsuperscript{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®; Digifab®

0 hr ASSESSMENT
No Treatment
Monitor

<table>
<thead>
<tr>
<th>R -</th>
<th>R +</th>
</tr>
</thead>
</table>

Loading dose:
160 mg (4 vials) over 0.25 - 1 h

2 hr Surveillance

? 160 mg /7 hours if symptomatic

<table>
<thead>
<tr>
<th>R -</th>
<th>R +</th>
</tr>
</thead>
</table>

9 hr other cause?

Surveillance

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

<table>
<thead>
<tr>
<th>Iron Salt</th>
<th>Tablet Size</th>
<th>Elemental Iron Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous fumarate</td>
<td>200 mg</td>
<td>65 mg</td>
</tr>
<tr>
<td>Ferrous gluconate</td>
<td>300 mg</td>
<td>35 mg</td>
</tr>
<tr>
<td>Ferrous succinate</td>
<td>100 mg</td>
<td>35 mg</td>
</tr>
<tr>
<td>Ferrous sulphate</td>
<td>300 mg</td>
<td>60 mg</td>
</tr>
<tr>
<td>Ferrous sulphate (dried)</td>
<td>200 mg</td>
<td>65 mg</td>
</tr>
</tbody>
</table>
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
TABLE 2. Relationship of Serum Iron Concentrations Above and Below 500 μg/dL and the Presence of Various Clinical or Laboratory Variables

<table>
<thead>
<tr>
<th>Variable and Serum Iron (μg/dL)</th>
<th>No. of Patients</th>
<th>Predictive Value</th>
<th>Predictive Value</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Variable Present</td>
<td>Variable Absent</td>
<td>Positive</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Coma*</td>
<td>1 83</td>
<td></td>
<td>0.67</td>
<td>0.93</td>
<td>27.67</td>
</tr>
<tr>
<td>Radiopacities</td>
<td>24 46</td>
<td></td>
<td>0.17</td>
<td>0.96</td>
<td>4.79 0.97</td>
</tr>
<tr>
<td>WBC &gt;15,000 neutropenia</td>
<td>15 54</td>
<td></td>
<td>0.21</td>
<td>0.93</td>
<td>3.60 0.85</td>
</tr>
<tr>
<td>Anion gap &gt;15</td>
<td>21 41</td>
<td></td>
<td>0.19</td>
<td>0.93</td>
<td>3.25 0.74</td>
</tr>
<tr>
<td>Glucose &gt;150 μg/dL</td>
<td>14 45</td>
<td></td>
<td>0.12</td>
<td>0.90</td>
<td>1.29 0.22</td>
</tr>
<tr>
<td>Vomiting</td>
<td>56 28</td>
<td></td>
<td>0.08</td>
<td>0.90</td>
<td>0.83 0.16</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>37 47</td>
<td></td>
<td>0.08</td>
<td>0.90</td>
<td>0.76 0.17</td>
</tr>
</tbody>
</table>

Abbreviation: WBC, white blood cell count.
* P = .02; all others not significant at P < .05.
Figure 1. Serum iron concentrations after time of ingestion for patients categorized as no symptoms (○), gastrointestinal symptoms (□), CNS changes (○), or cardiovascular instability (△).
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 20 mg/kg Features likely
- 150 – 300 mg/kg Severe - possibly fatal
- US textbooks suggest >60 mg/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 $1^{st}$ 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

Ferrioxamine VD 0.2 L/kg
(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:

  \[150 \times 50 = 7,500 \text{ mg} = >100 \text{ tablets FeSO}_4\]

US Texts >60mg /kg possibly fatal
  \[60 \times 50 = 3,000 \text{ mg} = 50 \text{ Tablets FeSO}_4\]
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 thalassaemia

- **Ocular toxicity**: All in chronic iron overload with “high dose” DFO

- **Yersinina 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

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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 1\text{st} 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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