Iron mobilization in thalassemia and other hemoglobinopathies

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Haemoglobinopathies:

- A group of hereditary diseases, the most common hereditary disease in the world.

- WHO estimates that 7 % of the population in the world are carriers of the disease.

- About 400,000 children are born yearly with a serious haemoglobinopathy, such as e.g. thalassemia major.

Geographic Distribution of the Haemoglobinopathies
Transfusion-requiring thalassemia in Norway and Sweden

• About 60 patients, average age below 20 years
• Blood transfusions usually administered every 3rd week
• About 40% are treated with deferiprone p.o., many with a combination with deferoxamine s.c.c.i.

• More than 40% of the patients have ferritin >2000 ug/L
• There are no consensus as to follow-up and therapy.
Thalassemia: Treatement of siderosis

• Deferoxamine s.c.c.i. intermittent courses, or

• Deferiprone (Ferriprox) p.o. daily or

• Deferasirox (Exjade) p.o. daily
Deferiprone (Ferriprox)

- Dose: dose 75mg/kg/day
- About 4,500 mg/d = 3 tabl (= 1,500 mg) x 3
Pharmacology Deferiprone

- **Deferiprone** is rapidly absorbed

- Max serum concentration about 60 min after an oral dose

- The deferiprone-iron chelate is a 3-to-1 chelate

- A minor part of the drug is metabolized in liver

- The Fe-chelate is eliminated via the kidneys
Classes of Chelators to Immobilize and Remove Iron

- **Hexadentate**
  - 1:1 complex
  - *Deferoxamine (Desferal)*

- **Bidentate**
  - 3:1 complex
  - *Deferiprone*

- **Tridentate**
  - 2:1 complex
  - *Deferasirox*
CHELATION OF IRON - the hexavalent iron ions, prefer nitrogen or oxygen ligands

![Chemical structures of Oxyhemoglobin, Carbaminohemoglobin, and Carboxyhemoglobin](image-url)
Kaplan-Meier Analysis of Survival in 257 Consecutive Thalassemic Patients
According to Mean Compliance with subcutaneous DFO Therapy

Thalassemia Centre, Dept. of Pediatrics
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Iron Accumulation in Transfusion-dependent Anemias

In a 60kg person

15-25 mg/day

Iron Excretion (Urine & Feces)
1-2 mg/day

Iron Accumulation
13-24 mg/day
When is chelation treatment indicated in potential transfusional siderosis cases?

- After the initial 10-15 blood transfusions (WHO-recommendation)

- Or when ferritin concentration increases above 1000 μg/l (WHO-recommendation)
Complications of siderosis:

- 0-10 year-old children: Retarded growth. Thyroid dysfunction

- 10-20 år: Impaired glucose tolerance or diabetes, Hypoparathyroidism, Delayed puberty. Hypogonadism

The goal of an iron chelator is to prevent iron-induced toxicity:

- Prevent organ damage
- Prevent premature death
The classical deferoxamine: is given as s.c.c. infusion during 12 hours per night.

- If ferritin is > 1000 ug/L: Deferoxamine 25 mg/kg/day for 5 day-periods.

- Deferoxamine is then recommended after each blood transfusion.
Causes of Death in 248 Thalassemia Major Patients, Born Between 1960 and 1984

Cardiac causes 171 (71%)
Infections 28 (12%)
Liver 15 (6%)
Tumors 7 (3%)
Endocrine 6 (3%)
Other 5 (2%)
Thrombosis 3 (1%)
Unknown 3 (1%)
Anemia 2 (1%)

Monitoring Chelation Therapy and Iron Overload

- Frequent determination of serum ferritin
- Liver biopsy
- Cardiac MRI
- Liver MRI
Why cardiac MR?

- Cardiac iron: presumed responsible for cardiomyopathy

- Heart disease is asymptomatic until late stages, and echo and systolic function remain normal. Once cardiac symptoms develop, outlook is poor

- Risk assessment from ferritin or liver iron is difficult
Advantages of combined chelation: deferoxamin s.c. and deferiprone p.o.

- Different iron pools of chelation (‘the shuttling hypothesis’)
- Increasing efficacy
- Decreased dose → toxicity decrease
- Better tolerability → better compliance
- Improved quality of life

- Use of oral chelators as “shuttling” agents
Incidence of agranulocytosis during Ferriprox p.o. therapy

Clinical trials 1995-2010 in Thalassemia Major patients:

- Neutropenia:
  - 5% of patients

- Agranulocytosis:
  - 1% of patients
Conclusion:

IRON MOBILIZATION – in thalassemia and some other hemoglobinopathies

- Deferoxamine (Desferal) s.c.c.i. intermittently

- Deferiprone or Deferasirox p.o. daily

- Combination therapy: Desferal + ‘shuttling agent’
Thank you for listening!