Sampling, pharmacokinetics and logistics during ITI

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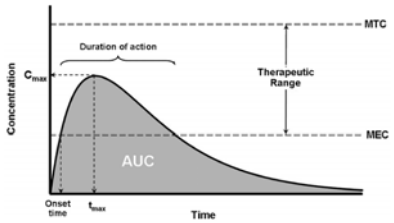
Pharmacokinetics - definition

- **Definiton:** *mathematical characterization of the process by which a drug is absorbed, distributed, metabolized, and eliminated by the body*



Recovery & Half-life

- **Recovery: a measure of the increase in plasma concentration (IU/dl) per injected dose (IU/kg) and is most often defined from the highest measured plasma concentration of FVIII/FIX within the first hour post-infusion**
- **Half-life: the period of time required for the concentration or amount of drug in the body to be reduced to exactly one-half of a given concentration or amount (FVIII 12h /6-25h/; FIX 18-34h)**

Pharmacokinetics - target points

- Wash out period:
  - *Hemophilia A*: 72 hours or at least 48 hours
  - *Hemophilia B*: 72 hours up to 5 days
- Dose of FVIII/FIX 50IU/kg
- Trough level >1 IU/dL = >1 % before ongoing administration of FVIII/FIX derivate within prophylaxis

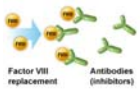
Pharmacokinetics - sampling

- Hemophilia A
  - < 30 min prior FVIII infusion
  - 7 time-points post infusion in older kids
    - 30min, 1, 3, 6, 12, 24, 48 hours
  - At least 5 time-points in patients ≤ 6 years old
- Hemophilia B
  - 7 samples over a period of 72 hours

ISTH recommendation

Inhibitor

- Definiton: antibody againts administred plasma derived/recombinant FVIII/FIX developing when the body's immune system stops accepting the factor as a normal part of blood
- Reason of the difference in PK between hemophiliacs with and without inhibitor



Inhibitor & Bethesda Units

- Low responder: 0,5 – 5 BU
- High responder: > 5BU

- 1 BU decreases the level of FVIII/FIX by 50%
  Faster FVIII/FIX wash-out in patients with inhibitor

⟹ Faster FVIII/FIX wash-out in patients with inhibitor

Pharmacokinetics and ITI

- Useful when assessing whether a patient achieve full tolerance at the end of ITI

ITI monitoring

- Inhibitor levels
  - Start of ITI when inhibitor is lower than 10BU
  - To be monitored repeatedly (e.g.every 6 weeks)
- Recovery
  - Depending of the protocol (at least every 3 months)
- Half –life
  - Depending of the protocol (at least every 3 months)

When we could stop ITI

- *Hemophilia A*
  - Negative inhibitor titer
  - Recovery of more than 66%
  - Half-life greater than 7 hours
- *Hemophilia B*
  - No equivalent consensus on FIX half-life for the definiton of tolerance

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"Troubles" with ITI

- Three different points of view

Patients Parents Hospital

Patients

- Necessity of cooperation
  - Small kids are afraid of more frequent drug administrations
  - Teenagers "don't like it at all"
- Decreased quality of life

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Parents

- **Necessity of cooperation**
  - **Drug administration**
    - at home
    - at the GP's
    - at Heamatology Clinic
  - **More frequent appointments at heamatology**
- **Concern for the child**
- **Changed quality of life**

Hospital – cost of care - disadvantages

- **Caring for people with inhibitors poses a special challenge.**
- **Overall medical treatment costs increased**
  - **Increased usage of concentrates**
  - **Expensive bypassing agents**
  - **Potentially related healthcare – e.g. surgery**
  - **Patients with hemophilia who developed inhibitors are twice as likely to be admitted for a bleeding complication**

Lower in-patient care costs – children´s advantage

lower weight

⇩

less amount of administered drugs

⇩

lower cost of care than in adults

Quality of life – patients prospective

- Choose convenient i.v. acess → frequent infusions
- Joint disease is more severe in these patients than in non-inhibitor patients *Morfini 2007*
- Chronic pain
- Days off-school and limitations in daily activities

Quality of life – small children

- Venous access can be painful and difficult

- Frequent prophylactic treatment in younger children is compensated by better health-related QoL with fewer bleeding episodes later in life *Gringeri 2004*

Quality of life – teenagers

- QoL impairment is felt more in social domains compared to younger children
  - „feeling strange" because they need frequent i.v. treatment
  - more often at the doctor's than their mates
  - less time spent with friends
  - limited in sport and other activities

Quality of life - parents

- Fear ⟹ Overprotection
- Necessity to learn new uncommon skills
- Absenteesm from work

↳ Lower family income

Home treatment - advantages

- Better prevention of profuse bleeding by immediate treatment of incipient bleed
- Time and economic savings in terms of transportations to and from hospital, waiting time and days of treatment
- Reduced absence from school and work
- Helping patients to live independent and „normal“ life

Quality of life – doctors and nurses

- Comprehensive support system
  - Educational efforts
  - Infusion training
  - 24/7 availability of „over-the-phone“ or personal consultation
  - Psychological support for both children and parents

Quality of life - conclusion

- QoL in patients with inhibitor is impaired more than in healthy children or in non-inhibitor patients, but much better when comparing with the past times (70-90´s)
- Cooperation between patients, parents and hospital staff is necessary

Thank you for you attention