Sampling, pharmacokinetics and logistics during ITI

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Pharmacokinetics - definition

- **Definition:** 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 derivates within prophylaxis

Pharmacokinetics - sampling

- Hemophilia A
  - < 30 min prior FVIII infusion
  - 7 time-points post infusion in older kids
  - At least 5 time-points in patients ≤ 6 years old

- Hemophilia B
  - 7 samples over a period of 72 hours

ISTH recommendation

Inhibitor

- Definition: antibody against administered 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

Pharmacokinetics and ITI

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

- 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 definition of tolerance

“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
Parents

- Necessity of cooperation
  - Drug administration
    - at home
    - at the GP’s
    - at Hematology Clinic
  - More frequent appointments at hematology
- 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 inhibitors 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. access ➔ 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 apart with friends
  – limited in sport and other activities
Quality of life - parents

- Fear  ➔ Overprotection
- Necessity to learn new uncommon skills
- Absenteeism 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 transportation 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