indication of differences in the tertiary structure of HC and LC in N8, Advate® and ReFacto® was found.
Disclosure of interest: A. Gruhler, Novo Nordisk A/S, employee.
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Biophysical characterization of glycopegylated recombinant human FVIIa

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PEGylation has become widely used as a modification methodology for improving the biomedical efficacy and physicochemical properties of therapeutic proteins. In this study various biophysical techniques were used to compare biophysical properties of long acting rFVIIa (LA-rFVIIa) and rFVIIa. LA-rFVIIa is a 40K glycoPEGylated recombinant human FVIIa derivative. Spectroscopic techniques, such as near and far UV Circular Dichroism (CD) in combination with GuHCl induced unfolding have shown that the secondary and tertiary structure of the protein in LA-rFVIIa and rFVIIa are similar. Further biophysical characterization of LA-rFVIIa demonstrates that solubility has been significantly improved. Thermal stability has been investigated using Differential Scanning Calorimetry (DSC) and High Resolution Ultrasonic Spectroscopy (HR-US). The apparent denaturation temperature of LA-rFVIIa is approximately 2°C higher as compared to rFVIIa. More importantly the reversibility is significantly improved upon PEGylation. Denaturation of rFVIIa is irreversible and it is not possible to separate thermally induced unfolding and aggregation processes. In contrast the unfolding of LA-rFVIIa is characterized by being partly reversible and less prone to thermal induced protein aggregation. We expect that the enhanced stability and reversibility will result in improved long term stability.
Disclosure of interest: none declared.

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Continuous infusion practice in 22 haemophilia comprehensive care centres in 16 European countries

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Introduction: Continuous infusion (CI) of FVIII used for the intensive treatment of haemophilia has proven to be a haemostatically effective mode of factor replacement. However, there is a wide variation in the technique and treatment protocols employed and recent anectodal reports of inhibitor development after CI in mild/moderate haemophilia have raised concerns.
Methods: Current practice in the use of CI was surveyed in 22 European haemophilia comprehensive care centres. Treatment efficacy and inhibitor development after CI were evaluated.
Results: CI is used in 13/22 (57%) of the centres surveyed. A total of 1072 CI procedures were performed in 868 haemophilia A patients (779 severe; 89 moderate /mild), including 126 in 111 children. All centres use CI for surgery, five centres also for major bleeds and six center in patients with inhibitors. All centres use concentrated FVIII solutions. Syringe pumps, portable minipumps, or both delivery devices are used in four, five and four centres respectively. Ten centres employ the adjusted dose CI and three fixed rate CI protocols. Preprocedure pharmacokinetics testing was performed in six centres, and intervals for exchange of infusion sets are 12, 24 and up to 72 h in three, six and two centres, respectively. The treatment with CI (duration 2–15 days) is regularly followed with factor bolus injections (BI) in 12/13 centers. The wide range of initial doses of FVIII (3.0–5.0IU/kg/h) reflects the different FVIII level targets in days 1–3 (0.6–1.0 IU/mL.CI was rated as haemostatically effective by all centres. Only ten of 868 (1.5%) patients developed inhibitor after intensive treatment with continuous infusion, three (0.4%) with severe hemophilia, seven (7.9%) mild.
Conclusion: CI is an effective and safe treatment mode for haemophilia. The inhibitor formation seen in mild haemophilia after intensive treatment for surgery (either CI or BI) requires thorough investigation with respect to all confounding risk factors.
Disclosure of interest: none declared.

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Peripheral arterio-venous shunts for venous access in children with haemophilia

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Background: Venous access is essential for administration of clotting factor concentrates to treat or prevent bleeding complications in patients with haemophilia. The primary choice for venous access is peripheral venipuncture but may be problematic, particularly in young children. In these instances, central venous access devices are frequently required but these carry the risk of infection, thrombosis, and mechanical complications. An alternative for venous access are peripheral arterio-venous (AV) shunts. We report our experience with 11 boys with severe haemophilia who received AV shunts over the last 4 years.
Results: Patients had a median age of 2.5 years (8 months to 12 years) at the time of shunt insertion. Reasons for shunt insertions were initiation of prophylaxis (n = 7) and immune tolerance therapy (n = 4). Shunts were inserted at the wrist (Cimino shunts, n = 8) or the forearm (Gracz shunts, n = 3). Median observation time since insertion is 11 months (2 months to 4 years). Reliable venous access could be achieved within a median of 4 weeks after shunt insertion. Home treatment has since been established in eight patients. Complications were a post-operative local haematoma in one patient and relatively large shunt volumes in two patients. There was no shunt thrombosis, infection or traumatic complication. Two patients already had their shunts taken down because peripheral venous access could reliably be established. Patients with AV shunts in average had prophylaxis and home therapy established at an earlier age compared to other haemophiliacs at our center.
Conclusions: AV shunts provide a good alternative to central venous access devices as they carry a lower risk of complications. AV shunts allow early start of prophylaxis and home therapy.
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