New challenges and best practices for the laboratory monitoring of factor VIII and factor IX replacement.

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Disclosures

Employment -
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Scientific Advisory Board Bayer, Roche
Patents -
Other -

Will the real FVIII please stand up?
Lusher J 1995 Blood 86 suppl 1 abstract 755

Will the real FVIII please stand up?
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2800 % of expected value with a one-stage assay

10-fold underestimation with some one-stage clotting assays
Available FVIII concentrates

- plasma derived FVIII (Factane"
- full length rFVIII (Advate"
- B-domain deleted rFVIII (NovoVeg""

Fcγ-rFVIII

Afstyla (CSL-Behring)

FcRn

endocytic vesicle
acidified endosome

lyosome

Elocta"
- types of assays
  - one-stage clotting test
  - chromogenic substrate assay

chromogenic assay

purified proteins

cleavage of a chromogenic substrate

coaugulation assay (APTT-based)

Factor deficient plasma

activator:
  - silica
  - kaolin
  - ellagic acid

coaugulation time

APTT activators:
  - non physiological surface
    - silica
    - kaolin
    - ellagic acid

Silica: \( \text{SiO}_2 \)

- colloidal silica
- micronised silica
Kaolin
silicate d’aluminium hydraté
$\text{Al}_2\text{Si}_2\text{O}_5(\text{OH})_4$

Ellagic acid (soluble) + Ca$^{++}$, Zn$^{++}$, Co$^{++}$ or Fe$^{++}$

insoluble material
negatively charged


mechanisms of bias?

2800 % of expected value with a one-stage assay

Factor IX
Factor IXa
Factor Xa

wild type FIX

micronisated silica
Communication with the clinicians
Monitoring: guidelines for the local laboratories

The official guidelines for local laboratories = manufacturer’s dosing guidelines
no other official guidelines (neither from ISTH SSC neither from EMA)

Expert opinion

“acceptable” assay:
± 30 % of the value determined with the reference assay(s)

“acceptable” assays?

Kitchen 2017 Semin Thromb Hemost 43: 331

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Kitchen 2017 Semin Thromb Hemost 43: 331
Spiked samples

Idelvion® (albumin-rFIX) provided by CSL-Behring

No published data with SynthaSil®
St Ledger K et al. Haemophilia 2016;22(5):80

Spiked samples

<table>
<thead>
<tr>
<th>Expected FIX activity (IU/dl)</th>
<th>Recovery (% of expected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>80</td>
<td>92</td>
</tr>
<tr>
<td>30</td>
<td>102</td>
</tr>
<tr>
<td>5</td>
<td>131</td>
</tr>
</tbody>
</table>

Belgium laboratory survey
WIV/ISP
Marjan Van Blerk

Elocta (patient plasma)

plasma after administration of Elocta®
(FcγrFVIII.Sobi)

ISP/WIV
lyophilised
local labs

plasma FVIII (normal donor)

Coamatic Factor VIII
Biophen FVIII:C
FVIII chromogenic
Trinichrom FVIII:C

SynthaSil APTT-SP
Actin FS
Actin FSL
Pathrombin SL
STA-Chromotest

Coagmatic Factor VIII chromogenic
Trinichrom FVIII:C

Biophen FVIII:C
FVIII chromogenic
Trinichrom FVIII:C

global median + 30%

<全球中位值+30%>
Use of correction factor

Conclusions
- communication with the laboratory: diagnostic? monitoring? product?
- "allowed assays": manufacturer's guidelines
- "acceptable assays": ± 30% of the target value
- severe biases with SOME rFVIIIs or rFIXs/reagents combinations
- quality controls should be available

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