Analytical and Clinical Validation of Beta-trace Protein BTP, a New Marker of Glomerular filtration Rate .

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I. Background :

1.Functions & synthesis :

Beta trace protein (BTP) is a low molecular weight protein synthesized mainly in the central nervous system **(CNS)**. Expressed in tissues of the blood-brain barrier and secreted into **cerebro-spinal fluid**. It catalyses the conversion of **PGH2 to PGD2**, a prostaglandin involved in smooth muscle contraction/relaxation and a potent inhibitor of platelet aggregation. Involved in a variety of CNS functions, such as sedation, NREM sleep and PGE-2 allodynia and may have an anti-apoptotic role in oligodendrocytes. Binds small non –substrate lipophilic molecules : bilirubin, biliverdin, retinal, retinoic acid and thyroid hormone, and may act as a scavenger for harmful hydrophobic molecules and as a secretory retinoid and thyroid hormone **transporter**.

2. BTP as renal marker :

It is freely filtrated in the glomerules and cleared by the tubules, its amount in plasma depends mainly from its renal clearance. Thus different authors have proposed to use it as a marker of renal function. However little is known regarding the analytical performances of its determination, as well as its stability in serum. We thus storage and compare its clinical characteristics with different well –established markers of the Glomerular Filtration Rate (GFR).

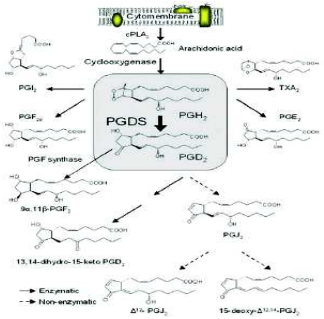
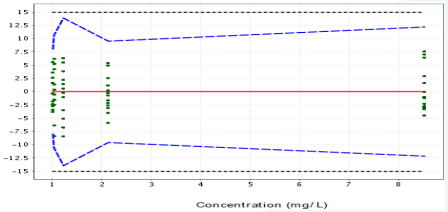


Fig- BTP , Beta trace protein (BTP) or lipocaline-type PGD2 (prostaglandin D2) synthase and role in prostaglandin pathway.

II. Material & Methods:

We have assessed the accuracy and precision (according to the CLI EP 5A-2 guideline) of BTP determination using the Siemens BN 2 (Siemens diagnostics , Tarrytown, NY) nephelometer. We built the accuracy profile on 10 serum pools (ranging from 0,62 to 20,4 mg/L). We calculated the **β expectation limits with β = 0,95** and considered the method as valid if they were comprised in the ± **15%** interval. **For stability studies,** 10 sample assayed in duplicate at T0 and after 1, 4, 7 and 14 days and after 1, 3, 6 and 12 months. Then we evaluated BTP performances as a marker of renal function compared to **Cystatin C** (Cys C; Siemens Diagnostics) in a population of patients for whom **GFR** had been previously determined with a reference method **(plasma iohexol clearance)**.

- **The accuracy profile** built with the predictive tolerance interval method shows that, on average, 95% of the future results that will be generated by this method will be included in the computed tolerance intervals of ± **15%** in the studied range.

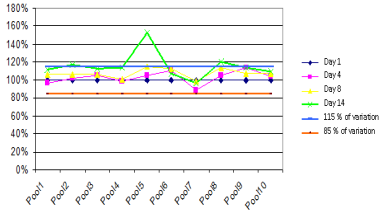


III. Results & discussion:

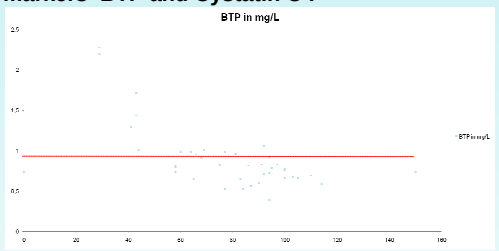
- **Repeatability** did not exceed 3,1% and the intermediate precision 5,4% in the studied range (from 1 to 8,5 mg/L).

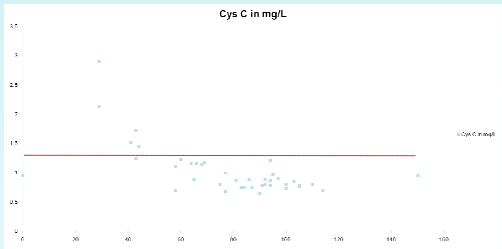
Concentration's level	Means of concentrations (mg/L)	Repeatability (CV%)	intermediate precision(CV%)
1.0	1.014	1.487	2.984
2.0	1.036	2.945	4.287
3.0	1.223	3.089	5.365
4.0	2.125	1.862	3.595
5.0	8.523	1.968	4.427

-**Stability :**
BTP was shown to be stable after 14 days of storage at + 4℃ and up to 1 year at -20℃.



- Correlation between GFR in mL/min, determined with a reference method (plasma iohexol clearance) and two renal markers BTP and Cystatin C :





BTP and Cys c shows the same classical exponential profile when compared to the GFR in mL/min determined with the reference method. However, we observed a grey- zone in the range 60-80 mL /min and we could not determine which parameter is the earlier to rise.

N.B :The upper limit of reference range is shown by the red line : 0,738 mg/L for BTP and 0,95 mg/L for Cystatin C.

IV. Conclusion :

BTP determination on BN2 is a reliable method that presents interesting analytical characteristics. However, 15% of total variability should probably be improved, compared to the analytical performances of some other GFR markers (8% of total variability for Cystatin C and creatinine). BTP was shown to be very stable molecule at + 4℃ and -20℃. Finally , studies with a re ference method in a greater number of patients presenting a GFR in the grey zone of 60-80 ml/min are needed in order to see if BTP could be an earlier marker of renal impairment compared to Cys C and creatinine.