Background

Haematopoietic stem cell transplantation (HSCT) is the only current curative treatment for Sickle Cell Disease (SCD), with potential life-threatening consequences. Busulfan is an alkylating agent used in HSCT conditioning regimen. Because of its narrow therapeutic window, determining the optimal first dose a priori remains a challenge.

Busulfan is metabolized in the liver by conjugation with glutathione, which is catalyzed by Glutathione-S-Transferases (GSTs). GSTA1 is a known determinant of Busulfan clearance (just like age and weight) suggesting that those characteristics should be known a priori to adjust the first dose of Busulfan.

Haemoglobinopathies (SCD and thalassemia) are not associated with changes in Busulfan clearance in a recent study. However, SCD is known to alter pharmacokinetics of other drugs. As it leads namely to liver dysfunction it may affect busulfan pharmacokinetics independently from genetic or anthropometric factors.

Our aim is to compare the clearance of the first dose of Bu between patients with and without SCD, considering other constitutional factors.

Methods

Patients with SCD were paired to patients without SCD on known Busulfan clearance’s covariates including GSTA1 group, age and frequency of administration.

Data were collected retrospectively from the HSCT Unit database at Sainte-Justine Hospital and also used in previous studies. Weight adjusted clearance was compared between the two paired groups using a mixed procedure on SAS software.

Results

Among the 129 patients included, 16 had SCD. Each patient was matched with up to 4 controls (total of 50 controls). Mean weight adjusted clearance was 3.04 ml/min/kg [SD=0.18] in patients with SCD versus 3.11 ml/min/kg [SD=0.14] in controls (difference 0.07 ml/min/kg F=0.14 p>F=0.714).

Conclusions

The diagnosis of SCD did not reveal to influence independently the clearance of the first dose of Bu. Consequently, no dose tailoring is needed in those patients only by the fact of being affected by SCD.

REFERENCES


Disclosure(s)

Nothing to disclose

Background

Recipient genotyping for CYP2D6 activity is an essential step prior to tramadol administration and has been recommended by international guidelines.1,2 However, prevalence of CYP2D6 ultra-rapid (UM) and poor (PM) metabolizers varies among different populations.3-5

We plan to include 53 children receiving tramadol at the Emergency Department (ED) of the Geneva Children’s Hospital. Children with concomitant inhibitors/inducers of CYP2D6 and CYP3A or drug with an impact on pupil size are excluded. Standard CYP2D6 phenotyping is performed by measuring blood dextromorphan/dextrorphan (DOR/DEM) using dried blood spots (DBS) at least 90min after dextromorphan and tramadol administration. Tramadol and its active metabolite, M1, concentrations are also performed using DBS at the same time. Pupillometry is performed at time of tramadol administration and 1 to twice per hour, during the stay in the ED.

Results

We included 26 children, median age 10.7 years, of which 2 are UM (8%) and 3 PM (12%), corresponding to what is expected in the Caucasian population. We found a positive correlation between DOR/DEM and M1/tramadol ratio (R²= 0.389, p = 0.0006). Pupillometry analyses are in progress. Tramadol 2 mg/kg orally was well tolerated in all children, including UM and PM.

Conclusion

Our study shows that it is possible to determine CYP2D6 activity in order to provide safe and effective tramadol prescription in children in a less invasive manner than by administering a probe drug, by directly determining the metabolic ratio between tramadol and its metabolite, M1 in children treated with tramadol.

REFERENCES