IFOSFAMIDE (IFX) AND MAIN METABOLITES IN 11 CHILDREN FOLLOWING A CONTINUOUS INFUSION OF 3 G/M²/D DURING 7 DAYS.

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Gaol of the study : Although the metabolism of IFX is well documented, few pharmacokinetics (PK)data are available. We have carried out a study on IFX and its 2 and 3 dechlorethylated metabolites (2D IFX, 3D IFX) as well as its active metabolite (4 OH IFX) in 11 patients (p)(aged from 5 to 19 y) treated with a daily dose of 3 g/m²/d during 7 days (d). The goal of the study was to verify if an induction of parent compound, as previously described, was observed and its influence on PK data of metabolites under these employed conditions.

Methods : 1 ml of blood samples were collected at 12 h, 24 h the first day, then every 24 h and 3, 6, 12 and 24 h after the end of the infusion and immediately decanted into tubes containing the trapping agent to stabilise the 4 OH IFX. The 4 compounds levels were determined by a Gaz Chromatography method equipped with an Nitrogen-Phosphorus Selective Detector after chloroformic extraction of the supernatant of the tubes. « MK Model » soft ware was used to estimate PK constants, based on a non compartmental approach where AUC and AUMC were determined using a log/trapezoidal method.

Results : For the 11 studied p. the **IFX initial concentrations** (T24 h) are quite homogeneous and reach from 20 to 30 µg/ml. **Repartition and elimination curves show a general decrease from the 1st to the 5th day** followed by a constant concentration level on days 6 and 7. This curve aspect was noted for each p and can be considered **as the drug auto-induction effect**. The average of the half life on the last day is : 3.69 +/- 1.95 h, the total clearance : 11.9 +/- 3.9 l/h and the volume of distribution : 68.9 +/- 45.11.

At the opposite the **metabolites levels are constant from the 1st or 2nd day through the end of the infusion for a given patient**. The mean metabolites index indicate a 3 D IFX production (17.7 %) slightly greater than that of 2 D IFX (13.2 %). Only 2.8 % were calculated for the active metabolite with a constant level too. The terminal half-lifes were respectively 9.1, 14.6, 7.5 h.

Conclusion : It is clear from our results that a stimulation of the metabolism of the parent compound is observed in children upon such doses. The AUC decrease of IFX from d 1 to d 5 cannot be explain by a greater metabolites production. However 2 D IFX and 3 D IFX remain in peripheral circulation following their synthesis. In the opposite, 4 OH IFX is the sole component able to move into the intracellular compartment and thus, its blood level does not reflect this intracellular one. An increase in the intracellular concentration could not be excluded for this active metabolite.