Oral

[O25-4] O25-4: Clinical toxicology (1)

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[O25-4-3] Designer benzodiazepines and opioids: the risk of metabolic interactions

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Background

Designer benzodiazepines (DBZD) are frequently implicated in cases of opioid overdoses when taken to enhance or to prolong the high and to reduce the descent effects of opioids. Possible metabolic interactions between DBZD and opioids have been poorly investigated yet. The aim of this study was to determine the interaction between diclazepam and oxycodone, two of the most misused DBZD and opioids, respectively. Therefore, we explored, *in vitro*, the metabolic pathways of diclazepam and then the influence of diclazepam on the metabolism of oxycodone.

Methods

Diclazepam was incubated at 37˚C in the presence of NADPH (4 mM diluted in Tris HCl pH 7.4) with 9 different hepatic recombinants isoenzymes (P450 1A2, 2B6, 2C19, 2C8+b5, 2C9+b5, 2E1+b5, 3A4, 3A5 et 2D6) (SUPERSOME® BD Bioscience). To evaluate the implication of each isoenzyme, the production of the 2 metabolites of diclazepam (lormetazepam and deslorazepam) were measured and the respective relative activity factors (RAF) were applied. After optimization, oxycodone (1 mg/L) was incubated with hepatic microsomes (0.5 mg/mL) and NADPH. The production of 2 oxycodone metabolites (oxymorphone and noroxycodone) was evaluated in the presence and the absence of diclazepam at 2 concentrations (5 and 10 mg/L). All determinations were performed on an LC-MS/MS system (Shimadzu® 8050).

Results

The isoenzymes responsible of the metabolism of diclazepam were 2B6, 2C19, 3A4 and 3A5 for the production of deslorazepam and 2C19, 3A4 and 3A5 for lormetazepam. The implication of CYP 3A4 was found to be 10 folds higher than the other isoenzymes. Diclazepam significantly decreased the metabolism of oxycodone. The production of oxymorphone was 36 to 57 % lower in the presence of 5 and 10 mg/L of diclazepam ($p=0.007$, $n=7$) and 25 to 37 % for oxymorphone ($p=0.004$, $n=7$).

Conclusions

Our results suggest that diclazepam decreases the hepatic metabolism of oxycodone. This interaction could partly explain the occurrence of oxycodone overdoses when combined to diclazepam. Other DBZD combined to other opioids may present similar interactions.