

THE ROLE OF LIVER CYTOCHROME ISOFORMS ON BUPRENORPHINE METABOLISM AND IT'S CLINICAL RELEVANCE

Somaini Lorenzo¹, Gola Mauro²

¹ Addiction Treatment Centre, Health Local Unit ASL 12 Biella

² Laboratory of Pharmacogenetics Lugano (CH)

Methadone (MTD) and buprenorphine (BPN) produce morphine-like agonist effects and cross substitute for heroin. Both have proven to be extremely effective in reducing illicit opioid use and maintaining patient in treatment. Pharmacokinetics of MTD differ from person to person, so, after the administration of the same dose, different concentrations are obtained in different subject, and the pharmacological effect may be too small or too strong and prolonged in some patients. The activity of cytochrome CYP 3A4, 2D6 and of 1A2, that are responsible for liver metabolism of methadone, varies considerably among the individuals, and such variability is the responsible for the large differences in MTD bioavailability. Although, the BPN has been used clinically for years, its metabolism has still not been fully elucidated. The aims of this study were firstly to compare the clinical efficacy of different doses of BPN and MTD in heroin addict patients and then to studies the role of different isoforms of CYP3A4 (1B, 3, 7, 10) and CYP2D6 (3, 4, 6) on BPN metabolism. For this reason, we studied the retention in treatment and the illicit opioid use in 4 groups of patients: group A patients in treatment with MTD < 60 mg/die; group B in treatment with MTD > 60 mg/die; group C patients in treatment with BPN < 8 mg/die; group D patients in treatment with BPN > 8 mg/die. In the groups C and D we also studied the distribution and the role of different isoforms of liver cytochrome on BPN metabolism in 24 hours collected urinary specimens. The different isoform of cytochrome were prepared from DNA of blood samples. The BPN and metabolite nor-BPN were detected by mean GC/Mass Spectrometry and the different cytochrome isoforms were identified by mean of Western-Blot analysis.

Retention in treatment was higher in patients treated with high doses of MTD and BPN and the differences were significant versus patients treated with low dose of both drugs. There were not significant differences in terms of retention in treatment among group B and D. Patients receiving high doses of MTD and BPN submitted fewer opioid-positive urine specimens than patients receiving low doses of each drugs and the differences were significant among these two groups. The concentration of BPN and nor-BPN in 24 hours urinary specimens were similar in patients with different isoforms of cytochrome suggesting that, differently from MTD, fewer interferences were seen by the liver isoforms of cytochrome on BPN metabolism, and these may contribute to maintain stability of plasma level of BPN in time and consequently it's clinical efficacy.