

Liver cytochrome overexpression in human HCV infection

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Sir,

The manuscript by S. Maxwell et al., "Correlation between hepatitis C serostatus and methadone dose requirement in 1,163 methadone-maintained patients", published in *Heroin Add & Rel Clin Probl* 2002, 4(2): 5-10, suggests the need for higher maintenance doses of methadone in HCV-infected patients. It is stated in the discussion that "whereas most other hepatitides impair the activity of the Cytochrome P450 enzyme system, our clinical observations are more consistent with a cytochrome induction phenomenon. This possibility deserves further study, as it could have significant impact on the treatment of HCV and related conditions".

Indeed, a correlation between viral hepatitis and the induction of selected isozymes of the cytochrome P450 family was published in 1996 by G.M. Kirby and coworkers⁽⁶⁾. The Authors report that in HCV-infected human liver, CYP2A6, CYP3A4 and CYP2B1 were overexpressed in hepatocytes with hemosiderin pigmentation.

It is known that the main catabolic pathway for methadone depends on CYP3A4, with minor contributions from other isozymes^(3,4).

Hence, the overexpression of CYP3A4 may be at least partly, responsible for the higher methadone doses reported by Maxwell and coworkers for HCV-infected opioid-dependent subjects. Since cannabinoids and diazepam are known to inhibit CYP3A4, a pharmacokinetic interference determining lower clearance of methadone and less craving and discomfort could contribute to their use by these patient populations.

Interestingly, buprenorphine is also metabolized by CYP3A4⁽⁵⁾; this calls for an evaluation of required dosages in HCV-infected vs. seronegative individuals.

Other mechanisms might also influence the bioavailability of opiate drugs in viral hepatitis. P-glycoprotein (PGP), a membrane transporter which extracts various cationic xenobiotics, including methadone, from cytoplasm could be a candidate. To our knowl-

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edge, no published studies have reported clinically significant effects on methadone pharmacokinetics by PGP inhibition, but the Italian drug package insert for methadone hydrochloride states that PGP inhibitors may increase methadone blood levels⁽¹⁾. Some *in vitro* investigations suggest that HBV infection with integration of the virus into hepatocyte DNA may induce the synthesis of PGP⁽²⁾. To date, no reports are available on the effects of HCV infection on the hepatic expression of that transporter. The direction and magnitude of those effects on PGP function, and their possible clinical relevance, could be an interesting additional route open to investigation.

References

1. Decreto Legislativo Ministero della Salute (July 4th, 2002). In: Gazzetta Ufficiale della Repubblica Italiana, 142, June 19th, 2002
2. Doong, S.L., Lin, M.H., Tsai, M.M., Li, T.R., Chuang, S.E., Cheng, A.L. (1998): Transactivation of the human MDR1 gene by hepatitis B virus X gene product. *J. Hepatol.* 29 (6): 872-878
3. Foster, D.J., Somogyi, A.A., Bochner, F. (1999): Methadone N-demethylation in human liver microsomes: lack of stereoselectivity and involvement of CYP3A4. *Br J Clin Pharmacol* 46 (4): 403-412
4. Iribarne, C., Berthou, F., Baird, S., Dreano, Y., Picart, D., Bail, J.P., Beaune, P., Menez, J.F. (1996): Involvement of cythochrome P450 3A4 enzyme in the N-demethylation of methadone in human liver microsomes. *Chem Res Toxicol* 9(2): 365-373
5. Iribarne, C., Picart, D., Dreano, Y., Bail, J.P., Berthou, F. (1997): Involvement of cytochrome P450 3A4 in N-dealkylation of buprenorphine in human liver microsomes; *Life Sci* 60(22): 1953-1964
6. Kirby, G.M., Batist, G., Alpert, L., Lamoureux, E., Cameron, R.G., Alaoui-Jamali, M.A. (1996): Overexpression of cytochrome P-450 isoforms involved in aflatoxin B1 bioactivation in Human liver with cirrhosis and hepatitis. *Toxicol Pathol* 24(4): 458-467

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