Alkoholizm i Narkomania 2003, Tom 16: nr 3-4, 127-137

DIFFICULTIES IN ANTIRETROVIRAL TREATMENT IN OPIOID DEPENDENT PATIENTS TREATED IN SUBSTITUTION PROGRAMS

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Abstract – The introduction of potent antiretroviral therapies, including triple regiment, has dramatically improved the prognosis for HIV-infected individuals. The widespread use of highly active antiretroviral therapy (HAART) has had a significant impact on HIV pandemic by reducing mortality and morbidity. Most patients will be on the antiretroviral therapy for the rest of their lives, so it could potentially cause severe adverse effects and drug toxicity. Unfortunately, long-term use of antiretroviral treatment is associated with several limitations and drawbacks. On the average, virological failure occurs in ca. 25% subjects. Treatment failure may be dependent on several factors, including low drug potency, selection of drug-resistant virus variants, poor drug compliance and pharmacokinetic interactions. An understanding of pharmacokinetics and drug mechanism is essential to predict interaction occurrence. In general, pharmacokinetic interactions are considered clinically significant, when at least a 30% change in maximum drug concentration (C_{max}), minimum (trough) conentration (C_{min}), or area under the concentration time curve (AUC) occurs. Currently, many clinical data show, that methadone may be involved in clinically significant drug interactions. For example, when the NNRTI's nevirapine or efavirenz were added to patients receiving methadone maintenance treatment, methadone concentration was decreased by average 50% (during 24-hour area under the curve), and some patients experienced withdrawal symptoms. Other antiretroviral agents – protease inhibitors (PI's), like boosted ritonavir/saquinavir and nelfinavir, have been reported to decrease methadone concentration, although the clinical significance of these changes is uncertain. HIV health care providers should be aware of potential ineraction between methadone and antiretroviral

drugs, when methadone dose adjustment is necessary. The most common type of pharmacokinetic drug interactions with HAART involves drug metabolism, because the non-nucleoside analogues reverse transcriptase inhibitors (NNRTI's) and Protease inhibitors (PI's) are extensively metabolized via the cytochrome P-450 (CYP 450) enzyme system. Methadone is metabolized via isoenzyms CYP 3A4 and CYP 2D6. Because of NNRTI's and PI's are also metabolized by CYP 3A4, drug interactions are likely to occur when these agents are used concurrently with methadone. The methadone-HAART associated drug interactions most likely to result in clinically significant ruduction in methadone level in serum, required methadone dose increasing. Among most methadone-treated individuals were observed HIV virological failure, drug resistance, and/or side effects occurrence and sometimes require discontinuation of HAART regimen. Drug interaction data for HAART are often lacking. An understanding of the drug interactions should allow clinicians to predict and avoid those drug combinations, that are likely to result in adverse events in HAART, and methadone dose change.

Key words: methadone, substitution therapy, antiretroviral drugs, pharmacokinetic interactions.