Journal of NeuroVirology (2000) 6, Suppl 1, S33–S37

www.jneurovirol.com

Neurologic disease in injection drug users: therapeutic issues

Walter Royal III*,[1]

[1]*Johns Hopkins University School of Medicine, 600 North Wolfe Street, Baltimore, Maryland, MD 21287, USA*

Illicit drug use may cause nervous system impairment as a result of direct and indirect effects on the integrity and function of nervous system tissue and, potentially, through immune effects. HIV-1 infection poses an additional risk of impairment, and this risk may be decreased as a result of antiretroviral drug treatment. Obviously, the goal of such therapy is to improve the potential clinical course of infection. However, interactions between antiretroviral drugs, abused drugs, and hepatic metabolic enzyme systems may result in impaired or more efficient drug clearance and, consequently, antiretroviral or substance abuse treatment failure. The clinical outcome of this interaction may potentially include drug-related neurotoxicity or neurologic disease induced by HIV infection. The actual impact of these interactions on the occurrence of neurologic impairment and disease are unknown at this time, and, therefore, require study. *Journal of NeuroVirology* (2000) **6,** S33–S37.

Keywords: human immunodeficiency; methadone; cocaine; nervous system; antiretroviral therapy; injection drug use

Introduction

The use of illicit drugs has been associated with more than a third of all cases of AIDS among adults and children (Centers for Disease Control and Prevention, 1998). Clinical neurological abnormalities, such as cognitive impairment and symptoms and signs of peripheral neuropathy, are common in injection drug users (IDU) and, early in HIV-1 infection, may occur with similar frequencies among HIV-1 seropositive and seronegative subjects (Royal, 1991; Selnes, 1997). In infected individuals, dementia may potentially occur as a direct result of effects of viral product such as gp 120, tat, and nef, or due to mediators or by-products of inflammation (Lipton and Gendelman, 1995). Among IDU, the mechanisms of the neurological impairment may be also multifactorial and include the effects of abused drugs. It has been observed that, in most cases, such structural damage results from effects of ischemia (Andersen and Skellerud, 1999). This has been suggested in numerous reports that clearly demonstrate that cocaine, opiates, and amphetamine derivatives may lead to the development of inflammation in the medium and small arteries in the brain (Margolis and Newton 1971; Fredericks *et al*, 1991; Levine *et al*, 1991) and, in rare cases, ischemia of the spinal cord (Richter and Rosenberg, 1968; Judice *et al*, 1978; Ell *et al*, 1981; Sawaya and Kaminski, 1990). It is now also apparent that HIV-1-infected IDU may be at increased risk for developing HIV encephalitis and cognitive impairment and may have more rapid clinical progression of HIV dementia as compared to gay men (Bell *et al*, 1998; Bouwman *et al*, 1998). Therefore, HIV-1 infection and illicit drugs may act synergistically to cause neurologic impairment in IDU.

The signs and symptoms of HIV dementia include impaired memory, concentration, and ability to perform simple and complex psychomotor tasks (Miller *et al*, 1990; Selnes *et al*, 1992, 1997). Individuals with late dementia become withdrawn and demonstrate more severe motor abnormalities such as lower extremity weakness and spacticity, caused by myelopathy, and tremor (Petito *et al*, 1985; Price and Brew, 1988). These HIV-related sequelae may be potentially exacerbated by the effects of abused drugs. The primary clinical effects of opiate drugs include euphoria, drowsiness, nausea, vomiting, blurred vision, constipation, urinary retention, and sweating (Brust, 1993). The pharmacologic effects of these drugs are achieved through the modulation of tolerance through changes in glutamate, norepinephrine, dopamine,

*Correspondence: W Royal, Morehouse School of Medicine, 7200 Westview Drive SW, Atlanta, GA 30310, USA

adenosine, acetyl choline, serotonin, and cholecystekinine levels in brain. Cocaine use causes dizziness, eurphoria, syncope, paresthesias, blurred vision, headache, tremor, weakness, movement disorders, seizures, lethargy, and coma (Brust, 1993). Tolerance to cocaine appears to be modulated through the expression of dopamine, norepinephrine, and serotonin receptors. Recent studies demonstrated that production of dopamine transporters in cells of the striatum are increased in cocaine (Little *et al*, 1999) and decreased in methamphetamine users (McCann *et al*, 1998). These findings suggest that, even in cases where obvious gross or microscopic neuropathologic abnormalities may be absent, cellular changes may be induced by drugs of abuse that may account for the pharmacologic properties and clinical manifestations observed with use of the substances.

Immune effects of drugs of abuse

In humans, chronic cocaine use has been associated with increased NK cell and decreased T cell numbers and impaired macrophage function (Baldwin *et al*, 1998). Lymphocytes exposed *in vitro* to cocaine produce lower than expected levels of IFN-γ and IL-8 and normal levels of IL-4, -5 and -10 (Baldwin *et al*, 1998). In contrast to what has been observed for cocaine, morphine has been shown to suppress NK cell activity and numbers with no consistent effect on T cell parameters being demonstrated (Eisenstein and Hilburger, 1998). Lymphocyte proliferation and production of IFN-α and -β was found by one investigator to be decreased by morphine (Nair *et al*, 1997), whereas another observed no effect (Palm *et al*, 1996). Such inconsistencies in data obtained from human cells are common and are often in conflict with results obtained from studies involving animals. Among the explanations proposed to explain these discrepancies are that (1) IDU may use multiple drugs with varying patterns of use; (2) documentation of use is generally based on self-reports, and the reported drug use may be inaccurate or not reported at all; (3) control groups that are used for comparison in statistical analyses may include users of non-injected illicit drugs (Donahoe and Vlahov, 1998).

Interactions between antiretroviral agents and drugs of abuse

Currently there are 15 antiretroviral drugs available for the treatment of HIV infection. Included in the spectrum of adverse effects associated with treatment with these agents are those which can involve the nervous system (Table 1). In most instances, the frequency of the reported neurologic side-effects and the mechanisms associated with their occurrence have not been systematically studied. Among drug users, the occurrence of various adverse effects may be even more difficult to anticipate due to the ability of illicit compounds to modify the activity of factors and pathways that are important for metabolizing anti-HIV drugs. Many pharmacologic agents are metabolized in the liver via two enzymatic pathways. Modification of the primary structure of the compound occurs due to the action of the cytochrome P450 enzymes (phase I metabolism; Figure 1). There are three known families of these enzymes, which share the characteristic of containing a heme group and demonstrating maximum absorbance at 450 nm. They have rate-limiting effects on drug inactivation and elimination and can be either inducible or non-inducible. Subtypes of the cytochrome P450 enzymes have also been identified in the intestine where they are responsible for intraluminal conversion of drugs and other compounds. As a result of the chemical modification that occurs in the intestinal lumen, absorption can be either increased or decreased. A second set of reactions, comprising phase 2 metabolism (Figure 1), frequently take place following modification of a compound by a phase 1 reaction and involve covalent linkage of the modified compound to a polar substance (e.g. glucuronic acid, sulfate, glutathione, or amino acids). The effect of phase 2 reactions is to increase the water solubility of the compound, thereby enhancing excretion in the urine and stool, the latter by inhibiting reabsorption from the intestines following excretion in bile (Watkins, 1995).

The protease inhibitors are metabolized by enzymes of the cytochrome P450 system, primarily cytochrome P450-3A (CYP3A), and act as inhibitors

Table 1 Neurological symptoms associated with currently available antiretroviral drugs

Nucleoside analogs	
Zidovudine (AZT; Retrivir)	Myopathy, minor headache
Didanosine (ddI, Videx)	Peripheral neuropathy
Zalcitabine (Dideoxycytidine; ddc; Hivid)	Peripheral neuropathy
Lamivudine (3TC, Epivir)	Minor headache, fatigue
Stavudine (d4T; Zerit)	Peripheral neuropathy
Abacavir (Ziagen)	Headache
Non-nucleoside inhibitors	
Nevirapine (Viramune)	Mild headache, somnolence
Efavirenz (Sustiva)	Dizziness, lightheadedness, agitation, anxiety, impaired concentration, drunken feeling
Delvirdine (Rescriptor)	Myalgias
Protease inhibitors	
Saquinivir mesylate (Invirase; Fortovase)	Headache, dizziness, paresthesia, peripheral neuropathy, muscle pain
Indinavir (Crixivan)	Minor headache, fatigue, drowsiness or insomnia, dizziness, metallic taste
Ritonavor (Norvir)	Dysgeusia, perioral or extremity numbness
Nelfinavir (Viracept)	Headaches, impaired concentration
Amprenavir (Agenerase)	Perioal numbness

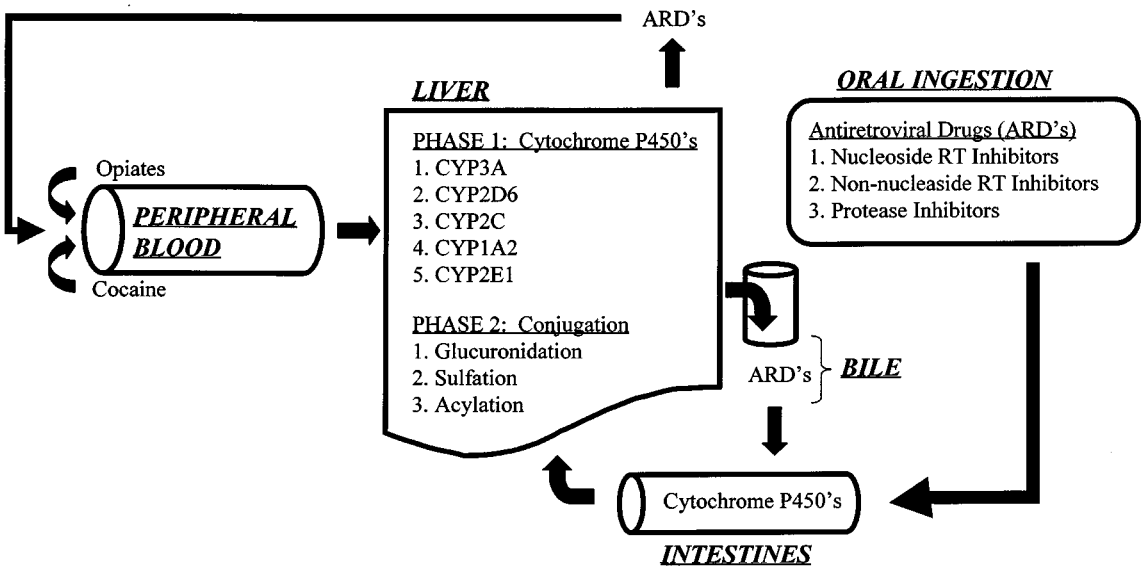

Figure 1 Orally administered antiretroviral drugs (ARD's) are exposed to cytochrome P (CYP) 450 enzymes in the intestines, and are then metabolized in the liver following absorption and with subsequent recirculation. Opiate drugs and/or cocaine (as well as other drugs) present in peripheral blood can interact with phase 1 and 2 metabolism of ARD'S. This may result in either increased or decreased levels of the abused drug or of the reverse transcriptase (RT) or the protease inhibitor (see text). The major cytochrome P450 enzymes and the categories of chemical reactions involved in phase 1 and 2 metabolism, respectively are listed (Benet *et al*, 1996).

of these enzymes (Decker *et al*, 1998; Flexner, 1998). Metabolism of zidovudine and other nucleoside reverse transcriptase inhibitors involves glucuronidation and, to a lesser extent, conversion by cytochrome P450 enzymes (Veal and Back, 1995; McCance-Katz *et al*, 1998; Trapnell *et al*, 1998). Concomitant administration of two protease inhibitors will increase the concentration of both drugs; nelfinavir and ritonavir increase the plasma-concentration-time curve of saquinavir by 392 and >2000 per cent, respectively. Similarly, the protease inhibitors may decrease the clearance of number of other drugs that are metabolized by CYP3A, including rifampin, rifabutin (which, consequently, should not be administered with ritonavir or saquinavir), amiodarone, astemizole, cisapride, ergot alkaloids and derivatives, quinidine, terfenadine, and medazolam and triazolam. Enzyme inhibitors such as ketoconazole, clarithromycin, fluconazole, and fluoxetine, and inducers, such as rifabutin and rifampin, increase and decrease, respectively, protease inhibitor levels (Flexner, 1998). Ritonavir, the most potent CYP3A inhibitor of this class of antiretroviral agents, also inhibits other cytochrome P450 enzymes to a lesser extent as well as glucuronosyl transferase, the essential enzyme for glucuronidation (Hsu *et al*, 1998). Therefore, the metabolism of many other drugs may be potentially affected by ritonavir, including other classes of antiretroviral compounds.

Methadone, buprenorphine and L-alpha-acetylmethadol (LAAM) have also been shown to undergo extensive modification by cytochrome P450 3A4 (Iribarne *et al*, 1997a, b; Moody *et al*, 1997); methadone is also processed via glucuronidation (Sanchez *et al*, 1978). The potential effect of cocaine on these enzyme systems is less well understood. However, it is likely that cytochrome P450 3A4 is also responsible for the cocaine demethylase activity that has been observed in liver (LeDuc *et al*, 1993). Therefore, it is possible that, for drug users who are either on methadone maintenance, undergoing treatment with LAAM or buprenorphine, or are actively using another opioid or cocaine, co-administration of an antiretroviral agent may potentially result in an increase in either drug level with multiple potential effects. Conversely, co-administration of CYP34A inducers may result in decreased levels these drugs and symptoms of withdrawal. Serum levels of zidovudine are increased by methadone (McCance-Katz *et al*, 1998). Therefore, specific drug related toxicities, including those involving the nervous system, may potentially result from co-administration of antiretroviral agents with substances of abuse. The precipitation of opiate withdrawal has been reported in a drug user on treatment with methadone after the initiation of nevirapine (Heelon and Meade, 1999), demonstrating that methadone metabolism may be induced by the protease inhibitors. In addition, a case of fatal ecstasy overdose induced by ritonavir has been also described, presumably due to induction of an increased half-life of the hallucinogen (Mirken, 1997). These cases demonstrate the dramatic and potentially catastrophic outcomes that can result from the effects of antiretroviral agents on

the hepatic catabolic enzyme systems and the fact that more needs to be learned about these interactions and their effects on the nervous system.

Conclusion

In addition to the demonstrated effects of abused drugs on nervous system and their speculated effects on immune function, the consequences of altered drug metabolism may be also associated with an increased risk of neurologic abnormalities occurring in IDU. The described interactions may result in either higher levels of a concomitantly administered antiretroviral agent, thereby increasing the risk of nervous system toxicity, or lower serum and CSF levels of the compound, increasing the risk of treatment failure and increased immunosuppression. The efficacy of treatment regimens that include protease inhibitors may be most affected by the metabolic effects of abused drugs since the CNS penetration of the protease inhibitors is quite low (Flexner, 1998). Even in those cases where there may be no anticipated interaction between an antiretroviral regimen and known abused substances, the drug intoxication or withdrawal may lead to antiretroviral non-compliance. Therefore, the risks of developing nervous system complications in the context of illicit drug use and treatment with currently recommended antiretroviral drug combinations require further study.

References

Andersen SN, Skellerud K (1999). Hypoxic/ischemic brain damage, especially pallidal lesions, in heroin addicts. *Forensic Sci Int* **102:** 51–59.

Baldwin GC, Roth MD, Tashkin DP (1998). Acute and chronic effects of cocaine on the immune system and the possible link to AIDS. *J Neuroimmunol* **83:** 133–138.

Bell JE, Brettle RP, Chiswick A, Simmonds P (1998). HIV encephalitis, proviral load and dementia in drug users and homosexuals with AIDS. Effect of neocortical involvement. *Brain* **121:** 2043–2052.

Benet LZ, Kroetz DL, Sheiner LB (1996). Pharmacokinetics. The dynamics of drug absorption, distribution, and elimination. In: *Goodman & Gilman's, The Pharmacological Basis of Therapeutics.* Hardman JG, Limbird LE, Milinoff PB, Ruddon RW, and Goodman A, (eds.) McGraw-Hill: New York, pp. 11–17.

Bouwman FH, Skolasky RL, Hes D, Selnes OA, Glass JD, Nance-Sproson TE, Royal W, Dal Pan GJ, McArthur JC (1998). Bariable progression of HIV-associated dementia. *Neurology* **50:** 1814–1820.

Brust JCM (1993). Neurological aspects of substance abuse. (Stoneham: Butterworth-Heinemann).

Centers for Disease Control and Prevention (1999). *HIV/AIDS Surveillance Report* **11:** 12.

Decker CJ, Laitinen LM, Bridson GW, Raybuck SA, Tung RD, Chaturvedi PR (1998). Metabolism of amprenavir in liver microsomes: role of CYP3A4 inhibition for drug interactions. *J Pharm Sci* **87:** 803–807.

Donahoe RM, Vlahov D (1998). Opiates as potential cofactors in progression of HIV-1 infections to AIDS. *J Neuroimmunol* **83:** 77–87.

Eisenstein TK, Hilburger ME (1998). Opioid modulation of immune responses: effects on phagocyte and lymphoid cell populations. *J Neuroimmunol* **83:** 36–44.

Ell JJ, Uttley D, Silver JR (1981). Acute myelopathy in association with heroin addiction. *J Neurol Neurosurg Psychiatry* **44:** 448–450.

Flexner C (1998). HIV-Protease Inhibitors. *New Engl J Med* **338:** 1281–1292.

Fredericks RK, Lefkowitz DS, Challa VER, Troost BT (1991). Cerebral vasculitis associated with cocaine abuse. *Stroke* **22:** 1437–1439.

Heelon MW, Meade LB (1999). Methadone withdrawal when starting an antiretroviral regimen including nevirapine. *Pharmacotherapy* **19:** 471–472.

Hsu A, Granneman GR, Bertz RJ (1998). Ritonavir. Clinical pharmacokinetics and interactions with other anti-HIV agents. *Clin Pharmacokinet* **35:** 275–291.

Iribarne C, Dreano Y, Bardou LG, Menez JF, Berthou F (1997a). Interaction of methadone with substrates of human hepatic cytochrome P450 3A4. *Toxicology* **117:** 13–23.

Iribarne C, Picart D, Dreano Y, Bail JP, Berthou F (1997b). Involvement of cytochrome P450 3A4 in N-dealkylation of buprenorphine in human liver microsomes. *Life Sci* **60:** 1953–1964.

Judice DJ, Leblanc HJ, *et al* (1978). Spinal cord vasculitis presenting as a spinal cord tumor in a heroin addict. *J Neurosurg* **48:** 131

LeDuc BW, Sinclair PR, Shusterk L, Sinclair JF, Evans JE, Greenblatt DJ (1993). Norcocaine and n-hydroxynorcocaine formation in human liver microsomes: role of cytochrome P-450 3A4. *Pharmacology* **46:** 294–300.

Levine SR, Brust JCM, Futrell N, Brass LM, Blake D, Fayad P, Schultz LR, Millikan CH, Ho K-L, Welch KMA (1991). A comparative study of the cerebrovascular complications of cocaine: alkaloidal versus hydrochloride - a review. *Neurology* **41:** 1173–1177.

Lipton SA, Gendelman HE (1995). Dementia associated with the acquired immunodeficiency syndrome. *N Engl J Med* **332:** 934–940.

Little KY, Zhang L, Frey KA, Dalack GW, Cassin BJ (1999). Striatal dopaminergic abnormalities in human cocaine users. *Am J Psychiatry* **156:** 238–245.

Margolis MT, Newton TH (1971). Methamphetamine (''Speed'') arteritis. *Neurorad* **2:** 179–182.

McCance-Katz EF, Rainey PM, Jatlow P, Friedland G (1998). Methadone effects on zidovudine disposition (AIDS Clinical Trials Group 262). *J Acquir Immune Defic Syndr Hum Retrovirol* **18:** 435–443.

McCann UD, Wong DF, Yokoi F, Billemange B, Dannals RG, Ricaurte GA (1998). Reduced striatal dopamine transporter density in abstinent methamphetamine and methcathinone users: evidence from positron emission tomography studies with [11C]WIN-35, 428. *J Neurosci* **18:** 8417–8422.

Miller EN, Selnes OA, McArthur JC, Satz P, Becker JT, Cohen BA, Sheridan K, Machado AM, Van Gorp WG, Visscher B (1990). Neuropsychological performance in HV-1-infected homosexual men: the Multicenter AIDS Cohort Study. *Neurology* **40:** 197–203.

Mirken B (1997). Danger: possibly fatal interactions between ritonavir and ''ecstasy,'' some other psychoactive drugs. *AIDS Treat News* **265:** 5.

Moody DE, Alburges ME, Parker RJ, Collins JM, Strong JM (1997). The involvement of cytochrome P450 34A in the H-demethylation of L-alpha-acetylmethadol (LAAM), norLAAM, and methadone. *Drug Metab Dispos* **25:** 1347–1353.

Nair MPN, Schwartz SA, Polasani R, Hou J, Sweet A, Chadha KC (1997). Immunoregulatory effects of morphine on human lymphocytes. *Clin Diag Immunol* **4:** 127–132.

Palm S, Mignat C, Kuhn K, Umbreit H, Barth J, Stuber F, Maier C (1996). Phytohemagglutinin-dependent T cell proliferation is not impaired by morphine. *Methods Find Exp Clin Pharmacol* **18:** 159–165.

Petito CK, Navia BA, Cho ES, Jordan BD, George DC, Price RW (1985). Vacuolar myelopathy pathologically resembling subacute combined degeneration in patients with the acquired immunodeficiency syndrome. *N Engl J Med* **312:** 874–879.

Price RW, Brew BJ (1988). The AIDS dementia complex. *J Infect Dis* **158:** 1079–1083.

Richter RW, Rosenberg RN (1968). Transverse myelitis associated with heroin addiction. *JAMA* **206:** 1255–1258.

Royal III W, Updike M, Selnes OA, Proctor TV, Nance-Sproson L, Solomon L, Vlahov D, Cornblath DR, McArthur JC (1991). HIV-1 infection and nervous system abnormalities among a cohort of intravenous drug users. *Neurology* **41:** 1905–1910.

Sanchez E, Villar D, Tephly TR (1978). Structural requirements in the reaction of morphine uridine diphosphare glucuronyltransferase with opioid substances. *Biochem J* **169:** 173–177.

Sawaya GR, Kaminski MJ (1990). Infarction of spinal cord after intranasal cocaine. *South Med J* **83:** 601–602.

Selnes OA, McArthur JC, Royal III W, Updike ML, Nance-Sporson T, Concha M, Gordon B, Solomon L, Vlahov D (1992). HIV-1 infection and intravenous drug use: longitudinal neuropsychological evaluation of asymptomatic subjects. *Neurology* **42:** 1924–1930.

Selnes OA, Galai N, McArthur JC, Cohn S, Royal III W, Esposito D, Vlahov D (1997). HIV infection and cognition in intravenous drug users: long-term follow-up. *Neurology* **48:** 223–230.

Trapnell CB, Klecker RW, Jamis-Dow C, Collins JM (1998). Glucuronidation of 3′-azido-3′deoxythymidine (zidovudine) by human liver microsomes: relevance to clinical pharmacokinetic interactions with atovaquine, fluconazole, methadone, and valproic acid. *Antimicrob Agents Chemother* **42:** 1592–1596.

Veal GJ, Back DJ (1995). Metabolism of zidovudine. *Gen Pharmacol* **26:** 1469–1475.

Watkins PB (1995). Gastrointestinal toxicology. In: *Textbook of gastroenterology*. Yamada T, Alpers DH, Powell DW, Owyang C, and Silverstein FE, (eds.) JB Lippincott Company: Philadelphia, pp. 599–605.