CASE REPORT

Problems in three Japanese drug users with Human Immunodeficiency Virus infection

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Abstract : Numbers of individuals infected with Human Immunodeficiency Virus (HIV) are increasing in Japan. The majority of them are Men who have sex with men and a part of them take drugs as 'Sex drug' at their sexual intercourse. Especially, Amyl nitrite, Methamphetamine, 5-methoxy-N, N-diisopropyltryptamine (5-MeO-DIPT ; Foxy), and 3, 4-methylenedioxy- methamphetamine (MDMA ; Ecstasy) are used, and they sometimes cause the physical and mental disorders. However, the actual drug inducing troubles among Japanese HIV-infected drug users had not yet been discussed enough.

In this report, we describe three cases with HIV infection ; a case developed severe neuroleptic malignant syndrome (NMS) after taking 5-MeO-DIPT, a case with persistent convulsion due to multiple drug intake and a case with rhabdomyolysis due to the non-subjective methamphetamine intake. Through these cases, we raise and discuss several underlying problems associated with drug use among HIV-infected individuals. J. Med. Invest. 55 : 156-160, February, 2008

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INTRODUCTION

Numbers of individuals infected with Human Immunodeficiency Virus (HIV) are increasing in Japan (1, 2). The majority of them are Men who have sex with men (MSM), who infect with HIV through sexual intercourse (1, 3). A part of MSM with high sexual activity takes multiple drugs as 'Sex drug' at their sexual intercourse, and the sexual behavior using the drugs is correlated with the high risk of HIV infection in Japanese MSM as well (4).

Among HIV- infected Japanese drug users, in addition to a casual snort of amyl nitrate, methamphetamine, 3, 4-methylenedioxy- methamphetamine (MDMA ; called as 'Ecstasy') and 5-methoxy-N, N-diisopropyltryptamine (5-MeO-DIPT ; amphetamine analog, 'Foxy') are preferentially ingested, and these had been reported to induce the rhabdomyolysis (5-7). And several reports describe the interaction between these drugs and anti-HIV reagents as the elevated drug concentration in plasma (8-10). Nowadays, the drugs are taken without the concern about the interaction or the toxicity, and some drug users are carried to emergency hospitals due to the drug-induced troubles. However, the actual drug-induced trouble among Japanese HIV-infected drug users

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In this report, we describe three cases with HIV infection ; a case developed severe neuroleptic malignant syndrome (NMS) after taking 5-MeO-DIPT, a case with persistent convulsion due to multiple drugs intake and a case with rhabdomyolysis due to the non-subjective methamphetamine intake. Through these cases, we raise and discuss the problems associated with drug use among HIV-infected individuals.

CASE REPORT

Case 1

A 28-year-old MSM was a 5-MeO-DIPT user for two years. He took duplicate dose of 5-MeO-DIPT rectally concomitant with sildenafil citrate (Viagra) orally for homosexual intercourse. Fifteen hours after the drug intake, he was transferred with unconsciousness to the department of critical care medicine of our hospital. His consciousness level was low at Glasgow Coma Scale E1V1M4 and Japan Coma Scale 200. His body temperature was over 40°C, blood pressure 140/ 87 mmHg and pulse rate 107/ min. His respiratory sound was normal vesicular. He was positive in HIV screening test. His CD4+ count was 220/μl with a viral load of 1,500 copies/ml. Laboratory data was as follows ; CPK 122,700 IU/L (normal : 62-287), CPK-MB 1,560 IU/L (0-16), Myoglobin 700 ng /ml (0-76), AST 1381 IU/L (13-33), ALT 515 IU/L (8-42), LDH 5040 IU/L (119-229), T-bil 1.0 mg/dl (0.3-1.2), Glucose 113 mg/dl (69-104), BUN 45 mg/dl (8-22), Cre 4.75 mg/dl (0.6-1.1), WBC 15,300/μl (4,000-8,000), Hb 13.7 g/dl (14-17), Platelet 113,000 /μl (130,000-350,000). He was negative in HBs-antigen, HCV-antibody, Rapid plasma reagin test (RPR) and Treponema pallidum hemagglutination test (TPHA). Blood gas analysis (with oxygen mask ; O_2 10L/min) was as follows ; pH 7.23 (Normal : 7.35-7.45), PaO_2 341.0 torr (over 75), ABE -10.2mmol/L ((-2.2) -1.2), $PaCO_2$ 41.9 torr (35-45) and HCO_3- 16.8 mmol/L (23-28). Alcohol or other drugs were not detected in his blood screening.

Drip infusion therapy for the high level of Cre didn't increase his urination because his acute renal failure had already progressed. Immediately, hemo-dialysis with continuous hemodia filtration (CHDF) started. Even three days later, his high fever over 38.2°C, elevated CPK (181,200 IU/L) were not yet improved and myotonia with muscle rigidity appeared. Diagnosis of NMS was made by the diagnostic criteria (11, 12). Then dantrolene (1mg/kg) treatment was administrated. In the next day, his CPK began to decrease and reached 2,733 IU/L within a week. His consciousness recovered after the forth day. His clinical presentations and laboratory data improved within two months completely. However, he complained a mild disturbance in memory, speech and finger movement. Then, his blood brain scintigraphy showed a decreased blood flow in whole cerebrum although his brain magnetic resonance imaging (MRI) showed no abnormal findings. The Japanese version of the neurobehavioral cognitive status examination showed very slight word dumbness and decrease of ability in both attention and concentration although all items of cognitive status profile were within normal range. He discharged from hospital two months later.

Passing three years of this episode, his HIV infection had been controlled well. However, his neurological disorders in memory, speech and finger movement remained.

Case 2

A 28-year-old MSM had been followed up at our hospital under highly active anti-retroviral therapy (HAART) with Tenofovir (TDF) /Lamivudine (3 TC) and Atazanavir (ATV). He took a 5-MeO-DIPT, MDMA, and amyl nitrite. The next morning he was transferred to our hospital with pain on muscle and knee joint, convulsions and consciousness loss. At arrival, he showed multiple tonic-clonic convulsions in every 15 minutes. His blood pressure was 100/50 mmHg, respiratory rate was 18 /min regularly, and his body temperature was 35.9°C.

His CD4+ count was 901 /μl with undetectable viral load of under 50 copies/ml. His laboratory data was as follows ; AST 25 IU/L, ALT 24 IU/L, LDH 159 IU/L, T-bil 1.1 mg/dl, CPK 240 IU/L, BUN 10 mg/dl, Cre 0.84 mg/dl, WBC 5,700/μl, Hb 15.0 g/dl, Plt 250,000 /μl, Na 140 mEq/l, K 3.9 mEq/l, Cl 108 mEq/l, Ca 8.7mg/dl. His brain computed tomography (CT) and MRI did not show any abnormal findings.

However, a treatment with diazepam and phenytoin for his tonic-clonic convulsion was not effective and the convulsion was observed in every 8 hours with following 30 to 90 second apnea. His respiratory was controlled under intra-tracheal intubations with anti-convulsion therapy via propofol 3 mg/kg/hr and phenytoin 500-650 mg/day. His electric encephalography (EEG) showed no specific disorder

in resting time while it showed three Hz slow wave at bilateral frontal and temporal lobes in convulsing time. His brain blood scintigraphy pointed out a decreased brain blood flow in the whole cerebrum.

He was a multiple-drug user as follows ; Marijuana and cocaine for more than 10 years, amyl nitrate more than 7 years, MDMA more than 7 months and crystal methamphetamine for one month. However, he had concealed the history of multiple-drug addiction from our medical staff. He had no episode of convulsions before this administration.

Then he was diagnosed as epilepsy, drug-induced mental disorder and poly-drug dependence. Two months later, he could discharge the hospital under HAART administration in tight control of the convulsion with sodium valproate. However, he incurred convulsions by taking the multiple drugs again. His convulsion was barely controlled by sodium valproate for two weeks and he quitted drugs. Four month later, he still showed multiple convulsions regardless of drug use. Instead of the prophylaxis with sodium valproate, his convulsion remains a major problem.

Case 3

A 32-year-old MSM had been treated with TDF / Emtricitabin (FTC) and ATV boosted by Ritonavir (RTV). He had a homosexual intercourse with unknown beverage at five days ago. The next day, he visited outpatient ward due to dark-red urine, general fatigue, muscular pain and appetite loss. His CD4+ count was 823 /μl and HIV-RNA was under 50 copies/ml. His laboratory data were as follows ; AST 44 IU/L, ALT 27 IU/L, LDH 239 IU/L, T-bil 7.3 mg/dl, Glucose 122 mg/dl, CPK 713 IU/L, BUN 12 mg/dl, Cre 0.68 mg/dl, haptoglobin 201mg/dl (19-170), WBC 4,900/μl, Hb 13.6 mg/dl, Plt 200,000 / μl, Na 142 mEq/l, K 4.0 mEq/l, Cl 108 mEq/l. Myoglobin was not measured. Drug screening test of urine showed positive reaction to amphetamine whereas the other drug reaction was not pointed out. He did not have any episodes of the fall or the injury. Drip infusion therapy for elevated CPK was performed for four days. Then his CPK was normalized up to 205 IU/L and his symptoms were improved within three days as well. He was an amyl nitrate, 5-MeO-DIPT and 4-methoxy-N-methyl-N-isopropyltryptamine (4-MeO-MIPT) user occasionally at sexual intercourse for these ten years. However, this was his first amphetamine intake and was his first experience of physical disorders by drugs as well.

DISCUSSION

In this report, we described three cases with various kinds of problems, which are related to drug users with HIV infection. The first problem is found in Case 1 as the unknown physical toxicity of 5-MeO-DIPT which is a hallucinogenic reagent that modulates neuron's activity in the forebrain like MDMA (13-16). Pharmacologically, 5-MeO-DIPT is mainly metabolized in Cytochrome P450 2D6 (CYP2D6) (17). However, the genetic polymorphism analysis of CYP2D6 revealed many variations including the 5-10% of poor metabolizers (18, 19). On the other hand, the detection method of 5-MeO-DIPT is still in an investigational stage (20, 21). In such background, we discuss the reason why Case 1 showed acute renal failure due to rhabdomyolysis and eventually developed NMS which is severer than the cases described in the previous reports (7, 22). Certainly, the frequent drug use increases the opportunities of accident on a poor metabolizer by the drug. Moreover, it is uncertain whether he is a poor metabolizer genetically. However, it is impossible to understand that NMS may happen by only the double doses of 5-MeO-DIPT even if Case 1 is a poor metabolizer. Then we consider additional factors with HIV infection. Even if the HIV-infected individuals do not need HAART yet, they hold higher risk of physical troubles or allergic reaction than non-infected individuals do (23, 24). These reports indicate that HIV certainly induces physical instability although the mechanism is not yet clear. The patient of Case 1 actually developed severer fatal NMS than the cases that had ever reported and he had complained the mental/ neurological disorder for followed three years. Thus, we should always consider that drug may cause unknown physical toxicity on HIV infected drug users.

The second problem is the unknown neurological toxicity of the drugs. Case 2 caused intractable convulsion after multiple drug use including 5-MeO-DIPT, MDMA and amyl nitrate. However, intractable convulsion after 5-MeO-DIPT use had not been reported. Each of 5-MeO-DIPT and MDMA were reported to show the overlapping toxicity on neurons (25, 26). Thus, multiple drugs use might cause the unknown neurological toxicity. We consider that Case 2 might potentially possess the genetic/ immunologic factors to cause neurological toxicity like Case 1. It should be considered that multiple drug use by Case 2 increased a risk of organ damage more, and it resulted in persistent intractable con-

vulsion, actually.

The third problem is an unexpected non-subjective drug intake and drug interaction under HAART administration. Case 3 caused rhabdomyolysis by taking methamphetamine contained in beverage without his intent. Methamphetamine intake is impermissible especially for HIV-infected individuals on HAART. Case 3 took HAART with TDF/FTC and ATV boosted by RTV at this episode. RTV, one of the HIV-Protease Inhibitors (PIs), can elevate plasma concentration of other PIs through the inhibitory effect on a metabolism at cytochrome P450 3A4 (CYP3A4) (27, 28). However, methamphetamine, 5-MeO-DIPT and MDMA should be alternatively metabolized by CYP3A4 although they are metabolized mainly by P450 2D6 (CYP2D6) (17, 19). On the other hand, RTV is a potent inhibitor of cytochrome CYP2D6 as well (29). Thus, the concomitant intake of drug on RTV would elevate plasma concentration of the drugs over the toxicity limit. A previous paper reported that RTV increase the MDMA concentration up to 8.8 fold and methamphetamine up to 2 to 3 fold in blood (8). As a matter of fact, the fatal cases by MDMA and methamphetamine with RTV are also reported (9, 10). These days, many of HIV individuals on HAART use RTV as a booster of PIs. Though it is not clear how RTV effected on the onset of rhabdomyolysis in Case 3, non-subjective drug intake out of the consideration of RTV including HAART is impermissible.

Thus, we strongly insist that a dangerous behavior concerning the drug use should be monitored in patient health care because the interaction by RTV is not well known in general.

In this report, we described several problems on HIV-infected drug users. The problem of drug users with HIV infection had not yet discussed intensively in Japan. Even though HIV infection was controllable, the problems of drug use remained in these cases certainly. Through these cases in our report, we wish that the underlying problems were recognized, discussed and reflected on medication and education for the HIV patient care.

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