ORIGINAL ARTICLE

Methadone Reduced Nevirapine Pharmacokinetic Parameters in People Living With HIV in Malaysia

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ABSTRACT

Introduction: The HIV epidemic in Malaysia predominantly affects males (90% of total HIV cases) mostly intravenous drugs users. Nevirapine-based of highly active antiretroviral therapy (HAART) once- or twice-daily dosage improve accessibility and effectiveness of antiretroviral treatment for HIV positive intravenous drug users (IDUs) receiving methadone maintenance treatment. Studies reported that concomitant administration of nevirapine with methadone reduced methadone plasma concentration. Since methadone and nevirapine were both known to be the substrate for cytochrome 2B6 (CYP 2B6), concomitant use of both drugs may affect nevirapine concentration too. However, methadone effect on nevirapine concentration is still unclear. This is a cross sectional study which reports how methadone co-administration affects the pharmacokinetic parameters of nevirapine in people living with HIV (PLHIV). **Methods:** 112 patients receiving nevirapine-based antiretroviral drugs were recruited. Seventeen were maintained with methadone without withdrawal symptoms. High-performance liquid chromatography was used to measure plasma nevirapine concentrations. Nevirapine population pharmacokinetics was modelled with a non-parametric approach using Pmetrics software. **Result:** According to univariate analysis, concurrent methadone administration increased the clearance of nevirapine by 25.3% (p = 0.046). Multivariate analysis showed that methadone medication was independently linked with lower nevirapine concentrations and area-under-curve (Cmin was reduced by 15.2%, p = 0.011, Cmax 19.5%; p = 0.003, AUC12 16.2%; p = 0.021 respectively). **Conclusion:** This study provides in-vivo evidence of methadone co-administration reducing nevirapine exposure. Since a low concentration of nevirapine will lead to treatment failure, monitoring is essential for PLHIV using both medications at the same time.
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INTRODUCTION

Human immunodeficiency virus (HIV) infection affected the world globally. In the year 2019, one point seven million people were newly infected out of an estimated 38 million HIV-positive individuals and 690 000 have died due to HIV-related deaths (1). In 1986 after the first HIV case in Malaysia was discovered in a 45-year-old man, HIV infection has emerged as one of the nation's most pressing health issues and development difficulties (2). The number of reported HIV infections (including AIDS) in Malaysia continued to increase until a peak of 6,978 detected new cases in 2002. After a tremendous effort of harm reduction programme by the country, the HIV reported infection in Malaysia showed a plateau starting from 2010 with 0.9% decline in the new HIV infection (3).

Most of Malaysia's HIV epidemic is confined to the most vulnerable groups, including intravenous drug users (IDUs), sex workers, and the transgender community (4,5). The majority of those affected by this epidemic are men, who account for 85% of all HIV cases (3). It was reported that 57% of PLHIV in Malaysia were on antiretrovirals and 85% of them were virally suppressed in 2019 (3). The main factor which affects the HIV viral suppression include drug adherence (6–8). A study reported that single tablet regiment of antiretrovirals could improve drug adherence and virologic suppression outcome (9).

Nevirapine is one of antiretroviral which is administered in a form of a single tablet once daily for the first 14 days. It belongs to the class of antiretrovirals known as non-nucleoside reverse transcriptase inhibitors (NNRTIs).

Nevirapine has a lengthy half-life and its steady state concentration achieved were within the range for 50% viral killing (IC50) (10) and metabolized mainly by enzymes CYP 2B6 and CYP3A4 (11). Nevirapine was reported to show good efficacy, safe and convenient to be used in HIV (12). Recently, nevirapine was also reported to be safe for use in HIV treatment of high-risk neonates (13).

Nevirapine however, was reported to have interactions with other drugs. For example, anti-tuberculosis drugs such as isoniazid significantly increase clearance of nevirapine (14,15). As CYP2B6 and CYP3A4 inducer, nevirapine was reported to lower the methadone plasma levels (drug used in management of opioid dependence) in some studies hence higher methadone maintenance doses were required (16,17). In some cases, methadone withdrawal were also reported with concomitant use of both drugs (18).

In Malaysia where many HIV patients were also intravenous drug users, the concomitant use of antiretroviral drugs and methadone maintenance therapy (MMT) was inevitable. Combinations of nevirapine-based HAART that provide once- or twice-daily dose are chosen for HIV-infected IDUs taking methadone replacement therapy in order to increase the accessibility, compliance, and effectiveness of antiretroviral medication. (19). Since methadone and nevirapine were both known to be the substrate for cytochrome 2B6 (CYP 2B6), concomitant use of both drugs may also affect nevirapine concentration (17,20). However, there is no published report on the pharmacokinetic parameters of nevirapine are affected by methadone. Therefore, in this study, the influence of methadone co-administration on nevirapine pharmacokinetics (PK) characteristics in PLHIV was investigated.

MATERIALS AND METHODS

Subjects

This is a cross sectional study involving adult PLHIV who received nevirapine-based HAART for at least two months in Hospital Raja Perempuan Zainab II, Hospital Sultanah Nur Zahirah, and Hospital Sultanah Bahiyah (in northern Malaysia) from January 2014 until December 2015. The exclusion criteria for the study include non-adherence to medications, and concurrent liver disease or renal disease.

All study participants gave their voluntarily informed consent. The Human Research Ethics Committee of Universiti Sains Malaysia (USMKK/PP/JEPeM[249.3.18]) and the Malaysia Ministry of Health (NMRR-13-687-16175) ethics committee approved the study. The protocols were drafted in conformity with the 1975 and 1983 versions of the Helsinki Declaration.

A total of 112 PLHIV with 17 of them were well maintained with methadone were recruited. Methadone was administered as direct-observed-therapy (DOT) in respective hospitals between 8.0 a.m. to 10.0 a.m. every day while nevirapine and other antiretrovirals were self-administered by the patients.

Blood sampling

Following the morning dosage of nevirapine, blood samples were taken at 0, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, and 8.0 hours. Time of the last nevirapine dose was obtained by patient report. Nevirapine concentration was determined and quantified by HPLC-UV analysis according to the method previously described (21). In summary, a reverse phase chromatography using C8 column with mobile phase (80% ammonium acetate and 20% acetonitrile, v/v) was used with carbamazepine as internal standard. A gradient flow rate was performed for the HPLC system, 1ml/min for 17 minutes and later increased to 2ml/min. The total analysis time was 30 minutes with detection performed at 280 nm. The parameters acquired from the analysis were absorption constant rate (Ka), volume of distribution (Vd), minimum blood plasma concentration reached by a drug during the time interval between administration of two doses (Cmin), maximum blood plasma concentration reached by a drug during the time interval between administration of two doses (Cmax), area under the curve (AUC), Clearance, elimination rate constant (Ke) and half-life of the nevirapine. Nevirapine population pharmacokinetics was modelled with a non-parametric approach using Pmetrics software (22,23).

Statistical method

SPSS version 24 (SPSS Inc., Chicago, Illinois) was used to conduct all statistical tests. Demographic information was analysed using descriptive statistics. Clinical characteristics were analysed using Independent T-test. A p-value of < 0.05 (two-tailed) was regarded as statistically significant.

The simple linear regression test for normally distributed or Mann-Whitney test for not normally distributed were used to compare independent factors to nevirapine pharmacokinetic parameters. Multiple linear regression testing was used to study predictors of nevirapine pharmacokinetic parameters. Based on univariate analyses, independent variables with the p-value <0.25 were being considered for the multiple linear regression analysis. To fit the categorical variables into the regression database, dummy variables were created before analysis could be conducted. Statistical significance was defined as a p-value <0.05.

RESULTS

One hundred and twelve subjects were recruited for the study. The social demographic and HAART regime are shown in Table I. Majority of them were Malays with nearly equal numbers of males and females in those

Table I: Subjects' social demography and treatment regime

Parameters	Without methadone (N= 95) n (%)	With methadone (N=17) n (%)
Gender		
Male	46 (48.42)	17 (100)
Female	49 (51.58)	0
Race		
Malay	80 (84.21)	15 (88.24)
Chinese	8 (8.42)	0
Indian	1 (1.05)	2 (11.76)
Others	6 (6.32)	0
HAART regime		
Nevirapine/combivir	66 (69.5)	13 (76.5)
Nevirapine/Truvada	15 (15.8)	4 (23.5)
Stavudine/lamivudine/nevirapine	5 (5.3)	0
Lamivudine/zidovudine/nevirapine	6 (6.3)	0
Lamivudine/tenofovir/nevirapine	2 (2.1)	0
Nevirapine/zidovudine/abacavir	1 (1.1)	0

(Abbreviations: HAART = highly active antiretroviral therapy)

Table III: Descriptive analysis nevirapine pharmacokinetic parameters

Parameters	Without methadone (N=95) Median (IQR)	With methadone (N=17) Median (IQR)
K_a	5.30 (21.00)	2.25 (21.44)
V_d (L)	81.01 (56.99)	78.40 (47.56)
C_{min}	5.26 (2.45)	4.46 (3.68)
C_{max}	8.11 (3.46)	6.53 (4.87)
AUC	71.30 (32.38)	74.69 (38.63)
K_e	0.04 (0.03)	0.04 (0.03)
Clearance	3.21 (2.06)	2.67 (2.20)
t	15.74 (10.82)	17.36 (13.41)

Abbreviation: IQR = interquartile range, K_a=rate of absorption, V_d=volume of distribution, C_{min}=minimum concentration C_{max}=maximum concentration AUC=area under curve, K_e=rate of elimination, CL=clearance, t =half life

without methadone while all the subjects on methadone were male. Those who were on methadone therapy in this study did not experience any symptoms of abstinence. Table II showed the clinical characteristics of the subjects. All PLHIV demonstrated normal renal and liver functions. In addition, there was no significant differences between subjects with or without methadone except ALP and AST. Fifty-one percent of the subjects not on methadone and 41% of the subjects on methadone showed undetectable VL. However, the mean VL did not significantly differ between the two groups. The descriptive nevirapine pharmacokinetic parameters was higher in those without methadone compared to those with methadone as shown in Table III. The effects of methadone to nevirapine pharmacokinetic parameters were shown in Table IV indicating that nevirapine concentrations and exposure were significantly decreased with concurrent methadone intake.

DISCUSSION

In this study, reduced nevirapine concentrations were independently and substantially associated with methadone therapy where the Cmin was 15.2% (p = 0.011) and the Cmax was 19.5 percent (p = 0.003). In PLHIV on methadone therapy, nevirapine's projected Cmin and Cmax values are 1.47 mg/L and 2.65 mg/L lower, respectively. Nearly half (47%) of PLHIV on methadone therapy also had low levels of nevirapine below the desired limit of 3.0 g/mL. In the

Table II: Clinical characteristics of subjects

Parameters	Without Methadone (N= 95) Mean (SD)	With Methadone (N=17) Mean (SD)	Mean difference (95% CI)	*t*-statistic (df)	*p*-value
Age (years)	41.20 (8.62)	43.59 (7.11)	-2.39 (-6.78,2.00)	-1.08 (110)	0.284
Weight (kg)	60.35 (14.04)	59.36 (8.25)	0.99 (-5.98,7.96)	0.28 (110)	0.779
BMI (kg/m^2)	23.07 (5.29)	21.44 (3.16)	1.64 (-0.99,4.26)	1.23 (110)	0.220
eGFR	91.69 (24.70)	85.14 (18.49)	6.55 (-5.92,19.02)	1.04 (110)	0.300
ALP (IU/L)	99.92 (28.60)	119.82 (69.92)	-19.91 (-39.50, -0.31)	-1.16 (17)	0.047
AST (IU/L)	36.24 (17.86)	45.94 (16.64)	-9.70 (-18.93, -0.47)	-2.08 (110)	0.040
ALT (IU/L)	35.36 (29.82)	36.41 (17.23)	-1.05 (-15.84, 13.74)	0.14 (110)	0.888
CD4 (cell/mm3)	413.24 (207.16)	346.88 (174.55)	66.36 (-39.52,172.24)	1.24 (110)	0.217
VL (copies/ml)	375.82 (2010.13)	17026.69 (63207.84)	-16650.87 (-50333.94, 17032.21)	-1.05 (15)	0.309

Independent T-test was applied. (Abbreviations SD = standard deviation, df= degree of freedom, e-GFR= estimated glomerular filtration rate, ALP=alkaline phosphatase, AST= aspartate transaminase, ALT=alanine transaminase, VL = viral load)

Table IV: Effects of methadone to nevirapine PK parameters

PK parameters	Effects of methadone	Univariate analysis	Multivariate analysis	
		p-value	Adjusted b (95% CI)	*p*-value[c]
C_{min}	15.2% reduction	0.096[a]	-1.47 (-2.61, -0.35)	0.011*
C_{max}	19.5% reduction	0.086[a]	-2.65 (-4.40, -0.90)	0.003*
AUC_{12}	16.2% reduction	0.051[a]	-19.00 (-35.25, -2.96)	0.021*
Clearance	25.3% increment	0.046[b]		NS

[a] *Mann-Whitney U test* [b] *independent t-test*
[c] *Multiple Linear Regression with Stepwise method. Adjusted for liver profile, CYP2B6 polymorphism, age and creatinine clearance (there is no interaction and multi-collinearity problem)*
**Significant. Abbreviations: CI = Confidence Interval, PK = Pharmacokinetic*

univariate study, concurrent methadone administration significantly increased the nevirapine clearance by 25.3 percent (p=0.046). In the univariate study, concurrent methadone administration significantly increased the nevirapine clearance by 25.3 percent (p=0.046). This was correlated to the earlier decrease in nevirapine concentration brought on by methadone.

With concurrent methadone administration, the nevirapine AUC12 was considerably reduced by 16.2% in this study. This was consistent with the reported reduction in nevirapine concentrations and suggested a potential methadone drug interaction. Given that nevirapine has been shown to reduce methadone AUC by up to 41%, this necessitates additional monitoring for the successful treatment of both medications (24). It was previously reported that nevirapine trough concentrations below 3.0 g/mL increase the risk of virological failure by five-fold (25), and if the concentration is below the target, dose modification should be considered (26). As mentioned before, since 47% of the subjects on methadone experienced low nevirapine concentration, the nevirapine dosage for these patients need to be adjusted to avoid the risk of virological failure. However, in this study, although the nevirapine exposure among subjects taking concurrent methadone were reduced, the difference in the VL between the concurrent methadone and non-methadone groups was not significant. The result is expected since the treatment regime for the patients involve more than one antiretroviral drug which covers the killing of the virus by other antiretroviral drugs given concurrently.
Nevirapine was known to induce both CYP3A4 and CYP2B6 enzymes which was reported to be the cause of methadone-nevirapine interaction resulting in methadone withdrawal in some cases as mentioned before. Nevirapine is metabolised primarily by CYP3A4, CYP2D6, and CYP2B6 isoforms of the cytochrome P450 family, which can be induced by a variety of medications, including methadone. (11,27). Nevirapine pharmacokinetic parameters were significantly decreased by concurrent medication such as rifampicin (28,29). However, there is no published report regarding nevirapine pharmacokinetics upon interaction with methadone. Since methadone is also CYP3A4 and CYP2B6 inducer and nevirapine is a substrate for both enzymes mentioned, nevirapine pharmacokinetics may be affected when concurrently administered.

Methadone is a complex drug, and its metabolism can be altered by many drugs that inhibit or induce cytochrome P450 (CYP 450) enzymes. Additionally, drug-drug interactions between methadone and several antiretroviral medications such zidovudine, atazanavir, and didanosine have been documented (17). However, co-administration of methadone with other antiretroviral drugs at times, may be inevitable. Methadone can either reduce the concentration of the antiretroviral drugs causing reduction in the antiretroviral efficacy or its concentration also can be reduced causing methadone withdrawal. Previous studies have described symptoms of opioid withdrawal resulted from significant interaction between methadone and nevirapine suggesting the necessity of dose adjustment for methadone (16,24).

Pharmacokinetics of drugs are affected by many factors including age, renal function and liver function. In this study, there were no significant difference in the mean value for age and renal function of the subjects. However, for the liver function, the ALP and AST results in patients taking methadone and not taking methadone showed significant difference (p-value 0.047 and 0.040 respectively). The mean ALP for both methadone and non-methadone subjects were within normal range (30-120 IU/L) whereas for AST was slightly elevated (normal range 8-33 IU/L)(30,31). However, the elevation was not clinically significant since they were not more than two times the normal range for AST as previously described by Giannini et al. (30). Therefore, the altered liver function may not be the major factor causing the alteration in nevirapine pharmacokinetics in this study. The other cause of alteration in the pharmacokinetics values are drug-drug interaction. Drug interaction occurs in several conditions such as competing for the same protein (in case of highly protein bound drugs) and enzyme metabolism when the drug is the substrate to the enzyme.

Methadone is highly protein bound (90%) and when

administered with nevirapine may affect each other's fraction binding and its intrinsic clearance (32,33). The plasma protein involved in the protein binding for methadone is mainly α1-acid glycoprotein (AAG) (34) while nevirapine is bound mainly to albumin (60%) (10). Therefore, although methadone and nevirapine are both highly protein bound, they do not compete with each other and the effects of protein binding increasing the unbound fraction of nevirapine leading to its higher metabolism is less likely.

When two or more medications that are of the same CYP's metabolic substrates taken at the same time, pharmacokinetic interaction may occur. (35). The CYP2B6 enzyme which is responsible for metabolism of nevirapine, is also responsible for methadone metabolism (27). Nevirapine and methadone usage together may result in an increase in CYP2B6 enzyme activities since nevirapine and methadone are CYP2B6 and CYP3A4 enzyme inducers (17,36). Consequently, nevirapine metabolism and clearance may be increased which will subsequently reduce nevirapine concentrations and exposure. None of the study subjects showed sign and symptoms of methadone withdrawal. However, unfortunately in this study, methadone levels were not quantified to show the methadone effects on concurrent treatment with nevirapine. So far, there was no published report on the effects of methadone on nevirapine concentration. However, there were other drugs which was reported to reduce nevirapine exposure when concurrently administered such as rifampicin, rifapentine and isoniazid (14,15). Since methadone may affect the efficacy of nevirapine treatment by reducing nevirapine concentrations, monitoring of the nevirapine plasma concentration is recommended. Furthermore, it was recommended to increase the dose of methadone in patients on concurrent treatment with nevirapine. The nevirapine concentration reduction effect is dose dependent need further evaluation.

This study had several limitations. Results presented in this study should be interpreted with caution, owing to the relatively small sample size of this study since only a small number of patients taking concurrent methadone and nevirapine were available during the study period of 2 years. Other variables which may affect nevirapine concentration such as dosing in relation to food or concurrent medications were not studied. A majority (85%) of the recruited PLHIV were Malays and one race may not represent the heterogeneous community of the Malaysian population. There were difficulties in recruiting other races as they were small in numbers compared to the Malays in the study settings (Kelantan, Terengganu and Kedah).

CONCLUSION

This study provides the first in vivo evidence that co-administration of nevirapine and methadone resulted in reduction of nevirapine exposure as evidenced by reduction in nevirapine pharmacokinetic parameters (Ka, Vd, Cmin, Cmax, AUC, Clearance, Ke and half-life). It is important to highlight that 40% of PLHIV in Malaysia used injectable drugs, with the majority of them receiving methadone replacement therapy (MOH, 2012), indicating the necessity of nevirapine level monitoring in high-risk group of patients such as those with poor compliance and on high dose of methadone.

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