Available online at www.sciencedirect.com
SCIENCE DIRECT®
International Journal of Drug Policy 16 (2005) 171–175
THE INTERNATIONAL JOURNAL OF DRUG POLICY
www.elsevier.com/locate/drugpo

Trends in the injection of midazolam and other drugs and needle sharing among injection drug users enrolled in the AIDSVAX B/E HIV-1 vaccine trial in Bangkok, Thailand

Frits Van Griensven [a,b,*], Punnee Pitisuttithum [c], Suphak Vanichseni [d], Paula Wichienkuer [a], Jordan W. Tappero [a,b], Udomsak Sangkum [d], Dwip Kitayaporn [c], Boonrawd Phasithiphol [d], Karin Orelind [e], Kachit Choopanya [d]

[a] *Thailand Ministry of Public Health, US Centers for Disease Control and Prevention Collaboration, DDC 7 Building, Nonthaburi 11000, Thailand*
[b] *Centers for Disease Control and Prevention, Atlanta, GA, USA*
[c] *Mahidol University, Bangkok, Thailand*
[d] *Bangkok Vaccine Evaluation Group, Bangkok, Thailand*
[e] *VaxGen Inc., Brisbane, CA, USA*

Received 4 June 2004; received in revised form 18 February 2005; accepted 21 February 2005

Abstract

Midazolam injection may increase the hazards of drug use. Its ability to cause amnesia may be associated with increased HIV risk behaviour and its interaction with other licit and illicit drugs may cause overdose and death. We analysed midazolam injection among injecting drug users (IDUs) participating in the AIDSVAX B/E HIV-1 vaccine trial in Bangkok, Thailand. From March 1999 to August 2000, 2545 IDUs were enrolled and randomised to receive AIDSVAX B/E or placebo. An interviewer-administered questionnaire assessed demographics (at baseline) and drug use behaviour (every 6 months). Reports of midazolam injection were statistically evaluated. During 36 months of follow-up, injection of any drug decreased from 94 to 51% and needle sharing decreased from 33 to 16%. Among those who continued to inject, midazolam injection increased from 10 to 31% (all $p < 0.0001$). Earlier study visit, lower education and less frequent injection were independently associated with less frequent midazolam injection; younger age, reports of needle sharing and receiving methadone treatment were independently associated with more frequent midazolam injection. Preventive interventions to educate IDUs and midazolam prescribers are urgently needed.

Keywords: HIV-1; Midazolam; Vaccines; Risk behaviour; Injection drug use; Thailand

1. Introduction

In March 1999, a phase III HIV vaccine trial (AIDSVAX B/E, VaxGen, Inc., Brisbane, CA, USA) was initiated among injection drug users (IDUs) attending drug treatment clinics of the Bangkok Metropolitan Administration (BMA) (Vanichseni, Tappero, Pitisuttitham, Kitayaporn, Mastro, Vimutisunthorn 2004). Participants were asked at every study visit whether they had injected drugs, and if so, whether they had injected heroin, methamphetamine or 'other drugs'. We noted that a drug called Dormicum® was frequently mentioned under the category other drugs.

Dormicum® is the Thai brand name for midazolam, a rapid-onset, short-duration benzodiazepine, also known as Versed and Hypnovel. It has anxiolytic, sedative, hypnotic, muscle relaxant, and anticonvulsant effects. It is used primarily for sedation in hospital, emergency, and preoperative settings. Parenteral administration of midazolam induces short-term anterograde amnesia. Physical dependence can develop with prolonged use, and abrupt discontinuation of the drug can lead to withdrawal symptoms (F Hoffmann-La

* Corresponding author. Tel.: +66 25800669; fax: +66 25800712.
E-mail address: favl@tuc.or.th (F. Van Griensven).

0955-3959/$ – see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.drugpo.2005.02.003

Roche Ltd., 1997; Perera and Lim, 1998; Munzar, Yasar, Redhi, Justinova, & Goldberg, 2001).

In Thailand, midazolam is usually prescribed in tablet form (15 mg) and classified as a psychotropic substance, schedule 2, meaning that it is legally accessible with no associated registration system. Some Thai physicians prescribe midazolam over methadone for drug addiction treatment, on account of its sedative effects. IDUs, in turn, inject midazolam in combination with heroin or as a substitute for heroin, if the latter is in short supply or too expensive.

The ability of midazolam to induce amnesia may affect IDUs' recall following injection, which may increase their HIV risk behaviour. Drug injection in Thailand usually is a social behaviour, practiced by circles of friends or 'brothers'. Since midazolam injection may involve multiple injections during consecutive or overlapping periods of time, IDUs may not be able to identify their own injection equipment, which may lead to needle sharing. There are also reports of interaction with other illicit and licit drugs, notably HIV antiretroviral drugs, increasing the risk of overdose and death (Centers for Disease Control and Prevention, 2001). In light of the dangers of midazolam injection, we analysed its frequency of use and association with other drug-use risk behaviours among IDUs enrolled in the AIDSVAX B/E vaccine trial.

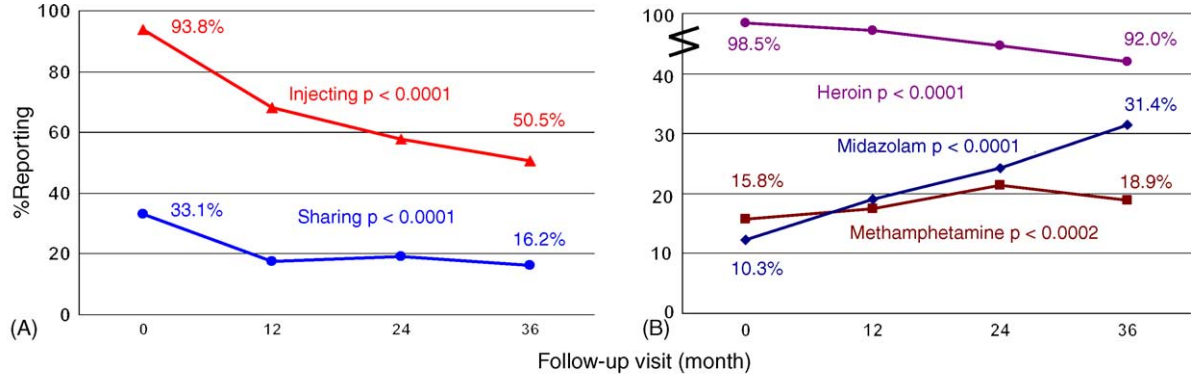
2. Method

A description of the study design is presented elsewhere (Vanichseni et al., 2004). Briefly, between March 1999 and August 2000, 2545 IDUs were enrolled and randomised to receive AIDSVAX B/E or placebo. The trial was completed in June 2003. Risk-reduction counselling was provided at every study visit and male condoms and bleach to clean injection equipment were demonstrated and provided free of charge. An interviewer-administered questionnaire assessed demographics (at baseline) and HIV risk behaviour (every 6 months). Those who reported to have injected drugs other than heroin and methamphetamine were prompted to specify the type of drugs. All participants whose answers included 'Dormicum' or 'midazolam' were classified as having injected midazolam. An Institutional Review Board of the Centers for Disease Control and Prevention, Atlanta, GA, USA, and the Ethical Review Committee of the Thailand Ministry of Public Health approved the study.

Reports of midazolam injection and needle sharing over time were statistically evaluated using chi-square tests. We adjusted for repeated within-subject measures to evaluate variables independently associated with midazolam injection. To do this, we used generalised estimating equation analysis for logistic model estimation with statistical inferences and 95% confidence intervals (Diggle, Liang, & Zeger, 1994). Variables significant in univariate analysis ($p < 0.05$) were evaluated in multivariate models to analyse midazolam injection as a function of time and these covariates.

3. Results

Participants were 93% (2376) male, their median age was 26 years (range: 20–59 years) and 1711 (67%) had at least completed 9th grade education. During the 6 months prior to baseline, 2388 (94%) reported having injected drugs, of whom 789 (33%) reported having shared needles, and 2092 (82%) reported receiving methadone treatment. Heroin injection was reported by 2351 (99%) participants, methamphetamine by 376 (16%), and midazolam by 243 (10%). Daily injection was reported by 936 (39%). Reports of injection during the past 6 months decreased over time (Fig. 1A)



Number of participants

Injecting*	2388	1614	1289	980
Sharing†	789	283	248	159

Number of participants injecting

Heroin†	2351	1569	1220	902
Midazolam†	243	274	282	307
Methamphetamine†	376	283	276	185

Fig. 1. Drug injection and needle sharing (A) and types of drugs injected (B) among injection drug users participating in the AIDSVAX B/E vaccine trial in Bangkok, Thailand, through 36 months of follow-up, by study visit.

Table 1
Univariate and multivariate analyses of midazolam injection among IDUs in the AIDSVAX B/E trial

Variable	Number[a] (%)	Injecting midazolam[b]	Midazolam injection	
		Number (%)	Univariate OR (95% CI)	Multivariate OR (95% CI)
Study visit				
Baseline	2545 (100)	243/2352 (10.3)	0.3 (0.2-0.3)	0.2 (0.2-0.3)
12 months	2426 (95.3)	274/1608 (17.0)	0.5 (0.4-0.5)	0.4 (0.3-0.5)
24 months	2274 (89.4)	282/1287 (21.9)	0.6 (0.5-0.7)	0.6 (0.5-0.7)
36 months	1941 (76.3)	307/979 (31.4)	1	1
Sex[c]				
Male	2376 (93.4)	1871/10003 (18.7)	1.2 (0.8-1.7)	
Female	169 (6.6)	113/657 (17.2)	1	
Age[c] (years)				
<30	1634 (64.2)	1331/6599 (20.2)	1.9 (1.5-2.5)	1.8 (1.4-2.3)
30-39	536 (21.1)	447/2323 (19.2)	1.8 (1.3-2.3)	1.7 (1.3-2.3)
≥40	375 (14.8)	206/1738 (11.9)	1	1
Education[c]				
<9th grade	834 (32.8)	520/3439 (15.1)	0.7 (0.6-0.8)	0.7 (0.6-0.9)
9th grade	959 (37.7)	786/3979 (19.8)	0.9 (0.8-1.1)	0.9 (0.8-1.1)
>9th grade	752 (29.6)	678/3242 (20.9)	1	1
Methadone treatment[c,d]				
Detoxification	1559 (61.3)	978/4590 (21.5)	1.6 (1.4-1.9)	1.5 (1.3-1.8)
Maintenance	532 (20.9)	647/4096 (15.8)	1.3 (1.1-1.5)	1.3 (1.1-1.5)
None	454 (17.8)	350/1974 (17.7)	1	1
Drug injected[c,e]				
Heroin[f]	2351 (98.5)			
Methamphetamine[g]	376 (15.8)			
Midazolam[g]	243 (10.3)			
Frequency of injection[c]				
<Weekly	664 (27.0)	545/3854 (14.1)	0.6 (0.5-0.7)	0.7 (0.6-0.7)
Weekly, but <daily	776 (32.7)	636/3407 (18.7)	0.8 (0.7-0.8)	0.8 (0.7-0.9)
Daily	936 (39.4)	802/3380 (23.7)	1	1
Needle sharing[c]				
Yes	789 (33.1)	557/1980 (28.1)	1.5 (1.3-1.7)	1.4 (1.3-1.6)
No	1598 (66.9)	1563/8663 (18.0)	1	

[a] During the course of the trial 230 (9.0%) participants reached the primary endpoint of HIV-1 infection, 105 (4.1%) were lost to follow-up, 38 (1.5%) withdrew consent and 102 (4.0%) died; data for 129 (5.1%) participants were missing or follow-up was not completed when the database was locked for final analysis.
[b] Denominators are those who reported injecting and may vary because of missing values.
[c] As assessed at baseline.
[d] Detoxification with or without maintenance or maintenance only.
[e] Association with midazolam injection could not be evaluated because of co-linearity and similarity between predictor and outcome variables.
[f] Reference category is 'no heroin injection'.
[g] Reference category is heroin injection only.

($p < 0.0001$). Among those who reported injecting drugs, needle sharing (Fig. 1A) and injection of heroin decreased, while methamphetamine and midazolam injection increased (Fig. 1B) (all $p < 0.0001$). Multivariate analysis showed that earlier study visit, lower education and less frequent injection were associated with less frequent midazolam injection, while younger age, reports of needle sharing and receiving methadone treatment were associated with more frequent midazolam injection (Table 1). The association between injection of heroin, injection of methamphetamine and midazolam injection could not be evaluated due to co-linearity of these variables (e.g., all midazolam injectors injected heroin).

4. Discussion

Despite a substantial decrease in injecting and needle sharing among AIDSVAX B/E trial participants, those who continued to inject reported a significant increase in midazolam injection. Earlier study visit, lower education and less frequent injection were independently associated with less frequent midazolam injection, while younger age, reports of needle sharing and receiving methadone treatment were independently associated with more frequent midazolam injection.

The decrease in reports of injecting and needle sharing is likely the result of repeat HIV-1 testing, education, coun-

selling and interviewing during the course of the trial (Van Griensven, Kaewkungwal, Vanichseni, Tappero, Sangkom, Pitisuttithum 2004). Several observational cohort studies among IDUs and other groups at risk for HIV infection have reported similar decreases in risk behaviour, which were largely interpreted as effects of study participation (Shore, Marmor, Titus, & Des Jarlais, 1996; Stimson, Des Jarlais, & Ball 1998; Choopanya, Des Jarlais, Vanicheni, Mock, Kitayaporn, Sangkhum 2004).

It is possible that some of the observed increase in midazolam injection was due to an increase in awareness about its use, prompting interviewers in our study to ask more systematically about midazolam injection. This is unlikely, however, since most of the data on midazolam injection had already been collected by the time its use and associated risks became more widely known. On the contrary, the real frequency of midazolam injection may have been higher, since no specific questions about midazolam were included in the questionnaire. Rather, participants named midazolam when prompted whether drugs other than heroin and methamphetamine had been injected. In addition, midazolam injection may impair day-to-day recall and some of its use may therefore have gone unreported.

Since injecting drug use in Thailand is a social behaviour, midazolam injection is likely to have increased outside the vaccine trial context as well, e.g., among Bangkok IDUs at large. The increase in midazolam injection observed among our study participants coincided with the Thai Government's 'war on drugs' (The Wire, 2003). As a result of this campaign, the street price of heroin in Bangkok has more than tripled from approximately 2500 to 10000 Thai baht (approximately 50 to 200 €) and more per 1000 mg, whereas the price of a midazolam tablet increased from 10 to 50 Thai baht (approximately 0.25 to 1 €), leaving midazolam as a cheaper and legally accessible alternative.

In our analyses, younger age, needle sharing and methadone treatment were found associated with increased midazolam injection. The association with younger age may be explained by the fact that midazolam is a relatively new drug of injection, with which younger injectors may be more likely to experiment. Older injection drug users may have more established drug use patterns and may be less likely to experiment with newer drugs. The higher levels of needle sharing may be due to a higher risk profile among midazolam injectors, who may inject midazolam as a last resort if no heroin is available and may be less prepared for injection. Since midazolam use impairs recall, the real frequency of needle sharing is likely to have been higher, and its association with midazolam injection therefore an underestimate of its real effect. The association between methadone treatment and midazolam injection may be the result of IDUs perception that midazolam can be used as a substitute for methadone, when the latter is not available or if they experience withdrawal during or after methadone detoxification. Indeed, anecdotal evidence shows that several physicians in Bangkok prescribe midazolam in lieu of methadone, on account of its sedative effects, or as a supplement to methadone, if recipients already get their daily dosage of methadone elsewhere. Little is known about the efficacy of midazolam for the treatment of heroin addiction, and additional research in this area is needed. Such research should also include an evaluation of methadone dosage and the duration of methadone treatment and their associations with midazolam use.

Our analysis identified lower education and less frequent injection as predictors of lower levels of midazolam injection. Lower educated participants may have lower income and therefore a reduced ability to buy midazolam and other injection drugs. Those who inject less frequently may be in less severe stages of addiction and may not have the need to inject midazolam.

Targeted, evidence-based, public health preventive interventions are urgently needed to educate midazolam injectors and to reduce associated risks, such as needle sharing, HIV infection, and overdose and death. Educating IDUs and prescribers of midazolam about its adverse effects and interaction with other drugs can be started immediately while additional data are collected. Little is known about the mental and behavioural aspects of midazolam injection, such as psychological dependence and impairment, injection practices (intravenous, intramuscular, subcutaneous), combinations with other drugs, frequency of injection, and preparation of drug solution, sharing of solution and sharing and disposal of used syringes. Research in these areas is necessary and may reveal opportunities for intervention. Since highly active antiretroviral treatment for HIV infection has become only recently available in Thailand, surveillance of overdose mortality among IDUs is needed to identify possible associations with midazolam injection.

A limitation is that our study data consist of self-reports of stigmatized and illegal behaviour, assessment of which has traditionally been problematic (Konigs, 1995). Moreover, during our study period, the Thai Government implemented its 'war on drugs', and some underreporting of injecting and sharing is therefore likely.

In conclusion, midazolam injection increased among IDUs in the Bangkok AIDSVAX B/E trial and likely reflects increasing midazolam injection among the general population of Bangkok IDUs. Needle sharing was independently associated with midazolam injection and may contribute to the spread of HIV and other health hazards. Preventive interventions, such as educating IDUs and midazolam prescribers about midazolam adverse effects are urgently needed.

Acknowledgements

VaxGen Inc., Brisbane, CA, USA sponsored the AIDSVAX B/E HIV-1 vaccine trial. The Centers for Disease Control and Prevention, Atlanta, GA, USA, supported the work reported in this paper. The sponsors of this study had no role in data analysis, data interpretation and writing of this report. We thank the personnel of the drug treatment clinics

of the Bangkok Metropolitan Administration for their dedication and support; Philip Mock, Dr. Michael Martin, and the staff of the Thailand MOPH – U.S. CDC collaboration; Drs. Pravan Suntarasamai and Jaranit Keawkungwal of Mahidol University; Drs. Timothy Mastro, Dale Hu, Charles Vitek, Alan Greenberg and Ms. Lynne Stockton of the U.S. Centers for Disease Control and Prevention; Carolyn Gee and Aimee Luck of VaxGen, Inc., for their help. We are greatly indebted to the 2545 participants in our study.

References

Centers for Disease Control Prevention. (2001). Appendix C: Basic and expanded HIV postexposure prophylaxis regimens. *MMWR Morbidity and Mortality Weekly Report*, *50*(RR11), 47–52.

Choopanya, K., Des Jarlais, D. C., Vanichseni, S., et al. (2004). HIV risk reduction in a cohort of injecting drug users in Bangkok, Thailand. *Journal of Acquired Immune Deficiency Syndromes*, *37*, 1170–1179.

Diggle, P. J., Liang, K., & Zeger, S. L. (1994). *Analysis of longitudinal data*. Oxford: Oxford University Press.

F Hoffmann-La Roche Ltd., 1997. Dormicum (midazolam) tablets package insert. 2374056 FE 9903.1016.

Konigs, F. (1995). Validating population surveys for the measurement of HIV/STD prevention indicators. *AIDS*, *9*, 867–873.

Munzar, P., Yasar, S., Redhi, G. H., Justinova, Z., & Goldberg, S. R. (2001). High rates of midazolam self-administration in squirrel monkeys. *Behavioural Pharmacology*, *12*, 257–265.

Perera, I., & Lim, L. (1998). Amineptine and midazolam dependence. *Singapore Medical Journal*, *39*, 129–131.

Shore, R. E., Marmor, M., Titus, S., & Des Jarlais, D. C. (1996). Methadone maintenance and other factors associated with intraindividual temporal trends in injection drug use. *Journal Substance Abuse Treatment*, *13*, 241–248.

Stimson, G. V., Des Jarlais, D. C., & Ball, A. (1998). *Drug injecting and HIV infection: global dimensions and local responses*. London: UCL Press.

Van Griensven, F., Kaewkungwal, J., Vanichseni, S., et al. (2004). Lack of increased HIV risk behavior among injection drug users participating in the AIDSVAX B/E HIV vaccine efficacy trial in Bangkok, Thailand. *AIDS*, *18*, 295–301.

The Wire, (2003). Amnesty International's Monthly Magazine. Thailand's 'war on drugs'. http://web.amnesty.org/web/wire.nsf/May2003/Thailand (accessed 04 June 2004).

Vanichseni, S., Tappero, J. W., Pitisuttitham, P., et al. (2004). Recruitment, screening and baseline epidemiologic characteristics of injection drug users enrolled in the AIDSVAX® B/E HIV vaccine trial in Bangkok Thailand: Comparison of characteristics with a preparatory cohort study. *AIDS*, *18*, 1–6.