A COMPARISON OF BLOOD TOXICOLOGY OF HEROIN-RELATED DEATHS AND CURRENT HEROIN USERS IN SOUTH WESTERN SYDNEY

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EXECUTIVE SUMMARY

Blood toxicology results for all accidental heroin `overdose' deaths that occurred in the south western Sydney region during 1995 (N=39) were compared to those of a sample of 100 current south western Sydney heroin users who had injected within the preceding 24 hours. Overall, fatal overdose cases had a higher median concentration of morphine than the needle exchange attendees (0.35mg/L v 0.09 mg/L). However, there was substantial overlap between blood morphine concentrations of the two groups, ranging from 0.08 mg/L to 1.45 mg/L. The overlap covered 90% of heroin-related deaths. A third of current users had morphine concentrations more than twice the toxic morphine blood level employed by the analytical laboratories, and 7% had morphine levels higher than the median recorded for fatal cases. Only 4 of the 39 heroin-related fatalities had blood morphine concentrations exceeding the highest recording for the current user group.

There was a marked contrast in the prevalence of alcohol detected in the groups. Alcohol was detected in 51% of fatal cases (median=0.10g/100ml) compared to only one current heroin user (1%). There was a significant negative correlation among fatal cases between blood morphine and blood alcohol concentrations (r_s=-0.41). The overlap between the morphine distributions of current heroin users and fatalities involving alcohol was substantially greater than between current users and alcohol negative cases.

There was no significant difference between the proportions of fatalities and current heroin users in which benzodiazepines were detected in the blood. Both alcohol and benzodiazepines were detected in 10% of fatal cases compared to 1% of current heroin users. Methadone was detected in one (2%) fatal case, and in 27% of current heroin users.

These data further call into question the assumed mechanisms underlying heroin fatalities. It is clear that a conclusion of heroin overdose cannot be based on blood morphine concentrations alone.

The study also supports previous work implicating the role of alcohol in what are reported as heroin overdoses. Alcohol was detected in over a half of heroin fatalities, compared to only one current heroin user. These data, taken in conjunction with previous studies, indicate that strategies to reduce the morbidity and mortality of heroin overdose should focus on the role of alcohol.

1.0 INTRODUCTION

Deaths attributed to overdose remain the single largest contributor to the excess mortality associated with heroin use, even in countries with a high HIV seroprevalence (Eskild et al, 1993; Frischer et al, 1993; Joe & Simpson, 1987; Oppenheimer et al, 1994; Perucci et al, 1991). Recent research has also indicated that the incidence of non-fatal overdose is high (Bammer & Sengoz, 1994; Darke et al, 1996, Gossop et al, 1996). Two thirds of a sample of Australian heroin users reported having experienced an overdose (Darke et al, 1996), a quarter in the preceding twelve months. A quarter of a sample of British heroin users reported an overdose (Gossop et al, 1996), 9% in the preceding twelve months. This widespread exposure to overdose, and to other causes of mortality such as HIV and violence, is reflected in an estimated excess mortality rate among heroin users 13 times that of peers of the same age and gender (English et al, 1995).

Contrary to popular belief, the `typical' overdose victim is an older, dependent user, the mean age of heroin fatalities being in the late twenties and early thirties (Cottrell et al, 1985; Oppenheimer et al, 1994 Ruttenber & Luke, 1984; Zador et al, 1996). Given that heroin using careers typically start in the late teens (Kandel & Logan, 1984), most fatal cases have been using heroin for ten or more years prior to their deaths.

Despite the pattern of long-term heroin use and, presumably, high tolerance to heroin, morphine concentrations in studies where they have been reported have been skewed towards the lower end of the range (e.g. Chan et al, 1988; Fugelstad, 1994; Kintz et al, 1989; Monforte, 1977; Zador et al, 1996). For instance, a third of cases reported by Zador et al (1996) had morphine concentrations below 0.16mg/L, which is considered by the analytical laboratories that conducted the analyses to be the toxic level for opioid-naive individuals.

Few studies have compared the morphine concentrations of fatal overdose cases to other groups. Monforte (1977) compared U.S. heroin overdose fatalities with narcotic users who died due to homicide. What was noticeable was the overlap of blood morphine concentrations between `overdose' cases and those detected in other groups. All of the homicide deaths had blood morphine concentrations lower than 0.19 mg/L. Two thirds of the overdose deaths, however, also had blood morphine concentrations lower than 0.19 mg/L.

Fugelstad (1994) compared blood morphine concentrations of Swedish heroin overdose fatalities with survivors of overdose presenting to hospitals. While the majority (78%) of survivors had blood morphine concentrations lower than 0.20 µgm/gm, 43% of fatalities also had blood morphine concentrations in this range. Approximately equal proportions of survivors (4%) and fatalities (3%) had concentrations in excess of 1.0 µgm/gm.

The only study known to the authors in which the toxicology of fatalities attributed to heroin overdose have been compared to that of living heroin users was reported by Aderjan et al (1995). Morphine concentrations among heroin users in police custody were compared with those of heroin overdose fatalities. While the morphine concentrations in fatalities were higher than those of the living group, there was substantial overlap, with 6 out of 20 of the living having morphine concentrations higher than the median morphine level of the overdose fatalities.

The data on morphine concentrations raises questions regarding the attribution of heroin overdose (cf. Darke & Zador, 1996; Zador et al, 1996). Recent research has indicated that the concomitant use of heroin with the CNS depressants alcohol (Ruttenber et al, 1990; Ruttenber & Luke, 1984; Zador et al, 1996) and benzodiazepines (Gutierrez-Cebollada et al, 1994; Zador et al, 1996) is associated with heroin overdose in a large proportion of cases, focusing attention on aetiological factors other than heroin purity *per se*.

To date, no study has examined the blood toxicology of a sample of current heroin users attending needle exchanges. This is clearly relevant in providing a general comparison group of the heroin using population. The South Western Sydney (SWS) region represented an ideal location to examine the comparative toxicology of current heroin users and accidental heroin-related fatalities. The region has, in recent years, become a major distribution point for high purity heroin (O'Brien et al, 1996). A recent study reported a mean purity of 59% for street seizures of heroin in the SWS region, with purity ranging up to 80% (Weatherburn & Lind, 1995). In order to provide a broad comparison group for fatal overdose, the current study aimed to compare the toxicology of current heroin users attending needle exchanges in SWS, and heroin overdose fatalities from the same region.

1.1 *Study Aims*

The objectives of the study were:

1. To compare blood morphine concentrations in all accidental heroin-related fatalities in the SWS area in 1995 with a sample of current heroin users who had injected within the preceding 24 hours.

2. To compare the prevalence of other CNS depressants among accidental heroin-related fatalities and current heroin users who had recently injected.

2.0 METHOD

2.1 *Procedure*

2.1.1 Structured interviews

All subjects were volunteers who were paid A$20 for participation in the study. Recruitment took place from December 1995 to February 1996, by means of advertisements placed in SWS needle and syringe exchanges. Heroin users presented to the Liverpool Hospital Drug and Alcohol Centre on a designated day, in response to advertisements at a fixed needle and syringe exchange in Liverpool, needle and syringe exchanges in Cabramatta, or by snowballing. Those who presented for the study were asked by the receptionist to be seated in the waiting area, and were seen by the registered nurse in order of presentation. Subjects were screened for suitability for the study through questions about their use of heroin. Those who indicated they had used heroin in the preceding 24 hours were admitted into the study.

Informed consent was obtained from subjects, and the brief questionnaire administered. The structured interview examined demographic characteristics, drug use history, recent drug use and history of heroin overdose. Time elapsed since last use of heroin, alcohol, benzodiazepines and other opioids were also recorded.

2.1.2 Blood sampling

After completion of the brief questionnaire, the registered nurse collected 10mls of blood by venipuncture from each subject. The blood samples were stored and preserved in vacutainers. Each blood sample was coded with the subject's study number, and refrigerated until being transported to the Analytical Laboratories for analysis.

Interviews, and blood sampling, took approximately 15 minutes.

2.1.3 Heroin-related fatalities

All fatalities were identified in the South Western Sydney Area Health Service region during 1995 in which blood morphine was detected by the Government Analytical Laboratories. Each coronial file was then inspected by a member of the research team to ascertain whether it was a heroin-related fatality or due to other causes. Heroin-related fatalities were determined by circumstances of death (e.g. presence of injecting equipment), police investigations and autopsy pathology conclusions. Those cases due to other causes were excluded from the study. Demographic characteristics, toxicological results and circumstances of death of fatal overdose cases were recorded.

12.2 *Analyses*

2.2.1 Toxicological analyses

All toxicological analyses, both for current heroin users and overdose fatalities, were conducted by the Division of Analytical Laboratories, NSW Department of Health.

Total morphine was quantitated using GC/MS with deuterated internal standards and derivatisation. The blood samples were initially hydrolysed with acid under pressure followed by extraction with organic solvent, The final extracts, with deuterated internal standards were then derivatised using acetic anhydride for final quantitation by GC/MS. This method allows fro simultaneous quantitation of morphine and codeine in SIM mode. Analyses for methadone, benzodiazepines and morphine were conducted at the Division's Forensic Toxicology Laboratory.

Alcohol was quantitated by GC in the Division's Blood Toxicology Laboratory. Immunoassay screens were initially performed for methadone and benzodiazepines, which were then quantitatively confirmed on the GC and IIPLC respectively.

2.2.2 Statistical analyses

For continuous variables t-tests were employed. Categorical variables were analysed using chi^2, and corresponding odds ratios (O.R.) and 95% confidence intervals (C.I.) were calculated. Where distributions were highly skewed, medians were reported. Highly skewed continuous data were analysed using the Mann-Whitney U statistic, a non-parametric analogue of the t-test.

In order to ascertain whether elapsed time between death and autopsy was related to blood morphine concentrations in fatal cases, a Spearman rank order correlation was conducted. In cases where there was a range of time in which death could have occurred, the mid-point was chosen for these analyses. Spearman rank order correlations were also calculated to determine the relationship between blood morphine and alcohol concentrations. All analyses were conducted using SYSTAT (Wilkinson, 1990).

3.0 RESULTS

3.1 *Study Cases*

3.1.1 Current heroin users

One hundred and twelve heroin users presented to the Drug and Alcohol Centre for screening. In 10 cases, the last use of heroin was more than 24 hours prior to presentation. In two cases, no blood could be drawn from the subject. The sample thus consisted of 100 heroin users, recruited from the SWS region. The mean age of subjects was 28.0 years (SD 6.1, range 17-39), with 70% of subjects being male. The majority were born in Australia (90%). Eighty eight percent of subjects were not currently enrolled in a drug treatment program, with 12% currently enrolled in methadone maintenance (MM). Those enrolled in MM had a median length of enrolment of 13.5 months (range 1-120). The mean years of formal school education was 9.1 (SD 2.0, range 1-12). The majority of subjects (86%) were currently unemployed, with 3% in full-time employment. In terms of key demographic variables such as age, gender and employment status, the sample was comparable to other samples of heroin users, both in Australia and elsewhere (Griffiths et al, 1994; Hall et al, 1993).

The mean age of first heroin use was 19.3 (SD 4.9, range 12-35), with a mean age of regular heroin use of 20.9 years (SD 5.0, range 12-36). The mean length of heroin using career was 8.7 years (SD 6.8, range 1-24). Fifty three percent of subjects reported having overdosed, on a median of three occasions. Nearly a third (31%) reported having overdosed in the twelve months preceding interview. The opioid antagonist naloxone had been administered to 41% of subjects.

Table 1 presents the prevalence of drug use by drug class over the month preceding interview.

Table 1: Prevalence of drug use by 100 current heroin users in month preceding interview

Drug Class	%
Heroin	100
Cannabis	80
Alcohol	52
Benzodiazepines	40
Other opioids*	24
Cocaine	12
Amphetamines	9
Hallucinogens	4
Inhalants	2
Barbiturates	0
Inhalants	2

* Excludes prescribed methadone

In addition to heroin, the major drug classes used in the preceding month were cannabis (80%), alcohol (52%) and benzodiazepines (40%). The median number of drug classes used by subjects in the month preceding interview was 4 (range 2-9). Tobacco use was prevalent, with 91% using tobacco in the month preceding interview.

The frequency of use of CNS depressant drugs in the month preceding interview is presented in Table 2. Heroin was used on a regular basis by 94% of subjects. Few subjects, however, reported regular use of other CNS depressants. Alcohol was reported to have been used on a weekly or less frequent basis in the preceding month by 85% of subjects. Similar proportions reported no use, or weekly or less frequent use, of both benzodiazepines (84%) and other opioids (94%).

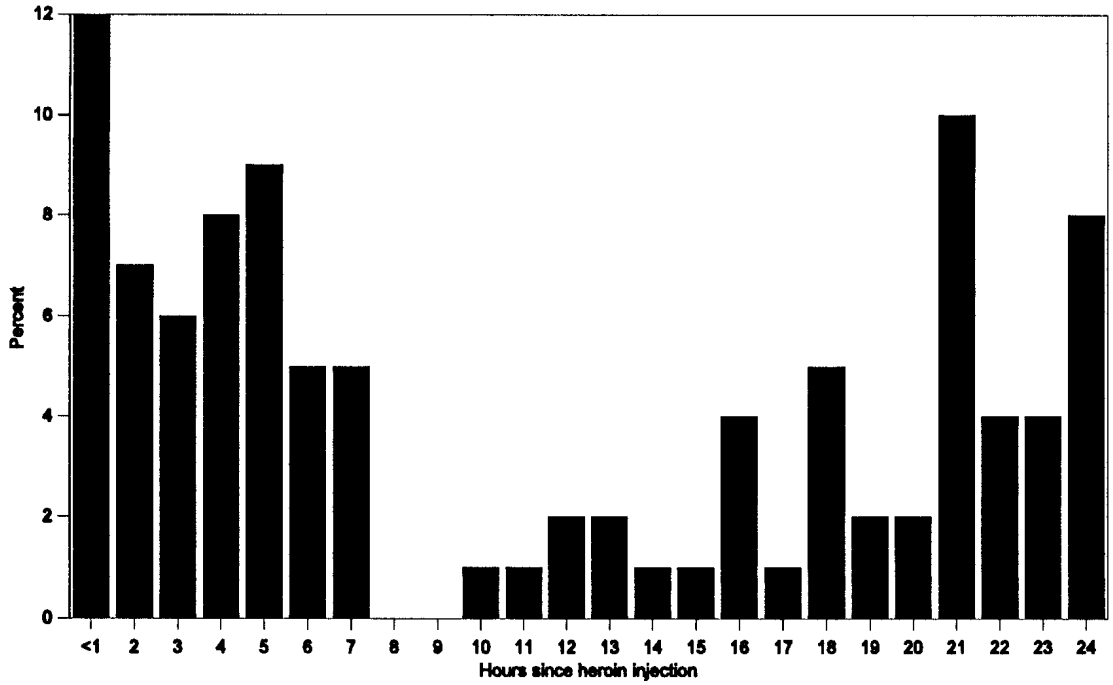
Table 2: Frequency of heroin and other CNS depressant drug use by current heroin users in month preceding interview

Drug Class	%
Heroin	
Daily	62
More than weekly	32
Weekly or less	6
No use in month	0
Alcohol	
Daily	6
More than weekly	9
Weekly or less	37
No use in month	48
Benzodiazepines	
Daily	7
More than weekly	9
Weekly or less	24
No use in month	60
*Other opioids**	
Daily	0
More than weekly	6
Weekly or less	18
No use in month	76

* Excludes prescribed methadone

The reported time elapsed since the most recent heroin injection of current heroin users is presented in Figure 1.

Figure 1: Reported elapsed time in hours since most recent heroin injection among current heroin users



Twelve percent of subjects reported injection within the hour preceding interview, 25% having reporting a heroin injection within the preceding three 3 hours.

Minorities of subjects reported the use of the CNS depressant drugs alcohol (10%), benzodiazepines (13%) and other opioids (2%) within the preceding 24 hours.

3.1.2 Heroin-related fatalities

Fifty seven cases were identified where morphine was detected at autopsy. Eleven cases were identified where the person was not a heroin user, and cause of death was not due to heroin administration. Two cases were identified as suicides who were known to be heroin users, but who employed other means for suicide (gunshot, carbon monoxide). A further three cases were identified as suicides who deliberately administered heroin as a means of suicide. In all cases of suicide, suicide notes were found with the body. Suicides were excluded from the analyses, as the current study aimed to compare current heroin users with accidental heroin-related deaths.

In one documented heroin overdose, the person was transported to hospital and maintained on life support for 72 hours until life was pronounced extinct. In one

further case of documented heroin overdose the body was in a state of advanced decomposition, and no toxicological analyses were performed.

These 18 cases were excluded from the analyses, leaving a total of 39 accidental heroin-related fatalities in the SWS area health region during 1995 in which toxicological analyses were conducted.

The mean age of fatal cases was 32.2 years (SD 7.1, range 19-45), with 95% being male. Fifty six percent were unemployed at the time of death. The majority (83%) of cases were born in Australia.

3.1.3 Comparison of demographic characteristics

Fatal cases were significantly older than the sample of current heroin users (32.2yrs v 28.0yrs, t=3.5, p<.001), more likely to be male (95% v 70%, OR 7.9, 95% CI 1.8-35.0), and less likely to be unemployed (86% v 56%, OR 0.2, 95% CI 0.1-0.5).

While 12% of current heroin users stated they were enrolled in methadone maintenance, no fatal case was enrolled in methadone maintenance at the time of death.

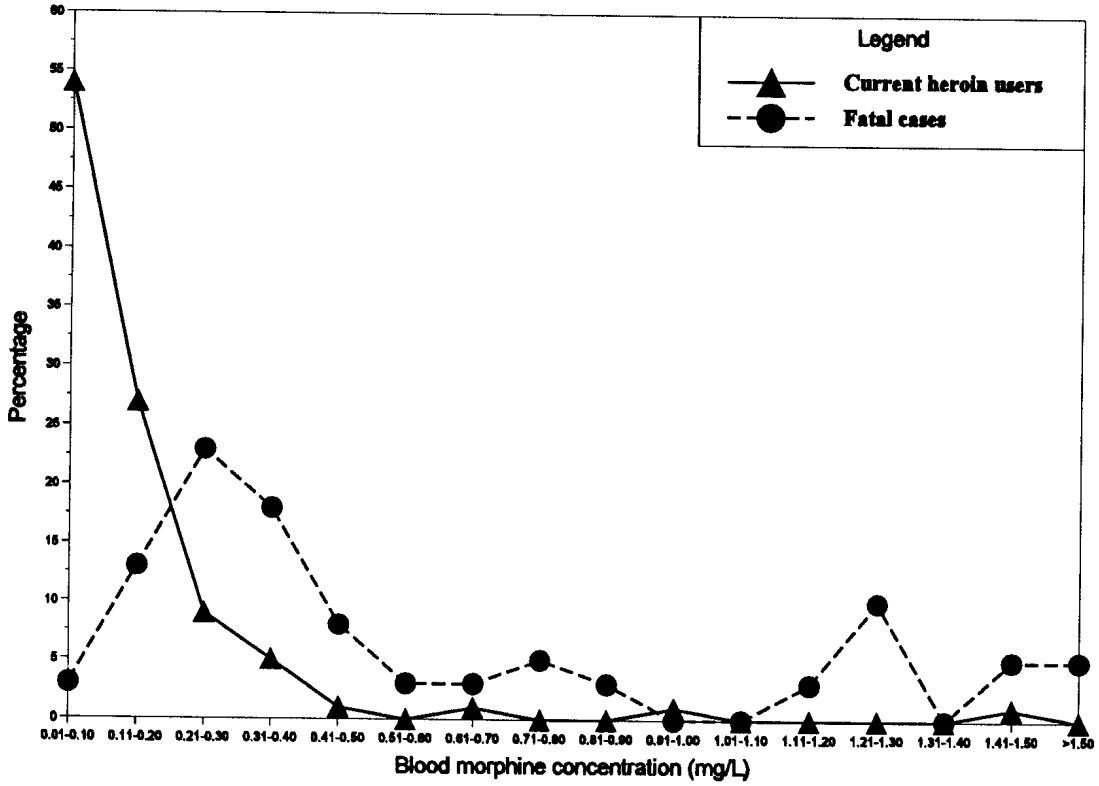
3.2 *Toxicological findings*

3.2.1 Blood morphine concentrations

Blood morphine was detected in 82% of current heroin users, 18% having no detectable blood morphine. The 18 subjects in which morphine was not detected were excluded from all subsequent analyses. The self-reported median time since last injection for these subjects was 18 hrs. Four of these subjects reported heroin use within the preceding seven hours, yet had no detectable morphine concentrations. Overall, there was a significant negative correlation among the 100 current heroin users between time since last reported heroin injection and blood morphine concentration (r_s=-0.51, p<.001).

Blood morphine concentrations of the 82 current heroin users in which morphine was detected and 1995 SWS overdose fatalities are presented in Figure 2.

Figure 2: Blood morphine concentrations in 1995 accidental heroin-related fatalities and current heroin users in South Western Sydney



The median blood morphine concentration among fatal cases was 0.35 mg/L (range 0.08mg/L-3.2mg/L), while that of the current heroin users was 0.09 mg/L (range 0.05mg/L-1.45mg/L) (U=3553.5, p<.001). While the blood morphine concentrations were higher in fatalities, there was substantial overlap between the two distributions. Seventeen percent of fatalities had blood morphine concentrations lower than 0.20 mg/L. Conversely, 7% of the sample of current heroin users had blood morphine concentrations in excess of the median level detected in `overdose' fatalities. A third (33%) of current heroin users had morphine concentrations in excess of the designated toxic level employed by the analytical laboratories that conducted the toxicological analyses (0.16 mg/L). Only 4 of the 39 (10%) fatal cases had blood morphine concentrations higher than the 1.45 mg/L detected in the current heroin user who recorded the highest morphine concentration in that group.

There were no significant relationship between either gender or age and blood morphine concentrations in either current heroin users or fatal cases.

There was no correlation between the estimated elapsed time between death and autopsy, and blood morphine concentrations in fatal cases (r_s=-0.06).

While not a formal component of this study, the toxicological data from the five

suicides that occurred in SWS in 1995 in which morphine was detected at autopsy are of interest. Three of these case involved self-administration of heroin as a means of suicide, while two employed other means (gunshot and carbon monoxide poisoning). All were known heroin users, and suicide notes were found with each body. The toxicological results for these cases are presented in Table 3. As can be seen, the blood morphine concentrations of the three deliberate heroin `overdoses' are all substantially lower than the two cases where other means of suicide were employed. It should also be noted that 6% of the sample of current heroin users had higher blood morphine concentrations than the highest level recorded by an overdose suicide.

Table 3: Blood toxicology of suicide cases of heroin users in South Western Sydney in 1995 in which morphine was detected at autopsy

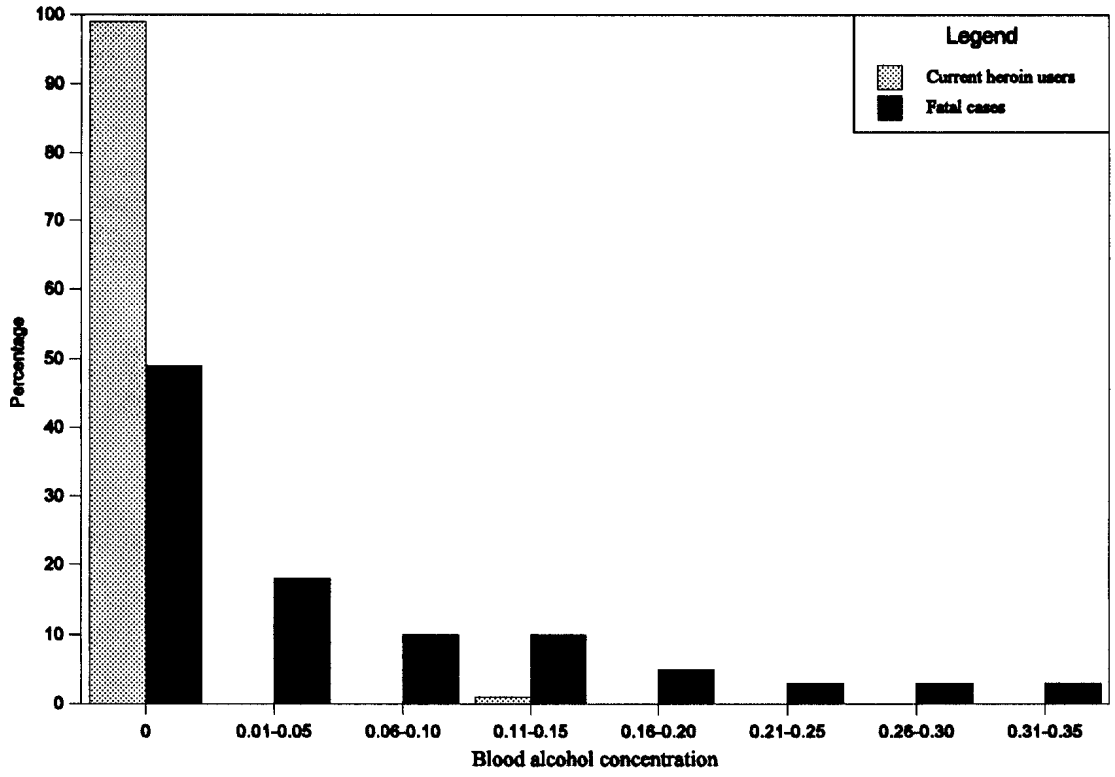
Suicide by heroin administration	Suicide by other means
Case 1 *Male, 31* Morphine: 0.14 mg/L Alcohol: 0.16g/100ml Benzodiazepines: Positive Antidepressants: Positive	*Case 4* *Female, 24 (gunshot to head)* Morphine: 1.2 mg/L Cocaine: 0.15 mg/L
Case 2 *Male, 28* Morphine: 0.39 mg/L Alcohol: 0.24 g/100ml	*Case 5* *Male, 38 (carbon monoxide)* Morphine: 0.68 mg/L CO: 74% saturation
Case 3 *Male, 18* Morphine: 0.32 mg/L Benzodiazepines: Positive	

3.2.2 Blood alcohol concentrations

Alcohol was detected in 51% of fatal cases compared to only one subject in the sample of current heroin users (OR 85.3, 95% CI 10.8-675.4). The median blood alcohol concentration of fatal overdose cases in which alcohol was present was 0.10 g/100ml (range 0.01-0.33 g/100ml). The distributions of blood alcohol

concentrations are presented in Figure 3. A third (33%) of fatal overdose cases had blood alcohol concentrations in excess of 0.05 g/100ml.

Figure 3: Distribution of blood alcohol concentrations among heroin-related fatalities and current heroin users



There was a significant negative correlation between blood alcohol and blood morphine concentrations among fatal cases (r_s=-0.41, p<.001). The median blood morphine concentration in cases in which alcohol was detected at autopsy was significantly lower than in cases where alcohol was not detected (0.26mg/L v 0.70mg/L, U=281.5, p<.01).

Figure 4 presents the distribution of blood morphine concentrations of the 82 current heroin users in whom morphine was detected and the 20 fatalities in which alcohol was detected. Figure 5 compares blood morphine concentrations of the current heroin users in whom morphine was detected and the 19 fatalities in which alcohol was *not* detected. As can be seen, there is substantially more overlap between the morphine concentrations of current heroin users and alcohol positive fatalities than between current heroin users and alcohol negative fatalities. While 90% of current heroin users had blood morphine concentrations ≤0.30mg/L, 60% of alcohol positive also had concentrations within this range, and only 16% of alcohol negative cases.

Figure 4: Blood morphine concentrations in current heroin users and fatal cases in which alcohol was detected

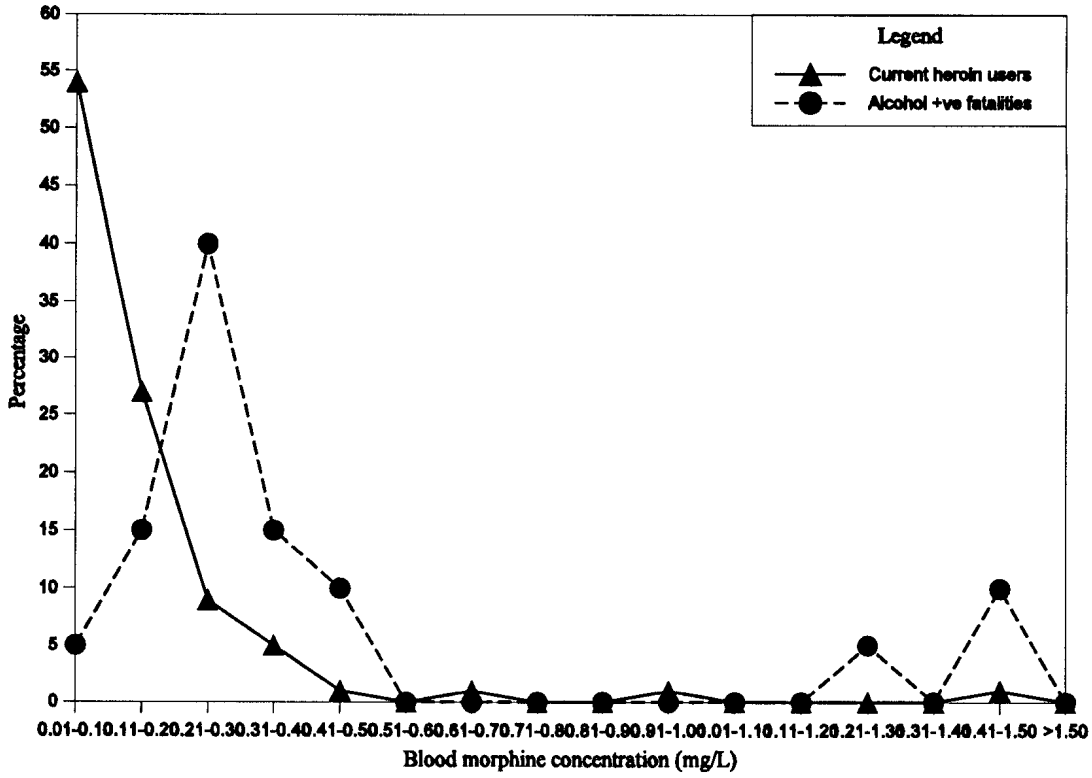
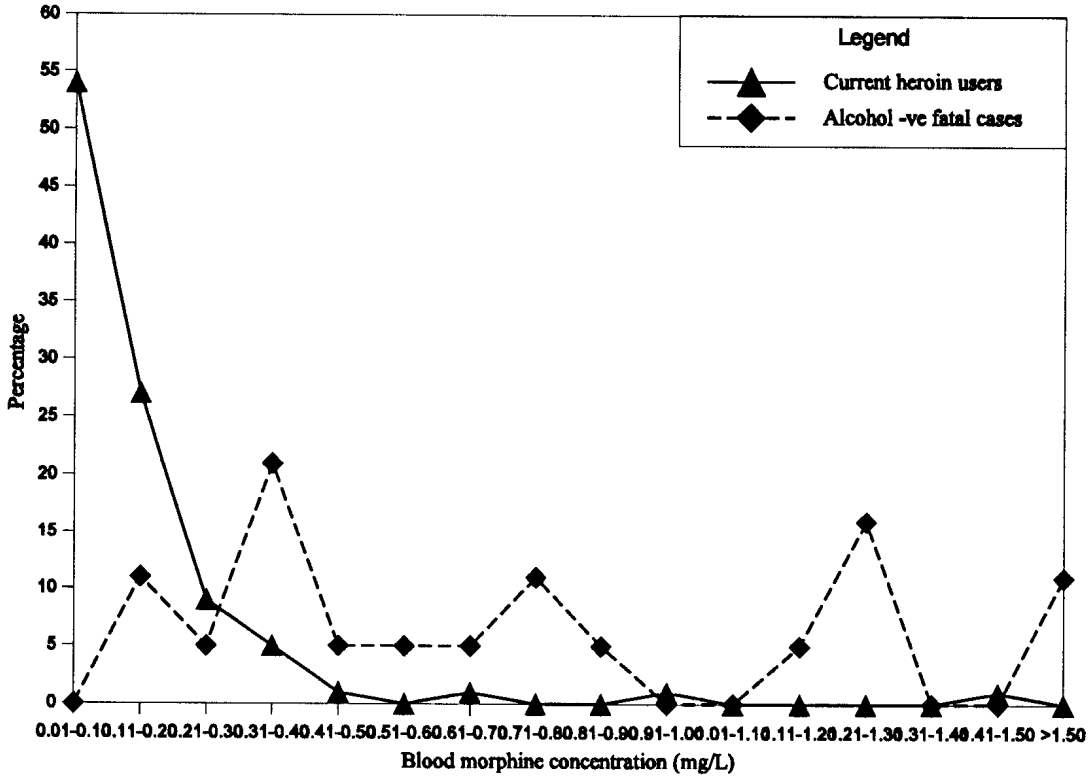


Figure 5: Blood morphine concentrations in current heroin users and fatal cases in which alcohol was *not* detected



3.2.3 Benzodiazepines

The proportions of cases in which benzodiazepines were detected is presented in Table 4. There was no significant difference between the proportions of fatalities and current heroin users in which benzodiazepines were detected in the blood.

Table 4: Prevalence of benzodiazepines in heroin-related fatalities and current heroin users

Benzodiazepines	**Current heroin users (N=82)** %	**Fatal cases (N=39)** %
Detected	27	21
Not detected	73	79

The specific benzodiazepines and metabolites detected were diazepam (14% of fatal cases v 12% of current heroin users), nordiazepam (17% v 15%), temazepam (5% v 6%), oxazepam (10% v 12%) and nitrazepam (0% v 1%). In 10% of fatal cases both alcohol and benzodiazepines were detected at autopsy, compared to 1% of current heroin users (OR 10.4, 95% CI 1.1-96.2).

3.2.4 Methadone

Methadone was detected in one (2%) fatal case, and in 27% of current heroin users (OR 14.9, 95% CI 2.0-113.6) (Table 5). All of the current heroin users who stated they were enrolled in methadone maintenance had methadone detected in their blood. Methadone was detected in eleven subjects who stated they were not enrolled in methadone.

Table 5: Prevalence of methadone in heroin-related fatalities and current heroin users

Methadone	**Current heroin users (N=82)** %	**Fatal cases (N=39)** %
Detected	27	2
Not detected	73	98

4.0 DISCUSSION

4.1 *Major findings of the study*

The major finding of this study was the large overlap between blood morphine concentrations in a sample of current heroin users who had injected in the preceding 24 hours, and in cases of fatal heroin `overdose'. Only 4 of the 39 fatalities had higher blood morphine concentrations than that recorded in the current heroin user with the highest morphine concentration in that group.

The second major finding was the marked difference in the prevalence of alcohol detected in the groups. While over a half of fatal cases had alcohol detected at autopsy, only one current heroin user had blood alcohol detected.

4.2 *Morphine concentrations*

The overlap between blood morphine concentrations among a sample of heroin users who reported heroin injection in the preceding 24 hours and accidental heroin-related deaths ranged from 0.08 mg/L to 1.45 mg/L. This range incorporates 90% of fatal cases. Overall, fatal cases had a higher median concentration of morphine than the needle exchange attendees. However, a third of living users had morphine concentrations more than twice the designated toxic morphine blood level, and 7% had morphine levels higher than the median recorded for fatal cases. Thus, there were many current users who had `toxic' levels of morphine in their blood, and fatal cases who had moderate levels detected.

These data further call into question the term `overdose' as a mechanism for all heroin deaths and near deaths. The extent of the overlap in morphine concentrations between the two groups is consistent with that found by Monforte (1977), Fugelstad (1994) and Aderjan et al (1995). The significance of this overlap should be considered in the light of the extremely high purity of heroin that is available within the SWS region in recent years. Even with purity ranging up to 80%, the overlap exists. High heroin purity alone would not appear to be an explanatory mechanism for all overdose fatalities in SWS.

At this point the issue of tolerance should be addressed. It is clear that an individual's's tolerance for heroin will be a factor in whether a dose will result in death. The tolerance of individuals for heroin in this study, however, cannot be determined. As such, it cannot be ascertained whether there were specific differences in tolerance between the two groups.

It should be noted that there was no correlation between estimated elapsed time between death and autopsy and blood morphine concentrations in fatal cases. If there had been a significant relationship, then the blood morphine

concentrations detected at autopsy could be underestimates of concentrations at death, due to post-mortem reductions in morphine concentrations. This, however, was not the case.

The suicide fatalities are of relevance for two reasons to the role played by heroin in heroin `overdose'. Firstly, both cases where other means of suicide were employed had substantially higher morphine concentrations than those detected in the fatal cases who deliberately attempted to overdose. In fact, the higher morphine concentrations of the two cases where other means were employed were higher than 80% (case 4) and 67% (case 5) of the accidental overdose fatalities. Second, 6% of current heroin users had higher blood morphine concentrations than the highest level recorded by an overdose suicide, and 43% higher than the lowest level recorded.

4.3 *Alcohol*

One of the most marked toxicological differences detected between the two groups was the prevalence of alcohol. Alcohol was almost completely absent among living users, detected in only one of the 82 subjects of this sample. Importantly, this was consistent with the self-reported alcohol consumption of this group, with 85% reporting weekly, less frequent or no alcohol use over the month preceding interview. Alcohol did not appear to be a prominent drug in this sample of heroin users. In contrast, a half of fatal cases had alcohol in their blood at the time of death. Furthermore, inspection of the coronial files of these cases indicated that 43% were known heavy alcohol users.

It is important to note that the difference between the groups in the current study was not an artefact of the time of day that blood sample were taken from current users (generally between 8am-7pm). Of the 16 fatalities that were determined to have occurred within this time period, 63% had alcohol detected at autopsy.

These findings are consistent with the findings of previous Australian (Zador et al, 1996) and overseas research (Ruttenber et al, 1990) concerning the role of alcohol in what are generally designated *heroin* fatalities. As was also found by both Zador et al (1996) and Ruttenber et al (1990), there was a significant negative correlation among fatal cases between blood morphine and blood alcohol concentrations. Of particular relevance here, however, is the greater extent of overlap between the morphine distributions of current heroin users and fatalities involving alcohol compared to alcohol negative cases.

4.4 *Benzodiazepines*

There was no significant difference in the proportions of current heroin users

and overdose fatalities in which benzodiazepines were detected. This is in contrast to many previous studies of heroin overdose, in which benzodiazepines have been implicated. The combination of alcohol and benzodiazepines, however, was detected in significantly more fatal cases than among current heroin users. The effects of benzodiazepines on overdose may possibly be reflected in the combination of these CNS depressants, rather than in combination with heroin alone.

4.5 *Methadone*

Methadone was detected in only one fatal case, who was not enrolled in methadone maintenance at the time of death. In contrast, methadone was detected in a quarter of current heroin users. It is possible that some of those subjects who stated they were not in treatment and in whom methadone was detected were enrolled in treatment. As the interviews were anonymous, this was not possible to ascertain.

The low prevalence of methadone detected at autopsy in fatal heroin overdose cases was noted in a previous Australian study (Zador et al, 1996), where only 2% of cases in NSW were enrolled in methadone maintenance at the time of death. The data is also consistent with a recent study of non-fatal heroin use that indicated that despite continued heroin use, current enrolment in methadone maintenance was protective against overdose (Darke & Ross, in press). This reduced exposure to overdose may reflect a combination a higher tolerance to opioids while being maintained on methadone.

4.6 *Representativeness of sample*

In terms of key demographic variables, drug use patterns and exposure to overdose the sample of heroin users recruited for this study are typical of previous samples recruited in Australia, and in SWS in particular (Darke et al, 1994; Hall et al, 1993). The group were experienced heroin users. They had used heroin for a mean of 8.7 years, and 53% had experienced a non-fatal overdose.

It was the original intention of the authors to obtain subjects within an hour of injection. This was not possible due to concerns expressed by the relevant area health service ethics committee, because it could be seen as offering an inducement to inject heroin. The adoption of a criterion of heroin injection within the preceding 24 hours was a compromise agreed upon with the committee. As such, the blood morphine concentrations of the sample of current heroin users were not peak plasma concentrations in some cases. Therefore, it would be expected that the range of overlap between morphine concentrations in the two groups is, in all probability, an *underestimate* of the degree of overlap between heavily intoxicated current users who do not die, and those who have

experienced a fatal `overdose'. Thus, for instance, subjects who reported their most recent injection as seven hours prior to blood sampling would, presumably, have had higher blood morphine concentrations closer to the time of injection.

4.7 *Clinical Implications*

The major clinical consideration that arises from this study concerns the concurrent use of alcohol with heroin. The data from the current study, in conjunction with those of previous studies, strongly implicate alcohol in the causation of many heroin overdoses. The current data clearly indicate that `overdose' is not simply a matter relating to the amount of heroin used by the individual. A dose of heroin that may not be lethal to a particular individual when sober may be a lethal dose when alcohol has been consumed. The reduction of concomitant use of alcohol and/or benzodiazepines with heroin may reduce the frequency of heroin-related deaths. Interventions targeted towards reduction of concurrent depressant drug use would seem warranted.

4.8 *Conclusions*

The current study supports the few previous studies that have compared morphine concentrations of heroin-related deaths with other groups. As in those studies, the current study found substantial overlap between those who had `overdosed' and died and current, intoxicated heroin users. These data further call into question the mechanisms underlying heroin overdose fatalities. It is clear that a conclusion of `overdose' cannot be based on blood morphine concentrations alone.

The study also supports previous work implicating the role of alcohol in what are designated heroin overdoses. Alcohol was detected in over a half of fatalities, compared to only one current heroin user. These data, taken in conjunction with previous studies, indicate that strategies to reduce the morbidity and mortality of heroin `overdose' should focus on the role of alcohol.

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