Factors associated with non-fatal heroin overdose: assessing the effect of frequency and route of heroin administration

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ABSTRACT

Aims To examine risk factors associated with non-fatal heroin overdose, particularly frequency and route of heroin administration.

Design Data from cross-sectional surveys were analysed as a case–control and as a case cross-over design.

Setting and participants 2556 subjects treated for heroin dependence in 164 outpatient facilities in Spain.

Measurements Prevalence of overdose involving emergency care in the 12 months before treatment admission.

Case control design Odds ratio (OR) adjusted by logistic regression.

Case–crossover design Estimated relative risk (RR) of transient risk of injecting heroin.

Findings The prevalence of overdose was 10%. In the case control analysis the cumulative risk of overdose increased as the frequency of heroin use decreased. However, among daily heroin users this risk increased as the frequency of heroin injection rose, with an OR of 6.0 (95% CI: 3.9–9.6) for daily injectors versus non-injectors. Sniffers had a higher risk than smokers among non-daily users, but not among daily users. Other factors associated with increased risk of overdose were: tranquillizers, alcohol or cocaine use, living in certain regions and being long-term HIV+ 0. In the case–crossover analysis, the RR for injecting heroin versus using other routes immediately before overdose was 15.9 (95%CI: 9.5–26.6), and was much higher for non-daily heroin users than for daily users.

Conclusions These findings suggest that the rapid entry of a large quantity of heroin into the blood (as occurs when injecting) involves a high risk of overdose, especially when the heroin tolerance level is low (as occurs in sporadic users).

KEYWORDS Administration route, frequency of use, heroin, non-fatal overdose.

INTRODUCTION

Acute heroin overdose is a major cause of death and demand for emergency care among heroin users (Sporer 1999). It is estimated that the annual rate of mortality from all causes among heroin users is 1–4% (6–30 times higher than that of their peers in the general population), with overdose and HIV infection being the main causes of death (Darke & Zador 1996; Ortí *et al.* 1996; Davoli *et al.* 1997; Haastrup 1999; Sporer 1999). In some large

cities such as Barcelona or Madrid, mortality related to drug use has been observed to be the primary reason for the rise in mortality among young people (De La Fuente *et al.* 1995; Torralba *et al.* 1996; Hulse *et al.* 1999). Studies have also shown that heroin users frequently suffer non-fatal overdoses (annual prevalence 9–32%) (Darke *et al.* 1996a; Gossop *et al.* 1996; Taylor *et al.* 1996; Powis *et al.* 1999). However, many non-fatal heroin overdoses do not result in medical attention being sought (56% of the witnessed overdoses in an Australian study) (Darke *et al.* 1996b). Among the factors most commonly cited as being associated with an increased probability of both fatal and-non-fatal heroin overdose are: heroin use by injection (Darke & Zador 1996; Gossop *et al.* 1996; Van Haastrecht *et al.* 1996; Powis *et al.* 1999; Sporer 1999; Van Ameijden *et al.* 1999; Darke *et al.* 2000; Darke & Ross 2000), use in conjunction with other central nervous system (CNS) depressants, such as alcohol or tranquillizers (Darke & Zador 1996; Van Haastrecht *et al.* 1996; Sporer 1999; Van Ameijden *et al.* 1999; Darke & Ross 2000), use following a period of abstinence (e.g. due to incarceration or treatment for dependence) (Darke & Zador 1996; Taylor *et al.* 1996; Sporer 1999; Van Haastrecht *et al.* 1996; Van Ameijden *et al.* 1999) and not being in methadone treatment (Darke & Zador 1996; Taylor *et al.* 1996; Van Haastrecht *et al.* 1996; Sporer 1999; Darke & Ross 2000). High or increased heroin purity (Darke & Ross 2000), being HIV positive (Van Haastrecht *et al.* 1996; Van Ameijden *et al.* 1999) or prolonged duration of heroin use (Darke & Zador 1996; Van Haastrecht *et al.* 1996; Davoli *et al.* 1997; Sporer 1999), have also been implicated.

However, evidence regarding the relative importance of many of these risk factors is lacking, in particular where frequency and route of heroin administration are concerned. Clarifying the implication of these factors is important, because major decreases in injecting and increases in smoking or sniffing have recently been reported in Europe and the USA (Strang *et al.* 1996; De La Fuente *et al.* 1997; National Institute on Drug Abuse 1998; Delegación Del Gobierno Para El Plan Nacional Sobre Dogas 2000), although a relatively high proportion of smokers or sniffers occasionally inject heroin (De La Fuente *et al.* 1997, 1999). Nevertheless, most of these studies have dealt exclusively with injectors, or have not included enough variables or participants to quantify the independent effect of different levels of heroin use or heroin injection (sporadic, daily), or that of the different main routes of heroin administration (injecting, smoking, sniffing). Therefore, it is not surprising that serious doubts remain. For example, if injecting heroin is a risk factor for overdose, it seems logical to expect that the risk of overdose would increase with increasing frequency of heroin injection. This, however, has not been observed, and sporadic injectors seem to have a risk of overdose as high as daily injectors (Van Haastrecht *et al.* 1996; Van Ameijden *et al.* 1999). Such results may be due to the lack of control for variables that may modify strongly the effect of frequency of injection, such as the frequency of heroin use by any route of administration (or its correlates, dependence or tolerance level). The existence of a sizeable subgroup of sporadic heroin users who occasionally inject (with low tolerance to heroin and a high risk of overdose) could account for this finding. Thus, to measure the independent effect of frequency of heroin injection on overdose, it is advisable to adjust for other relevant variables, i.e. frequency of heroin use or dependence level.

This study focuses mainly on the effect of frequency and route of heroin administration on the occurrence of non-fatal heroin overdose, controlling for other relevant variables. However, other risk factors associated with overdose are also examined.

METHODS

Subjects

The sample consisted of 2556 people admitted to treatment for heroin dependence in Spain during 1996, regardless of the therapy employed. An independent sample was selected for all but two of Spain's 17 regions. The sample size in each region was proportional to the square root of the number of treatments reported to the national information system SEIT. A two-stage sampling method was used. First, 164 outpatient centres were selected randomly from the 391 centres that participate in the SEIT. These centres are the main gateway to the treatment system for drug abuse in Spain. Within centres, a systematic random sample of subjects was selected, based on the order of admission to treatment. Subjects were replaced only if they refused or prematurely interrupted the interview or missed three appointments.

Interviews and measurements

The interview was carried out during the evaluation process, before the beginning of the treatment intervention, by trained professionals who generally did not participate in the subsequent treatment. A structured questionnaire with closed and precoded questions was used. Each person was asked to report the number of episodes involving emergency medical care in the 12 months before treatment admission that were self-perceived as 'drug overdoses'. They were also asked whether or not they had used heroin, tranquillizers,

alcohol, cocaine and other drugs before the most recent overdose, whether they considered heroin to be the main drug responsible for the overdose and, if so, what the route of admission was. Questions were also asked concerning socio-demographic characteristics, history and pattern of drug use, such as the main administration route of heroin, frequency of heroin use and frequency of heroin injection. The reference period for questions about patterns of drug use or socio-demographic information was the 12 months before treatment except for alcohol and tobacco, for which it was 30 days. HIV serostatus was investigated by direct questioning, as well as from clinical records. A 'heroin overdose episode' was defined as one meeting the following three criteria: (1) self-perceived by the subject as overdose or acute reaction following drug consumption; (2) requiring emergency medical care; and (3) existence of heroin consumption in the 24 hours before episode. This definition is more restrictive than those used by other authors, because it does not include overdoses without medical care (Darke *et al.* 1996a; Gossop *et al.* 1996; Powis *et al.* 1999).

Analysis

To identify the main factors associated with heroin overdose, the data were analysed as a case–control design (Kleinbaum *et al.* 1982). Comparisons were made of people with and without overdose in the 12 months before treatment, with respect to the variables mentioned above. The measure of effect was the prevalence odds ratio (OR), adjusted by logistic regression. To show more clearly the independent effect of frequency of injection, adjusting for frequency of heroin use, separate logistic models were constructed for sporadic and daily heroin users. To construct the logistic models a bivariate analysis was carried out, and the variables that were found to be associated significantly with overdose were included in the models. The final variables included were selected using the stepwise regression method.

Overdose is an acute-onset event and heroin use is a brief exposure with a transient effect. Therefore, it is possible to study to what extent injecting heroin is an immediate determinant of overdose by a case–crossover analysis of the 168 subjects who attributed the overdose mainly to heroin. Unlike the case–control design where two groups of subjects are compared, here the behaviour of each case in a short period immediately before overdose is compared with the same subject's usual behaviour. All subjects served as their own controls, thus eliminating confounding by characteristics of the subject that remain constant over time, as well as possible control-selection bias (MacLure 1991; Redelmeier & Tibshirani 1997). To estimate the effect at 95% confidence intervals (95% CI) a matched-pair analysis was carried out, calculating the Mantel–Haenszel estimate of relative risk (RR) and an estimator of the variance of its logarithm for sparse person-time data (Greenland & Robins 1985; MacLure 1991). The estimated RR was obtained by dividing the number of days without heroin injection in the year before treatment for subjects who injected heroin immediately before overdose by the number of days with heroin injection for subjects who did not inject heroin before overdose. The number of days with and without heroin injection was estimated from the 'usual frequency of heroin injection in the 12 months before treatment'.

Weighting by region had little effect on the results, thus all data shown below are not weighted. The proportion of non-responses for all variables analysed was less than 2%, except for length of heroin use (2.4%), frequency of heroin injecting (2.6%) and type (colour) of heroin (7.6%).

RESULTS

General characteristics of heroin users

Most of the subjects were male (81.5%), between 25 and 34 years old (58.8%), single (69.7%), with less than 9 years of education (81%) and lived in a house or apartment (84.8%). The income of 56.8% of the subjects came from work, family or social assistance, and 27.6% made their living from illegal activities. Some 40.6% had been in prison, and at least 19.4% were HIV positive. Most of them were daily heroin users (80.8%), chiefly of brown heroin (77.6%), and had been using heroin for 5 years or more (80.2%). Smoking was the main route of heroin administration for 48%, injecting for 34.8%, sniffing for 6.3%, and 10.9% used various main routes. Some 47.4% injected heroin daily and 19.9% sporadically. A higher proportion of smokers than sniffers had sometimes injected heroin in the 12 months before treatment (19.1% versus 11.1%, $p = 0.08$), and used heroin on a daily basis (81.7% versus 70.2%, $p = 0.0008$).

History of non-fatal heroin overdose

In the 12 months before treatment, 10% had experienced at least one heroin overdose involving emergency medical care. Among them, 61.8% had only one episode, 18.9% two and 19.3% three or more. Along with heroin, 43.5% of subjects had also taken tranquillizers, 32.8% cocaine and 31.8% alcohol in the 24 hours prior to the most recent overdose. Some 75% attributed the last overdose to heroin, and 20.2% to tranquillizers. Of those who attributed it to heroin, 79.8% had injected before the overdose.

Table 1 Main factors associated with non-fatal heroin overdoses.

Associated factors[a]	*Number of subjects in each category*	*Last 12 months prevalence of overdose (%)*	*Adjusted OR*[b]	*95% CI*
Main area of residence				
Balearic Islands	111	26.1	3.8	2.0–7.3
North-east (Catalonia, Aragón, Basque C., Cantabria, Navarra)	766	13.7	2.2	1.3–3.6
Canary Islands	370	8.1	2.3	1.1–4.7
Center-East (Madrid, Valencia, Murcia)	560	10.0	1.7	0.9–2.9
South (C-La Mancha, Extremadura, Andalucía, Ceuta)	518	5.0	1.1	0.6–2.0
North-west (Asturias, Castilla y León)	186	5.7	1.0	
Frequency of heroin use				
<Monthly	190	13.2	2.6[c]	1.4–4.8
Monthly	300	13.7	2.3	1.4–3.8
Daily	2066	9.2	1.0	
Frequency of heroin injecting				
Daily	1181	15.1	4.1[c]	2.6–6.3
Monthly	248	16.2	2.9	1.7–5.0
<Monthly	247	14.9	3.1	1.8–5.2
No injection	814	3.6	1.0	
Length of heroin use				
<5 years	442	10.5	1.3	1.1–1.6
5 years or more	2074	9.9	1.0	
Frequency of tranquilizers/sleeping pills use				
Weekly	1059	14.4	3.5[c]	1.8–6.7
<Weekly	1119	8.0	2.0	1.1–4.0
None	357	3.4	1.0	
Cocaine use (including crack)				
Yes	1865	11.3	1.8	1.2–2.6
No	691	6.7	1.0	
Level of use of pure alcohol				
100 ml/day or more	158	20.3	1.9[c]	1.1–3.1
<100 ml/day	1574	9.4	0.9	0.6–1.2
No use	818	9.2	1.0	
HIV status and year subject knew positive status				
Negative	1807	9.9	2.0	0.9–4.6
Unknown	246	4.9	1.2	0.4–3.4
Positive, 1982–88	113	19.5	3.6	1.4–9.3
Positive, 1989–94	264	12.9	1.8	0.8–4.4
Positive, 1995–96	118	6.8	1.0	

[a] The reference period for patterns of drug use was 12 months before treatment admission, except for level of alcohol use, for which the period was 30 days before treatment admission. Main area of residence refers to the area where the subject lived longest in the 12 months before treatment admission.
[b] Odds ratio adjusted for all variables in the table.
[c] Linear trend was statistically significant ($p < 0.05$).

Factors associated with heroin overdose

An association was found between frequency of heroin use and overdose, with a significant linear trend toward decreasing risk of overdose with increasing frequency of use. Furthermore, a strong association between heroin injecting and overdose was found, but with a significant linear trend in the opposite direction. Subjects who had used heroin for less than 5 years had a slightly higher risk of overdose than those who were more long-term heroin users. Concomitant use of tranquillizers showed a trend toward increasing risk of heroin overdose with increasing frequency of use. Other factors associated with higher risk of overdose were cocaine use, having been diagnosed as HIV+ between 1982 and1988, and living in the Balearic or Canary Islands or in the North-east of Peninsular Spain (Table 1).

When the variable 'frequency of heroin injection' was replaced by 'main route of heroin administration' in the model of Table 1, it was found that heroin injectors had a risk of overdose higher than that of smokers (OR = 3.8; 95% CI: 2.6–5.6). This was also the case for those who used various main routes (OR = 3.1; 95% CI: 1.9–4.9) and with sniffers (OR = 1.6; CI95%: 0.8–3.2).

Table 2 Effect of route of heroin administration on overdose occurrence among daily and non-daily heroin users[a].

	Number of subjects in each category	*Last 12 months prevalence of overdose (%)*	*Adjusted OR*	*95% CI*
Daily heroin users				
Frequency of heroin injection				
Daily	814	15.1	4.4[b]	2.7–7.1
Monthly	121	13.2	3.7	1.9–7.5
< Monthly	138	9.4	2.9	1.4–6.0
No injection	941	2.9	1.0	
Main route of heroin administration				
Injecting	714	17.1	4.1	2.6–6.5
Sniffing	113	3.5	0.7	0.2–2.2
Smoking	994	3.8	1.0	
More than one main route	243	10.7	2.3	1.4–4.1
Non-daily heroin users				
Frequency of heroin injection				
Monthly	126	19.0	2.2	1.0–4.8
< Monthly	110	21.8	3.0	1.4–6.5
No injection	240	6.7	1.0	
Main route of heroin administration				
Injecting	169	18.9	3.3	1.4–7.7
Sniffing	48	16.7	4.5	1.5–13.4
Smoking	223	4.5	1.0	
More than one main route	33	33.3	7.4	2.6–21.1

[a] Four multivariate logistic models were constructed: two for daily users and two for non-daily users. In each model, ORs were adjusted for all variables in Table 2, except for the stratification variable (frequency of heroin use).
[b] Linear trend was statistically significant ($p < 0.0001$).

Effect of frequency of heroin use on the relation between administration route and overdose

It could be hypothesized that the frequency of heroin use can seriously affect the relation between overdose and administration route. Both the crude and multivariate analyses should be considered in studying this issue. In the crude analysis, no significant linear trend is seen toward increasing risk of overdose with increasing frequency of heroin injection: the ORs for non-daily and daily heroin injectors versus non-injectors were 4.8 and 4.7, respectively. Such a trend, nevertheless, becomes clear in the multivariate analysis after adjusting for the variables shown in Table 1.

When the logistic analysis is stratified by daily and non-daily heroin users, it can be observed that the risk of overdose increases with increasing frequency of heroin injection among daily users, but not among non-daily users (Table 2). If in the two models the variable 'frequency of heroin injection' is replaced by 'main route of administration', it is found that among daily users there is no difference in overdose risk between smokers and sniffers, whereas among non-daily users, the risk for sniffers is much higher. This stratified analysis further reveals that among non-daily users the risk for subjects who used various main routes of administration is very high (Table 2).

Another way to explore this issue is by constructing a logistic model similar to that of Table 1, combining the variables 'frequency of heroin use' (daily/non-daily users) and 'frequency of heroin injection' (daily/non-daily/non- injection) in a new variable of five categories. This analysis show that daily heroin users who do not inject have the lowest risk of overdose, and that sporadic heroin users who do inject this drug have an even higher risk (OR versus daily users who do not inject = 7.2; 95% CI: 4.1–12.4) than daily injectors do (OR = 4.2; 95% CI: 2.6–6.8).

Case–cross-over analysis to estimate the transient relative risk of overdose from injecting heroin

Among 256 subjects who had some non-fatal heroin overdose in the12 months before treatment, 168 attributed their most recent episode to heroin. Of those, 134 had injected this drug in the last use before overdose and 34 had not. The estimated RR for injecting heroin before overdose versus using by other routes was 15.9 (95% CI: 9.5–26.6), and was much higher for sporadic users

(RR = 80.0; 95% CI: 24.5–261.3) than for daily users (RR = 5.5; 95% CI: 2.7–11.0).

To control for possible within-individual confounding of use of other central nervous system (CNS) depressants, a case–crossover analysis was carried out only for subjects who did not use these drugs in the 24 hours before overdose. The estimated RR of injecting was 14.3 (95% CI: 8.3–24.7) for tranquillizers abstainers, 12.4 (95% CI: 7.2–21.2) for alcohol abstainers, 19.5 (95% CI: 10.7–35.6) for abstainers from opioids other than heroin, and 11.6 (95% CI: 6.6–20.4) for abstainers from all of the mentioned drugs. The differences mentioned in estimated RR between sporadic and daily heroin users remained.

DISCUSSION

Clarifying the relation between overdose, and frequency and route of heroin administration

This study can help to clarify how the frequency of heroin use and route of administration affect the risk of overdose. Several findings should be emphasized: (a) the cumulative risk of heroin overdose in a given period increases as the frequency of heroin use decreases; (b) it is several times greater among heroin injectors than among non-injectors; (c) this risk increases with increasing usual frequency of heroin injection among daily heroin users, but not among non-daily users; (d) the estimated RR of injecting heroin immediately before overdose versus using other administration routes is very high (15.9), and much higher for non-daily than for daily users; and (e) among non-daily heroin users the overdose risk of sniffers is much higher than that of smokers, but there are no differences among daily users.

After controlling for frequency of heroin injecting, it seems clear that non-daily heroin users (including irregular users or intermittent abstainers) have a higher cumulative risk of non-fatal overdose than do daily users. This may be because non-daily users have a lower or more fluctuating tolerance level than do daily users, or a higher frequency of risky behaviours or circumstances surrounding overdose. The scarcity of available information, often contradictory, makes this an important finding. Our results are consistent with recent data showing that most fatal overdoses occur in heroin users with a much lower hair morphine content than that usually found in active, chronic users (Tagliaro *et al.* 1998). They are also consistent with a London study, which shows that the occurrence of non-fatal overdose is not related to the frequency or quantity of heroin use (Gossop *et al.* 1996). On the other hand, the often-cited evidence that most fatal overdoses occur among regular heroin users (Darke & Zador 1996; Sporer 1999) does not necessarily mean that they had a greater risk of overdose than did sporadic users. In fact, this figure depends both on the proportion of regular users in the whole population of users and on the risk of fatal overdose among regular users. Nevertheless, the annual risk of overdose among daily heroin users is high (9.2% of study subjects had a non-fatal overdose requiring emergency care), and this may be partly because the tolerance to respiratory depression is lower and is reached more slowly than other opioids effects (White & Irvine 1999).

The higher overdose risk of injecting heroin has already been shown and explained in previous studies (Darke & Zador 1996; Gossop *et al.* 1996; Powis *et al.* 1999; Van Ameijden *et al.* 1999; Darke *et al.* 2000; Darke & Ross 2000). Sniffers and smokers are not risk-free (Sporer 1999; Darke & Ross 2000), but they are at a much lower risk of both overdose and of HIV infection (White & Irvine 1999). Therefore, it can be predicted that the transition from injecting to smoking or sniffing heroin will be accompanied by a sharp decline in heroin-related mortality, as seems to be occurring in Spain (Brugal *et al.* 1999; Delegación Del Gobierno Para El Plan Nacional Sobre Dogas 2000).

An increased cumulative risk of overdose in a period as the usual frequency of heroin injecting increases is seen clearly in the multivariate but not in the bivariate analysis, mainly because of the confounding effect of frequency of heroin use. In fact, both frequency of heroin injection and overdose are associated simultaneously with frequency of heroin use in the opposite direction, i.e. the risk of overdose decreases as frequency of use increases (negative association), and the frequency of use increases as the frequency of injection increases (positive association). The inability to control for this confounding effect may also explain the results of some studies in Amsterdam and Baltimore, showing a higher risk of death from overdose/suicide among heroin injectors than among non-injectors, with the highest risk among the more infrequent injectors (Van Ameijden *et al.* 1999), or with no significant differences by frequency of injection (Van Haastrecht *et al.* 1996; Van Ameijden *et al.* 1999).

The estimated RR of overdose for injecting heroin immediately before overdose versus heroin use by other routes, as calculated in the case–crossover analysis, can be considered an estimation of the transient (or very short-term) relative risk associated with injecting heroin (Delegación Del Gobierno Para El Plan Nacional Sobre Dogas 1996). The high transient risk in non-daily heroin users can be explained by the rapid entry into the blood of a large amount of heroin that overwhelms an organism's low capacity to compensate (tolerance level). This evidence, taken together with the increased cumulative risk of overdose with increasing usual frequency of

heroin injection, suggests the hypothesis that when heroin is only injected, each additional new injection increases the cumulative annual risk of overdose, but this marginal increase is lower for each new injection, at least until the frequency of daily injecting is reached. The very high transient risk of overdose for injecting heroin among non-daily heroin users also accounts for the fact that some groups of non-daily heroin users who occasionally injected this drug had an annual risk of overdose even higher than those who injected daily.

The differences in overdose risk between heroin sniffers and smokers have not, to our knowledge, been studied before. Previous studies have generally focused on differences between heroin injectors and non-injectors, perhaps because of the difficulties in recruiting sniffers or smokers. This is probably the first study to compare these two subgroups. The results show that among daily heroin users there are no differences in overdose risk between smokers and sniffers. However, among sporadic users the risk of sniffers was much higher than that of smokers. This finding cannot be explained by a higher frequency of heroin injection among sniffers than among smokers. Some possible explanations could be a lower capacity to self-regulate the absorbed dose when heroin is sniffed than when it is smoked, or a higher efficiency of heroin to reach the receptor sites in the brain when sniffed than when smoked.

Other factors associated with overdose

No increase in the risk of non-fatal overdose was found with increasing length of heroin use, after controlling for other risk factors. However, this may be different for fatal overdose, because long-term heroin users could accumulate other health problems which could increase their mortality risk when they overdose. Some mortality studies have found no statistically significant trend toward increasing risk of fatal overdose as length of heroin use increases (Van Haastrecht *et al*. 1996; Davoli *et al*. 1997). Nevertheless, the isolated evidence that most of those who die from overdose are old enough to have been using heroin for a long time (Darke & Zador 1996; Sporer 1999) does not mean that long-term users have a higher risk of non-fatal overdose than do short-term users.

The strong association of overdose with area of residence, even after controlling for other individual factors, shows the dangers of carrying out studies like this in a single city. This association would indicate that some ecological or supraindividual factors, which were not controlled for, may have been at play. One such factor could be the characteristics of the available heroin, particularly the variability in its purity. In fact, in Spain, important differences in purity have been detected among regions, with the North-east of Peninsular Spain and the Balearic Islands showing the highest levels (De La Fuente *et al*. 1996). These are precisely the areas that show the highest risk of non-fatal and fatal overdoses (Brugal *et al*. 1999; Delegación Del Gobierno Para El Plan Nacional Sobre Dogas 2000). Moreover, in these areas, unlike the rest of Spain, white heroin is predominant (Brugal *et al*. 1999). Other possible explanations for the regional differences may be differences in medical help-seeking behaviour or in psychosocial or behavioural risk factors that were not studied.

The association of overdose with the concurrent use of alcohol, tranquillizers or cocaine has already been well described in previous studies (Darke *et al*. 1996a; Van Haastrecht *et al*. 1996; Powis *et al*. 1999; White & Irvine 1999; Darke & Ross 2000), making it clear that polydrug use, especially CNS depressants, presents a greater risk of overdose than does single-substance use (Darke & Zador 1996). This is consistent with the evidence that many cases of apparent fatal overdose have blood levels of morphine no higher than those detected in heroin users who died from other causes or those who survived an overdose (Darke & Zador 1996; Sporer 1999; White & Irvine 1999).

The HIV+ heroin users who were diagnosed between 1982 and 1988 had a higher risk of overdose than those who were diagnosed later, but the HIV+ group as a whole did not show a higher risk than those who were HIV-. This could be explained by a higher susceptibility to overdose due to poor physical health, or by a higher frequency of risky or suicidal behaviours among long-term HIV+. This is in line with data from a Baltimore–Amsterdam study, in which patients with CD4 counts lower than $200/mm^3$ had a higher risk of fatal overdose than patients with higher CD4 counts (Van Haastrecht *et al*. 1996; Tagliaro *et al*. 1998). Data from other studies on this issue are contradictory (Van Ameijden *et al*. 1999).

Study limitations

The main limitations lie in the cross-sectional design of the study. There may be survival or recall biases. The variables that change over time may have been reported after the overdose, which limits causal inferences. The definition of overdose is self-perceived, which can produce misclassification. Nevertheless, the low non-response rate and previous studies (Darke & Zador 1996) suggest that users recognize overdoses well. In addition, since only overdoses involving emergency medial care were analysed, it is probable that less clear-cut clinical situations were excluded. When a subject had various overdoses, only the last one was analysed, but this is not a problem because results were similar for subjects with a single overdose.

The heroin users in this sample have similar characteristics to those reported to SEIT (Delegación Del Gobierno Para El Plan Nacional Sobre Dogas 1996) or those in street samples (De La Fuente *et al*. 1997, 1999). However, they may not be totally representative of all Spanish heroin users, because short-term users without important problems begin dependence treatment less frequently, and street samples also often fail to adequately represent newer heroin users. In any case, even if the sample was not representative, this would probably not affect the main study findings.

The case–crossover analysis has some advantages over the case–control analysis, because it eliminates confounding by characteristics of the subject that remain constant over time, it has a lower probability of selection bias and it is statistically more powerful (MacLure 1991; Redelmeier & Tibshirani 1997). However, there are some validity problems mainly derived from the study data. First, only the 168 subjects who attributed their overdose to heroin were asked about route of heroin administration before the overdose and analysed later. This might have resulted in biased estimates of RR if the remaining 88 subjects with overdose, who were not asked which heroin route of administration they used before the overdose, behaved differently from those studied. Secondly, we assumed an effect-period for heroin of 24 hours, because we did not know the number of heroin injections administered daily. This is an overestimation of the effect-period, but fortunately results only in a non-differential exposure misclassification, diluting the association (Delegación Del Gobierno Para El Plan Nacional Sobre Dogas 1996). Thirdly, this design does not eliminate confounding by characteristics of the subjects that change over time (MacLure 1991). For example, subjects may have more frequently used CNS depressants concurrently with heroin when this drug was injected before overdose than when it was not. However, when we conducted the analysis only for subjects who did not use these concurrent drugs before overdose the RR remained very high, with the mentioned differences between sporadic and daily heroin users. It is also possible that some subjects self-select times, circumstances or protective behaviours (not explored here) in order to minimize harmful effects. If that selection was related to route of heroin administration (for example, if they only injected heroin when it was of poor quality), a biased estimate of RR would result.

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