23 Bennish ML, Salam MA, Haider R, Barza M. Therapy for shigellosis. II. Randomized, double-blind comparison of ciprofloxacin and ampicillin. *J Infect Dis* 1990;162:711-6.
24 Wolbach SB, Howe PR. Tissue changes following deprivation of fat-soluble vitamin A. *J Exp Med* 1925;42:753-73.
25 DeLuca L, Little EP, Wolf G. Vitamin A and protein synthesis by rat intestinal mucosa. *J Biol Chem* 1969;244:701-8.
26 DeLuca L, Maestri N, Bonanni F, Nelson D. Maintenance of epithelial cell differentiation: mode of action of vitamin A. *Cancer* 1972;30:1326-31.
27 Olson JA. The biological role of vitamin A in maintaining epithelial tissues. *Isr J Med Sci* 1972;8:1170-8.
28 Zile M, Bunge E, Deluca HF. Effect of vitamin A deficiency on intestinal cell proliferation in rat. *J Nutr* 1977;107:552-60.
29 Nauss KM, Mark DA, Suskind RM. The effect of vitamin A deficiency on the in vitro cellular immune response of rats. *J Nutr* 1979;109:1815-23.
30 Chandra RK, Au B. Single nutrient deficiency and cell mediated immune responses. III. Vitamin A. *Nutr Res* 1981;1:181.
31 Hatchigian EA, Santos JI, Broitman SA, Vitale JJ. Vitamin A supplementation improves macrophage function and bacterial clearance during experimental salmonella infection. *Proc Soc Exp Biol Med* 1989;191:47-54.
32 World Health Organisation. *Programme for control of diarrhoeal diseases. Manual for laboratory investigations of acute enteric infections*. Geneva: WHO, 1983. (WHO/CDD/83.3)
33 Alam AN, Islam MR, Hossain MS, Mahalanabis D, Hye HKMA. Comparison of pivmecillinam and nalidixic acid in the treatment of acute shigellosis in children. *Scand J Gastroenterol* 1994;29:313-7.
34 Dupont WD, Plummer WD Jr. Power and sample size calculations: a review and computer program. *Controlled Clin Trials* 1990;11:116-28.
35 Sivakumar B, Reddy V. Absorption of labelled vitamin A in children during infection. *Br J Nutr* 1972;27:299-304.
36 Molla A, Islam A, Molla AM, Jahan F. Change in serum vitamin A concentration after an oral dose in children with acute diarrhoea. *J Pediatr* 1983;103:1000-2.
37 Reddy V. Absorption of vitamin A by children with diarrhoea during treatment with oral rehydration salt solution. *Bull WHO* 1986;64: 721-4.
38 Coutsoudis A, Kiepiela P, Coovadia HM, Broughton M. Vitamin A supplementation enhances specific IgG antibody levels and total lymphocyte numbers while improving morbidity in measles. *Pediatr Infect Dis J* 1992;11:203-9
39 Barker BM. Vitamin A. In: Barker BM, Bender DA, eds. *Vitamins in medicine*. Vol 2. 4th ed. London: Heinemann 1983:211-90.
40 Glaziou PP, Mackerras DEM. Vitamin A supplementation and infectious disease: a meta-analysis. *BMJ* 1993;306:366-70.
41 Barreto ML, Santos LMP, Assis AMO, Araujo MP, Farenzena GH, Santos PAB, et al. Effect of vitamin A supplementation on diarrhoea and acute lower respiratory infection in young children in Brazil. *Lancet* 1994;344:228-31.
42 Ghana VAST Study Team. Vitamin A supplementation in northern Ghana: effects on clinic attendances, hospital admissions and child mortality. *Lancet* 1993;342:7-12.
43 Henning B, Stewart K, Zaman K, Alam AN, Brown KH, Black RE. Lack of therapeutic efficacy of vitamin A for non-cholera, watery diarrhoea in Bangladeshi children. *Eur J Clin Nutr* 1992;46:437-43.
44 Campos F, Flores H, Underwood BA. Effect of an infection on vitamin A status of children as measured by relative dose response (RDR). *Am J Clin Nutr* 1987;46:91-4.
45 Stephensen CB, Alvarez JO, Kohatsu J, Hardmeier R, Kennedy Jr JI, Gammon Jr RB. Vitamin A is excreted in the urine during acute infection. *Am J Clin Nutr* 1994;60:388-92.
46 Danton H. Vitamin A deficiency in Bangladesh. *Health Policy Plann* 1988;3:205-13.

(Accepted 3 October 1997)

Mortality from overdose among injecting drug users recently released from prison: database linkage study

S R Seaman, R P Brettle, S M Gore

Medical Research Council Biostatistics Unit, Institute of Public Health, Cambridge CB2 2SR

S R Seaman, *PhD student*

S M Gore, *senior statistician*

Regional Infectious Diseases Unit, City Hospital, Edinburgh EH11 3XA

R P Brettle, *consultant*

Correspondence to: Dr Gore sheila.gore@mrc-bsu.cam.ac.uk

BMJ 1998;316:426–8

Abstract

Objective: To assess whether injecting drug users have a higher than usual risk of death from overdose in the 2 weeks after release from prison.

Design: Soundex coding of surnames and information on date of birth were used to link entry and release dates from the local prison between 1983 and 1994 with clinical data from Edinburgh City Hospital's cohort of male injecting drug users who are infected with HIV.

Setting: Edinburgh City Hospital and Edinburgh Prison.

Subjects: 316/332 male injecting drug users infected with HIV in the City Hospital HIV cohort; 16 were excluded because they were enrolled after developing AIDS or because their precise date of death was not available.

Main outcome measure: Relative risk of dying from overdose before developing AIDS and relative risk of dying of all causes before developing AIDS during the 2 weeks after release from prison; this was compared with relative risks of death during other time at liberty.

Results: 238/316 (75%) injecting drug users served time in the prison between 1983 and 1994. 33 out of 316 injecting drug users who were infected with HIV died before developing AIDS during 517 177 days at risk. 20 of these men died of an overdose; 6 of these deaths occurred within 2 weeks of release during 5903 days at risk. Death rates from overdose before the development of AIDS were 1.02/1000 days during the 2 weeks after release (recently released) and 0.029/1000 days during other times of liberty. The relative risk of death from overdose became 7.7 (1.5 to 39.1) after temporal matching (when the comparison was limited to the first 2 weeks after release *v* the next 10 weeks). The crude relative risk in an analysis combining stratified prison term and the 2 weeks after release was 4.5 (1.7 to 11.7) for death from overdose. After temporal matching these risks became 1.8 (0.4 to 9.2).

Conclusion: Prisons should evaluate interventions to reduce the risk of death from overdose after release.

Introduction

The risk of death from overdose may be greater in injecting drug users who resume drug use after a period of abstinence during which their tolerance may have declined.[1] Imprisonment is an enforced period of abstinence from, or may lead to a radical reduction in, drug use.[2] We investigated the risk of death from overdose among male injecting drug users in the Edinburgh City Hospital HIV cohort[3] in the 2 weeks after release from the local prison and compared the risk with that of death from overdose at other times.

Subjects and methods

An alphabetical and soundex coded list of 704 names and dates of birth was compiled by RPB. The list included all male patients infected with HIV in the Edinburgh City Hospital cohort (injecting drug users who used mainly heroin, drug users who did not inject drugs, and patients who did not use drugs) and male

patients at the regional infectious diseases unit who were not infected with HIV (injecting drug users who used mainly heroin, drug users who did not inject drugs, and patients who did not use drugs). The list did not identify whether the men were injecting drug users or were infected with HIV.

Edinburgh Prison keeps records on all inmates. These records give each inmate's dates of entry to and departure from the prison. SMG searched for records for each name on the list. When a record was found all dates of entry and departure between 1983 and 1994 were entered by SRS on to a database that was indexed by soundex code and date of birth but did not include names. Two validation checks evaluated the completeness of searching and accuracy of transcribing information (details on request).

The list of names was destroyed. Only soundex codes and dates of birth were used by SRS to link the prison database with the HIV clinical database up to 30 September 1994 for injecting drug users who were infected with HIV. This method was designed to avoid RPB knowing whether his patients had spent time in prison, but a difficulty arose. On re-reading this paper, RPB remembered that one of his patients who was an injecting drug user had committed suicide in the prison between 1983 and 1994. The study database was checked using the soundex code and date of birth provided by RPB. The man had committed suicide before he developed AIDS, but we had no record of him having spent time in prison. It is possible that because of the circumstances of his death his record card had been moved to a special file. This has no effect on our estimates of overdose deaths, but does mean that our estimates of the relative risk of all deaths occurring before the development of AIDS are conservative.

Patients were assumed to be at risk of dying of an overdose from the time of enrolment in the Edinburgh City Hospital HIV cohort until censoring at the time of development of AIDS, at 30 September 1994, or at 31 March 1994 if they had been lost to follow up for more than 6 months and were not known to have developed AIDS or died. Total mortality and mortality from overdose before developing AIDS during the 2 weeks after release from prison (recent release) were compared with the same death rates during other time outside prison (other liberty). Relative risks were obtained from Cox's proportional hazards models adjusted for age and CD4 count for the crude comparison, stratified to account for the frequency of imprisonment, or temporally restricted to the first 12 weeks after release to allow comparability of injecting habits.

Results

Data from 316 out of 332 male injecting drug users infected with HIV in the City Hospital cohort were analysed. Sixteen were excluded because they were enrolled after they developed AIDS or because no precise date of death was available.

Crude comparison

Among the 316 injecting drug users infected with HIV, 33 died before developing AIDS (20 from an overdose); 238 (75%) of them had spent time in the prison between 1983 and 1994. Eight deaths occurred among injecting drug users for whom no prison terms were recorded. We later realised that one of these men had committed suicide while in prison (see Subjects and methods). Of the 33 deaths, three occurred within 2 days of release, two at 5 days after release, and one death each at 9, 12, 66, and 74 days after release. The remaining deaths occurred more than 100 days after release.

Of the seven deaths that occurred within 2 weeks of release (during 5903 days at risk), six were caused by overdose (1.02 deaths from overdose/1000 days during the 2 weeks after release) and the seventh resulted from injecting into an artery. Of the 26 deaths that occurred later (during 478 245 days at risk), 14 were caused by overdose (0.029 deaths from overdose/1000 days during the 2 weeks after release). Compared with other time spent outside prison the risk ratio for all deaths occurring before the development of AIDS for those recently released was 22 (95% confidence interval 9 to 50), and for deaths caused by overdose was 35 (13 to 90). The table shows the corresponding crude relative risks adjusted for age and CD4 count alone.

Crude and adjusted Cox's relative risks (95% confidence interval) of death from all causes and from overdose among injecting drug users in first 2 weeks after release from prison

Death before development of AIDS	Crude	Stratified*	First 12 weeks after release
All causes†:			
First 2 weeks after release from prison	23.1 (9.6 to 55.8)	17.6 (5.9 to 53.0)	9.4 (1.9 to 46.0)
From overdose:			
First 2 weeks after release from prison	34.2 (12.3 to 94.6)	18.5 (5.4 to 64.0)	7.7 (1.5 to 39.1)
In prison or during first 2 weeks after release	4.5 (1.7 to 11.7)	3.1 (1.7 to 5.7)	1.8 (0.4 to 9.2)

*Stratified by average number of terms spent in prison.
†This is a conservative estimate. See Subjects and Methods.

Adjusted comparisons

Heavier drug use could cause increased risks of both imprisonment and overdose. Two methods were used to investigate this.

Firstly, to account for heterogeneity in the frequency of imprisonment, injecting drug users were stratified into three groups according to the average number of prison terms they served each year. (This was the ratio of the number of prison terms served by each subject to the number of years between 1983 and 1994 or to the number of years between 1983 and time of death if earlier.) The first group consisted of injecting drug users with at least one prison term but a ratio of <0.8; the second group consisted of those with a ratio of between 0.8 and 1.5; and the third group consisted of those with a ratio >1.5. These cut off points were chosen so that the total number of prison terms served by injecting drug users in each group was the same. The pooled relative risk of overdose was 18.5 (5.4 to 64.0) (table).

Secondly, we compared the risk of dying from an overdose before developing AIDS during the 2 weeks after release with the risk of dying from an overdose during the 10 weeks that followed so that only the eight deaths from overdose that occurred within 12 weeks of release were critical; periods of recent release and other time spent outside prison were thus more comparable in terms of patients' injecting history. The relative risk of overdose was reduced to 7.7 (1.5 to 39.1).

To account for the fact that no deaths from overdose occurred in prison, recent periods of release were analysed with the prison terms to measure the

Key messages

- Overall, imprisonment does not seem to increase injecting drug users' risks of dying from an overdose
- Between 1983 and 1994 the risk of death from overdose was eight times higher within 2 weeks after release from prison among injecting drug users infected with HIV than it was during the next 10 weeks after release
- Further studies will need to determine if the estimate of 1 death from overdose per 1000 days spent recently released can be generalised to those who are not infected with HIV, and to dependent drug users who do not inject drugs
- Deaths from overdose occurring in the 2 weeks after release from prison may outnumber the deaths from suicide in Scottish prisons by 3 to 1
- Lives could be saved by implementing prison based, randomised trials of interventions to reduce the number of deaths from overdose that occur soon after release

effect of the entire prison experience. With the second method of adjustment, the relative risk of death from overdose was 1.8 (0.4 to 9.2).

Discussion

For injecting drug users infected with HIV the risk of death from overdose during the 2 weeks after release from prison was 34 times higher than during other time spent outside prison; the risk of death from any cause before developing AIDS was 23 times higher. The estimated relative risk for dying from an overdose was reduced to about 8 when temporal matching was used to control for heterogeneity in drug use by restricting analysis to the next 10 weeks after release; when prison term and the 2 weeks immediately after release were analysed together this risk became 1.8 and was no longer significant. Prison may not markedly increase the overall risk of injecting drug users dying from an overdose, but the time immediately after release is one of intensified risk, probably caused by a decrease in tolerance to drugs as a result of less frequent injecting while in prison or the lower purity of drugs found in prison.

The Scottish Prison Service has approved an additional study to determine whether the relative risks found in this paper can be generalised to the present, to those who are not infected with HIV, and to dependent drug users who do not inject. Results from a Dutch study, however, suggest that the absolute risk of death from overdose may be lower in injecting drug users who are not infected with HIV.[4] We took the findings of the Dutch study into account to estimate conservatively the number of deaths caused by overdose among men recently released from prison and compared this with the number of suicides in prisons in Scotland.

About 36 000 prisoners are released each year from Scottish prisons.[5] Five sixths of all inmates are men aged <35,[6] and 30% of male prisoners have a history of injecting drugs.[7] We estimate that 9000 of those released each year are male injecting drug users aged <35 ($36\,000 \times 5/6 \times 0.3$). Extrapolation to all of Scotland of the death rate from overdose during the 2 weeks after release that we found in this paper leads us to predict that 126 deaths from overdose each year would occur soon after release among male injecting drug users aged <35 ($9000 \times 0.001 \times 14$). If the relative risk of death from overdose during this time is about 8, then one eighth of these deaths would have occurred anyway; this leaves 110 deaths apparently resulting from the transition from prison to the community. This number may be too high as the mortality from overdose among injecting drug users not infected with HIV may be only one third of that of injecting drug users who are infected with HIV.[4] However, even if the excess number of deaths from overdose soon after release is only 37 rather than 110, this is still more than three times the annual suicide rate of 11 found in Scottish prisons between 1992 and 1997.[5]

Prison services might reduce the risk of recently released inmates dying from overdose by implementing randomised evaluations of interventions—such as providing an information sheet to prisoners who are about to be released, obtaining permission from the inmate for communication between the prison doctor and the inmate's general practitioner, or providing an appointment for inmates before they are released with prison healthcare staff.[1] In the United Kingdom random mandatory drug testing identifies over 3000 prisoners each year who use opiates while in prison (not all of them are injecting drug users). These inmates could be randomised by the prison governor at the time of identification of their drug use inside prison to one or more active interventions. The effectiveness of the interventions could be compared by telling the registrar general which prisoners had been randomised so that any deaths would be notified; this would allow determination of which interventions were successful in bringing about a 50% reduction in deaths from overdose occurring immediately after release. Such a trial would be proactive, inexpensive, and simple to run. It would last 1 to 3 years and would introduce all prison governors to the advantages of randomised trials.

Clive Fairweather, the chief inspector of prisons for Scotland, provided inspiration for the comparison of deaths from overdose among recently released inmates with death by suicide in prison; he noted that prisoners could recall many more names of drug users who had died from overdose shortly after being released than of inmates who had committed suicide in prison.

Contributors: RPB manages the Edinburgh City Hospital cohort of patients with HIV, classified the deaths, and participated in designing this study. SMG participated in designing the study, in extracting the data from prison records, and is guarantor for the study. SRS participated in extracting the data from prison records and performed the statistical analysis.

Funding: Medical Research Council grant G9102b32.

Conflict of interest: None.

1 Strang J, Darke S, Hall W, Farrell M, Ali R. Heroin overdose: the case for take-home naloxone. *BMJ* 1996;312:1435.
2 Bird AG, Gore SM, Hutchinson SJ, Lewis SC, Cameron S, Burns S. Harm reduction measures and injecting inside prison versus mandatory drug testing. *BMJ* 1997;315:21-4.
3 Brettle RP, McNeil AJ, Gore SM, Bird AG, Leen CSL, Richardson A. The Edinburgh City Hospital cohort: analysis of enrolment, progression and mortality by baseline covariates. *Q J Med* 1995;88:479-91.
4 Van Haastrecht HJA, van Ameijden EJC, van den Hoek JAR, Mientjes GHC, Bax JS, Coutinho RA. Predictors of mortality in the Amsterdam cohort of human immunodeficiency virus (HIV)-positive and HIV-negative drug users. *Am J Epidemiol* 1996;143:380-91.
5 Fairweather C. *Her Majesty's chief inspector of prisons for Scotland: report for 1996-7*. Edinburgh: Inspectorate of Prisons for Scotland, 1997.
6 Bird AG, Gore SM, Cameron S, Ross AJ, Goldberg DJ. Anonymous HIV surveillance with risk factor elicitation at Scotland's largest prison, Barlinnie. *AIDS* 1995;9:801-8.
7 Gore SM, Bird AG. Cross-sectional willing anonymous HIV salivary (WASH) surveillance studies and self-completion risk factor questionnaire in establishments of the Scottish Prison Service. *ANSWER (AIDS News Supplement to the Weekly Report of the Scottish Centre for Infection and Environmental Health)* 1995; No 39:1-3.

(Accepted 30 December 1997)