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RESEARCH REPORT

Methadone maintenance and hepatitis C virus infection among injecting drug users

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Abstract

Harm reduction strategies for the prevention of transmission of human immunodeficiency virus (HIV) transmission among injecting drug users (IDUs) have been widely implemented in Australia and are seen to have been effective in preventing the spread of HIV. A major strategy has been increasing the availability of and accessibility to methadone maintenance therapy (MMT) programmes. We have reviewed the experience of a major MMT general practice with hepatitis C virus (HCV) infection from 1991 to 1995. Of 1741 individuals tested for HCV antibodies at least once 66.7% were positive. Of 73 IDUs who were initially seronegative and were retested at least once, 19 were subsequently seropositive. Seroconverters to HCV were younger than non-seroconverters, and were more likely to have evidence of previous hepatitis B infection. The overall HCV incidence rate was 22 cases per 100 person-years, and this did not differ between those on MMT programs (continuous or interrupted) between HCV tests and those not on MMT. These findings suggest that the role of MMT in the control of the spread of HCV infection among IDUs needs further assessment, and that control of the current epidemic of HCV infection among IDUs in Australia will be very difficult.

Introduction

There is evidence that spread of the human immunodeficiency virus (HIV) among injecting drug users (IDUs) has been slowed or prevented in some places over the last decade,[1] generally by the application of the principles of what has become known as 'harm reduction'.[2] In their successful application, harm reduction strategies have relied on multifaceted approaches rather than single measures, directed towards decreasing sharing of contaminated injecting equipment. Strategies include needle and syringe distribution and exchange, education about and provision of the means for disinfecting injecting equipment, and efforts to decrease the frequency of injecting among IDUs, leading to decreased sharing opportunities.[3] In many western countries, including most jurisdictions in Australia, prime among these last has been methadone maintenance therapy (MMT).

In Victoria, Australia (population 4.3 million) sterile injecting equipment is widely available

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through government-funded needle and syringe distribution programmes (167 free outlets) and through approximately 70% of the State's 1300 pharmacies (Geoff Milne, Department of Human Services, personal communication). MMT is also freely available and accessible, through formal drug treatment programmes and through general practices and private pharmacies; up to 3200 people were on a programme at any time during 1992–94 and waiting times to enrol in a programme were generally less than one day (Mark Blackburn, Department of Human Services, personal communication). The proportion of injecting drug users estimated to be currently infected with HIV in Victoria is estimated as less than 4%;[4] only 130 IDUs (not including homosexual men with histories of injecting drug use) had been diagnosed with HIV infection, of whom 23 had developed AIDS, to the end of March 1996,[5] in an estimated population of between 50,000 and 80,000 IDUs (pers. comm., Geoff Milne, Department of Human Services). Exposure to the hepatitis C virus (HCV) is, however, much more common: 68% of entrants to a prospective follow-up study of field-recruited IDUs in 1990–91[6] and 64% of prison entrants who gave a history of IDU in 1991–92[7] in Victoria had antibody to HCV. Incidence of HCV infection was 19.6 cases per 100 person-years (py) in the former and 38 per 100 py among prison entrants aged less than 30 years who gave a history of injecting drug use in the latter, indicating continued spread of bloodborne viruses in Victorian IDUs.

MMT has been shown to decrease injecting drug use[8] and to decrease HIV transmission among IDUs where doses are high enough to significantly reduce needle use.[9] There is an urgent need for strategies to control the continuing spread of HCV. Given its much higher prevalence in this population, with much higher incidences and higher efficiencies of transmission,[10] it cannot be assumed that harm reduction strategies which have been effective for control of HIV infection among IDUs will work unmodified for HCV. Calls for increases in MMT programmes to control HCV transmission among IDUs are premature; the programmes must be re-evaluated for their effectiveness in diminishing spread of HCV. As part of this process, we have therefore begun to assess the impact of MMT on the transmission of HCV among IDUs, and report here the first observational results from this research. Does MMT have a role in the control of HCV infection among IDUs, and does it need to be delivered differently as part of an HCV control programme?

Methods

We selected a large and busy general practice in inner metropolitan Melbourne, in an area renowned for high concentrations of IDUs. As well as general primary care, the clinic provides supervision of methadone maintenance therapy to 500–600 clients annually; strict abstinence among methadone maintenance patients is not enforced. Since 1990, testing for HCV antibody has been routinely performed when patients start or restart methadone. For patients not on methadone, the need for HCV testing is determined by the clinical judgement of the individual doctors, with no set protocol for when HCV testing should be performed or repeated. Minimal demographic data (date of birth, gender, postcode of current residence) has been collected at the testing laboratory on all patients tested. These data were reviewed to describe patterns of diagnosis of HCV infection at this practice, and to identify patients who had had repeat testing for HCV. Patients who had had repeat testing and were initially seronegative were included in the second part of the study, classified into seroconverters and non-seroconverters: the former being initially seronegative, and seropositive on a subsequent test, and the latter remaining seronegative for two or more tests. Only tests conducted using second generation anti-HCV assays were included in this analysis (Abbott Laboratories, Chicago, ILL). The histories of all patients who were classified after this process as initially seronegative and subsequently retested on at least one occasion were retrieved where possible and reviewed in detail for: age at seroconversion or at the last negative hepatitis C test, the number of years of injecting drug use prior to seroconversion or the last negative test, the interval between hepatitis C tests, evidence of either an elevated ALT or seroconversion illness, the pattern of methadone use before, between or after the first and last tests, written evidence in the medical file of injecting drug use between tests, evidence of injecting drug use based on urine testing while on methadone between tests, and dosages of methadone administered. Information mentioned in some but not all histories included

Table 1. *Testing for, diagnosis of and incidence of hepatitis C virus infection at the Barkly St Clinic, January 1991 to December 1995*

	1991	1992	1993	1994	1995	Total
Testing for anti-HCV						
Number of people tested	439	492	469	318	263	1981
Number of first tests	430	440	403	258	210	1741
Mean age at first test (SD)	32.9 (6.8)	33.8 (6.5)	32.1 (6.6)	31.8 (6.7)	30.3 (6.7)	32.5 (6.8)
Proportion first tests male (%)	*59.3*	*58.4*	*58.3*	*59.6*	*52.3*	*58.1*
Diagnosis of HCV						
Proportion first tests + ve (%)	*71.1*	*75.2*	*67.2*	*55.8*	*50.0*	*66.5*
Male:female ratio (positives)	1.57	1.38	1.30	1.36	1.28	1.40
Mean age (years) (SD)	34.3 (6.8)	34.8 (6.1)	33.2 (6.6)	33.7 (6.7)	33.0 (6.4)	34.1 (6.6)
Seroconverters						
Person-years of follow-up	6.0	19.3	26.4	24.5	9.2	85.4
Number of seroconverters*	1	6	2	3	7	19
Incidence rate (95% CI):						
by year of diagnosis	16.6 (2.3, 118)	10.3 (4.6, 23)	22.7 (5.7, 91)	12.2 (3.9, 38)	76.0 (36, 159)	22.2 (14.2, 34.8)
by mid-point**	33.3 (8.3, 133)	10.3 (4.6, 23)	34.0 (18, 65)	24.0 (11, 53)	—	

*By year of diagnosis; **by mid-point between last negative and first positive tests.

Table 2. *Seroconversion rate to HCV among IDUs at Barkly St Clinic, by methadone maintenance therapy (MMT) program status, 1991 to 1995*

	Continuous MMT	Interrupted MMT	Not on MMT
Number	25	26	22
Person-years observation	24.4	42.3	18.7
Number of seroconverters	9	6	4
Cumulative incidence rate	36.9	14.2	21.4
95% CI	19.1, 70.9	6.3, 31.6	8.0, 57.0

previous methadone use and previous history of participation in drug treatment programs. All information removed from the premises of the clinic was coded to protect the identities of the patients. No information from outside the clinic was reviewed, and patients were not contacted for further information or for clarification of information obtained in the history. Details of the histories of seroconverters and non-seroconverters were compared to identify factors which differentiated those at risk of HCV infection from those not becoming infected in the same time period.

Data were coded and analysed using EpiInfo Version 5.00. This study was approved by the Ethics Committee of the Department of Health and Community Services, Victoria.

Results

There were 1981 tests for antibody to hepatitis C on 1741 individuals between January 1991, (when testing with the second generation assay began at this clinic) and December 1995. Of these, 1157 people (66.5%) were initially seropositive. This proportion was the same for males (674/1010, 66.7%) as for females (483/730, 65.3%). On average those who were HCV antibody positive were 5.2 years older than those who were negative (34.7 years, SD 6.5, *cf.* 29.5 years, SD 6.1, $p < 0.001$).

The number of tests and of first tests remained reasonably constant from 1991 to 1993, and thereafter both declined (Table 1). Mean age at first test and the proportion of those being tested who were male did not change substantially over this period. However, the proportion of those being tested for the first time who were seropositive did decrease substantially from 1991 to 1995, from 71.1% to 52.3% (χ^2 for trend, $p < 0.001$). The ratio of males to females among the first positive tests declined somewhat through this period, from 1.57:1 to 1.28:1, but this did not account for the overall decline in seropositivity as there was no significant difference in prevalence between males and females for any year. Mean age at diagnosis also did not change over the period.

During the 5-year period there were 73 people whose first test was negative and who had a subsequent test. Of these, a subsequent test result was positive for 19 (26%). The cumulative period between tests for these 73 was 85.4 years, so the overall incidence in this group was 22.2 seroconversions per 100 py (95% CI 14.2, 34.8). The annual seroconversion rate is shown in Table 1, calculated by two different methods; there is great annual variation because of small numbers, but the annual rate is generally between 10 and 35 infections per 100 py, with no indication of a trend.

Of the 73 initially seronegative people, about equal proportions were on continuous MMT from before the last negative test to after the first positive, on interrupted MMT or not on MMT at any stage (Table 2). There was no significant difference in cumulative incidence rate over the 5 years between the three groups.

Seroconverters were on average younger at first injection and at first HCV test, and were more likely to have been exposed to hepatitis B (Table 3). Otherwise they did not differ from non-seroconverters, especially in the proportions on MMT, the doses of methadone or the concurrent use of heroin between tests whether on methadone or not.

Of the 19 seroconverters nine had elevated ALT levels at some time, in three of whom ALT levels reached more than three times the upper limit of normal. These three also reported nausea, vomiting and lethargy but jaundice was not reported or observed. Of the non-seroconverters,

Table 3. *Comparison of seroconverters to HCV and non-seroconverters at Barkly St Clinic, January 1991 through December 1995*

	Seroconverters	Non-seroconverters	*p* value for difference
Number	19	54	
Proportion male	47.4%	53.7%	NS
Mean age (years) (SD) at first injection	21.7 (4.5)	25.2 (6.6)	0.01
Mean age (years) (SD) at first HCV test	29.2 (4.3)	32.8 (6.3)	0.09
Mean length of IDU (years) (SD)	7.5 (3.2)	7.9 (2.9)	NS
Previous exposure to hepatitis B	6 (31.6%)	5 (9.2%)	0.03
Altered LFTs	9 (47.4%)	5 (9.2%)	0.001
Methadone:			
mean starting dose (mgs) (SD)	33.9 (16.4)	35.3 (15.5)	NS
mean maximum dose (mgs) (SD)	44.5 (18.4)	49.2 (22.4)	NS
On methadone between HCV tests			
continuous	9	16	
interrupted	6	20	
total	15	36	
Never on MMT between tests	4	18	NS
Evidence of heroin use between tests	17 (89.5%)	50 (92.6%)	NS

NS: not significant at f = 0.05 level.

five had, at some point, an elevated ALT measurement, none greater than three times the upper limit of normal, and none had symptoms suggestive of acute hepatitis.

Discussion

In a review of testing for HCV infection at a general practice with a large group of patients on methadone maintenance therapy, we have found a very high proportion infected with HCV, a very high incidence of HCV infection among those initially seronegative and retested, and evidence of IDUs becoming infected with HCV while on MMT at the same rate as those not on MMT. Other studies have also found high seroprevalences of HCV antibody among IDUs on methadone programmes,[11–15] and an association of HCV seropositivity with having been on a methadone programme, at least for female IDUs.[6] IDUs who became infected with HCV in this study were younger, had begun injecting drugs at a younger age and were more likely to have serological evidence of past infection with HBV. These observations are also in keeping with existing data, comparing HCV positive and negative IDUs.[4,7]

Non-seroconverters in this study were just as likely while on MMT to have evidence of continuing injecting drug use documented in their histories and to have urine specimens positive for opiates as were seroconverters. Non-seroconverters were also as likely to be on methadone continuously, and to have gaps in methadone maintenance therapy. As there is no set policy for retesting HCV negative methadone patients unless they restart methadone, it is likely that the non-seroconverters identified by this study are not representative of all methadone patients who remained seronegative, many of whom were perceived to have no reason to be retested. This provides the major weaknesses of this exploratory study, in that investigation for HCV serostatus was not routine, and as a result sample size of those in whom incidence could be measured was small and potentially biased. In contrast to our results, one Italian study has found that participation in a methadone maintenance programme may have provided some protection from HCV infection, but comparison of such programmes between countries is difficult.[16]

In general, methadone patients who seroconverted often had gaps in methadone therapy or had evidence of some injecting drug use between HCV tests. Some were infected prior to first starting methadone, and methadone maintenance therapy could not have been expected to prevent these infections. In order to determine factors which differentiate seroconverters from non-seroconverters, a policy needs to be adopted of screening all methadone maintenance patients

regularly in order to obtain a truly representative seronegative control group. Such a policy will give a more accurate estimate of the incidence of seroconversion among all methadone maintenance patients, and is perhaps justified on clinical grounds given the high likelihood of HCV infection in these patients, and the probability that this acute infection will be asymptomatic.

Evidence strongly suggests that MMT programmes decrease frequency of injecting, and less strongly that they decrease risk of HIV infection, among IDUs.[9] In a study where individuals on a waiting list for a formal methadone programme were randomized to receive either counselling and urine testing alone, or methadone plus counselling and urine testing, 88% of the control group compared to 33% of the methadone group were injecting drugs at the time of entry into the formal methadone programme.[17] In another study, 71% of individuals who were still on a methadone maintenance program after 1 year had given up injecting drug use and 10% reported sharing needles during the study period while 82% of individuals who left the programme within 1 year of starting were still injecting drugs with 27% sharing needles.[18] A clear relationship has been demonstrated between methadone dose and frequency of injecting.[19] On the other hand, even long-term retention in MMT does not guarantee cessation of injecting drug use. In another study, of subjects who had been on MMT for an average of 70.9 weeks, 82% had injected a street drug in the past month, and 20% had shared needles with one other person. While these subjects were knowledgeable about HIV, this did not necessarily translate into behaviour change.[20]

There is a challenge in these data for those attempting to control the spread of HCV among IDUs. The simple provision of methadone to IDUs at risk of infection with or of transmitting HCV is not necessarily prophylactic against HCV transmission occurring. Does methadone maintenance *diminish* this risk? Are the differing characteristics of differing methadone programmes which have an impact on HIV transmission the same for HCV transmission?[21] In addition to providing methadone, patients who are seronegative for HCV must be counselled in depth about the very likely danger of becoming infected with HCV (as well as the smaller risk of becoming infected with HIV) in the face of continuing risk-taking behaviour. Patients who are seropositive for HCV need counselling about all aspects of their infection, including methods to minimize the risk of further transmission. This counselling must emphasize not sharing *any* injecting equipment or allowing any blood contamination of objects or surfaces which can carry the virus to others; this is relevant for both HCV-infected and uninfected individuals, as there is some suggestion of possible reinfection with other genotypes. This information should also be carried in targeted education campaigns for IDUs.

It is clear that despite low HIV rates among IDUs in Australia, HCV continues to spread at high rates in the same populations. Our data suggest that the role of MMT in slowing that spread requires further examination, in two ways: first, the majority of IDUs have already been exposed to HCV by the time they enter a methadone programme and secondly, the prevalence and infectiousness of HCV are so great as to virtually require total avoidance of injecting to significantly decrease risk of transmission. While a dose–response gradient may exist for methadone maintenance and HCV infection (as for HIV infection), these data do not support this and suggest that it may only exist at the highest levels of methadone dosage. On average participants in this MM programme were receiving doses of methadone below those associated with complete cessation of injecting. These data are yet further evidence that the epidemic of HCV infection among Australian IDUs will prove extremely difficult to contain, and requires the strongest commitment and action to do so.

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