Unsafe Injections and the transmission of Hepatitis B and C in a periurban community in Pakistan

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Following reports of frequent deaths associated with jaundice and chronic liver disease among adults in a periurban community of Karachi, Pakistan, an investigation was conducted to evaluate the relationship between injections and viral hepatitis infections, to identify the reasons why patients received frequent injections, and to observe the injection practices employed in clinics. Two hundred and three adult patients were interviewed as they left each of the 18 area clinics. Practitioners were interviewed and three consecutive injections were observed at each clinic. Eighty-one per cent of patients received an injection on the day of the interview. Of the 135 patients who provided a serum sample, 59 (44%) had antibodies against hepatitis C virus and 26 (19%) had antibodies against hepatitis B virus. Patients who received more injections were more likely to be infected with hepatitis C. If oral and injected medications were equally effective, 44% of patients preferred injected medication. None of the practitioners knew that hepatitis C could be transmitted by injections. Non-sterile syringes and needles that had been used earlier in the day on other patients were used for 94% of the observed injections. Interventions to limit injections to those which are safe and clinically indicated are needed to prevent injectionassociated infections in Pakistan and other low-income countries.
Keywords: hepatitis B, transmission; hepatitis C, transmission; injections, adverse effects; epidemiological studies; Pakistan.

Introduction

Hepatitis C virus (HCV) is a blood borne pathogen responsible for a substantial proportion of cases of post- transfusion hepatitis, liver cirrhosis and hepato-cellular carcinoma.[1,2] The most commonly identified routes of HCV transmission in developed countries include intravenous drug use, blood transfusions, haemodialysis, needle-stick injuries among health professionals, tattooing, sexual intercourse and perinatal infections.[3-8] In developing countries, there use of needles and syringes without sterilization for therapeutic injections has been implicated as a vehicle for transmission of blood- borne organisms including hepatitis B virus (HBV), human immunodeficiency virus (HIV), Ebola virus, Lassa fever virus, and HCV.[9-15]

In 1993 a community-based survey in Hafizabad, Pakistan, found the prevalence of antibody against HCV to be 6.5%, and a follow-up case-control study showed that patients infected with HCV were seven times more likely than control store port averaging ten or more therapeutic injections per year in the previous ten years.[13] The study design did not permit assessment of the practices of health care providers or their perceptions regarding the potential risks of needle reuse.

In 1995 we received reports of increasingly frequent deaths of adults which were associated with jaundice and chronic liver disease in Darsano Channo, a pen urban agricultural community of Karachi

over 1100 kilometres from Hafizabad. These reports led us to conduct an investigation in to the relationship between hepatitis infections and injections, the reasons why patients received frequent injections, and the injection practices employed in clinics.

Methods

Setting

Darsano Channo is a periurban sub-district 20 kilo- metres north-east of Karachi, comprising nearly 30 village centres with, according to the most reliable estimate available, approximately 13000 people of Sindhi and Balochi descent. The primary source of income for most families is agricultural labour on land owned by a small number of landowners; a small proportion of educated men are employed by the government in local service or in Karachi. The adult population is largely unable to read or write.

Design

On five days in January 1995 a group of final year medical students from the Aga Khan University approached consecutive patients as they left 18 health clinics in Darsano Channo. If the patients consented and were at least 20 years of age the students administered a structured questionnaire on presenting health complaints, injections given on the day and previously, and attitudes towards injections. A blood specimen was collected from each patient who gave informed consent. Patients aged 20 or more were enrolled to provide sufficient data for statistical analysis, a previous study in Pakistan having demonstrated that HCV infection increased markedly with age.[13]

The study team asked the health care providers at the clinics about their qualifications, work experience, patient turnover and injecting practices. A questionnaire asked the practitioners to state the common medical indications for which they prescribed injections, the types of injectable drugs prescribed why they preferred injectable drugs over oral forms and the diseases likely to be transmitted through the reuse of non-sterile needles. A structured form was used to record observations made on three consecutive patients who received injections in each clinic. This number was chosen because of the limited time and numbers of observers, the desire to make observations in all the clinics, and the expectation that three observations per practitioner would give an adequate picture of routine practice.

Three periods of patient exposure to therapeutic injections were considered: the 12 months preceding the study, i.e.1994; 1989 to 1993; and, for persons aged 30 or more, 1978 to 1988. Respondents were asked to report their average number of yearly injections in the following categories: zero, 1-4, 5-10 and more than ten.

Laboratory procedures

Serum was separated and stored at-7OoC at the laboratory of the Aga Khan University Hospital. HCV infection was defined as the presence of serum HCV antibodies detected by a third-generation enzyme-linked immunosorbent assay (Abbott EIA).Because the prevalence of HCV infection in the study population was much higher than expected we selected a random sample often HCV antibody-positive aliquots and repeated the HCV antibody test from a different batch of kits. We also tested the serum for antibodies against HBV core antigen (anti-HBc, Abbott EIA).We interpreted the presence of anti-HBc as evidence of past HBV infection.

Statistics

Interview forms were coded and double-entered into Epilnfo software.[16] We compared the prevalences of infection between groups on the basis of X2 prevalence ratios and used the w-test and Yate's corrected P-values to evaluate statistical significance, with Taylor Series 95% confidence limits. The w-test for linear trend was employed to evaluate the relationship between current infection and number of injections overtime.

Results

Patients

We interviewed 203 patients aged at least 20 years as they left the clinics. Their mean age was 36 years (range 20- 80); there were 127 females (63%) and 76 males (37%). The mean ages for females and males were 35 and 37 years respectively. Seventy-six percent of the females were house wives and 55% of the males were involved in agricultural labour; 75% of the females and 54% of the males were unable to read or write.

One hundred and thirty-five patients (67%) agreed to provide a serum sample. The sex distribution (63% male versus 62% female) and mean age (38 versus 35 years)of those who refused to give a blood sample and those who agreed were similar. Of the females and males who did not provide a serum sample, 90% and 69% respectively could not read or write.

Of the 135 serum samples procured and tested, 59 (44%) had antibodies against HCV and 26 (19%) had antibodies against HBV core antigen. Forty-three of 85 females (5 1%) and 16 of 50 males (32%) were infected with HCV (prevalence ratio=1.6, P = 0.05). Compared to patients aged 20-24 years, all older age groups were 4 to 6 times more likely to be infected with HCV. The prevalence of anti-HBc antibodies did not differ significantly by sex or age group (Table 1).

Table 1. Prevalence of antibodies to hepatitis C and hepatitis B core antigen by age group and gender in 135 patients leaving clinics in Darsano Channo, 1995.

	Positive for HCV antibody n (%)				Positive for anti-HBV core antigen n (%)			
Age group (years)	Females %	Males	Total	Prevalence ratio across age groups[a]	Females %	Males	Total	Prevalence ratio across age groups[a]
20-24	3/18 (17)	0/10	3/28 (11)	Baseline	3/18 (17)	3/10 (30)	6/22 (21)	Baseline
25-29	7/12 (58)	7/14 (50)	14/26 (54)	5 (1.60-15.5)	2/12 (17)	1/14 (7)	3/23 (11)	0.5 (0.1-1.7)
30-34	10/14 (71)	2/7 (29)	12/21 (57)	5.3 (1.7-16.5)	4/10 (29)	3/7 (43)	7/21 (33)	1.2 (0.5-3)
35-39	6/11 (54)	3/10 (30)	9/21 (43)	4 (1.2-13)	2/11 (18)	1/10 (10)	3/21 (14)	0.5 (0.1-1.8)
40-49	9/13 (69)	0/1	9/14 (64)	6 (1.9-18.7)	1/13 (8)	0/1	1/14	0.3 (0.04-1.9)
≥ 50	8/17 (47)	4/8 (50)	12/25 (48)	4.5 (1.4-14.1)	4/17 (24)	2/8 (25)	6/25 (24)	0.9 (0.3-2.3)
All age groups	43/85 (51)	16/50 (32)	59/135 (44)	NA[b]	16/85 (19)	10/50 (20)	26/135 (19)	NA[b]

[a] Prevalence ratio across age groups using the 20-24 years age group as the baseline. Values in parentheses are Taylor Series95% confidence intervals for prevalence ratios.

[b] Not applicable.

The primary symptoms prompting these patients to visit the clinic included generalized muscular and joint aches (22%), abdominal discomfort (20%), acute febrile illness (18%) and respiratory tract infections (13%). An injection was received during the visit to the clinic by 165 patients (81 %), including 90% of those aged 20-24 years. Seventy-three percent of patients did not know whether the

needle and syringe used to inject them were sterile; 17% reported them to be reused and 10% observed a new syringe being drawn from its packet.

Among all 203 exit patients, the percentage who reported averaging more than ten injections per year increased from 52% in 1978- 88 to 69% during 1989-93 and to 73% during 1994. Those averaging zero injections per year decreased from 34% during 1978-88 to 16% during 1989-93 and to 5% during 1994. Women were twice as likely as men to report receiving over ten injections per year during 1994 (prevalence ratio=1.9, 95% confidence interval (CI) 1.2-3.0, P<0.01). In comparison to men in corresponding age groups, women aged 30-39 years were twice as likely to report receiving more than ten injections per year during 1994 (prevalence ratio 2.1, 95% CI 1.2-3.9, P<0.02), and women aged 25-29 years of age were five times more likely than similarly aged men to report receiving over ten injections per year during the same year (prevalence ratio=5.0, 95%CI 1.2-20.3, P<0.02). Such increased exposure for women was not statistically evident prior to 1994.

Among the 135 patients for whom serology results were available, those who received more injections during 1994 and during 1989-93 were significantly more likely to be infected with HCV (Table 2).

Table 2. Association between anti-HCV reactivity and average number of injections received in 1994, 1989-93 and 1978-88, Darsano Channo[a].

	No. positive for HCV antibody	No. negative for HCV antibody	HCV odds ratio
Average number of injections in the last year			
0	1	6	1.0 (baseline)
1-4	2	9	1.3
5-9	5	14	2.2
≥ 10	51	47	6.5
X^2 for linear trend, P=0.002			
Average number of injections per year, 1989-93			
0	6	15	1.0 (baseline)
1-4	1	4	0.63
5-9	5	9	1.4
≥10	47	48	2.4
X^2 for linear tremd, P=0.048			
Average number of injections per year, 1978-88			
0	17	29	1.0 (baseline)
1-4	2	3	1.1
5-9	4	6	1.1
> 10	36	38	1.6
X^2 for linear trend, P=0.21			

[a] Persons who responded"don't know" when questionned as to the average number of injections for a particular time frame were excluded from the analysis

Antibody to HBV core antigen was not associated with the average number of injections received during the same time periods.

Fifteen percent of patients reported that they had previously received a blood transfusion, and these patients were 1.9 times more likely to be infected with HCV. However, this and other associations between parenteral exposures and HCV and HBV infection were not statistically significant (Table 3).

Table 3. Lack of association between HCV and HBV infection with other potential routes of transmission, Darsano Channo, 1995.

Other risk factors	Total n (%)	No. positive for HCV antibody[a]	HCV prevalence ratio[b]	No. positive for HBV core antigen antibody[a]
Receiving blood transfusion	31/203 (15)	12/22 (55)	1.9 (0.7-5.4)	4/22 (18)
Injecting drug use	8/203 (4)	2/7 (28)	0.5 (0.1-3.1)	2/7 (28)
Extramarital sexual intercourse	26/203 (13)	7/19 (37)	0.7 (0.2-2.2)	5/19 (26)

[a] No. positive among those who provided serum samples. Values in parentheses are percentages

[b] Values in parentheses are Taylor Series 95% confidence intervals for prevalence ratio

If oral and injectable medicines were equally effective in the treatment of a given illness, 90 of the patients (44%) said they would prefer an injectable. Twenty-nine (14%) said they always insisted on receiving injectable drugs when they visited health care practitioners; 41(20%) said they did so usually or occasionally. Forty-one percent of the patients thought that oral medication was more expensive than injectable medication. Only 48 patients (24%) reported ever having asked their practitioner for oral medication in preference to an injectable drug that had been prescribed.

Health care providers

We interviewed 18 health care providers during working hours in the clinics, which contained one to three rooms and lacked laboratory and radiology facilities. Ten of the providers were registered medical practitioners; the sole qualification of the others was previous apprenticeship under such practitioners. The registered practitioners reported an average of 60 patient visits a day; the unregistered practitioners reported 25 such visits. The mean duration of practice as an independent health care provider was 13 years.

Eight of the ten registered practitioners and six of the eight unregistered practitioners said that life-

threatening diseases could be spread through the reuse of non-sterile needles and syringes. When asked to mention diseases likely to be transmitted in this manner, none of the practitioners referred to HCV; only two mentioned HBV, and over half mentioned tuberculosis (Table 4).

Table 4. Perceptions of health care providers as to diseases like to be transmitted because of reuse of non-sterile needles for injections, Darsano Channo, 1995.

Disease	What diseases are likely to be transmitted because of reuse of non-sterile needles (n=18)? Registered practitioners[a] (n=10)	Unregistered practioners[b] (n=8)
AIDS	8 (80)	4 (50)
Hepatitis B	2 (20)	0 (0)
Hepatitis C	0 (0)	0 (0)
Malaria	5 (50)	5 (62)
Tuberculosis	5 (50)	5 (62)
Typhoid fever	5 (50)	5 (62)
Cancer	0 (0)	2 (25)

[a] Qualified medical graduates registered with the Pakistan Medical and Dental Council. Values in parentheses are percentages.

[b] Health care providers who were not medical school graduates and were not registered with the Pakistan Medical and Dental Council.Values in parentheses are percentages.

When asked to estimate the percentage of their patients seen on a working day for whom they prescribed an injectable drug, the responses ranged from 60% to 75%. The most common diseases reported for which these injectable drugs were administered included respiratory tract infections (9; 50%), malaria (8; 44%), gastroenteritis (8; 44%) and generalized weakness(4; 22%). According to the practitioners, their reasons for preferring injectable drugs over oral counterparts included the quick relief of symptoms (15; 83%), greater effectiveness (7;39%),lower frequency of side-effects (6; 33%)

and patient satisfaction (4; 22%).

Practitioners prescribed a wide range of injectable therapeutic agents including mixtures of two or more drugs. All 18 practitioners reported prescribing injectable antibiotics, most commonly gentamicin, penicillin G and cephalosporins for a broad range of suspected infectious diseases. Seven practitioners (39%) reported prescribing injectable chioroquine for suspected malaria. Seven (39%) also used mixtures of vitamins with analgesics administered intramuscularly for complaints of generalized weakness and muscular or joint aches.

Observations in clinics

The use of a new needle was observed on two occasions and the opening of a packet containing a syringe with a needle was seen on one occasion during observations on the administration of 54 injections. For the other 51 injections both the needle and the plastic disposable syringe had been used on another patient during the same working day. In all clinics, needles were observed either in a pan of tepid water or lying open on a table. Between uses, syringes were always placed on a table.

Discussion

Forty-four per cent of patients aged at least 20 years who visited health clinics in a periurban setting outside Karachi were infected with HCV. The primary route of transmission was evidently injection with reused, inadequately sterilized needles and syringes. There was a strong dose-dependent association between the numbers of injections received and HCV infection during two periods of exposure: the 12 months prior to interview and the five years preceding them. It is possible that persons with HCV were symptomatic and thus more likely to come to practitioners and receive injections, with the consequence that HCV infection was there as on for the injections rather than vice versa. However, if the injections were not responsible for HCV infection there would need to be another cause of the 44% prevalence of HCV in the population. Other parenteral risk factors were evaluated, but none were significantly associated with HCV. If the cause of this high prevalence was an unknown risk factor not covered in the questionnaire, the observation that 94% of injections were administered with unsterilized reused syringes and needles would be an irrelevant finding. This, given the limitations of a cross-sectional study, is arguable, but the more straight forward explanation that injections led to HCV infection is more plausible. Moreover, this relationship between unsafe injections and HCV infection has been observed elsewhere in Pakistan[13] and in Taiwan, China.[14,15] It is consistent with the associations observed between HCV transmission and injecting drug use[2] and needle-stick injuries.[5]

These data also suggest that most transmission of HCV in Darsano Channo occurred within the five years preceding the investigation. The strongest association was between HCV infection and the receipt of injections in the previous year; a weaker association occurred in respect of the preceding 2-6 years, and there was no association with injections given more than 6 years previously. Furthermore, persons aged at least 25 were at markedly greater risk of HCV infection than persons aged 20-24 years, but above the age of 30 there was no increased risk relative to the already elevated risk of persons aged 25-29 years. If the rate of infection were steady and longstanding, increased infection in each age group would be expected. Thus, although injections were commonly used in the 16 years prior to the study (1978- 94), the virus was apparently either introduced or reached sufficient prevalence for exponential spread within the population during the five years preceding the investigation. This is consistent with a study in a village in Taiwan, China, suggesting that most community-wide HCV transmission from injections occurred during distinct time frames.[14]

This model of widespread risk behaviour but episodic large-scale transmission is consistent with the varying prevalence of HCV reported in different communities. Two epidemics of HCV caused by injections from inadequately sterilized needles have been documented in Pakistan, one in the present study and the other in Hafizabad[13], a community with a different language and culture and separated

from Darsano Channo by over 1100 kilometres. Both communities were investigated following reports of liver disease. Although injections are widely popular in Pakistan[17], rates of HCV infection are below 2% in other communities, including voluntary blood donors in Karachi18 and residents in four squatter settlements in Karachi (S. Thobani, personal communication). Patchy outbreaks of HCV against a background of widespread unsafe injections suggest that interventions to improve needle hygiene could prevent an exponential increase in transmission in the many communities where HCV prevalence and injection behaviour resembled the conditions in Darsano Channo in the ten years preceding our study. However, it is not easy to bring about a reduction in unsafe and unnecessary injections. Patients in Darsano Channo actively sought injections. Seventy-three per cent of the patients had received more than ten injections in the preceding year, and 44% preferred injections to oral medications even where they were equally effective. Practitioners, unaware of many of the specific risks of bloodborne pathogen transmission through injections, were providing a service that people wanted at a modest price. Complete medical evaluation was not a part of this study; nevertheless, the fact that 81% of the patients visiting primary care clinics received a parenteral injection in the absence of laboratory or radiological evaluation pointed to unnecessary parenteral therapy.

The consequences of frequent unsafe injections were not borne equally within the community. Over half of all the women were infected with HCV. Women sought more care at these clinics, received more injections and were twice as likely as men to be infected with HCV. This increased exposure to injections was particularly evident in women aged 30-39 years, the peak reproductive age range of women in Pakistan. In Darsano Channo, women's social roles and mobility are strictly prescribed. Somatization, the expression of psychological stress as physical symptoms, is responsible globally for a large percentage of visits to health care providers[19] and is likely to account for many visits to clinics in Darsano Channo. When Darsano Channo residents felt unwell they sought injections.

Although hepatitis B virus can be transmitted by reused injection equipment the present study did not find an association between hepatitis B and injections. There are two likely reasons for this. First, 85% of the persons who have anti-HCV antibodies as detected by second-generation enzyme-linked immunosorbent assay have circulating HCV virus and so can readily transmit the infection.[20] In contrast, in a previous study in Pakistan, only 14% of persons with antibodies to hepatitis B core antigen had evidence of infectivity, i.e. circulating hepatitis B surface antigen.[13] In Darsano Channo, therefore, the opportunities for HCV transmission via contaminated injection equipment were more frequent than for HBV transmission. Second, hepatitis B is more efficiently transmitted vertically and sexually than hepatitis C.[21,22] In this relatively small study, substantial HBV transmission that was not associated with injection could have obscured an association between injections and HBV infection.

It is worth noting the following limitations of the present study.

Exposure to injections was assessed by questionnaire. Recall, especially over long time frames, is imperfect. However, patients were unaware of their HCV status when they were questioned, so imperfect recall would lead to non-differential misclassification of exposure which would bias associations to the null. Thus, while there may be additional associations between exposures and outcomes which the study failed to recognize, those that it did identify are probably valid.

Because this was a cross-sectional study it was impossible to distinguish completely how much of the varying prevalence of HCV with age was a result of an age effect, a period effect, or a cohort effect. However, in contrast to other populations with HCV which showed a steady increase in HCV prevalence with age[13,23,24] the prevalence in Darsano Channo peaked at 25- 29 years of age, indicating more than a simple age effect. Whether this unusual age distribution of infection was something that happened during a particular period, resulting in increased prevalence for all age groups, or whether persons in a specific birth cohort were susceptible to unique conditions of their birth cohort, cannot be resolved completely with cross-sectional data. Nevertheless, the retrospective data on exposure to injections identifies a particular period, i.e. the year prior to the study, as the time of strongest

association with infection. This contrasts with the results from Hafizabad: injections in the preceding year were not associated with HCV infection, whereas there was an association between injections in the preceding five and ten years and HCV infection.[13] Moreover, whether the responsible event occurred among all ages, i.e. a period effect, or among a particular age group, i.e. a cohort effect, it appears that at some time in the recent past HCV was widely transmitted through this community.

The study raised substantial ethical conflicts. At the outset the members of the team realized that they would probably observe clinical practices that could potentially transmit blood-borne infection, and careful consideration was therefore given to the acceptability of observation without immediate intervention. Because the project was of short duration, and because the Human Subjects Committee of the Aga Khan University met only quarterly, formal external ethical review was unavailable. It was decided to proceed for three reasons. Firstly, to insist on intervening at the time of observation would undercut both the project and effective public health intervention. We were invited into clinics where both clinicians and patients preferred injections. Had we violated the autonomy of the care providers and the patients and insisted on an immediate change in practice, we would not have been allowed to continue observing and the care providers would have been unwilling to cooperate in any follow-up activity aimed at reducing unsafe injections. Stopping the process at the time of initial observation would also have undercut the development of broader regional public health interventions that could only be rationally based if the problem was realistically understood. Secondly, giving three clean needles and syringes to each care provider on the day of observation would not have meaningfully lessened the risk of bloodborne infection in a population whereover three- quarters of the patients were receiving more than ten injections a year and the reuse of injection equipment was usual. Thirdly, had a different topic been chosen for study, a possibility that was considered, the end result would have been less controversy, the same number of unsafe injections administered on the days of planned observations, and no data to give back to the community or to examine on a national or international level. Although we did not intervene at the time of observation we did in fact plan and intervene. Once the data were analysed we returned to Darsano Channo, divulged the laboratory results and provided counselling and referral to the participants in the study. We also shared the results of the study with the larger community, and with the local health care providers, and with other health care providers and communities throughout the region. We shared the data with colleagues in the Sindh Government AIDS Prevention Programme, who subsequently included the avoidance of unsafe injections among the public health messages issued via the mass media throughout the province of Sindh, which has a population of 40 million. We also collaborated with a nongovernmental organization in including the reduction of unnecessary and unsafe injections in an intervention programme for improving clinical care in the area.

In developing countries, frequent injections are part of a mutually re-enforcing cycle. Injections are psychologically rewarding to patients, bring status and financial reward to the injector, and occasionally bring genuine health benefits.[25] Consequently, interventions should be addressed at the societal, practitioner and patient levels. An important long term goal is to prevent unnecessary injections. Research in developing countries which aimed at measuring the average percentage of adult outpatients in primary care settings who required parenteral therapy would permit the establishment of an evidencebased standard. Governments, nongovernmental organizations and communities could use such a standard to evaluate local practices and persuade practitioners and community members to make the necessary modifications.

Efforts are needed to ensure that all injections are administered with sterile syringes and needles. The incremental cost to practitioners of using new syringes or to community members of providing their own syringes is small compared to the cost of visits. A typical clinic visit in Karachi costs US$ 0.96, while a sterile needle and syringe cost $0.06 (G. Raglow, personal communication). It is more realistic to use cleaner injecting equipment in the short term than to expect rapid change in the psychological

and economic dynamic that drives unnecessary injections. Even in Hafizabad, where a community-wide HCV outbreak caused by unsafe injections was followed by an intensive two-year information and education campaign, the average number of injections per year among residents remained unchanged, although the majority of residents had started providing their own new syringe and needle each time they visited a clinic (Fauzia Hoodbhouy, personal communication). As there is no immediate prospect of a vaccine against HCV it is vital to combat unsafe injection practices in developing countries. This would not only help to diminish the morbidity and mortality associated with HCV but could also be expected to prevent disease from needle-transmitted hepatitis B virus, HIV and other bloodborne pathogens.

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