

EDITORIAL

A trial of naloxone for peer administration has merit, but will the lawyers let it happen?

The extent of the problem

In Australia, there has been a six-fold increase in the rate of heroin-related overdose deaths from 1979 to 1995 [1], with heroin overdose accounting for almost 9% of all deaths nationally, in the age range 15–44 years, during 1998 (Lynskey, 2000, personal communication). There has also been a sharp increase in the number of dependent heroin users in Australia, with estimates increasing from 40 000 in 1990 to 74 000 in 1997 [2]. The national prevalence of heroin dependence is estimated to be 6.9 per 1000 adults aged 15–54 years, comparable to that of the United Kingdom and other European countries [2]. It has been argued that we are now in the midst of a new cycle of recruitment into heroin use which began in the early 1990s. As heroin overdoses tend to peak about 10–15 years after initiation of use in any cohort, overdose mortality is unlikely to decrease and may actually increase [3–4]. There is, therefore, a clear need to continue to develop, implement, evaluate and modify strategies to prevent and manage heroin-related overdose.

A range of responses

Heroin overdose is like motor vehicle trauma in that there will not be any single solution to reduce the associated morbidity and mortality, and a range of interventions is likely to be required. To reduce vehicle-related harm we have road rules, driver training, blood alcohol limits, frangible poles, seat belts, air-bags, speed cameras, and so on. The range of options to reduce mortality and morbidity associated

with heroin-related overdose thus far includes: educating users about risk factors for overdose (eg polydrug use, using alone, reduced tolerance with abstinence, etc.) and how to minimize these; expanding treatment options, especially methadone; improving user response to overdose events by providing training in resuscitation and encouragement to call an ambulance; protocols between police, ambulance services and user representatives which clarify that police will not routinely attend ambulance calls to overdose; and peer outreach such as that targeted through hospital emergency departments.

It may respect it is early days for a number of these interventions

While these interventions are still being expanded it may be too early to see any impact on the number of deaths. Nevertheless, we need to consider other strategies which may have promise. The provision of naloxone hydrochloride ('Narcan') to users for peer administration has been suggested as one of these other strategies [e.g. 5–8]. Naloxone is an opioid antagonist which reverses the respiratory depression, sedation and hypotension associated with the use of heroin and other opioids. However, naloxone does not reduce the respiratory depression caused by non-opioid central nervous system (CNS) depressants, such as alcohol and benzodiazepines, and has no effect when administered to someone who has not used opioids [9].

Why naloxone might be an effective additional strategy

There tend to have been ample opportunities for intervention in many fatal heroin-related overdoses. Approximately 60% of deaths occur in the company of others [6,10–13], mostly other users, and instant death following injecting is rare, occurring in about 15% of cases [12,14]. Death occurs more than 3 hours after injection in between 22% and 52% of cases [10]. Furthermore, most overdoses occur in a home or other dwelling [14]. Witnesses to fatal overdose only call an ambulance in about 10% of cases [12], and there is no intervention before death in 79% of cases [10]. Reasons for not calling an ambulance include fear of police involvement [6,15] ambulance-related costs [13] and previous negative experiences with hospital staff [15].

Use of naloxone in medical settings

There are two medical settings where naloxone has been used extensively, postoperatively to reverse the effects of opioids administered during surgery, and in the prehospital treatment of overdose resulting from heroin and other opioids. Literature from these areas suggests that although complications have been documented, naloxone appears to be a safe drug overall. Postoperatively, complications such as hypertension, atrial and ventricular tachycardia, fibrillation, left ventricular failure, pulmonary oedema and sudden death have been documented [16–19]. However, where they have occurred they have often done so in patients with pre-existing medical conditions or where numerous drugs had been administered and thus interaction effects are possible [16,20]. As such it is difficult to determine whether the problems have been due to naloxone *per se*.

Treatment of heroin overdoses in the United Kingdom and Australia suggests that medical complications are rare, with no significant problems reported following hundreds of administrations [7]. Naloxone can precipitate withdrawal symptoms when given to those who are opioid-dependent, and sometimes the person in acute withdrawal can become aggressive and endanger themselves and others [21–22]. In general, withdrawal symptoms are typically less severe following intramuscular than intravenous administration [23].

There are potential problems

Whether making naloxone available for peer administration would likely result in a net reduction in harm will depend on a number of factors, including: the extent to which it is used as an additional component of a peer First Aid response to overdose; whether it undermines other strategies such as airway management and calling an ambulance; whether naloxone recipients receive a medical review; and what proportion of users engage in more hazardous use if they believe their friends can bring them round. For these kinds of reasons we believe a carefully controlled trial of naloxone provision for peer administration is needed before more widespread distribution is considered seriously.

There are some data to suggest caution is warranted. Some Australian and UK studies suggest that if naloxone is made available for peer administration a small minority of users may use more heroin, or use in a more hazardous way [8,24–25]. Seal [26] reported that 40% of their small San Francisco sample said that they would use more heroin if they had access to naloxone. Furthermore, one of the reasons given by users for wanting naloxone for peer administration is that it would alleviate many of the factors (e.g. fear of police involvement, cost and previous negative experiences with hospital staff), which currently prevent them calling for an ambulance [6,8,24]. Only 38% of the San Francisco sample said they would still call an ambulance if they had naloxone, compared to 59% who called an ambulance at their last witnessed overdose when naloxone was not available [26]. It is quite likely that, other things being equal, if users and their peers had access to naloxone they would be less likely to call an ambulance. As a result, fewer overdose survivors would be medically reviewed so any morbidity associated with non-fatal overdose may remain undetected. This issue could be addressed by educating users when they access naloxone, but the extent to which lack of medical review will become a problem in practice is, at present, unclear.

Concerns which should not preclude a trial of naloxone provision

There are a number of issues which have been raised with respect to peer naloxone administration which we believe can be addressed adequately and should not be a barrier to conducting a trial [25]. (1) Polydrug use: although the role of alcohol and/or benzodiazepines in

fatal overdoses involving heroin has been well documented, and naloxone is only effective in reversing respiratory depression due to opioids, it is considered that removing the opioid component could prevent the overdose becoming a fatality. (2) Naloxone is short-acting: the half-life of naloxone is estimated at between 30 and 90 minutes, which has particular implications where longer-acting opioids such as methadone have been used and points to a need for adequate follow-up care. Yet a user's peers may be in the best position to know what drugs the individual has used, monitor the response to the initial naloxone administration, maintain airway and, if necessary, administer a subsequent dose of naloxone. (3) Shelf life: the preloaded minijet system has a shelf-life of 18 months and any trial should ascertain whether users replace expired stock. (4) Product stability: naloxone appears stable at both extremes of temperature and would remain potent even if left in the glove box of a car, or carried around in pockets or bags for extended periods of time. (5) Intoxicated administration: it is reasonable to expect that on many occasions the person administering naloxone to their overdosed peer will themselves be intoxicated. However, this is likely to be the case whatever overdose management strategy is used, and administering naloxone intramuscularly via a pre-loaded minijet, designed for this purpose, may be no more difficult than would many other interventions, such as calling an ambulance and administering EAR. (6) Impact on heroin use: although it has been argued that provision of naloxone for peer administration may remove a significant barrier to heroin use, namely fear of overdose, and result in an increase in the total number of heroin users, we and others [e.g. 5] believe that for a number of reasons this will be unlikely. Similar concerns were raised about needle and syringe provision and these have not been borne out by the evidence.

Examples of distribution of naloxone for peer administration

There are at least four locations around the world where naloxone is being officially or unofficially provided for peer administration. It has been available over the counter from pharmacies in Italy since 1995 and there are unpublished reports of authorized distribution for peer administration in Jersey (B. Saunders, Preventing opiate overdose fatalities through the distribution of take-home naloxone: the Jersey experience. Alcohol and Drug Service, Channel

Islands, unpublished) and Berlin [27], plus underground distribution in San Francisco [26,28] and Chicago [29]. However, the use of naloxone by heroin users and their peers has not yet been thoroughly evaluated.

In Jersey naloxone has been given free to users through the Islands Alcohol and Drug Service to clients on the methadone programme since October 1998. Some 100 minijets have been given to users along with a one-page information sheet. According to anecdotal reports it has been used successfully on at least five occasions and there have been no reports of adverse consequences (B. Saunders, Preventing opiate overdose fatalities through the distribution of take-home naloxone: the Jersey experience. Alcohol and Drug Service, Channel Islands, unpublished).

The San Francisco Needle Exchange has been incorporating training in naloxone administration as part of its overdose management and prevention training course for drug users in the Haight-Ashbury area since mid-1999. Naloxone has been available to users in the area through underground sources over this period [28]. The two-session training includes causes of overdose; how it happens/stages; overdose prevention strategies (e.g. taste first); rescue breathing and CPR certification; 911 protocol; naloxone administration; and, importantly, the development of an overdose management plan. The plan is negotiated between the user, their peers, spouse, etc. and includes an agreement as to how the user will be managed should they overdose. This includes: in what circumstances an ambulance will be called; whether naloxone will be used and how much will be administered; as well as what support and after-care will be provided [29]. A very similar training programme, incorporating self-help resources, has been in place at the Chicago Recovery Alliance, where the addition of a naloxone component to the overdose management training has been seen as empowering users and has encouraged hard-to-reach users into making contact with the service [30].

In January 1999 a programme to distribute naloxone to opioid users for peer administration was begun in Berlin by Fixpunkt Mobilix (a health service for users incorporating a needle exchange programme). To be eligible for naloxone, users must attend a overdose prevention and First Aid course run by the service. Follow-up research with 103 participants failed to find a single case where naloxone provision had resulted in risky consumption by any of these individuals. Additionally naloxone had been used in 21 overdose

situations by this group, at least 18 of which were judged to be 'medically warranted' based on the accounts provided [27].

In Torino, Italy, outreach workers distributed 10 108 naloxone ampoules to clients between 1995 and 1998. They report that most users now carry naloxone routinely in their pocket or bag, believed to be due in part to a growing acceptance of its worth among users (Ronconi S, Gruppo Abele—ASL 4 Torino Outreach Project 1995–1998: prevention of overdoses among current heroin users in Torino, Italy for the period 1995–1998, unpublished). There has not been a formal evaluation of naloxone provision on the impact on fatal overdose statistics over the life of this project. However, interviews with 100 clients conducted as part of a larger study of needle exchange attendees found 99% knew what naloxone was and 47% had used it to help another user. Furthermore, 43% of male and 73% of female users were comfortable asking the outreach workers for naloxone.

Effectiveness can be addressed by a trial

Despite these encouraging case reports we believe we owe it to drug users to receive answers to the outstanding questions before recommending more widespread availability of naloxone. The best way to do this will be by a closely monitored trial of naloxone provision. Although there are some methodological difficulties in conducting such a trial, in our opinion these are not insurmountable [25]. More crucial are the considerable medico-legal barriers.

Legal barriers

There are a number of legal and ethical barriers to conducting a trial. Some of these are because naloxone is currently classified as a Schedule 4 medication in Australia and as such is only legally available on prescription. Given that naloxone is likely to be used among a network of peers, potential legal problems could result where an individual who has been granted access to naloxone then passes it on to another person. In practice this may not be a problem, as regulators may decide there is no benefit in pursuing such action and there may be other ways around this, such as rescheduling the drug for the purposes of a trial or issuing permits to access naloxone.

A more difficult legal problem is likely to be the need to limit the exposure to civil action of the participating parties (prescriber, person who administers the drug, organizations involved in running a trial). This could occur if someone died or suffered significant morbidity which loved ones or others attribute to the peer-administered naloxone.

Discussing the problems with peer-administered naloxone in the US context Burris [32], a lawyer, has noted that as it is possible someone will sue the individual practitioner and their employing organization, lawyers representing agencies considering participating in a trial will become involved. He makes the pertinent observation that while it is 'nice' for lawyers to save lives, their success is measured by their ability to protect the organization from lawsuits, and they will therefore advise their organizations against involvement in such a trial. We believe that a trial of distribution of naloxone for peer administration will not happen unless lawyers are engaged to find ways to make it happen, rather than reduce to zero any risks to the organizations involved of being sued. Burris [32] argues that someone needs to take the risk to get the ball rolling. He believes that if there are willing prescribers, a trial with sound research background and reasonable safeguards conducted in collaboration with users, medical practitioners with alcohol and drug experience and researchers may provide a context to weather the possible legal risks.

If there is medical merit then there is a need to find a way through legal impediments. Peer-administered naloxone will never be the magic bullet for heroin-related overdose and we need to continue to emphasize the range of other strategies to prevent overdoses, both fatal and non-fatal. While there is no guarantee that widespread availability of naloxone for peer administration will necessarily have a public health benefit, a carefully controlled trial will help determine whether it is worth proceeding with. If, as we and others believe, a trial has medical and public health merit, we must find a way through organizational anxiety about legal liability, otherwise an additional strategy to prevent heroin-related fatalities may be overlooked.

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