Public health

Medical use, misuse, and diversion of opioids in India

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In less-developed countries, opioids such as morphine are often not available for pain relief because of excessive regulations imposed to prevent their misuse and diversion. We describe the effect that these draconian measures have had on the availability of drugs for medical use in Kerala, India, and present results of a study, which we did to ascertain whether or not the misuse and diversion of opioids is as prevalent as the government reaction would suggest. We followed 1723 patients in Calicut, India, who were being treated for pain with oral morphine on an outpatient home-care basis. Over 2 years, we did not identify any instances of misuse or diversion. These results suggest that, in the context of India as a less-developed country, oral morphine can be dispensed safely to patients for use at home. We recommend that palliative care programmes talk to concerned governmental authorities, to make them aware of the medical need for opioids, and communicate with local news media to increase awareness of palliative care and the use of these analgesics. Our project has overcome regulatory barriers that had interrupted availability of morphine and its use in pain relief in India.

The WHO estimates that 10 million new cases of cancer are diagnosed every year, with over 6 million people dying from the diease annually.[1] According to projections, the annual incidence and mortality rates of cancer will double in the next 20 years, with over two-thirds of cases arising in less-developed countries[1] where the disease is often diagnosed at an advanced stage.[2]

Although not inevitable, pain requiring relief is prevalent in people with cancer, particularly in those with advanced disease.[3] Reports indicate that over 50% of cancer patients worldwide suffer unrelieved pain,[4] which can destroy quality of life by making ordinary activities difficult or impossible. In late-stage cancer, pain management and palliative care should be the primary aim of treatment.[3]

In 1986, the WHO announced a three-step analgesic plan that could relieve most pain caused by malignant disease.[4] The organisation stated that: "The greatest improvements in the quality of life for cancer patients and their families could be effected by implementation of existing knowledge of pain and symptom control."[3] Opioid analgesics such as morphine are safe, effective, and essential in the treatment of moderate to severe pain.[2,4,5] However, these drugs should be prescribed according to individual requirements of the patient, and must be available when and where they are needed.[3,6]

Several factors contribute to the underutilisation of opioids and to inadequate treatment of pain, including misinformation and exaggerated concerns about the risks of abuse and diversion.[2,7] Furthermore, the WHO and the International Narcotics Control Board, which is committed to trying to minimise the misuse and diversion of narcotic drugs while ensuring the availability of opioids for legitimate medical and scientific purposes, have identified excessive regulatory requirements as important factors affecting adequate availability of opioid analgesics for medical use, especially in less-developed countries. Complex and restrictive laws can undermine the dual imperative that governments should establish a system of narcotics control that prevents the misuse of drugs while, at the same time, ensuring their adequate and continuous availability for legitimate medical purposes.[7] This is the principle of balance.[8] When efforts to prevent drug abuse interfere with availability for medical and scientific purposes, there is a lack of balance. Such is the situation in India.

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Cancer pain and opioid availability in India

More than a million people are thought to have cancer pain in India.[9] However, pain relief is a new notion in this country and palliative care training has been available only since 1997. Palliative medicine and pain relief are being practised in some cancer hospitals and hospices, with more and more emphasis being placed on outpatient services, including home care.[9,10] Despite this trend, only a few of those who need such care receive it.

To make opioids available for palliative care on an outpatient basis in the state of Kerala, India, WHO set up a community-based demonstration project. When this project began, oral morphine products were, at least theoretically, available from several manufacturers in India. However, in practice the drug was not available to most patients for many reasons, including lack of awareness among professionals, patients, and the public, and excessively strict narcotic regulations. Although pethidine injection has always been available, this treatment is not recommended for chronic pain.[11] Transdermal fentanyl is now available in India. There are no other opioids available that could be substituted for oral morphine.

In 1985, the Narcotic Drugs and Psychotropic Substances (NDPS) act[12] was developed and adopted because of a concern that increases in the medical use of morphine and other opioids, which occurred in India in the early 1980s, would contribute to substantial increases in drug misuse (use for any reason other than therapeutic purpose) and diversion (when a drug moves from a licit to an illicit channel of distribution or use). This concern is based historically on frequent incidents involving misuse and diversion of these substances into illicit channels,

which occurred in the past because of a lack of consistent controls over their manufacture, distribution, and storage.

The act established a national framework of complex licensing requirements, which resulted in medical institutions having to obtain various paperwork before they were able to procure and possess opioids such as morphine. Every state adopted its own licensing rules to conform to the national law. A key feature is that every state government regulates import and export of narcotic drugs between states, much as national governments regulate the movement of narcotic drugs between countries. For a hospital to purchase morphine from another state, there is a complicated licensing procedure. This procedure involves obtaining five licenses from two different government bureaucracies in both states, each of which might have a different period of validity but all of which must be valid at the same time in order for shipment of morphine to be lawful. Inevitably, some licenses expire before others can be obtained, necessitating a repeat of the process and resulting in continued unavailability of morphine. Hospitals and pharmacies stopped procuring and stocking morphine because of a fear of penalties that might result from clerical errors and the impossibly burdensome licensing process.

The NDPS act, therefore, had a negative effect on availability of morphine in India for medical purposes; the country's consumption of morphine fell by 97%, from 716 kg in 1985[13] to 18 kg in 1997.[14] As a result, the International Narcotics Control Board, called attention to the decline in consumption of morphine in India and made a recommendation: "As the domestic consumption of morphine has decreased to an extremely low level over the last few years, the Government of India should take effective measures to ensure its adequate availability for medical purposes."[15] After all, what evidence is there to suggest that improving the availability of opioids for medical purposes by itself contributes to misuse and diversion of those drugs?

Misuse and diversion of opioids

There have been few empirical studies published that address the relation between opioid availability and misuse and diversion. We identified no such trials that were done in less-developed countries.

The International Narcotics Control Board commented that: "Despite the large quantities of substances involved and the large number of transactions no cases involving the diversion of narcotic drugs from licit international trade into the illicit traffic were detected during 1999".[16] This statement conforms to a previous comment by the board concerning the relatively low extent of diversion of narcotic drugs in 1995: "The international system to prevent diversion of narcotic drugs is working well. The number of incidents involving diversion of narcotic drugs is small considering the large number of transactions at the international and national level."[17] The International Narcotics Control Board attributes the successful global prevention of diversion of narcotic drugs to governments' continued compliance to the control requirements established by the 1961 Single Convention on Narcotic Drugs, and to their continued collaboration with the competent authorities in various countries.[16]

Japan, where morphine consumption increased by 1486% between 1985[13] and 1998,[17] reports little if any abuse or diversion.[18] And in Wisconsin, USA, another WHO demonstration project reported very low and stable morphine diversion despite a great increase in medical use.[19] Finally, results of an empirical study,[20] which assessed the relation in USA between trends in the medical use and abuse of opioids used to treat severe pain, revealed large increases in the medical use of opioid analgesics, including morphine, fentanyl, hydromorphone, and oxycodone, since 1990. However, rates of abuse remained very low and stable throughout the study. The findings contradict the perception that the abuse of opioids in the class of morphine is a direct consequence of their availability, and supports the International Narcotics Control Board's assertion that effective national and international drug control efforts have successfully limited the diversion and abuse of these drugs. If misuse or diversion of opioid analgesics should take place, the sources of diversion should be identified quickly and directly, without affecting drug availability or patient care. To ensure against drug misuse or diversion by refusing to prescribe, administer, or dispense opioids when their medical use is appropriate is not acceptable.

Figure 1: **Outpatient clinic of the Pain and Palliative Care Society**

Fight for availability of opioids

Various programmes and institutions have been set up worldwide to investigate the medical use, misuse, and diversion of opioids, and to develop ways to improve availability of these drugs while preventing their ilicit use. The WHO Collaborating Center for Policy and Communications in Cancer Care, based at the University of Wisconsin, for example, supports a programme of pain policy research, demonstration, and assessment. The centre develops ways to investigate regulatory barriers to opioid availability, to guide changes in national and state policy, and to monitor results.

The Pain and Palliative Care Society, formed in 1993, is a non-governmental organisation and a WHO demonstration project. Such projects aim to teach those in less-developed countries how to provide outpatient community-based palliative care. In 1997, the society established the Pain and Palliative Care Clinic (PPCC). Based at the Medical College Hospital, Calicut, the clinic is part of an outpatient programme that provides palliative care for cancer and other terminally ill patients in Calicut, a city of 2·8 million in the largely rural southern state of Kerala, India.[21] Over the past 7 years the society has helped to develop a further 19 outreach palliative care programmes throughout Kerala.[10]

Outpatient care is the main type of service provided by the PPCC (figure 1). Brief hospital admission is available for the very ill, and a home-care service is extended to those who are too sick to travel to a clinic. Over the 2 years of our study, based at the clinic, the PPCC treated

150–185 new patients every month. Every patient is cared for by trained staff with a minimum of 1 month's practical training. All staff also have to attend a 10-day foundation course in palliative care, which is held twice a year.

Most patients have late-stage cancer when they arrive at the PPCC. The location and type of pain is assessed and recorded by use of a body chart and a 0–10 numerical rating scale. Treatment of pain begins immediately and follows the WHO three-step analgesic ladder.[2,4] Dextropropoxyphene and codeine are the weak opioids used most often. Sublingual buprenorphine is available for patients who are unable to swallow tablets. However, oral morphine is the mainstay of treatment. If pain is severe at presentation, morphine is given first by injection, then orally.[22] Invasive procedures are available, but are reserved for the few patients who do not receive adequate pain relief from oral opioids.

Oral morphine is given free of charge to all patients who need it. Funds to support this action come from donations to the Pain and Palliative Care Society, by the community. When outpatient or home care begins, the patient and family members are told about how immediate release morphine tablets must be used to be effective, and also about how to store them safely. Most patients return home with a 2-4 week supply of opioids, depending on how far they live from the clinic, and are instructed to return for additional medication. Patients are rarely concerned about addiction, but when they are medical staff are ready with explanations and examples of other patients to help dispel any doubts.

New research

Over 2 years, from Jan 1, 1998, my colleagues and I investigated whether or not a continuous supply of morphine for community-based outpatient and home care could be maintained in a India, without misuse and diversion of drugs. We did this by following the treatment of 1723 patients being treated for pain at home or as outpatients by the PPCC.

Prevention of misuse and diversion of morphine is based on security of the stock, maintenance of records, and judicious prescribing. These are the essential components of managing opioids in any patient care setting in any country. Therefore, when we received a consignment of oral morphine at the clinic, we notified the local authorities by telephone, and the parcel was opened only with their concurrence (figure 2). The quantity received was verified and compared with both the amount ordered and the amount entered in the stock register. We then put the

Figure 2: **A shipment of morphine**

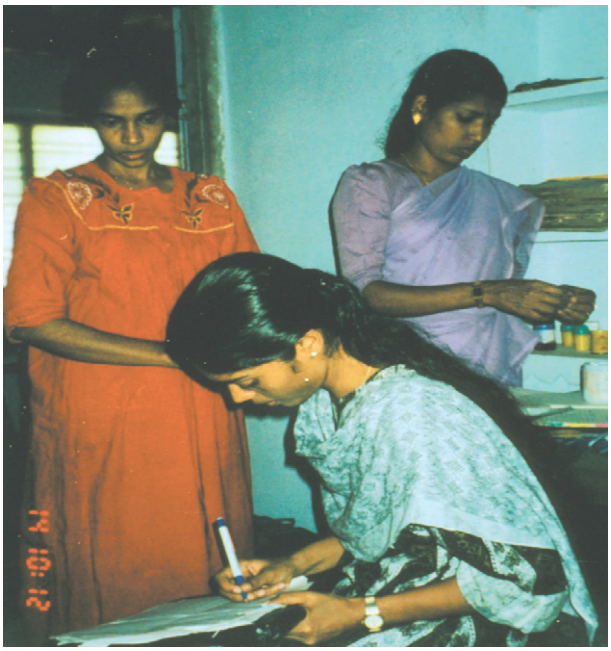

Figure 3: **Clinic physician entering the prescription into the patient's chart, nurse counting out morphine tablets, patient's wife looking on**

morphine in a locked cupboard in a locked room, to which only a few PPCC employees had access.

Throughout our study, morphine was prescribed only by licensed medical practitioners, as stipulated by Indian law. Such doctors had had training in pain management. Every time morphine was dispensed, we entered the patient's name, an identification number, and the quantity dispensed into the morphine stock register (figure 3). At the end of every working day, the nurse in charge of data collection verified whether the stock register amount was the same as the actual stock amount. Any disparity was noted and brought to the attention of the physician in charge so that the reason for the disparity could be identified. Unused quantities of morphine, returned by a patient or patient's family, were returned to the stockpile if not expired, and an appropriate entry was made in the stock register.

Nearly all patients were initially seen at the clinic (about 50 per day, 6 days a week). If patients were too sick to travel to the clinic and lived within 40 km of the clinic they were assessed and cared for at home by a home-visit team. Patients who needed pain relief quickly were started on 4-hourly immediate release morphine. Prescriptions were made in duplicate, one copy carried by the patient to establish legal possession and provide instructions for use, and the other entered on the case sheet in the patient chart held at the clinic. The dose was adjusted over the next 24 to 48 h if necessary. Once pain control was achieved with a stable dose of morphine, the patient returned home, usually with a fortnight's supply of the drug, including rescue doses. Patients were told that they could return to the clinic earlier than the next scheduled visit if pain control was inadequate or if side-effects were intolerable.

Patients and their relatives were informed about how to take the drug at regular intervals and asked to return any unused drug to the clinic. They were told about possible side-effects and given advice and measures for managing constipation. Patients were informed about the consequences of taking too much morphine, such as drowsiness, delirium, and myoclonus. This information

was printed on the medication schedule in the local language of Malayalam. At every visit, the patient was reminded to return any left-over drugs, including morphine.

All records were checked by one nurse to identify possible diversion or misuse of morphine. This nurse investigated the frequency and amount of stock shortages, any disparity between the quantity of morphine said to have been consumed by patients and the actual amounts left over, and any report of loss or theft of the drug. Misuse of morphine was indicated by a patient's increased use of the drug that could not be accounted for by worsening of disease or pain.

Findings

During our study, 13·6 kg of morphine was dispensed to 1723 patients, averaging 7·9 g per patient. The number of patients who received oral morphine represented 43% of the total patient population and 53% of patients diagnosed with cancer. 1637 patients (95%) were seen on an outpatient basis and only 86 (5%) were seen at home. Patients received opioids for between 1 day and 2 years.

Only one major discrepancy in stock position arose, when 100, 10 mg tablets went missing. As the loss could not be accounted for, the person who was responsible for dispensing drugs on that day was relieved of that job until an explanation was forthcoming. The missing amount was discovered 2 days later within the drug storage cupboard itself; two packets of 50 tablets had escaped our notice.

There were minor discrepancies between the quantity of morphine that was ordered and the quantity actually received. These discrepancies were not apparent at the time of receipt. The drug was supplied in packets of 50 tablets, and only the number of packets had been counted at the time of entry into stock. We later discovered that some packets contained more or less than 50 tablets. Most of these discrepancies arose two to three times a month and involved one or two tablets. There were a few initial discrepancies in stock that involved somewhat larger quantities. Six tablets could not be accounted for on one day, eight tablets were missing on another, and four tablets were missing on three separate occasions. Upon further inquiry, we ascertained that some batches of tablets were quite fragile and had been crushed into powder during transit. The amount of powder accounted for most of the missing tablets.

Overall, the negative discrepancies amounted to 44, 10 mg tablets and 24, 20 mg tablets. This represented 0·0068% of the total quantity dispensed. In our study there were actually more positive than negative discrepancies in stock position. Occasionally, one or two extra tablets were found in stock, and an excess of 18, 22, 27, and 57, 10 mg tablets was found on four different days. Furthermore, there was an excess of 22 and 50, 20 mg tablets on 2 other days. After careful consideration, we believe that this disparity was caused by our own failure to document several instances of tablets that were returned by patients or families. Once the personnel concerned were made conscious of this situation, such occurrences became rare. In fact, there were no great positive or negative discrepancies in the last 6 months of the study, because of increased staff awareness.

We considered whether the positive discrepancies could have been caused by an employee's failure to dispense the drug after it had been prescribed. We identified no such instances, probably because our staff are well-trained and committed to pain relief. Had there been staff misuse or diversion, we would have identified unaccounted failure of pain relief. Also, there were no reports of loss or theft of morphine throughout the study. Although many relatives returned all drugs upon the death of the patient, there were some who did not. Thus, we are unable to account for some amount of morphine that was probably left over. No relative tried to procure the drug by concealing the fact that the patient had died.

All patients' medical records were checked to determine whether increases in a patient's drug requirement could not be accounted for by worsening disease and pain. No instances of drug misuse were noted. Additionally, the Pain and Palliative Care Society asked regulatory officials whether they were aware of any misuse or diversion of morphine in the Calicut area; they were not.

What do these results mean?

Our study monitored accountability for morphine stock, prescription, dispensing, and documentation, and was a valuable management and accountability experience for the clinic staff. No changes were made to pre-existing PPCC procedures for management of patient care and documentation of morphine stock and use, although greater staff awareness toward the end of the study reduced positive discrepancies.

Several aspects of our morphine management strategy are open to criticism. Perhaps the small discrepancies would have been prevented if a pharmacist, or even a single individual, had been employed to dispense and keep all records of morphine. However, additional funds to cover such an expense were not available, and the use of existing resources would have taken resources away from the patient, which would have been an unacceptable trade-off in the Indian setting. In any event, the discrepancies were minor and were easily corrected by increased awareness and attention by nursing staff.

We allowed relatives, instead of the patient, to come to the clinic for periodic review, especially when patients lived far away and travel to the clinic was difficult. In such instances, we modified prescriptions based on the relatives' reports. This practice would be questionable if it were a general policy. However, we believe that this flexibility was necessary in some cases, especially in light of the need to provide palliative care services to patients in the periphery. For us to deprive such patients of pain relief simply because they could not travel to the clinic would have been unacceptable; however, we were unable to monitor morphine use as carefully as would ordinarily be possible in a typical outpatient situation.

The fact that all left-over drugs were not always returned to the PPCC after the patient's death might be a cause for concern. In India, however, this situation is probably inevitable, because the burial or cremation of medicines along with the person's body is a common custom. From a cultural perspective, to demand the return of unused drugs, at a time when the family is overwhelmed by the loss of their relative, would be awkward and possibly unacceptable.

While it is the practice in some countries to dispose of drugs returned by patients, the existing law allows them to be returned and we use them if they are intact and not expired. This might be a questionable practice in some places, but our staff believes that it would be wasteful to discard precious morphine in a country where the vast majority of those who need morphine still have no access to it.

The minor discrepancies in stock position could have been avoided if we took the time to count each tablet or if, instead of packs of loose tablets, they were available as foil packs. However, both of these strategies would have increased our costs with little benefit. We did not find

Morphine consumption (kg)	Year					
	1994	1995	1996	1997	1998	1999
Oral morphine	..	..	..	..	829	894
Cancer patients	299	543	1145	1304	1453	1823
Non-caner patients	87	137	280	369	399	387
All patients	680	680	1425	1673	1852	2205
All morphine	1·065	3·305	7·532	6·322	6·192	7·420

Consumption of oral morphine tablets in the pain and palliative

any instance in which a patient's increasing morphine requirement was out of proportion with progression of disease and pain. There were no cases of actual or suspected diversion and we were able to correct the reasons for the minor discrepancies in stock position. These results are reassuring and show that we were indeed able to maintain adequate control over morphine while still making it available to the patients who needed it. The time and effort required for documentation made us think about simplifying the procedures. However, we are also very much aware that decreasing our record-keeping could possibly lead to a failure to detect real difficulties in the future.

Future of pain relief

Poppy, from which morphine is derived, is grown under government license and inspection in three Indian states. The government-owned Opium and Alkaloid Factory at Ghazipur processes all the raw material from these poppy plants into morphine sulfate powder, most of which is exported to satisfy the increasing demand for pain relief in other countries. Several manufacturers in India procure morphine sulfate powder from the factory, which they then convert to morphine tablets and injections to sell to associations such as the PPCC.

Since 1997, the PPCC has been able to obtain an uninterrupted supply of morphine. From 1994 to 1996, however, there were several occassions when no morphine was available. Such situations normally arose as a result of the difficulties encountered when trying to obtain the required licences. At other times, manufacturers of the drugs simply did not have any stock to sell, because of a lack of morphine powder from the Opium and Alkaloid Factory; a direct result of low and unpredictable demand. During these times, morphine stocks at the PPCC would run out. In these emergencies, the clinic would resort to otherwise unethical and unacceptable cut-back measures, implemented in such a way so as to minimise the effect on patients and families. These measures included dispensing rationed amounts of drugs to patients who could reasonably return to the clinic more frequently than the usual once a fortnight, and use of medications—eg, codeine, buprenorphine—and routes of administration that are less effective for chronic severe pain, or are unnecessarily invasive and costly—eg, nerve blocks. When these alternative treatments failed to achieve adequate pain relief, as was usually the case, the staff would share in the helplessness, anger, and frustration of the patients and their families. To communicate the intensity of the dread felt by staff and patients when a morphine shipment was delayed, and the joy when the morphine finally arrived, is not possible.

To address the morphine availability problem in India, the PPCC, the Pain and Palliative Care Society, and the Indian Association for Palliative Care initiated a collaborative project in 1998 with the central Government of India and Kerala state government officials. After numerous meetings and communications about supply issues, the factory was instructed to maintain a minimum stock of morphine sulfate that would be available all the time. Additionally, a PPCC-sponsored workshop on morphine availability was held in Trivandrum, the state capital, for government officials and palliative care physicians. This initiative resulted in improved cooperation and the simplification of state licensing procedures. Furthermore, the PPCC was exempted from the state health department requirement of employing a pharmacist to dispense drugs, because doing so placed an undue financial burden on the programme. Instead, nurses are now trained to manage dispensing and record keeping for medications, including morphine, according to the physicians' prescription. Table 1 shows the amount of morphine and the number of patients treated at the PPCC over the past six years.

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