



A subcutaneous polymeric opioid delivery system for the treatment of cancer pain

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ABSTRACT

The optimal control of pain related to cancer requires the use of potent opioid analgesics. Despite significant efforts by the World Health Organization and other international agencies, oral morphine and other opioids remain largely unavailable to 80% of the world's population. As more cancer cases are being diagnosed in the developing world than elsewhere, large numbers of patients worldwide suffer from cancer-related pain without reasonable therapeutic options. This manuscript describes a polymeric opioid delivery system designed to provide opioids subcutaneously at a continuous rate for 1–3 months alleviating concerns regarding compliance, misuse, diversion and costs. This approach to opioid administration could substantially impact the global treatment of patients with cancer pain.

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1. Introduction

Pain in patients with terminal illness is often undertreated even in developed countries with abundant resources and easy access to oral, parenteral, and transdermal opioids. (Adult Cancer Pain Guidelines, 2010; Swarm et al., 2007; Fairchild, 2010) In developing nations, where opioids are generally not available, the challenges to providing adequate analgesia to patients with cancer and other serious diseases are often insurmountable. In spite of concerted efforts by the World Health Organization and other organizations to make oral opioids available and to educate physicians and government officials, limited progress has been made in relieving pain in patients with life limiting illnesses. (World Health Organization, 2000) Major obstacles to the procurement and distribution of opioids include significant limitations on funds for all pharmaceutical agents, a priority to distribute agents that prevent or cure diseases (i.e. vaccines or antibiotics), and a focus on treating children and young adults rather than terminally ill patients. In addition, health ministers from many countries express reasonable concerns regarding compliance in taking the affordable immediate release short acting opioids, the safe storage of these drugs in private homes, and the possible diversion of these agents into illicit channels. (Koshy et al., 1998; Joranson and Ryan, 2007) Finally, the documented association between drug diversion, addiction, violence, and AIDS is especially worrisome in nations with many other important health issues.

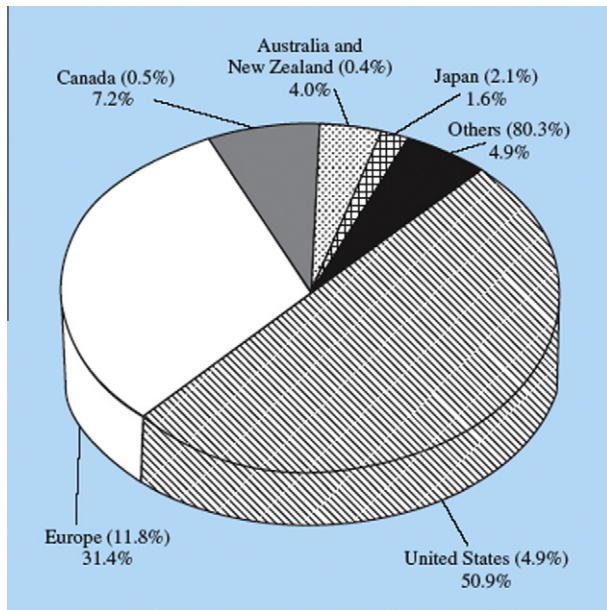
Issues regarding the treatment of pain will continue to grow in importance worldwide. The incidence of cancer is rapidly increasing in the developing world and currently more than 70% of all cancer deaths occur in low- and middle-income countries. (World Health Organization, 2000) Over 70% of cancer patients will experience severe pain during the course of their illness. The NCCN guidelines and other resources document that opioids are required to provide acceptable pain control in most patients with terminal malignancies. (Adult Cancer Pain Guidelines, 2010) Although morphine is not expensive, recent data from the International Narcotics Board clearly demonstrate that opioids remain unavailable to over 80% of the world's population (Fig. 1). (Narcotic Drugs, 2007; International Narcotics Control Board, 2005)

2. Description of the intervention/program, including funding source

Taking steps to ensure that patients with cancer and other terminal illnesses remain as comfortable and functional as possible is important to health care providers and public health officials. As a result, novel approaches that address fundamental concerns regarding opioid availability in these countries are needed. One such approach employs an inexpensive, non-biodegradable, polymeric implant designed to provide continuous hydromorphone to the subcutaneous tissue for 1–3 months (Lesser et al., 1996). This subcutaneous implant is constructed of materials that are approved by the FDA, can be implanted by a physician extender, and release an opioid at a continuous rate without an ini-

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*Percentages in parentheses refer to shares of the world population.

Fig. 1. Worldwide morphine consumption in 2005. Source: *Narcotic Drugs* (2007).

tial “burst”. The materials and manufacturing are designed to provide an inexpensive product suitable for use in developing nations. This novel opioid delivery system has the potential to reduce concerns about patient compliance, drug storage, and opioid diversion while making opioids available to patients in rural areas and reducing the number of follow-up visits necessary for medication refills.

2.1. Implementation challenges

The major obstacle encountered when any drug is placed within a slow release polymeric delivery system is the pattern of drug release. This is characterized by an initial rapid drug release followed by declining drug levels thereafter. If the drug being used is relatively non-toxic the initial burst release is of little consequence. However, if a one month or three month supply of opioid is placed into the polymer and a large percentage is released immediately it would result in the death of the patient. Our polymeric delivery system was specifically designed to prevent an initial burst release of opioids. This was accomplished by first combining the polymer and opioid and producing a polymeric disc about the size of a shirt button. This is then coated with an opioid impermeable covering that prevents all drug from leaving the polymer. Finally, a hole is created in the center of this coated disc. This hole extends from the top to the bottom of the disc (Fig. 2). It is this central uncoated channel's surface area that provides the only means for the opioid to be released from the polymer. This configuration provides a continuous release for over 30 days without a burst. In addition, the geometry permits formulations which will provide a wide range of drug release rates and durations of action. The polymer will release more milligrams per hour as the surface area of the uncoated central channel is increased. Thus, higher release rates with deeper polymers or larger central channels. The duration of release is regulated by the diameter of the polymer. As the diameter of the polymer is increased, the distance from the central channel to the most distant opioid is increased resulting in an extension of duration of the action. This polymeric drug delivery system was designed specifically to optimize the use of hydromorphone. This opioid is routinely administered to the subcutaneous tissue in cancer patients

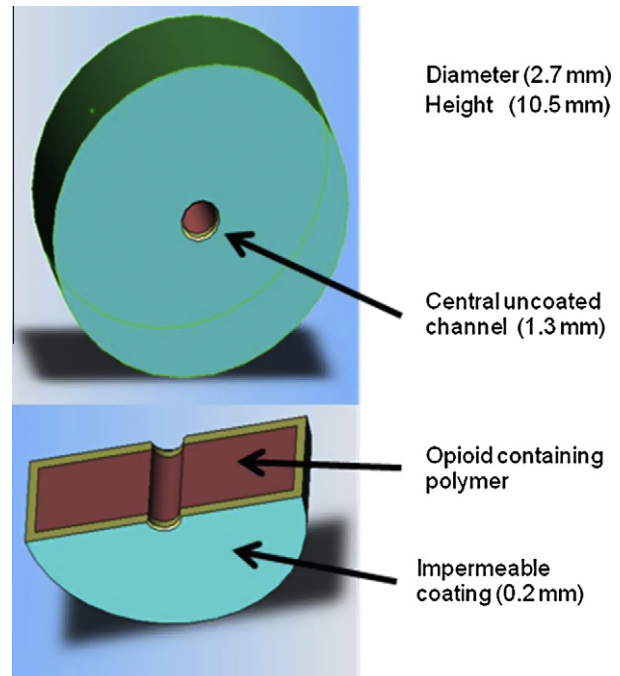


Fig. 2. Hydromorphone polymer implant.

using either intermittent injections or an external pump connected to an indwelling subcutaneous needle. As hydromorphone is six to seven times more potent than morphine, our polymeric implant is many times smaller than would be required for an equipotent morphine polymer.

3. Potential impact

This new opioid delivery system should have significant impact in the management of patients with pain from terminal illnesses. Care should begin with a thorough evaluation by a qualified health care professional. This would focus on better understanding the etiology of the pain, considering alternate treatment strategies, and evaluating other co-morbidities that would impact on a final treatment plan. If systemic opioids are felt to be the treatment of choice, opioid titration should be initiated using a short acting agent such as oral or parenteral morphine or hydromorphone. This would provide valuable information about the sensitivity of the pain to opioids and the daily dose of opioid required to control the pain. The effective dose would then be converted to parenteral hydromorphone equivalents using a narcotic equivalency table or opioid conversion software program which is available on the internet at no cost. The health care provider could then select the appropriate hydromorphone polymer based on the desired delivery rate (milligrams per hour of hydromorphone) and duration of action (1, 2 or 3 months). The polymer would be placed subcutaneously and the patient would be observed for 24 h. Thereafter, the patient would be discharged to his place of residence and follow-up phone calls or visits would be made to ensure that the patient is comfortable. Ideally, a short acting oral opioid would also be provided to be used as “rescue” doses for pain exacerbations. A second polymer could be placed if the pain is escalating or a polymer with a higher release rate could be administered when a new polymer is required. Old polymers can be left in place or removed when a new polymer is inserted.

This subcutaneous drug delivery device will provide a continuous infusion of subcutaneous hydromorphone to patients with life

limiting illnesses without attached pumps or needles. The risk of drug diversion will be substantially reduced as it will not be kept in private homes or stocked in pharmacies. Accidental misuse will be eliminated as the opioid will not be stored in the home. In addition, once the polymer is placed subcutaneously compliance is not an issue. Placement of the subcutaneous polymer could be performed by a health care extender, would occur after the administration of local anesthetics, and would not require the use of sutures. Finally, as the components and manufacturing of the implant are inexpensive, this approach to the palliation of pain should be within the limited budgets of countries around the world.

Conflict of interest statement

None

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