Opioids: maximizing efficacy, minimizing adverse effects

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The use of opioids in efforts to achieve pain relief for chronic noncancer pain has remained among the most controversial issues in medicine throughout the ages. Opioids are potent broad-spectrum analgesics that may provide significant analgesia to patients with severe chronic pain, but also possess qualities that make them prone to misuse in certain subpopulations of patients. Examinations of opioid therapy seem to repeatedly focus on their role as analgesics; however, in palliative medicine they may also be used as cough suppressants, sedatives or to ameliorate the uncomfortable sensation of dyspnea.

One of the earliest known written references to the medicinal use of opioids was found in the Eber Papyrus of 1552 BCE, which has been translated as:

"The goddess Isis gave the juice of the poppy to Ra, the sun god, to treat his headache."

(one can only assume that Isis was not a neurologist). After England and Portugal had developed a blossoming market for opium in China, the Emperor of China wrote to Queen Victoria in 1840 asking her to halt this trade, leading to the so-called 'Opium Wars'. In 1871, William Dale, a surgeon and physician in the UK, promoted opium for analgesia and sedation in palliative care patients near the end of life, but also recognized its abuse potential. He wrote:

"It is stated that some women, after having been hypodermically treated under medical surveillance, are in the habit of injecting morphia … on their own responsibility, when suffering from slight neuralgic pains, mental depression, or severe ennui, 'just as the drunkard takes his dram.'"

This dual nature of opioids has led the pendulum of medical opinion to swing back and forth between opiophobia and opiophilia. In the 1960s, it was considered inappropriate to prescribe opioids for chronic noncancer pain, and physicians spent considerable time trying to discontinue opioid therapy. A few decades later, some physicians began using opioids generously as a first-line treatment for a wide variety of painful conditions. Although there may have been nothing inherently wrong with this, primary care physicians with little training in pain medicine were also treating a variety of painful conditions solely with relatively high-dose opioids, some of which may have responded better to a combination of physical medicine approaches, interventional approaches and other pharmacologic approaches (e.g., trigeminal neuralgia and piriformis syndrome). The 1914 Harrison Narcotic Act in the USA required that opioids be prescribed by a physician.

In 1956, Schiffrin and Gross described one reaction of a patient in pain to the administration of morphine:

"The patient is aware of pain, but feels that it is no longer part of him. He recognizes it as he would an impersonal object in the room; and since his thoughts are no longer completely centered on pain; he can think and act in a rational manner."

They contrasted this with the administration of morphine to a patient who is not in pain and who may experience euphoria, described as a "patient who is uncooperative with his thoughts turned inward as he experiences a sense of exhilaration and exaltation" [1].

In the 1970s, the decades of work from Raymond Houde and Ada Rogers at Sloan-Kettering in New York (NY, USA), and of Cicely Saunders and Robert Twycross at St Christopher's Hospice in London, UK, re-established opioids as an important part of the medical treatment plan for patients suffering from cancer pain. Houde's pain fellows

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(e.g., Kathleen Foley, Russell Portenoy and Richard Payne) were among the first to demonstrate the safety and efficacy of opioid for the treatment of noncancer pain.

The 2009 version of the American Geriatric Society (AGS) Clinical Practice Guidelines: Pharmacological Management of Persistent Pain in Older Persons states: "All patients with moderate–severe pain, pain-related functional impairment or diminished quality of life due to pain should be considered for opioid therapy" [2].

In 2009, Chou *et al.*, with an expert panel convened by the American Pain Society and the American Academy of Pain Medicine, concluded that chronic opioid therapy should be utilized for carefully selected and monitored patients with chronic noncancer pain [3]. Currently, the use of opioid for chronic noncancer pain is well accepted, but controversial issues remain.

It has become apparent that the concept of 'balance' seems to be the most rational approach to prescribing opioids. Balance refers to practicing a 'middle-of-the-road' approach employing the appropriate use of opioids in the context of good medical practice, while at the same time focusing appropriate attention on risk assessment and management of opioid misuse. In fact, Raymond Houde had utilized the term balance in 1995 when he stated:

> *"We sought out a balance between a drug's good effects and its bad effects … the only way we could determine that, of course, was in relative terms"* [4].

In the new millennium, tools sprung up to help clinicians predict patients who may be at risk of opioid misuse. Furthermore, the use of a number of practices was promoted (e.g., opioid agreements and urine drug testing) in efforts to curb, as well as identify, opioid misuse.

The US FDA is in the process of drafting risk evaluation and mitigation strategies (REMS), which will apply to opioid analgesics in efforts to curb the potential abuse of these agents. It is hoped that REMS, which may be finalized as early as the end of 2009, will not reduce access to the appropriate medical use of opioids for the treatment of pain. Onsolis™ is a US FDA-approved fentanyl formulation for adult breakthrough cancer pain patients on 'around the clock' opioids, which uses BioErodible MucoAdhesive technology to deliver fentanyl via an absorbable film through the mouth's mucous membrane on the inner lining of the cheek. A specific REMS program for Onsolis exists that includes: a restricted distribution program called the FOCUS program, providing training and educational materials to prescribers and pharmacy personnel, as well as a counseling call to patients in efforts to ensure they have been adequately educated regarding the use of the medication.

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Opioid-induced adverse effects may be extremely important in certain patients, and may lead to increased suffering/distress, as well as discontinuation of opioid therapy, with the result of increased pain. Specific adverse effects may be associated with specific genes or specific receptors. For instance, in 2001, Dahan *et al.* studied μ-opioid receptor (MOR) knockout mice and concluded that opioid-induced respiratory depression is almost solely due to opioid activation of the μ-opioid receptor (and not δ, κ or opioid receptor-like 1 receptors) [5]. Thus, pharmacologic strategies to address opioid-induced respiratory depression should focus on the μ-opioid receptor.

Other strategies to diminish opioid-induced adverse effects may involve genetic techniques. Margarete Ribeiro Dasilva and colleagues from the University of Florida in Gainesville (FL, USA) examined three single nucleotide polymorphisms (SNPs) of the dopamine receptor D2 (*DRD2*) gene (which has been associated with opioid-induced vomiting) and presented their findings at the 2009 annual meeting of the American Pain Society in San Diego (CA, USA). The investigators genotyped the rs1800497, rs6279 and rs2734838 SNPs, and found that the presence of both the rs1800497 and rs6279 SNPs was significantly associated with both nausea ($p = 0.0460$) and vomiting ($p = 0.0056$) after intravenous morphine sulfate, and the haplotype formed by all three SNPs was also significantly associated with nausea ($p = 0.0277$) and vomiting ($p = 0.0019$) following the administration of intravenous morphine sulfate.

When attempting to design alternative opioids with reduced adverse effects, an extensive familiarity with structure–activity relationships of opioid activities is crucial. The classic example of altering opioid structure in efforts to diminish a specific unwanted effect is the removal of the hydroxyl group from the 6-position of morphine sulfate, which tends to diminish its emetic

potential. For example, hydromorphone, which has a double-bonded oxygen at this 6-position, tends to evoke less nausea than morphine.

In this special focus issue of *Therapy*, I propose a number of hypothetical future strategies to minimize various opioid-induced adverse effects, including: combining an opioid with a second agent in efforts to diminish opioid side effects (combination opioid analgesics); the use of alternative opioids that may possess novel qualities and/or work on various opioid receptors; and, finally, peripherally restricted opioid agonists that have the potential to produce analgesia with less side effects than traditional opioids, since they do not gain access to the CNS [6].

McCleane presents some of the many issues surrounding the prescribing of chronic opioid therapy for chronic noncancer pain [7]. Chu and Clark discuss opioid withdrawal, its mechanisms, current treatment strategies and future potential methods to modulate opioid withdrawal (e.g., 5HT3 receptor agonists) [8].

Drs Christup, Lundorff, and Werner present a concise state-of-the-art discussion of novel formulations and routes of administration for opioids in the treatment of breakthrough pain [9]. Dr Dahan delves into the issue of individual differences in response to opioid therapy [10]. Dr Brookoff presents some research highlights related to potential endocrinological effects of opioids [11].

Myself and Dr Kirsh explore the issue of identifying and managing the risk of opioid misuse [12]. Furthermore, they address the issue of assessing when it might be a good time to initiate chronic opioid therapy, and the 'readiness' of the patient for chronic opioid therapy (e.g., the readiness for chronic opioid therapy [RCOT] tool). Dr Mellar Davis, an expert in pain and palliative medicine, and the lead editor of an excellent text, *Opioids in Cancer Pain* [13], is interviewed [14].

I would like to thank all of the contributors who have really made this issue an exciting and insightful collection of various current issues associated with chronic opioid therapy, as well as provided projections and suggestions for future ideas, improvements and therapies with respect to the administration of opioid analgesic products for the alleviation of pain and suffering.

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