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Strategic Pain Management: The Identification and Development of the IAHPC Opioid Essential Prescription Package

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Abstract

The aim of this study was to determine by consensus the components of an opioid essential prescription package (OEPP) to be used when initiating a prescription for the control of moderate to severe chronic pain. Palliative care physicians ($n=60$) were sampled from the International Association for Hospice and Palliative Care (IAHPC) membership list to represent a range of countries of varying economic levels and diverse geographical regions. Using a Delphi study method, physicians were asked to rank preferences of drug and dosing schedule for first-line opioid, antiemetic, and laxative for the treatment of adults with chronic pain due to cancer and other life-threatening conditions.

Overall response rates after two Delphi survey rounds were 95% ($n=57$) and 82% ($n=49$), respectively. A consensus (set at $\geq 75\%$ agreement) was reached to include morphine as first-line opioid at a dose of 5 mg orally every 4 hours. Consensus was reached to include metoclopramide as a first-line antiemetic, but there was no consensus on "regular" or "as needed" administration. No consensus was reached regarding a first-line laxative, but a combination of senna and docusate secured 59% agreement. There was consensus (93% agreement) that laxatives should always be given regularly when opioid treatment is started. Further work is needed to establish a recommended dose of metoclopramide and a type and dose of laxative. The resulting OEPP is international in scope and is designed to ensure that opioids are better tolerated by reducing adverse effects of opioids, which could lead to more sustained improvements in pain management.

Introduction

Cancer-related pain is experienced by almost 50% of patients in all stages of the disease and by more than 70% in advanced and terminal stages.[1] People with human immunodeficiency virus (HIV) in early stages and almost 100% in very advanced stages of infection experience pain.[2,3] Opioid analgesics are the mainstay of management for moderate to severe pain.[4] Still, it is estimated that 80% of patients in pain do not have access to analgesics.[5,6] Even in countries with abundant health resources, such as those in Western Europe[7] and the United States with availability of opioids, inadequate training of health care professionals and poor communication between physicians and patients often lead to undertreated pain and the presence of adverse effects that are preventable or treatable.

Adverse effects of opioids, such as constipation and nausea, may limit the dosing of opioids and lead to early discontinuation and inadequate analgesia. Constipation affects up to 87% of terminally ill people who are receiving opioids.[8] There are some suggestions that laxative prophylaxis for prevention of constipation should be a priority when patients are starting

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opioid medication.[9] Laxatives can be broadly separated into two types: those that act by softening fecal matter and those that act through direct stimulation of peristalsis. The evidence to favor one laxative over another in palliative care is scarce. Only a few trials show that oral lactulose, polyethylene glycol/electrolyte solutions, and senna are effective in people with opioid-induced constipation.[10,11]

Nausea and vomiting occur in 15% to 40% of patients.[12,13] Some health care professionals suggest using antiemetics for the prevention of nausea and vomiting whenever opioids are prescribed, but there is limited evidence to support this recommendation.[14] Metoclopramide is generally recommended as a first-line therapy. Medications with central nervous system effects, such as haloperidol,[15] levomepromazine,[16] and cyclizine[17] have been shown to be effective but may cause sedation and other adverse effects. There are no studies to indicate the effectiveness of one antiemetic over another in the management of opioid-induced nausea.

In 2006, the International Association for Hospice and Palliative Care (IAHPC) developed a list of Essential Medicines in Palliative Care, which includes weak and strong opioids for the treatment of moderate and severe pain. It also includes antiemetics and laxatives for the management of nausea and constipation.[18] However, the IAHPC list does not specify dosages or combinations of opioids, laxatives, and antiemetics that may be most safe and effective in the prevention and treatment of chronic pain in patients who require initiation of strong opioids.

The IAHPC wanted to recommend an opioid essential prescription package (OEPP) that would: (a) ensure that opioids are better tolerated by patients and therefore lead to more sustained improvements in pain control and (b) be international in scope. The aim of this study was to determine by consensus the components of an OEPP to be used when initiating a prescription for the management of chronic pain due to cancer and other life-threatening conditions. The second objective was to determine the availability of OEPP components within each country and geographical region in order to ensure international applicability of the recommendations. The study was not intended to measure and compare the efficacy of any opioid, antiemetic, or laxative included in the IAHPC List of Essential Medicines for Palliative Care or in any other list.

Method

The IAHPC convened a working group (WG) of experts consisting of members of the IAHPC Board (MB, EB, LDL, CR, RW) and external palliative care experts from academic and research institutions (EV, CN).

Study design

A Delphi technique with two rounds was used to determine consensus. Participants confidentially accessed an online web-based survey system through the IAHPC website. The estimated time to complete each survey was 15 minutes. The survey contained medications listed in the IAHPC List of Essential Medicines for Palliative Care for the treatment of severe pain, nausea and vomiting, and constipation:

1. *Opioids:* morphine, oxycodone, methadone, and fentanyl (transdermal patch);
2. *Laxatives:* bisacodyl and senna;
3. *Antiemetics:* haloperidol, levomepromazine, and metoclopramide.

Since the development and publication of the IAHPC list in 2006, additional studies on the management of opioid-induced constipation have been conducted with lactulose and polyethylene glycol solutions with strong evidence demonstrating their effectiveness and safety.[7,8] In addition, new guidelines also recommend magnesium hydroxide (oral liquid) (Milk of Magnesia) for the treatment of constipation.[19,20] Based on these findings, the WG decided to include them in the study.

Sampling and participants

The study sample was selected using the principle of purposeful sampling[21] and the following criteria:

1. IAHPC members who were physicians.
2. Individuals working in countries that submit consumption reports to the International Narcotics Control Board (INCB).[22]

Using the list of potential participants, the following steps were taken:

1. Members were stratified using the World Health Organization (WHO) regional classification system (Africa, Americas, South East Asia, Europe, Eastern Mediterranean, and Western Pacific).
2. Based on the World Bank income classification,[23] countries were stratified as high, upper middle, lower middle, and low.
3. The first two individuals from the results in each category were selected. When the number of individuals in a socioeconomic category was insufficient, an individual from the next socioeconomic level was selected.

The selected individuals were contacted by e-mail and invited to participate. Whenever a person declined the invitation or if he/she did not reply, the individual following in the list was invited to participate.

An ethics review board from the Tornú Acute General Hospital in Buenos Aires, Argentina approved the study. Participants were informed about the study through a letter and an introduction to the survey. A signed informed consent was submitted by the participants before completing the survey.

Procedure

A description of the study and instructions for accessing the survey was sent to 60 participants who accepted the invitation. Two e-mail reminders were sent at 2-week intervals after initial contact for each round. The first Delphi round included information on: participant demographics; opioids, laxatives, and antiemetics; availability and access to medications; laxative and antiemetic administration times; and general comments. Participants were asked to rank a list of medications in order of preference from "most safe and effective" to "least safe and effective" in adults for whom they were initiating strong opioids for the treatment of moderate to severe chronic pain due to cancer and other life-threatening conditions. They were also given the opportunity to suggest other medications

not included in the survey. In the availability and access to medications section, participants were asked if their patients had difficulties accessing any of the medications listed in the study and if so, which medications.

For the second Delphi round, the cutoff point for consensus (the proportion of sample agreeing with the statement) was set at ≥75%. Medications rated lower than 15% after the first round were dropped from the list. In the second round, participants were provided with the results from the first round and asked to rank the remaining medications by identifying their first, second, and third drug of choice.

Data analysis

Quantitative data were analyzed using simple descriptive statistics. Open responses were coded, categorized, and used to inform the final OEPP. The components of the final OEPP were based on whether consensus was reached for drug and administration selection after both Delphi rounds.

Results

Sixty (60) pain and palliative care physicians agreed to participate in the study. Overall response rates of the first and second survey rounds were 95% (57/60) and 82% (49/60), respectively. More than a half of participants (57%) were from countries in the Americas and Europe. Sixty-three percent were from high and upper middle income countries.

Preferred opioid

In the first round, morphine was selected by 89.4% ($n=51$) of the participants, achieving consensus as the opioid of first choice to be included in the OEPP. In the first Delphi round hydromorphone was not included, but 35.1% ($n=20$) of the participants suggested it. It was therefore included in the second round as an alternative opioid of choice.

In the second round, 87.7% ($n=43$) agreed or strongly agreed with the use of oral morphine 5 mg every 4 hours as the first line of treatment. No consensus was reached regarding an alternative opioid of choice in case of lack of availability of morphine. Only oxycodone and methadone were chosen by more than 15% of the participants.

Preferred laxative

After both rounds, there was no clear consensus regarding a laxative of first choice with the combination of senna and docusate reaching the highest level of agreement (59.2%; $n=29$), followed by bisacodyl (24.5%; $n=12$). There was consensus that laxatives should always be given when opioid treatment is started (93%; $n=53$).

Preferred antiemetic

After both rounds metoclopramide reached consensus (75.5%; $n=37$) as the antiemetic of first choice. No consensus was reached regarding frequency of antiemetic administration. After both rounds 51.0% ($n=25$) chose "as needed," whereas 49.0% ($n=24$) selected "regularly."

Availability and access to medications

As shown in Table 1, a substantial proportion of participants had difficulty accessing opioids in their country, ranging from 33% (morphine) to 45% (methadone). Most laxatives are more readily available, although more than one-third of participants (38.8%) would have difficulty accessing senna and docusate. Of the three antiemetics, the highest frequency in terms of problems with medication access was for levomepromazine (46.9%). Poor access to opioids, except fentanyl, was significantly higher in lower middle and low income countries ($p<0.05$). No significant differences in accessibility for laxatives were found between high and low income countries. Access to levomepromazine was significantly more difficult in lower middle and low income countries. The number of participants in each geographical region was too small to determine significant differences among the responses from participants in each region.

Differences between gross national income levels

When comparing medication selection based on income classification (Table 2), a significantly higher proportion of participants in lower income regions selected oxycodone than participants in higher income regions ($p=0.03$).

Table 1. Responses of Participants Who Reported Problems with Availability and Access

		Total (n = *49*)		*HI/UMI* (n = *31*)		*LMI/LI* (n = *18*)		
Drug class	*Medication*	N	%	N	%	N	%	
Opioids	Methadone	22	44.9	9	29.0	13	72.2	*p = 0.003*
	Oxycodone	20	40.8	9	29.0	11	61.1	*p = .028*
	Fentanyl	19	38.8	10	32.3	9	50.0	
	Morphine	16	32.7	6	19.4	10	55.6	*p = 0.009*
Laxatives	Senna and docusate	19	38.8	10	32.3	9	50.0	
	Macrogols	15	30.6	7	22.6	8	44.4	
	Senna	10	20.4	5	16.1	5	27.8	
	Milk of Magnesia	5	10.2	2	6.5	3	16.7	
	Bisacodyl	4	8.2	2	6.5	2	11.1	
	Lactulose	4	8.2	2	6.5	2	11.1	
Antiemetics	Levomepromazine	23	46.9	10	32.3	13	72.2	*p = 0.007*
	Haloperidol	3	6.1	2	6.5	1	5.6	
	Metoclopramide	1	2.0	0		1	5.6	

HI, high income; UMI, upper middle income; LMI, lower middle income; LI, low income.

Table 2. Medication Selection Based on UN Gross National Income Classification (n = 49)

	HI/UMI (n = *31*)		*LMI/LI* (n = *18*)		
	N	%	N	%	
Morphine	27	87.1	17	84.4	
Oxycodone	13	41.9	14	77.8	*p = 0.03*
Methadone	9	29.0	3	16.7	
Senna/docusate	19	61.3	10	55.6	
Bisacodyl	7	22.6	5	27.8	
Metoclopramide	25	80.6	12	66.7	

HI, high income; UMI, upper middle income; LMI, lower middle income; LI, low income.

There were no significant differences for any of the other medications.

Opioid essential prescription package

Using the results from both rounds, members of the WG developed the OEPP and identified the appropriate dosage and route of administration for each medication in accordance with the U.S. Food and Drug Administration approved manufacturer's recommendation. Table 3 shows the resulting OEPP.

Discussion

The aim of this study was to develop a single prescription package (drugs and dosing) with one opioid, one laxative, and one antiemetic for the initiation of opioid treatment in cancer pain and other life-threatening conditions, with the intention to facilitate opioid use, improve patient compliance, and reduce adverse effects.

The selection of morphine as a first option for the start of pain treatment is in agreement with different clinical guidelines and critical reviews in pain management due to its efficacy, clinical experience, availability, and cost.[24,25]

Oxycodone and methadone were the alternative opioids selected for the start of pain treatment, the former chosen more by participants located in low income countries, and the latter more by those in high income countries. Data indicate that oxycodone is more expensive than methadone[26] and less safe to use in patients with renal failure.[27,28,29] This finding suggests that factors other than the price are influencing this preference and further studies may be useful to identify these factors.

Table 3. IAHPC Opioid Essential Prescription Package (OEPP)

Opioid:
Morphine, oral, 5 mg every 4 hours

Laxative:
Combination of senna and docusate, oral, 8.6 mg/50 mg every 12 hours.
OR:
Bisacodyl, oral, 5 mg every 12 hours.

Antiemetic:
Metoclopramide, oral, 10 mg every 4 hours OR as needed.

Constipation is the most common adverse effect of opioids, and in this study almost all participants recommended that laxative prophylaxis should be a priority when patients are starting opioid medication. The combination of senna and docusate was the most preferred option to prevent constipation, but more than one-third of the participants reported having access difficulties to the combination, both in high and low income countries. Bisacodyl was chosen as the second option in treating constipation and has the advantage of being more accessible in most of the countries represented in this study. Evidence on the superiority of one laxative over another in the management of opioid-induced constipation has not been demonstrated and recommendations have been made on the basis of expert opinion, unsupported by any prospective study or systematic evaluation of retrospective data. As in the case of the opioids, further studies would be useful to identify which factors are influencing this preference.

Metoclopramide was recommended as a first-line therapy in the management of opioid-induced nausea, but there was no consensus on dosing schedule. There are no studies to indicate the superiority of one antiemetic over another, or if they should be used for the prevention of opioid-induced nausea.

Further work is needed to establish a recommended type and dose of laxative, as well as a dosing schedule for metoclopramide and to compare the OEPP with standard pain management approaches on outcomes such as pain prevalence and intensity, improvements in patient compliance, and reduction of adverse effects of opioids.

More than one-third of participants reported problems with availability and access of medications and in low income countries this was reported by half of the participants. Challenges in the provision of pain treatment in many developing countries are complex and include poverty, illiteracy, language barriers, limited health care resources and facilities, lack of training, and unduly restrictive laws and regulations that limit the distribution, prescription, dispensation, and use of controlled medications.[30,31]

This study has several limitations. Findings were based on the opinions of physicians purposively selected from IAHPC membership list and may not reflect the views of a wider sample of palliative care and pain specialists. The majority of participants were located in high or upper middle income countries so the results may not reflect the preference of individuals working in lower middle or low income countries.

Conclusion

The IAHPC OEPP is designed for moderate to severe chronic pain in adult patients who require initiation of strong opioids. Further work is needed to examine the effectiveness of the OEPP compared with usual care in reducing adverse effects and improving tolerability of opioid treatment, leading to better pain management.

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The names and countries of the palliative care physicians who participated in both rounds of the Delphi are listed here.

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