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ORIGINAL ARTICLE

Prophylactic use of antiemetics for prevention of opioid-induced nausea and vomiting: a survey about Italian physicians' practice

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Abstract

Purpose Antiemetics are being used both for the treatment and prophylaxis of opioid-induced nausea and vomiting (OINV) in clinical practice, despite the lack of evidence for the prophylactic benefit. Studies among Japanese physicians demonstrated over 80% prescribe antiemetics, with neuroleptic antipsychotics as the most commonly prescribed drugs. Our objective was to elucidate the current scenario of the prophylactic use of antiemetics for OINV among Italian physicians.

Methods We conducted a web-based cross-sectional national survey. All the invited participants received an e-mail with an 11-item electronic questionnaire accessible through a direct link. Anonymity was guaranteed. According to the exploratory intent of the survey, we did not predefine any formal statistical hypothesis. Associations between variables were tested by the Pearson chi-square or the Fisher exact test.

Results From January to March 2017, 112 completed the electronic questionnaire (112/256, overall response rate, 43.7%). Nearly half of the participants were oncologists (54; 48.2%). Sixty-one (54.4%) physicians worked in palliative care units. About 45% of the interviewed prescribed prophylactic antiemetics at the beginning of opioid prescription. The most commonly chosen drugs for this purpose were prokinetics such as metoclopramide and domperidone (84%), followed by 5-HT3 antagonists (8%), neuroleptic antipsychotics (6%), and corticosteroids (2%). Ninety-one physicians (81%) declared to prescribe antiemetics at the occurrence of OINV, mainly prokinetics ($N = 70$; 77%).

Conclusion Italian physicians do not commonly prescribe prophylactic antiemetics for OINV. Unlike previously reported data, dopamine antagonists resulted the most commonly prescribed drugs. Prospective clinical trials are necessary to evaluate the real efficacy of this practice.

Keywords Opioid-induced nausea and vomiting · OINV · Antiemetics · Cancer pain · Prophylaxis

Introduction

Pain is common in cancer patients, particularly in the advanced stage of the disease. The most comprehensive systematic review indicates pain prevalence ranging from 33% in patients after curative treatment, to 59% in patients on active anticancer treatment and to 64% in patients with metastatic, advanced, or terminal disease [1, 2]. Opioids represent the mainstay of analgesic treatment in moderate to severe cancer-related pain. [3]. Unfortunately, among the adverse effects of opioids, there are nausea, vomiting, and/or retching. These side effects are commonly referred to as opioid-induced nausea and vomiting (OINV) and occur in up to 60% of patients who start to receive opioids [4, 5].

Patients generally develop tolerance to OINV within a few days. However, in some patients, OINV persists over time and

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may cause discontinuation of therapy and impairment of pain management.

Antiemetics are being used both for the treatment and prophylaxis of OINV in clinical practice, despite the lack of evidence for the prophylactic benefit. Studies among Japanese physicians trained in cancer pain management demonstrated over 80% prescribe antiemetics, with neuroleptic antipsychotics (prochlorperazine 88%) as the most commonly prescribed drugs [6].

OINV may be difficult to tease apart from chemotherapy-induced nausea/vomiting (CINV), radiation-induced emesis (RIE), or postoperative nausea/vomiting (PONV); thus, "pure" OINV has not been extensively well studied as a single entity. Although the precise mechanisms of OINV are not entirely certain, there are multiple and complex mechanisms involved. OINV may be due to multiple opioid effects, including (a) enhanced vestibular sensitivity (symptoms may include vertigo and worsening with motion), (b) direct effects on the chemoreceptor trigger zone, and (c) delayed gastric emptying (symptoms of early satiety and bloating, worsening post-prandially) [7]. The classic, straight treatment of OINV, partially due to the strong activity on μ-opioid receptors, consists of opioid antagonists (e.g., continuous naloxone infusion, naltrexone, nalmefene). Additionally, classic antiemetic drugs are also efficiently used for the treatment of OINV as well as for PONV or CINV, although some of them seem to be particularly useful for the treatment of OINV [7]. Despite the treatments, OINV may lead to the discontinuation of opioids in several patients, thereby compromising pain management [8]. For this reason, many physicians prefer to prescribe prophylactic antiemetic treatment while administering active painkillers. In this perspective, we aimed at elucidating the current scenario of the prophylactic use of antiemetics for OINV, among the Italian physicians. To pursue this objective, we conducted a cross-sectional analysis to investigate the use of prophylactic antiemetics for OINV prevention when starting opioid therapy.

Our final goal was to conduct a future randomized controlled clinical trial to validate the efficacy of the most commonly used antiemetic in this scenario based on the outcomes of this survey and on the other similar experience reported in literature.

Methods

Subjects

This survey was targeted among Italian physicians trained in supportive care in cancer. The participants were chosen among those attending several short-term clinical supportive care fellowship programs promoted by two of the authors (GP, LV) in the last 5 years.

Survey questionnaire

This was a web-based cross-sectional national survey. The survey was created using GoogleDocs™ online survey maker (https://docs.google.com—Fig. 1).

All the invited participants received an e-mail with the 11-items electronic questionnaire that was only accessible through a direct link. All participants were invited to anonymously fill the questionnaire that assessed the physicians' practice and beliefs regarding the prophylactic antiemetic prescription when they start opioids in patients with cancer pain (7 items) and other demographic data (4 items). After the first invitation, two further reminders were sent. Anonymity was warranted by the Secure Sockets Layer (SSL) encryption with no Internet Protocol (IP) address tracking.

Since the study did not involve patients' data, but is a physician's opinion collection, it was deemed as unnecessary to submit it to the Ethical committees. Absolute frequencies and percentages were collected and organized with Microsoft Excel™. According to the exploratory intent of the survey, we did not predefine any formal statistical hypothesis or sample size.

Statistical analysis

Descriptive statistics were used to describe the participants' characteristics. The association between variables was tested by the Pearson chi-square test or the Fisher exact test.

Variables testing significant at the univariate analysis were entered into multivariate analysis.

A multivariate logistic regression model was developed using a stepwise regression (forward selection) to compare the predictive power of different items. Enter limit and remove limit were $p = 0.10$ and $p = 0.15$, respectively. The SPSS (21.0) licensed statistical programs were used for all analyses.

Results

This survey was conducted from January to March 2017 and was addressed to a total of 256 Italian physicians trained on supportive care in cancer and pain management. One hundred twelve completed the electronic questionnaire (112/256, overall response rate, 43.7%).

Nearly half of the participants were oncologists (54; 48.2%). Overall, 61 (54.4%) physicians worked in palliative care units.

The Italian regions more represented were Lazio (22; 19.6%) and Lombardia (21; 18.8%), while 48 (42.9%) physicians declared to work in the north of Italy (Table 1).

According to the first answer of the survey, about 45% (50/112) of the physicians prescribe prophylactic antiemetics at the beginning of opioid prescription. The most commonly

1.	While prescribing opioids for the first time on a patient, do you also prescribe antiemetics prophylactically to prevent OINV?
2.	If yes, which antiemetic do you prescribe the most? [a]
3.	Besides the prophylactic antiemetics, do you also prescribe other antiemetics for treating possible OINV that could occur after initiating opioid intake?
4.	In the case of question 3, what is the antiemetic you most often prescribe? [b]
5.	Based on your clinical experience, do you believe that the prophylactic antiemetics are actually effective in preventing OINV?
6.	Approximately what percentage of patients do you believe develop OINV despite the use of prophylactic antiemetics?
7.	What would that percentage be if anti-emetic prophylaxis were not used?
8.	Please specify your medical specialization
9.	Please specify your structure of working
10.	Please specify your geographic site of work
11.	Please specify your age

[a] Applicable only to those physicians who reply "yes" to question 1.
[b] Applicable only to those physicians who reply "yes" to question 3.

Fig. 1 Survey questionnaire

prescribed drugs for this purpose were prokinetics such as metoclopramide and domperidone (84%), followed by 5-HT3 antagonists (8%), neuroleptic antipsychotics (6%), and corticosteroids (2%). Overall, 91 physicians (81%) declared to prescribe antiemetics at the occurrence of OINV, mainly prokinetics ($N = 70$; 77%).

Among the physicians who prescribed prophylactic antiemetics (50/112, 45%), 41 physicians (82%) also prescribed antiemetics for use as treatment at the occurrence of OINV (beforehand prescription for treatment in addition to prophylaxis). The commonest antiemetic used for this treatment purpose remains metoclopramide (66%; used by 27 physicians), followed by 5-HT3 antagonists (17%; used by seven), steroids (10%; used by four), antipsychotics (5%, used by two), and NK1 receptor antagonist used by one.

Moreover, 102 physicians (91%) agreed that antiemetics are effective against OINV and the majority declared that the incidence of OINV decreases with the association of antiemetics to opioids.

The factors associated with the prescribing of antiemetic prophylaxis while starting a new opioid treatment were "believe that antiemetic drugs are effective against OINV" ($p = 0.02$) and a higher presumed percentage of patients that develop OINV even with or without antiemetics ($p = 0.04$ and $p < 0.0001$, respectively). No statistic associations were found for physicians' age, region of provenience, working structure, and different specializations (Table 2).

At multivariate analysis, the only factor that seems to significantly influence the prescribing of an antiemetic therapy together with a new opioid treatment was the estimated number of patients who develop OINV without prophylaxis (OR 5.52, 95% CI 2.70–11.28, $p < 0.0001$).

Table 1 Background of questionnaire respondents

	N (%)
Age	
< 40 years	63 (56.3)
≥ 40 years	49 (43.7)
Medical specialization	
Oncology	54 (48.2)
Anesthesiology	16 (14.3)
Palliative care	6 (5.4)
Radiotherapy	11 (9.8)
Other	9 (8.0)
No specialization	16 (14.3)
Workplace	
Palliative care unit	61 (54.4)
Generic hospital	21 (18.8)
University hospital	20 (17.9)
IRCCS/oncologic center	10 (8.9)
Geographic region of work	
North Italy	48 (42.9)
Center Italy	40 (35.7)
South Italy + islands	24 (21.4)
Total	112 (100)

N number, % percentage, *IRCCS* Istituto di Ricovero e Cura a Carattere Scientifico

Discussion

To the best of our knowledge, this is the first cross-sectional survey performed among Italian physicians trained in supportive care in cancer about their common practice and beliefs regarding the prophylactic antiemetic prescription when they start opioids in patients with cancer.

There has been one similar study conducted among physicians experienced in cancer pain treatment at two institutions

Table 2 Statistic associations between physicians' attitude about prescribing prophylactic drugs for OINV (question #1) with other survey items

Survey item (#question number)	*N* (112)	Physicians prescribing prophylaxis for OINV, *N* (%)	*p* value
Antiemetic prescription at the occurrence of OINV (#3)			
Yes	91	41 (45.1)	0.85
No	21	9 (42.9)	
Physician's believe in the efficacy of prophylactic antiemetics for OINV (#5)			
Yes	102	49 (48.0)	0.02
No	10	1 (10.0)	
Estimated % of pts with OINV with antiemetics (#6)			
0–25%	97	39 (40.2)	
25–50%	10	8 (80.0)	0.04
> 50%	5	3 (60.0)	
Estimated % of pts with OINV without antiemetics (#7)			
0–25%	57	13 (22.8)	
25–50%	42	25 (59.5)	< 0.0001
> 50%	13	12 (92.3)	
Medical specialization (#8)			
None	16	8 (50.0)	
Palliative care/-anesthesiology	22	9 (40.9)	
Oncology	54	23 (42.6)	0.93
Radiotherapy	11	5 (45.5)	
Other	9	50 (44.6)	
Workplace (#9)			
IRCCS/oncologic center	10	2 (20.0)	
University hospital	20	8 (40.0)	0.26
Generic hospital	21	12 (57.1)	
Palliative care unit	61	28 (45.9)	
Age (#11)			
< 40	63	27 (42.9)	0.67
≥ 40	49	23 (46.9)	

N number, % percentage, *IRCCS* Istituto di Ricovero e Cura a Carattere Scientifico

of Japan which showed that many Japanese physicians prescribe prophylactic antiemetics while starting cancer patients on opioids [6]. Based on the report of this study, we decided to conduct the same analysis among the Italian physicians on the same setting. The most important results reported by Tsukuura et al. [6] was that 82% of Japanese physicians prescribed prophylactic antiemetics at the beginning of opioid prescription, and the most commonly prescribed drug for this purpose was prochlorperazine (88%), a dopamine D2 receptor (DRD2) antagonist with a piperazinyl phenothiazine structure. This finding is in line with the results from another retrospective study [9]. Unfortunately, this common and potentially distressing problem has been insufficiently studied to allow specific recommendations to be made and there are too few evidences to support this practice as the first-line treatment for OINV.

One, underpowered, placebo-controlled randomized trial of the therapeutic use of metoclopramide and ondansetron in established OINV showed no significant differences between the ondansetron, metoclopramide, or placebo groups [10]. The Japanese group conducted a placebo-controlled RCT of prophylactic prochlorperazine for preventing OINV among cancer patients starting on opioids which showed that prophylactic prochlorperazine—the most commonly used antiemetic for this purpose in Japan—was not effective in preventing OINV [11]. It is not sure whether metoclopramide and domperidone—the most commonly used prophylactic antiemetics in Italy—will hold similar results. It is indeed surprising that no RCTs have been conducted to test this important clinical question until the Japanese study was published, and these drugs have been routinely used without data.

Several antiemetics appear active in managing OINV. The choice may be empirical or based on the pathophysiology (e.g., a prokinetic for impaired gastric emptying or an antihistamine for vestibular apparatus sensitization). It is still unclear whether the use of other antiemetics, such as olanzapine, would have resulted in beneficial outcomes, and this remains a topic for future research. There is limited evidence to support opioid switching, i.e., changing the opioid or the route [4]. The 2016 Updated MASCC/ESMO consensus recommendations on the management of nausea and vomiting in advanced cancer support metoclopramide as the drug of choice and some other antidopaminergic agents (haloperidol, levomepromazine, or olanzapine) as alternatives in advanced cancer [12]. Our findings are in line with these recommendations. In our study, the most commonly prescribed drugs were prokinetics such as metoclopramide, very likely because the vast majority of participants were oncologists who are generally used to prescribing this type of medication. Nevertheless, clinical consensus and current practice indicate that this classes of drugs have a place in the management of OINV in advanced cancer, despite the lack of robust evidence but and this represents an important topic for future research.

According to the recent systematic reviews by Sande et al. [13], only weak recommendations can be made regarding opioid switching in the setting of opioid-induced nausea and vomiting. No recommendations can be given regarding the use of antiemetics or change of the route of administration of the opioid. Based on the existing evidence, it is still not known what the best approach is regarding these methods of management. The best practices for opioid switching, changing the route of administration, and the optimal antiemetic are all issues that need further examination. Whether one of these methods is better than the other is also unclear. The existing literature is of low quality and the challenges of researching

this area are likely to have contributed to this. There remains a need for high quality to be done before strong recommendations and guidelines on the management of opioid-induced nausea and vomiting can be made.

Our study had several limitations. First, this survey includes the convenience sample and the incomplete list of potential interviewed physicians existing in Italy. Nevertheless, the sample could be representative of the palliative care world in Italy. Second, the study population was heterogeneous in terms of medical specialization and structure of working. This is a key point because the characteristics of observed patients and related interventions can change according to the place of care (e.g., intensive care unit, medical oncology unit, palliative care or home care unit) and the expertise and field specialization of examining physician (anesthesiologist, oncologist, or no specialization). Finally, there was no formal hypothesis for this study but the purpose of the study was also to explore this topic more thoroughly in order to develop some specific hypothesis or prediction that can be tested in future research.

Conclusion

There is no good quality of evidence and powered strength of recommendations to support any antiemetic in OINV prophylaxis. By our experience, Italian physicians do not commonly prescribe prophylactic antiemetics for OINV. Unlike previously reported data, dopamine antagonists resulted the most commonly prescribed drugs. Prospective clinical trials are necessary to evaluate the real efficacy of this practice.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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