Tsuruoka, which is a typical rural town, had no formal specialized palliative care service at the time of survey.

Due to the lack of an established method to identify all cancer patients living in a specific area in Japan, we identified all hospitals in the study areas with reference to hospital lists from the Japan Hospital Association, the largest authorized organization of hospitals in Japan, and local resource information. Of the 54 hospitals identified, we excluded 20 hospitals primarily treating psychiatric, rehabilitation, and geriatric non-cancer patients. We approached the remaining 34 hospitals (11,033 beds), and a total of 23 hospitals (8,964 beds, 81%) participated in this survey: 3 hospitals (Tsuruoka), 7 hospitals (Kashiwa), 8 hospitals (Hamamatsu), and 5 hospitals (Nagasaki).

Patients

Inclusion criteria for patients in this study were: (1) adult cancer patients with a primary tumor site in the lung, esophagus, stomach, colon, rectum, pancreas, liver, biliary system, kidney, prostate, bladder, breast, ovary, or uterus; (2) presence of metastatic or recurrent cancer; (3) outpatient visits to the hospital between April and June 2008; and (4) disclosure of malignancy. Exclusion criteria included: (1) incapacity of the patient to complete the questionnaire (dementia, cognitive failure, or psychiatric illness), (2) severe emotional distress of the patient as determined by the principal treating physician, (3) poor physical condition unable to complete the questionnaire, and (4) language difficulty or visual loss. Patients were recruited consecutively, with hospitals either sending each eligible patient a questionnaire by mail or delivering it directly by hand to the patient.

Measurements

Data were collected on: (1) knowledge about opioids, beliefs about palliative care, and concerns about homecare; (2) sense of security; (3) pain intensity; and (4) patient-perceived quality of palliative care. The questionnaire (available from the authors) was constructed based on an extensive literature review, expert consensus among the authors, and a previous study [2–23, 25–27].

Knowledge about opioids, beliefs about palliative care, and concerns about homecare

We asked the respondents to rate the extent to which they agreed with the statements about their knowledge of opioids, beliefs about palliative care, and concerns about homecare on a 5-point Likert-type scale (1 strongly disagree, 2 disagree, 3 unsure, 4 agree, 5 strongly agree) [2]. Knowledge about opioids was examined using two items: "opioids can relieve most pain caused by cancer" and "opioids are addictive and/or shorten life". Beliefs about palliative care were examined using three items: "palliative care relieves pain and distress", "palliative care is provided along with chemotherapy and/or radiation therapy", and "palliative care is only for terminally ill patients". Concerns about homecare were examined based on five items: "pain can be alleviated as effectively through home-visit services as it can at the hospital", "home-visit services cannot respond to sudden changes in a patient's condition", "it is hard to find home-visiting physicians", and "being taken care of at home puts a burden on the family".

Sense of security about cancer care in the region

The sense of security was measured using the five-item scale to assess feelings of support and security about cancer care in a region [23]. The statements were: (1) "I would feel secure in receiving cancer treatment", (2) "my pain would be well-relieved", (3) "medical staffs will adequately respond to my concerns and pain", (4) "I would feel secure as a variety of medical care services are available", (5) "I would feel secure in receiving care at home". We asked participants to rate their level of agreement with the statements on a 7-point Likert scale (1 strongly disagree, 2 disagree, 3 slightly disagree, 4 not sure, 5 slightly agree, 6 agree, 7 strongly agree). The total score of five items, ranging from 5 to 35, quantifies the levels of the sense of security; a higher score indicates higher sense of security levels. Factor validity was established based on the emergence of one factor by explanatory factor analysis, and a high Cronbach's alpha coefficient (0.91) demonstrated sufficient internal consistency. Criterion-related validity established a significant difference among the total scores of general populations from several areas with various health care services in Japan.

Pain intensity

Pain intensity was measured using the Japanese adaptation of the Brief Pain Inventory, with a score given for the pain at its worst (0–10), at its least (0–10), and a score for the average pain felt (0–10) in the previous 24 h [25]. Its reliability and validity in Japanese populations has been established [25]. For this study, average pain was used for analyses.

Patient-perceived quality of palliative care

Patient-perceived quality of palliative care was measured using the Care Evaluation Scale [26, 27]. The Care Evaluation Scale is a well-validated and commonly used measurement tool in Japan to quantify the level of patient or family-perceived need for improvements in palliative care. The full version of the Care Evaluation Scale consists of eight subscales (three items for seven domains and two

items for one domain) with a 6-point Likert-type scale from "1 improvement is not necessary at all" to "6 highly necessary": physical care provided by physicians, physical care provided by nurses, psycho-existential care, help with decision making, coordination/consistency of care, environment, availability, and cost. For this study purpose, we used the first five subscales (15 items), because the study aim focused on interpersonal areas, not social areas (i.e., environment, availability, and cost). Each subscale score was calculated as an average of the items belonging to the subscale, and the total score was calculated as an average of subscale scores. All scores were proportionally adjusted to range from 0 to 100 following the original studies, and, thus, higher values indicate a lower perceived necessity for improvement.

In addition, information about the subjects' demographic characteristics (age, sex, and family), performance status, and medical status was collected through self-administered questionnaires. The performance status was measured using the European Organization for Research and Treatment of Cancer performance status: 0 (no symptoms, able to carry out all activities without restrictions), 1 (mild symptoms but ambulatory and able to carry out work of a light or sedentary nature), 2 (ambulatory and capable of self-care for more than 50% of their waking hours), 3 (laying in bed or sitting in a chair for more than 50% of their waking hours), and 4 (laying in bed or sitting in a chair for the entire day).

Statistical analysis

The 5-point scale to measure patients' knowledge, beliefs, and concerns was simplified into two categories ("strongly agree" and "agree" vs. others). As the age, sex, and regions of the subjects were considered to affect the knowledge, beliefs, and concerns, they were selected a priori as explanatory variables. The chi-square test was used to examine the rate of "agree" responses in relation to the age, sex, and region. The total sense of security scores were examined employing Student's *t* test and analysis of variance. To elucidate the influence of the age, sex, pain level, and patient-reported quality of palliative care on patients' knowledge, beliefs, and concerns, multiple logistic regression analyses were performed to determine odds ratios. With sense of security scores, multiple linear regression analyses were used. All models included the following covariates selected a priori: age in years (≤59, 60–74, ≥75); sex; region; number of family members living with the participant; performance status; current medical status; pain level; and the patient-reported quality of care measured by the Care Evaluation Score (≤49, 50–79, ≥80). Trend analysis was conducted, and the Care Evaluation Score was included as an ordinal variable. Comparisons were performed with analysis of covariance, adjusting for age and sex, because these two factors were significant covariates for confidence levels. As the results were essentially the same across the four regions (data not shown), we report only the overall results. All analyses were carried out using STATA ver. 9.1 (College Station, TX, USA).

Results

Of 2,087 patients who met the inclusion criteria, 367 patients were excluded due to: (1) mental incapacity of the patient to complete the questionnaire such as dementia, cognitive failure, or psychiatric illness (n=137), (2) patient death, admission, or changing hospitals during the procedure (n=101), (3) severe emotional distress (n=52), 4) responsible physicians unavailable for technical reasons (n=30), (5) poor physical conditions (n=28), (6) language difficulty or visual loss (n=5), as well as other unspecified reasons (n=14). In addition, 101 patients refused to receive the questionnaire. Questionnaires were thus sent to 1,619 patients, and 5 returned due to being sent to the wrong address. Overall, 925 responses (57%) were obtained, and 833 responses were finally analyzed due to missing values for some of the primary endpoints.

Participant characteristics

The participant characteristics are summarized in Table 1. The mean age ± standard deviation (SD) was 67±11 years, and 57% were men. The performance status was 0 or 1 in about 70% of the respondents, and 60% were receiving chemotherapy and/or radiation therapy.

Knowledge about opioids, beliefs about palliative care, and concerns about receiving care at home

As shown in Table 2, nearly 30% of the patients believed that opioids are addictive and/or shorten life, and about half believed that palliative care is only for terminally ill patients. Regarding concerns about receiving care at home, 75% agreed or strongly agreed that being taken care of at home puts a heavy burden on the family, and about 60% agreed that home-visit services cannot respond to sudden changes in a patient's condition.

Sense of security

The mean score of the sense of security was 27±5.6 (Table 2). The proportions of respondents who agreed (i.e., scored 5 or greater on the 7-point Likert-type scale) with each statement were: 82% ("I could feel secure on receiving

Table 1 Participant characteristics (N=833)

	Number	Percent
Age (years)		
< 60	208	25
60–74	405	49
75 or over	220	26
Sex		
Male	473	57
Female	360	43
Region		
Yamagata	135	16
Chiba	137	16
Shizuoka	302	36
Nagasaki	259	31
Family living with participant[a]		
Yes	771	93
No	61	7
Performance status (EORTC)[b]		
0	234	28
1	367	44
2	174	21
3 or 4	52	6
Current medical status		
Receiving chemotherapy and/or radiation therapy	491	60
Average pain score in previous 24 h		
0–4	721	89
5–10	92	11

[a] n=832, due to missing values

[b] n=827, due to missing values

cancer treatment"), 78% ("pain could be well-relieved"), 78% ("medical staff adequately responded to concerns and pain"), 59% ("I could feel secure as a variety of medical care services are available"), and 75% ("I could feel secure on receiving care at home").

Factors associated with the patients' knowledge about opioids, beliefs about palliative care, and concerns about homecare

Older respondents and patients who reported lower-level quality of palliative care they received were significantly more likely to have incorrect knowledge about opioids (Table 3). Although male patients were significantly more likely to know that opioids can relieve most pain caused by cancer, they were more likely to have incorrect knowledge that opioids were addictive and/or shorten life (p=0.03). Patients' beliefs about palliative care and concerns about homecare were not significantly influenced by age and gender, while the patient-reported quality of palliative care was significantly associated that positive beliefs about palliative care ("palliative care relieves pain and distress") and lower levels of concerns about homecare ("pain can be alleviated as effectively through home-visit services as it can at the hospital").

Associations between the sense of security and knowledge about opioids, beliefs about palliative care, and concerns about homecare

Sense of security levels were significantly higher in patients who agreed that "opioids can relieve most pain caused by cancer", "palliative care relieves pain and distress", "palliative care is provided along with chemotherapy and/or radiation therapy", and "pain can be alleviated as effectively through home-visit services as it can at the hospital", as well as in the patients who did not agree that "home-visit services cannot respond to sudden changes in a patient's condition" and "being taken care of at home puts a burden on the family" (Table 4).

In addition, higher senses of security levels were significantly associated with an older age, male gender, lower pain intensity, and higher patient-reported quality of palliative care (Table 3).

Discussion

This is the first large-scale survey designed to clarify knowledge about opioids, beliefs about palliative care, and concerns about homecare in advanced cancer patients as a representative sample of multiple regions, in addition to the sense of security; the factors associated with knowledge, beliefs and concerns; and associations between the sense of security levels and knowledge and beliefs. The most important findings of this study involved clarification of the patients' knowledge about opioids, beliefs about palliative care, and concerns about homecare.

First, about 30% of advanced cancer patients believed that opioids are addictive and/or shorten life. This figure is very close to that in previous surveys of the general population in Japan and other countries (i.e., 30–40%) [2, 5, 7]; and somewhat lower than some studies (i.e., 70%) [4, 6]. In addition, this study revealed that older and male patients were significantly more likely to have incorrect knowledge about opioids. As many studies have identified misconceptions about opioids as dominant barriers to optimal pain control [3, 5], these results confirm that providing appropriate information about opioids, especially to older and male patients, is of considerable importance to achieve maximum pain control.

Table 2 Knowledge about opioids, beliefs about palliative care, and concerns about receiving care at home

	All subjects	Age (years)			*P* value	Sex		*P* value
		<60	60–74	75+		Male	Female	
Knowledge about opioids								
Opioids can relieve most pain caused by cancer (n=743)	545 (73%)	143 (71%)	272 (75%)	130 (74%)	0.620	320 (77%)	225 (69%)	0.018
Opioids are addictive and/or shorten life (n=718)	202 (28%)	40 (20%)	105 (30%)	57 (34%)	0.007	126 (32%)	76 (24%)	0.002
Beliefs about palliative care								
Palliative care relieves pain and distress (n=753)	570 (76%)	155 (77%)	280 (75%)	135 (76%)	0.905	313 (74%)	257 (79%)	0.105
Palliative care is provided along with chemotherapy and/or radiation therapy (n=742)	474 (64%)	124 (62%)	230 (63%)	120 (69%)	0.278	147 (35%)	121 (37%)	0.578
Palliative care is only for terminally ill patients (n=727)	377 (52%)	97 (48%)	187 (52%)	93 (55%)	0.436	216 (53%)	161 (50%)	0.508
Concerns about receiving care at home								
Pain can be alleviated as effectively through home-visit services as it can at the hospital (n=748)	286 (38%)	67 (33%)	144 (39%)	75 (42%)	0.203	171 (41%)	115 (35%)	0.006
Home-visit services cannot respond to sudden changes in a patient's condition (n=744)	452 (61%)	103 (52%)	241 (66%)	108 (61%)	0.004	256 (62%)	196 (59%)	0.442
It is hard to find home-visiting physicians (n=742)	419 (57%)	113 (57%)	215 (59%)	91 (51%)	0.191	227 (55%)	192 (58%)	0.354
Being taken care of at home puts a burden on the family (n=748)	557 (75%)	152 (76%)	274 (75%)	131 (73%)	0.811	303 (73%)	254 (76%)	0.309
Sense of security score (n=833)	**27.0±5.6 (n=833)**	**25.5±5.5 (n=208)**	**27.3±5.6 (n=405)**	**27.8±5.1 (n=220)**	**<0.001**	**27.4±5.4 (n=473)**	**26.4±5.8 (n=360)**	**0.009**

Each column indicates the number (percentage) of respondents who agreed or strongly agreed with the statement, except for the last column, which indicates the mean ± S.D. (number of subjects)

Table 3 Factors associated with knowledge and beliefs about palliative care, and sense of security by multivariate analysis

	Age (years)			Sex		Pain	Care evaluation score (total)			
	<59	60–74	75+	Male	Female	Pain score	−49	50–79	80+	Trend P
Knowledge about opioids										
Opioids can relieve most pain caused by cancer (n=743)	1	1.1 0.7–1.6	0.9 0.6–1.5	1	0.6* 0.4–0.8	1.1 0.6–2.0	1	1.1 0.7–1.7	2.3* 1.4–3.7	P<0.001
Opioids are addictive and/or shorten life (n=718)	1	1.8 1.1–2.7	2.4* 1.4–4.0	1	0.7* 0.5–0.9	1.3 0.7–2.2	1	0.6 0.4–1.0	0.6* 0.4–0.9	P=0.04
Beliefs about palliative care										
Palliative care relieves pain and distress (n=753)	1	0.9 0.6–1.4	1.1 0.6–1.9	1	1.2 0.8–1.7	0.9 0.5–1.5	1	1.4 0.9–2.3	2.4* 1.5–4.0	P<0.001
Palliative care is provided along with chemotherapy and/or radiation therapy (n=742)	1	1.0 0.7–1.5	1.4 0.9–2.2	1	0.9 0.7–1.3	0.8 0.5–1.3	1	1.1 0.7–1.6	1.4 0.9–2.2	P=0.11
Palliative care is only for terminal patients (n=727)	1	1.2 0.8–1.7	1.4 0.9–2.2	1	0.9 0.7–1.3	0.9 0.9–1.5	1	0.8 0.5–1.2	0.8 0.5–1.2	P=0.39
Concerns about receiving care at home										
Pain can be alleviated as effectively through home-visit services as it can at the hospital (n=748)	1	1.1 0.7–1.6	1.2 0.7–1.9	1	0.8 0.5–1.0	0.6 0.3–1.0	1	0.8 0.5–1.3	1.7* 1.1–2.6	P=0.002
Home-visit services cannot respond to sudden changes in a patient's condition (n=744)	1	2.1* 1.4–3.0	1.8* 1.1–2.8	1	1.0 0.8–1.4	0.9 0.5–1.5	1	1.1 0.7–1.8	0.7 0.5–1.1	P=0.07
It is hard to find home-visiting physicians (n=742)	1	1.2 0.8–1.7	0.9 0.6–1.3	1	1.0 0.8–1.4	1.0 0.6–1.6	1	1.1 0.7–1.6	0.8 0.5–1.3	P=0.22
Being taken care of at home puts a burden on the family (n=748)	1	0.9 0.6–1.4	0.9 0.6–1.5	1	1.1 0.8–1.6	1.5 0.8–2.7	1	1.2 0.7–1.9	1.1 0.7–1.7	P=0.92
Sense of security score (n=833)	–	**+1.5* 0.6, 2.3**	**+2.4* 1.3, 3.4**	–	**−0.8* −1.5, −0.1**	**−1.8* −2.9, −0.7**	–	**+0.9* −0.1, 1.8**	**+4.4* 3.4, 5.3**	***P*<0.001**

Values in the table indicate odds ratios and 95% confidence interval. Multiple logistic regression analysis for knowledge about opioids and beliefs about palliative care indicates adjusted odds ratio and P value; multiple linear regression analysis for sense of security score indicates adjusted difference in score; all models include age (<60, 60–74, 75+; <60 as reference category), sex (male as reference category), region of residence, family living with participant, physical activity status, current medical status, average pain score in previous 24 h, and care evaluation score (<50, 50–79, 80+; <50 as reference category)

*p<0.05

Second, this study revealed that about half of the patients believed that palliative care is only for terminally ill patients, while similar percentages of the patients believed that palliative care is provided along with chemotherapy and/or radiotherapy. The findings are consistent with previous studies that revealed a negative image of palliative care among both patients and healthcare professionals [8–11]. In Japan, a strong policy change from end-of-life care to "early" palliative care resulting in the involvement of palliative care teams was significantly associated with patient- and family-perceived appropriate referrals to specialized palliative care services [12, 28]. These findings suggest that along with ongoing efforts of disseminating palliative care teams not only for terminally ill patients but also those with intense symptoms and suffering irrespective of disease stages, providing information about the emerging concept of palliative care to patients themselves is another area to be improved to maximize palliative care use for enhancing patients' quality of life

Third, this study revealed a high level of concern among advanced cancer patients about receiving homecare. The concerns most commonly reported included family burden, being unable to adequately respond to sudden changes in out-of-hours care, and availability of family physicians visiting the home. These figures are very close to data provided by the Ministry of Health, Labour, and Welfare, whereby the most common difficulties with homecare surround concerns about the burden to the family and sudden changes in physical conditions [15], and this is also consistent with Western studies which identified that

Table 4 Associations between the levels of feeling secure and knowledge about opioids, beliefs about palliative care, and concerns about homecare

		Number	Mean ± S.D.	*P* value
Knowledge about opioids				
Opioids can relieve most pain caused by cancer	Yes	545	27.9±6.5	<0.001
	No	198	25.8±5.9	
Opioids are addictive and/or shorten life	Yes	202	27.2±5.8	0.857
	No	516	27.3±6.9	
Beliefs about palliative care				
Palliative care relieves pain and distress	Yes	570	28.3±8.0	<0.001
	No	183	25.6±6.1	
Palliative care is provided along with chemotherapy and/or radiation therapy	Yes	474	28.1±6.5	<0.001
	No	268	25.9±6.1	
Palliative care is only for terminal patients	Yes	377	27.3±6.4	0.684
	No	350	27.2±6.4	
Concerns about receiving care at home				
Pain can be alleviated as effectively through home-visit services as it can at the hospital	Yes	286	29.3±5.7	<0.001
	No	462	26.1±6.4	
Home-visit services cannot respond to sudden changes in a patient's condition	Yes	452	27.1±6.4	0.026
	No	292	27.9±6.1	
It is hard to find home-visiting physicians	Yes	419	27.2±6.5	0.193
	No	323	27.7±6.1	
Being taken care of at home puts a burden on the family	Yes	557	27.1±6.8	0.027
	No	191	28.1±5.7	

concern about burden is a major factor affecting a cancer patient's decision regarding homecare [18, 29, 30]. The family burden is one of the most relevant issues in this population, and this includes the patient-perceived burden and actual family burden in caregiving. Multiple studies have indicated that the patient-perceived burden has one of the largest impacts on suffering in terminally ill cancer patients, even if family members do not report an actual caregiving burden [31, 32]. These findings indicate that clinicians should alleviate patient concerns about burden when they receive homecare through the provision of psychological support for patients themselves, as well as arranging regional resources to reduce the actual family burden.

Another important finding of this study was clarification of the levels of a sense of security and the significant association between the sense of security and patients' knowledge, beliefs, and concerns. To our best knowledge, this is the first reported study to demonstrate the significant association between the sense of security and patients' knowledge, beliefs, and concerns. This finding suggests that a sense of security is shaped at least partly by knowledge and beliefs, and providing appropriate information could be of marked importance to enhance patients' sense of security.

Despite the strengths of this study, including obtaining a relatively large number of patients from multiple regions of Japan and regional representative sampling, there are some limitations. First, it was a cross-sectional study, and, thus, the observed associations among variables might not be causal. Second, the response rate was moderate and no data were collected from the non-respondents. This could be a potential selection bias which may distort the study results. Third, unmeasured confounding factors, such as educational levels and family forms, could have distorted the study results, although adjustment was made for the confounders measured in the multivariate analyses. Finally, patients' knowledge, beliefs, and concerns are inevitably influenced by the social and cultural views in the societies they live in.

In conclusion, advanced cancer patients frequently had incorrect knowledge about opioids, a belief that palliative care is only for terminally ill patients, and concerns about homecare, especially the family burden and responses to sudden changes. The knowledge, beliefs, and concerns were significantly associated with the sense of security levels regarding receiving cancer care in the region. Providing appropriate information about the safety of opioids, availability of palliative care during the entire course of a disease, and realistic information about homecare is of marked importance to achieve the optimal quality of life for cancer patients.

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Conflict of interest None.

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●調査報告●

市民の緩和ケアに対するイメージの変化

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Changes in Public Images of Palliative Care

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背　景

緩和ケアや医療用麻薬に対する誤ったイメージは，緩和ケア普及の妨げとなることが示唆されている[1~3]。しかしながらわが国では，3～5割の国民，あるいはがん患者が「医療用麻薬は命を縮める」や「緩和ケアは末期だけのものである」といったイメージをもっており[4~5]，このような誤解を取り除くための対策が必要とされている。

緩和ケアや医療用麻薬に関する正しい知識を得てもらうために，一般市民やがん患者を対象とした教育講座やセミナーが各地で開かれているが，効果について評価した研究はほとんどない。1地域の住民を対象とした研究では，緩和ケアについての講演会は緩和ケアに対する誤ったイメージを取り除くために，短期的に有効であることが示されている[6]。しかし，複数の地域の一般市民を対象とした研究はこれまでに報告されていない。本調査は，複数の地域の一般市民を対象に，市民講座の受講前後での緩和ケアに対するイメージの変化を検証することを目的とする。

対象・方法

緩和ケア普及のための地域プロジェクト(OPTIM)[7]の介入の一部として，2008年度から2010年度にかけて，山形県鶴岡市と静岡県浜松市の一般市民を対象に緩和ケアに関する市民講座を行った。市民講座のテーマは，鶴岡では「地域で支えるがん緩和ケア―あなたらしく生きるために」(2008年11月15日実施：講義・パネルディスカッション)，浜松では「上手に使おうホスピス・緩和ケア」(2008年9月27日実施：講義)，

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「安心できるがん緩和医療をめざして―患者さんとご家族の明日のために」(2009年9月26日実施：講義)，「がんと向き合う―地域で支える」(2010年7月18日：講義) であった。

いずれも講演の中で，「緩和ケアは，化学療法や放射線治療など，がんに対する治療と一緒に行う」「モルヒネなど医療用麻薬は，麻薬中毒になったり命を縮める作用はない」「ホスピスは“末期”だけでなく，在宅療養を支える役割もある」ことを伝えた。また，地域で利用できる緩和ケアの資源を具体的に紹介することによって「がんであっても，苦痛や心配には十分に対処してもらえると思う」「がんであっても，安心して自宅で療養できる」ことを伝えた。

参加者1,200名を対象に調査を行った。鶴岡地域の参加者は319名，浜松地域の参加者は，2008年度は72名，2009年度は600名，2010年度は209名の計881名であった。質問紙は，講座開始前に全員に配布し，終了後に任意で回収した。1回の質問紙で受講前後のイメージを尋ねた。回答は匿名で行った。

緩和ケアのイメージについて，「緩和ケアは，化学療法や放射線治療などがんに対する治療と一緒に行う」「モルヒネなど医療用麻薬は，麻薬中毒になったり命を縮める」「ホスピスは“末期”だけでなく，在宅療養を支える役割もある」という緩和ケアの知識に関する3項目と，「がんであっても，苦痛や心配には十分に対処してもらえると思う」「がんであっても，安心して自宅で療養できる」という安心感に関する2項目で尋ねた。それぞれの項目ごとに，受講前のイメージと受講後のイメージを，「そう思っていなかった・そう思わない」(1)，「そう思っていた・そう思う」(2)，「とてもそう思っていた・とてもそう思う」(3)，の3件法で尋ねた[4, 8]。

緩和ケアの受講前後でのイメージについて平均値の比較を行った。受講前後でイメージに変化がみられた群とみられなかった群に分けて，カイ2乗検定を行った。イメージに変化がみられた群とは，受講前は各項目に対し「そう思わなかった」と答えたが，受講後は「そう思う，とてもそう思う」と答えた，否定的だったイメージが肯定的に変化した参加者を指す。

イメージに変化がみられなかった群とは，受講前に「そう思わなかった」，受講後に「そう思わない」を選択し，否定的なイメージをもち続けた参加者，または受講前は「そう思っていた，とてもそう思っていた」を選択したが，受講後は「そう思わない」を選択した，肯定的なイメージが否定的に変化した参加者を示す（いずれの群も，逆転項目の場合は反対の処理を行った)。

結　果

858名（回収率71.5％）から回答を得た。年代別では，60歳代（27.3％）が最も多く，続いて50歳代（22.9％），70歳代以上（21.3％），40歳代（17.6％），30歳代（7.3％），20歳代（3.6％）であった。男女比は1：4であった。参加者の内訳は，一般市民（55.1％）が最も多く，続いて医療関係者（18.5％），患者の家族（10.2％），患者（8.4％），その他（7.8％）であった。

全体として，市民講座の受講前後での緩和ケアに関するイメージを比較したところ，「緩和ケアは，化学療法や放射線治療などがんに対する治療と一緒に行う」「モルヒネなど医療用麻薬は，麻薬中毒になったり命を縮める」「ホスピスは“末期”だけでなく，在宅療養を支える役割もある」「がんであっても，苦痛や心配には十分に対処してもらえると思う」「がんであっても，安心して自宅で療養できる」のすべての項目で受講前より受講後の方がイメージが肯定的に変化した（表1)。

鶴岡と浜松の両地域で，すべての項目において，受講前より受講後の方が緩和ケアや医療用麻薬に対するイメージは肯定的に変化した（表1)。

また，受講前後で否定的なイメージが改善した割合は，性別による有意差はみられなかった。年齢別では，60歳以上の高齢者の方が「モルヒネなど医療用麻薬は，麻薬中毒になったり命を縮める」という認識が改善しない傾向がみられた。

表1　緩和ケアに対するイメージについての質問項目とその変化

質問項目	t検定			「とてもそう思う」「そう思う」と回答した対象者の割合			
	全体 ($n=858$)			鶴岡 ($n=208$)		浜松 ($n=650$)	
	講演会前	講演会後	p	講演会前	講演会後	講演会前	講演会後
1. 緩和ケアは，化学療法や放射線治療などがんに対する治療と一緒に行う	1.92 ± .68	2.52 ± .56	<0.01	67.3%	68.3%	59.1%	82.5%
2. モルヒネなど医療用麻薬は，麻薬中毒になったり命を縮める　※逆転項目	1.54 ± .66	1.29 ± .63	<0.01	30.3%	10.1%	40.0%	19.1%
3. ホスピスは「末期」だけでなく，在宅療養を支える役割もある	1.73 ± .72	2.45 ± .54	<0.01	56.3%	70.2%	45.5%	83.4%
4. がんであっても，苦痛や心配には十分に対処してもらえると思う	1.87 ± .64	2.43 ± .56	<0.01	57.7%	71.6%	61.8%	82.5%
5. がんであっても，安心して自宅で療養できる	1.57 ± .66	2.20 ± .63	<0.01	42.8%	64.4%	37.2%	73.5%

表2　緩和ケアに対する否定的なイメージが改善した割合

質問項目	性別			年齢			地域			性別		
	男性	女性	p	<60歳	≧60歳	p	鶴岡	浜松	p	市民	医療関係者	p
1. 緩和ケアは，化学療法や放射線治療などがんに対する治療と一緒に行う（$n=192$）	87.5%	89.3%	0.75	89.7%	88.9%	0.86	65.2%	92.3%	<0.01	89.0%	88.9%	0.98
2. モルヒネなど医療用麻薬は，麻薬中毒になったり命を縮める（$n=351$）	54.1%	64.2%	0.11	67.5%	58.1%	0.073	68.3%	60.4%	0.25	62.7%	54.3%	0.33
3. ホスピスは「末期」だけでなく，在宅療養を支える役割もある（$n=291$）	94.4%	95.7%	0.69	97.5%	92.9%	0.060	89.2%	96.5%	0.046	96.1%	91.9%	0.25
4. がんであっても，苦痛や心配には十分に対処してもらえると思う（$n=196$）	85.3%	88.7%	0.58	87.2%	91.3%	0.38	90.0%	87.8%	0.70	92.0%	57.1%	<0.01
5. がんであっても，安心して自宅で療養できる（$n=358$）	78.3%	77.9%	0.95	79.0%	77.1%	0.67	73.3%	78.5%	0.38	79.6%	63.6%	0.017

地域別では，「緩和ケアは，化学療法や放射線治療などがんに対する治療と一緒に行う」「ホスピスは“末期”だけでなく，在宅療養を支える役割もある」の知識に関する項目で，鶴岡に比較して浜松で有意な改善がみられた。

立場別では，「がんであっても，苦痛や心配には十分に対処してもらえると思う」「がんであっても，安心して自宅で療養できる」の安心感に関する項目で，市民に比較して医療従事者の認識が改善しにくかった（表2）。

考　察

本調査の結果から，緩和ケアに関する市民対象の教育講座は，市民の緩和ケアのイメージを少なくとも短期的に変化させる可能性が示唆された。「緩和ケアは，化学療法や放射線治療などがんに対する治療と一緒に行う」「ホスピスは“末期”だけでなく，在宅療養を支える役割もある」という項目について，受講後に「とてもそう思う・そう思う」と答えた参加者が増加したことから，緩和ケアに関する講座は「緩和ケア＝末期」という

イメージを取り除き，早期からの緩和ケアを推進するために効果的であることが示唆される。同様に，「モルヒネなど医療用麻薬は，麻薬中毒になったり命を縮める」という項目では，受講後に「とてもそう思う・そう思う」と答えた参加者が減少したことから，緩和ケアに関する講座は麻薬に関するそのような間違ったイメージを払拭するために有効であることが示唆される。

また，「がんであっても，苦痛や心配には十分に対処してもらえると思う」「がんであっても，安心して自宅で療養できる」という項目についても，受講後に「とてもそう思う・そう思う」と答えた参加者が増加したことから，参加者が講座を受講することで，がんに罹患しても住んでいる地域や自宅で治療を受けながら生活できるという安心感が得られていると考えられる。

今回，対象とした2地域では同じようなイメージの変化がみられたことから，このような市民講座はいずれの地域でも有効であると考えられる。

受講前後でのイメージに変化があった群となかった群で，対象者の性別に差がみられなかったことから，男女の違いによるイメージの認識に大きな変わりはないことが示唆されると考えられる。

また，年齢別では，60歳以上の高齢者の方が，緩和ケアの知識に関しての認識が変わりにくい傾向があった。高齢者向けの講演を行う場合には，知識に関する説明だけではなく，高齢者の経験や生活に即した情報提供を行うことがより効果的ではないかと考えられる。

地域別にみると，知識に関する項目で差はみられたが，これは鶴岡地域にもともと緩和ケアに肯定的なイメージを抱いていた参加者が多かったため，このような結果になったと考えられる。

同様に，参加者の立場別にみて，医療関係者の方が安心感に関するイメージが変わりにくいとの結果が得られたが，これは，医療関係者は実際に現場を知っており，現実的な経験に基づいたイメージを持っているためであると考えられる。

このように，市民に緩和ケアに関する正しいイメージを提示し，今後の緩和ケアの利用につなげるためにも，緩和ケアに関する教育講座は重要であるといえる。

本調査の限界として，市民講座を受講した前と後にイメージを聞いておらず，受講をした後のみに，受講前後のイメージを聞いているため，対象者の認識にバイアスがかかっている可能性が指摘される。また，本調査では市民講座の長期的な効果を検討していないため，今後，そのような調査を行うことも重要である。

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Usefulness of Olanzapine as an Adjunct to Opioid Treatment and for the Treatment of Neuropathic Pain

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ABSTRACT

Background: The use of opioids for pain management is often associated with nausea and vomiting. Although conventional antipsychotics are often used to counter emesis, they can be associated with extrapyramidal symptoms. However, chronic pain can induce sleep disturbance. The authors investigated the effects of the atypical antipsychotic olanzapine on morphine-induced emesis and the sleep dysregulation associated with chronic pain.

Methods: A receptor binding assay was performed using mouse whole brain tissue. The emetic response in ferrets was evaluated by counting retching and vomiting behaviors. Catalepsy in mice was evaluated by placing both of their forepaws over a horizontal bar. Released dopamine was measured by an *in vivo* microdialysis study. Sleep disturbance in mice in a neuropathic pain-like state was assayed by electroencephalogram and electromyogram recordings.

Results: Olanzapine showed high affinity for muscarinic M_1 receptor in brain tissue. Olanzapine decreased morphine-induced nausea and vomiting in a dose-dependent manner. However, olanzapine at a dose that had an antiemetic effect (0.03 mg/kg) did not induce catalepsy or hyperglycemia. In addition, olanzapine at this dose had no effect on the morphine-induced release of dopamine or inhibition of gastrointestinal transit. Finally, olanzapine inhibited thermal hyperalgesia and completely alleviated the sleep disturbance induced by sciatic nerve ligation.

Conclusion: These findings suggest that olanzapine may be useful for the treatment of morphine-induced emesis and as an adjunct for the treatment of neuropathic pain associated with sleep disturbance.

What We Already Know about This Topic

- Chronic pain is often associated with sleep disturbances
- Severe side effects of opioids given for pain treatment include nausea and vomiting

What This Article Tells Us That Is New

- In ferrets, olanzapine, an atypical thienobenzodiazepine antipsychotic drug, suppressed morphine-induced emesis and improved pain-related sleep disturbances

THE World Health Organization[1] has stated that morphine is the "gold standard" for the treatment of moderate to severe pain caused by cancer. However, the use of morphine for this purpose is often associated with distressing side effects, such as drowsiness, constipation, emesis, and delirium.[2,3] Many clinicians consider that dopamine receptor antagonists, including prochlorperazine, are the preferred drugs for combating opioid-induced nausea and vomiting.[2,3] However, these drugs often produce adverse effects, including extrapyramidal symptoms.[4] Therefore, new approaches are needed to prevent opioid-induced emesis, as is a better understanding of the mechanism of drug action.

Nausea and vomiting are controlled by the "vomiting center" in the medulla oblongata,[5] which receives signals from the chemoreceptor trigger zone (CTZ) in the area postrema, the gastrointestinal tract, the vestibular apparatus in the temporal lobe, and the cerebral cortex.[6] Opioids have emetogenic effects by stimulating the CTZ and the vestibular apparatus and by inhibiting gut motility.[7] Although stimu-

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lation of the CTZ by opioids involves opioid μ and δ receptors,[8] signals from the CTZ to the vomiting center mainly involve dopamine D_2 and serotonin ($5\text{-}HT_3$) receptors in the former. However, opioid-induced stimulation of the vestibular apparatus and subsequent sensory input to the vomiting center have both been suggested to involve histamine H_1 and muscarinic acetylcholine pathways.[9]

Atypical antipsychotic medications treat the positive symptoms of schizophrenia, such as hallucinations and delusions, more effectively than the negative symptoms, such as lack of motivation and social withdrawal. Olanzapine is a newer atypical antipsychotic that blocks dopaminergic, serotonergic, adrenergic, histaminergic, and muscarinic receptors for multiple neurotransmitters. Because it affects neurotransmitters that are associated with nausea, it may have potential as an antiemetic medication.[10]

In addition, patients with chronic pain commonly experience sleep disturbance[11–13] and may benefit from its treatment.[13] Sleep problems and daytime sleepiness seem to be related to depression and the severity of pain.[14] It has been suggested that olanzapine may improve sleep disturbance.[15]

The primary endpoint of the study was to investigate whether olanzapine at doses lower than those that would induce catalepsy could suppress morphine-induced emesis with few side effects. We also examined if olanzapine could improve sleep dysregulation under a neuropathic pain-like state.

Materials and Methods

The present study was conducted in accordance with the Guiding Principles for the Care and Use of Laboratory Animals at Hoshi University, as adopted by the Committee on Animal Research of Hoshi University (Tokyo, Japan). Every effort was made to minimize the numbers and suffering of animals used in the following experiments.

The observer was not blinded in all of the experiments.

Animals

In the present study, male Institute of Cancer Research mice (20–25 g) (Tokyo Laboratory Animals Science, Tokyo, Japan), male C57BL/6J mice (25–30 g) (CLEA Japan, Tokyo, Japan), and Sprague-Dawley rats (200–300 g) (Tokyo Laboratory Animals Science) were used. Animals were housed in a room maintained at 22° ± 1°C with a 12-h light–dark cycle. Food and water were available *ad libitum*. Each animal was used only once. Male ferrets weighing 1–1.5 kg were obtained from Marshall Research Labs (North Rose, NY) and housed individually in a room kept at 23° ± 1°C under a 12-h light–dark cycle (lights on 8:00 AM-8:00 PM). They were given a standard cat diet (70–80 g/animal, Oriental Yeast Co. Ltd., Chiba, Japan) and allowed free access to water.

Receptor Binding Assay

Mouse whole brain was treated as described previously,[16] and the resulting pellet was resuspended and used as the membrane fraction. The binding assay was performed in triplicate with [^{3}H]clozapine (specific activity, 70–87 Ci/mmol; American Radiolabeled Chemicals, St. Louis, MO) at 0.2 nM, [^{3}H]ketanserin hydrochloride (specific activity, 67 Ci/mmol; PerkinElmer, Waltham, MA) at 0.5 nM, [^{3}H]BRL-43694 (granisetron) (specific activity, 85.3 Ci/mmol; PerkinElmer) at 0.5 nM, [^{3}H]GR113808 (specific activity, 78.3 Ci/mmol; PerkinElmer) at 0.5 nM, [^{3}H]pyrilamine (specific activity, 30 Ci/mmol; PerkinElmer) at 0.5 nM, and [^{3}H]pirenzepine (specific activity, 72.8 Ci/mmol; PerkinElmer) at 0.5 nM, in a final volume of 500 ml that contained 50 mM Tris-HCl buffer, pH 7.4, and 200 ml homogenized membrane fraction. Ninety to 140 mg membrane proteins were used in each assay. Specific binding was defined as the difference in binding observed in the absence and presence of 1 mM unlabeled clozapine, ketanserin, granisetron, or GR113808, 10 mM unlabeled pyrilamine, or 100 mM unlabeled pirenzepine, respectively. All samples were incubated as described previously,[16] and radioactivity in the samples was determined with a liquid scintillation analyzer. All receptor binding curves were fitted using Prism software (version 5.0a; GraphPad Software, La Jolla, CA).

Evaluation of the Emetic Response

Emesis in ferrets after the administration of morphine (0.6 mg/kg, subcutaneous injection) was evaluated by counting the number of retching or vomiting behaviors as described elsewhere,[17] where retching was defined as a rhythmic abdominal contraction without expulsion and vomiting was the oral expulsion of solid or liquid from the gastrointestinal tract. Emesis was assessed for 30 min after the injection of morphine.[18] To determine the effect of olanzapine on morphine-induced emesis, groups of ferrets were pretreated with olanzapine 30 min before the injection of morphine.

An interval of at least 7 days was allowed between testing for each animal to allow for drug washout and to minimize the development of tolerance.

Horizontal Bar Test for the Evaluation of Catalepsy

Catalepsy[19,20] was evaluated using the horizontal bar test as described previously.[21] Briefly, animals were placed so that both forepaws were over a horizontal bar 5 cm above the floor, and the amount of time (s) the animal maintained this position was recorded for as long as 60 s. Catalepsy was considered to have finished when a forepaw touched the floor or when the mouse climbed on the bar. Scores were assigned based on the duration of the cataleptic posture (score 1: 15 to 29 s, score 2: 30 to 59 s, score 3: 60 s or more).

In vivo *Microdialysis Study and Quantification of Dopamine and Its Metabolites*

After 3 days of habituation to the main animal colony, all of the rats were anesthetized with sodium pentobarbital (50 mg/kg, intraperitoneal administration) for surgery as described previously.[21] Briefly, the anesthetized animals were placed in a stereotaxic apparatus, the skull was exposed, and a small hole was made using a dental drill. A guide cannula (AG-8; Eicom, Kyoto, Japan) was implanted into the nucleus accumbens (from the bregma: anterior, +4.0 mm; lateral, −0.8 mm; ventral, −6.8 mm; angle 16 degrees) according to the atlas of Paxinos and Watson[22] and fixed to the skull with cranioplastic cement. Three to 5 days after surgery, microdialysis probes (A-I-8−02; 2 mm membrane length; Eicom) were slowly inserted into the nucleus accumbens through guide cannulas during anesthesia with diethyl ether, and the rats were placed in experimental cages (30 cm wide × 30 cm deep × 30 cm high). The probes were perfused continuously (2 ml/min) with artificial cerebrospinal fluid: 0.9 mM $MgCl_2$, 147.0 mM NaCl, 4.0 mM KCl, and 1.2 mM $CaCl_2$. Outflow fractions were collected every 20 min. After three baseline fractions were collected from the rat nucleus accumbens, rats were given olanzapine (0.3 mg/kg, intraperitoneal administration), vehicle (5% dimethyl sulfoxide [DMSO]); 1 ml/kg, intraperitoneal administration) or saline (1 ml/kg, intraperitoneal administration) 30 min before treatment with morphine (10 mg/kg, intraperitoneal administration). Dialysis samples were collected for 180 min after treatment and analyzed by high-performance liquid chromatography (Eicom) with electrochemical detection (Eicom). Dopamine and its metabolites, 3,4-dihydroxyphenylacetic acid and 3-methoxy-4-hydroxyphenyl acetic acid, were separated by column chromatography and identified and quantified by the use of standards, as described previously.[21]

Gastrointestinal Transit

In the study of gastrointestinal transit,[23] Institute of Cancer Research mice were fasted for 12 h before the experiments. Groups of mice were pretreated with olanzapine (0.03–1 mg/kg, subcutaneous injection) or vehicle (5% DMSO) 30 min before the administration of morphine (0.7 mg/kg, subcutaneous injection) or saline, and ink (0.3 ml/mouse) was orally administered 20 min after the injection of morphine or saline. Twenty minutes after the administration of ink, the animal was killed by cervical dislocation, and the small intestine was removed. The percentage inhibition of gastrointestinal transit was calculated as follows: (distance traveled by the ink/length from the pylorus to the cecum) × 100.

Blood Glucose Measurement

C57BL/6J mice were administered olanzapine (0.03–1 mg/kg, subcutaneous injection) or vehicle (5% DMSO) once a day for 1 week. At 60 min after the final injection, the tail was cut and blood was collected. Blood glucose was measured using a self-monitoring blood glucose meter (Medisafe-Mini; Terumo, Tokyo, Japan). The Medisafe-Mini system is based on the optoelectric colorimetry method.

Neuropathic Pain Model

C57BL/6J mice were anesthetized with 3% isoflurane. A partial sciatic nerve ligation model was made by tying a tight ligature with 8−0 silk suture around approximately one third to one half the diameter of the sciatic nerve on the right side (ipsilateral side) under a light microscope (SD30; Olympus, Tokyo, Japan). In sham-operated mice, the nerve was exposed without ligation.

Measurement of Thermal Thresholds

The sensitivity to thermal stimulation was measured as described previously.[24] Briefly, the right plantar surface of mice was exposed to a well-focused radiant heat light source (model 33 Analgesia Meter; IITC/Life Science Instruments, Woodland Hills, CA) that had been adjusted so that the average baseline latency of paw withdrawal in naive mice was approximately 8–10 s. Only quick movements of the hind paw away from the stimulus were considered to be a withdrawal response: paw movements associated with locomotion or weight shifting were not counted as a response. The paws were measured alternating between left and right with an interval of more than 3 min between measurements. Before testing, mice were placed in a clear acrylic cylinder (15 cm high and 8 cm in diameter) for at least 30 min. The data represent the average latency of paw withdrawal for the right hind paw.

Electroencephalogram and Electromyogram Recordings

Electroencephalogram and electromyogram recordings were obtained as described previously.[24] Briefly, electroencephalogram signals were monitored with two stainless-steel electroencephalogram recording screws 1 mm anterior to the bregma or λ, both 1.5 mm lateral to the midline, and electromyogram activity was monitored by stainless steel, nonstick-coated wires placed bilaterally into both trapezius muscles. Electroencephalogram and electromyogram signals were amplified, filtered (0.5–30 Hz and 20–200 Hz, respectively), digitized at a sampling rate of 128 Hz, and recorded using SleepSign software (Kissei Comtec, Nagano, Japan), which was also used to automatically classify vigilance over 4-s epochs as wakefulness, rapid eye movement (REM) sleep, or non-REM sleep using standard criteria. Finally, defined sleep–wake stages were examined visually and corrected, if necessary. For each epoch, the electroencephalogram power density in the δ (0.75–4.0 Hz) and θ bands (6.25–9.0 Hz) and the integrated electromyogram value were displayed on a computer monitor. Electroencephalogram and electromyogram activities were monitored for 24 h at 7 days after sciatic nerve ligation. Recordings were started at 8:00 PM. Vehicle

(5% DMSO) or olanzapine (0.06 mg/kg, intraperitoneal administration) was injected every day at 8:00 AM.

Drugs

The drugs used in the current study were morphine hydrochloride (Daiichi-Sankyo, Tokyo, Japan), prochlorperazine maleate (Sigma–Aldrich, St. Louis, MO), clozapine (Wako Pure Chemical Industries, Osaka, Japan), olanzapine (Toronto Research Chemicals, Toronto, Ontario, Canada), telenzepine dihydrochloride hydrate (Sigma–Aldrich), ritanserin (Tocris Biotechnology, Ellisville, CA), pyrilamine maleate salt (Sigma–Aldrich), ketanserin tartrate (Wako Pure Chemical Industries), granisetron (Sigma–Aldrich), GR113808 (Sigma–Aldrich), haloperidol (Sigma–Aldrich), L745870 (Research Biochemicals International, Natick, MA), raclopride (Santa Cruz Biotechnology, Santa Cruz, CA), pirenzepine (Toronto Research Chemicals), and DL-trihexyphenidyl hydrochloride (Sigma–Aldrich).

Statistical Analysis

Data are expressed as the mean with SEM. The statistical significant of differences between the groups was assessed with one-way and two-way ANOVA followed by the Bonferroni multiple comparisons test or Student *t* test (unpaired, two-tailed). The concentration of the test compound that caused 50% inhibition of specific binding (IC_{50} value) was determined from each concentration-response curve. All statistical analyses and IC_{50} values were calculated by Prism software (version 5.0a, GraphPad Software). A P value of <0.05 was considered to reflect significance.

Results

Binding Properties of Clozapine

In mouse brain membranes, we determined the competitive displacement binding of [^{3}H]clozapine with graded concentrations (10^{-11}–10^{-4} M) of unlabeled clozapine, olanzapine, telenzepine, ritanserin, pyrilamine, ketanserin, GR113808, granisetron, haloperidol, L745870, and raclopride. The binding of [^{3}H]clozapine was displaced by olanzapine in a concentration-dependent manner (fig. 1A). In addition, the binding of [^{3}H]clozapine was partially displaced by telenzepine (M_1), ritanserin (5-HT_{2A}), pyrilamine (H_1), ketanserin (5-HT_{2C}), GR113808 (5-HT_4), granisetron (5-HT_3), haloperidol (D_2), L745870 (D_4), and raclopride (D_2) (fig. 1B).

Binding Properties of Olanzapine with 5-$HT_{2A/2C}$, 5-HT_3, 5-HT_4, H_1, and M_1 Receptors

In mouse brain membranes, we determined the competitive displacement binding of [^{3}H]ketanserin, [^{3}H]BRL-43694 (granisetron), [^{3}H]pyrilamine, [^{3}H]GR113808, and [^{3}H]pirenzepine with graded concentrations (10^{-11}–10^{-4} M) of unlabeled ketanserin, granisetron, pyrilamine, GR113808, telenzepine, pirenzepine and olanzapine. The binding of [^{3}H]ketanserin and [^{3}H]pirenzepine was displaced by olanzapine in a concentration-dependent manner (fig. 2, A and B). The binding of [^{3}H]pyrilamine, [^{3}H]BRL-43694, and [^{3}H]GR113808 was partially displaced by olanzapine (fig. 2, C, D, and E).

Suppression of Morphine-induced Emesis by Olanzapine or Prochlorperazine

Pretreatment with either olanzapine (0.03 mg/kg, subcutaneous injection) 30 min before the injection of morphine (0.6 mg/kg, subcutaneous injection) or prochlorperazine (0.3 mg/kg and 1.0 mg/kg, subcutaneous injection) 60 min before the injection of morphine reduced the number of retching and vomiting behaviors induced by morphine (fig. 3).

Effects of Antipsychotics on Catalepsy

The results from the horizontal bar test as a measure of catalepsy were obtained at 15, 30, 45, and 60 min after the subcutaneous injection of vehicle, prochlorperazine (0.3–1 mg/kg), haloperidol (0.03–0.3 mg/kg), risperidone (0.01–0.1 mg/kg), or olanzapine (0.03–0.3 mg/kg). Although the catalepsy scores were not affected by a single subcutaneous injection of olanzapine (0.03–0.3 mg/kg), catalepsy was observed with the other antipsychotics within this dose range (fig. 4).

Effects of Olanzapine on the Morphine-induced Increase in the Concentrations of Dopamine and its Metabolites in Dialysate

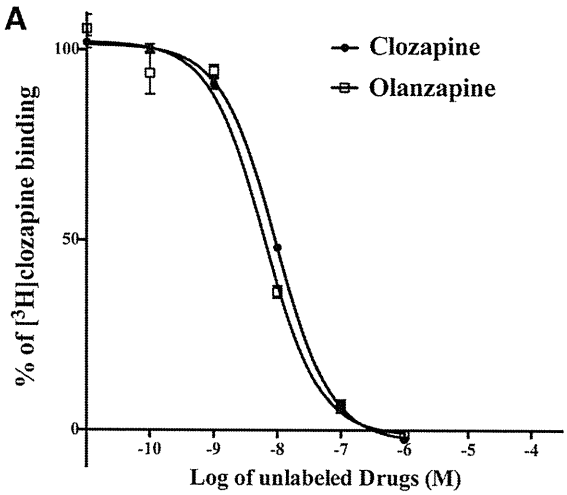
In the microdialysis study, the concentrations of dopamine and its metabolites 3,4-dihydroxyphenylacetic acid and 3-methoxy-4-hydroxyphenyl acetic acid in dialysate from the rat nucleus accumbens were markedly increased by the intraperitoneal administration of morphine at 10 mg/kg compared with those under the administration of saline. The increased concentrations of dopamine, 3,4-dihydroxyphenylacetic acid, and 3-methoxy-4-hydroxyphenyl acetic acid in the nucleus accumbens after the administration of morphine were not affected by olanzapine at 0.3 mg/kg (olanzapine-morphine *vs.* vehicle-morphine: $F_{(1,77)} = 0.1516$, $P = 0.7086$ fig. 5A; $F_{(1,77)} = 0.06326$, $P = 0.8086$ fig. 5B; $F_{(1,77)} = 1.851$, $P = 0.2158$ fig. 5C).

Effect of Olanzapine on the Morphine-induced Inhibition of Gastrointestinal Transit

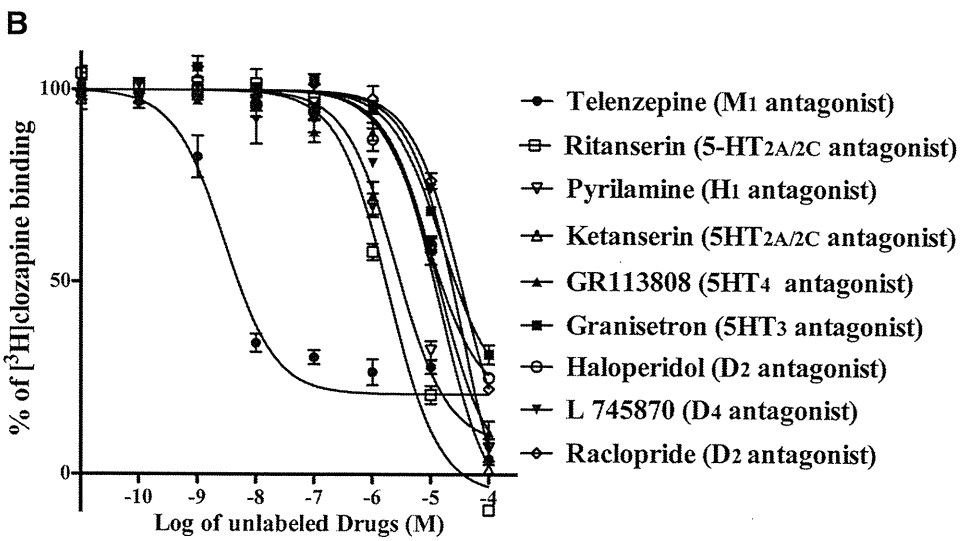
Morphine slowed gastrointestinal transit, and this effect was not significantly altered by the coadministration (subcutaneous injection) of olanzapine at 0.03–1 mg/kg (fig. 6A). Olanzapine itself did not slow gastrointestinal transit at doses of 0.03 and 0.1 mg/kg but significantly inhibited gastrointestinal transit at 0.3 and 1 mg/kg (fig. 6B).

Effects of Olanzapine on Blood Glucose

Blood glucose was measured after long-term treatment with olanzapine, saline, or vehicle (5% DMSO) in mice. Hypergly-



Antagonists	Clozapine	Olanzapine
IC50 (nM) for displacing [^{3}H]clozapine binding	9.56 (8.55-10.63)	6.26 (4.27-9.20)



Antagonists	IC50 (nM)
Telenzepine	2.91 (1.66-5.13)
Ritanserin	1885 (1368-2597)
Pyrilamine	2559 (1949-3339)
Ketanserin	> 10000
GR113808	> 10000
Granisetron	> 10000
Haloperidol	9127 (6329-13160)
L745870	> 10000
Raclopride	> 10000

Fig. 1. Displacement of the binding of [^{3}H]clozapine in membranes of mouse brain without the cerebellum by clozapine, olanzapine, telenzepine, ritanserin, pyrilamine, GR113808, granisetron, ketanserin, haloperidol, L745870, and raclopride. Experiments were performed in the presence of [^{3}H]clozapine (0.2 nM) and increasing concentrations of either clozapine or olanzapine (*A*) or of telenzepine, ritanserin, pyrilamine, GR113808, granisetron, ketanserin, haloperidol, L745870, or raclopride (*B*). The data represent the mean ± SEM of three to four samples. IC_{50} values were determined using an analysis of variance and linear regression techniques. To calculate the IC_{50} values, at least six drug doses were used, and three samples were used for each dose. Values in parentheses indicate the 95% confidence range.

cemia was not observed under treatment with olanzapine at 0.03, 0.1, or 0.3 mg/kg (subcutaneous injection) (fig. 7).

Thermal Hyperalgesia Induced by Sciatic Nerve Ligation in Mice

Sciatic nerve ligation markedly decreased the latency of paw withdrawal in response to a thermal stimulus on the ipsilateral side. This state of persistent pain caused by partial ligation of the sciatic nerve was suppressed by treatment with olanzapine at 0.06 mg/kg (fig. 8).

Changes in Sleep Vigilance in a Neuropathic Pain-like State Using Electroencephalogram and Electromyogram Recordings

We next investigated the changes in sleep patterns in sciatic nerve-ligated mice. Vigilance was classified automatically offline as wakefulness, REM sleep, or non-REM sleep. Mice with sciatic nerve ligation showed a statistically significant increase in wakefulness ($P = 0.0009$ *vs.* sham operated mice with vehicle, fig. 9A) and a decrease in non-REM sleep ($P = 0.0067$ *vs.* sham-operated mice with vehicle, fig. 9C) during the light phase. REM sleep during the light phase was not affected by sciatic nerve ligation ($P = 0.2896$ *vs.* sham-operated mice with vehicle, fig. 9B). On the other hand, there was no statistically significant difference in the sleep conditions during the dark phase between the two groups (wakefulness: $P = 0.6170$ *vs.* sham operated mice with vehicle, fig. 9D; REM: $P = 0.3936$ *vs.* sham operated mice with vehicle, fig. 9E; non-REM: $P = 0.5479$ *vs.* sham operated mice with vehicle, fig. 9F).

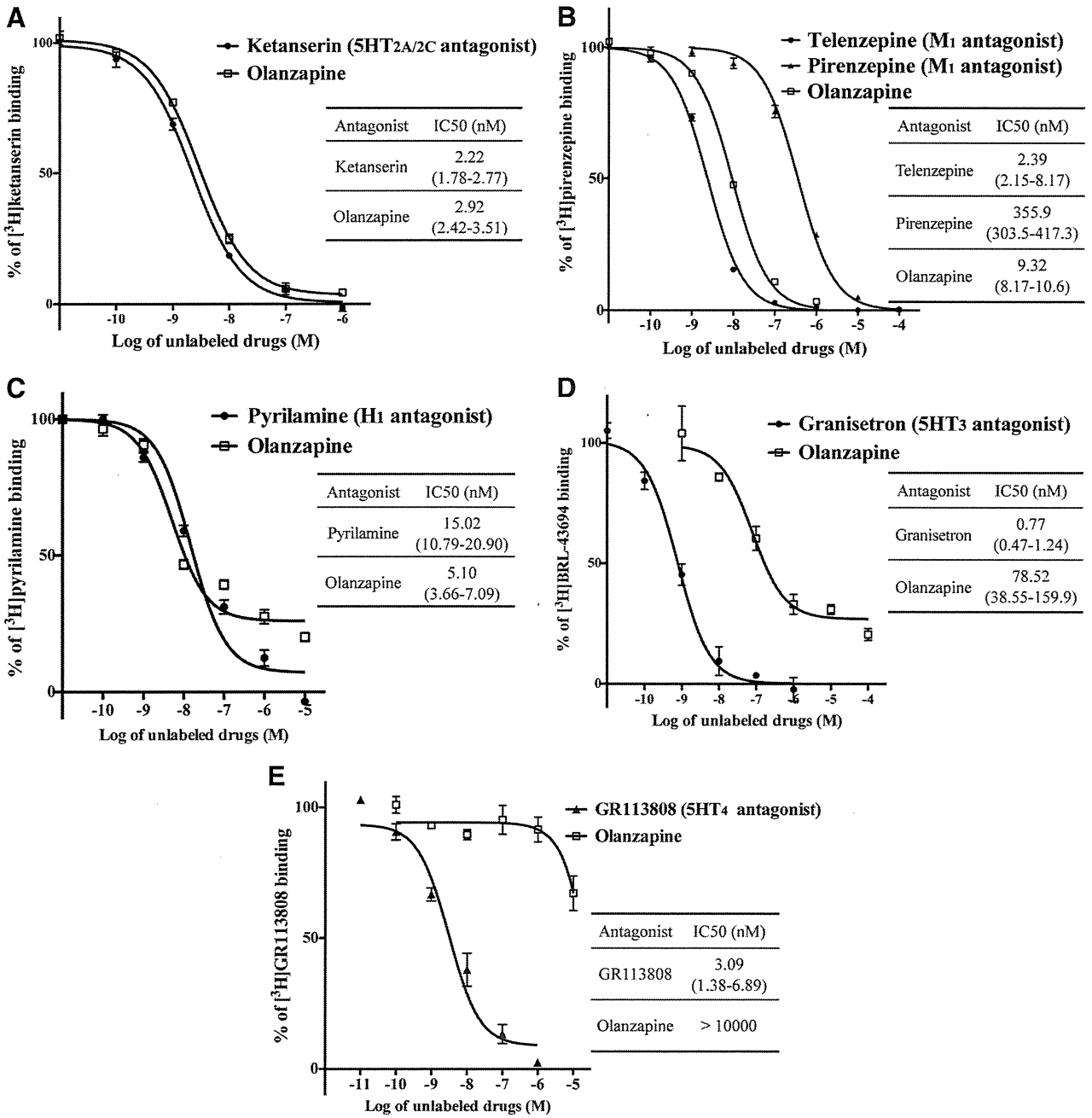


Fig. 2. Displacement of the binding of the serotonin (5-HT)$_{2A/C}$ receptor ligand [^{3}H]ketanserin (*A*), the muscarinic M_1 receptor ligand [^{3}H]pirenzepine (*B*), the H_1 receptor ligand [^{3}H] pyrilamine (*C*), the 5-HT_3 receptor ligand [^{3}H]BRL-43694 (granisetron) (*D*), or the 5-HT_4 receptor ligand [^{3}H]GR113808 (*E*) in membranes of mouse brain without the cerebellum by ketanserin, pirenzepine, telenzepine, pyrilamine, granisetron, GR113808, or olanzapine. Experiments were performed in the presence of [^{3}H]ketanserin (0.5 nM), [^{3}H]BRL-43694 (0.5 nM), [^{3}H]pyrilamine (0.5 nM), [^{3}H]GR113808 (0.5 nM), or [^{3}H]pirenzepine (0.5 nM) and increasing concentrations of ketanserin, granisetron, pyrilamine, GR113808, pirenzepine, telenzepine, or olanzapine. The data represent the mean ± SEM of three to four samples. IC_{50} values were determined using an analysis of variance and linear regression techniques. To calculate the IC_{50} values, at least six drug doses were used, and three samples were used for each dose. Values in parentheses indicate the 95% confidence range.

Changes in the Hypnotic Effects of Olanzapine in a Neuropathic Pain-like State Using Electroencephalogram and Electromyogram Recordings

To ascertain the hypnotic effect of olanzapine in a neuropathic pain-like state, we performed electroencephalogram and electromyogram recordings. The increased wakefulness and decreased non-REM during the light phase in nerve-ligated mice were significantly attenuated compared with those in sham-operated mice by the intraperitoneal administration of olanzapine (wakefulness: $P = 0.0006$ *vs.* nerve-

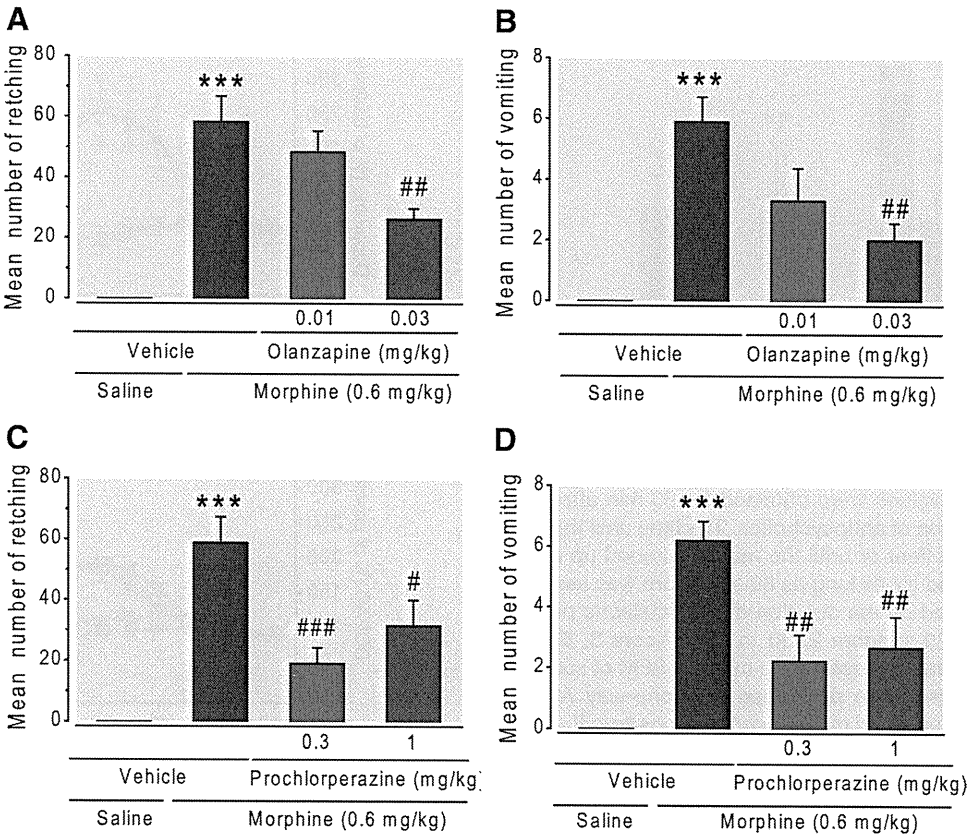


Fig. 3. Effects of olanzapine on subcutaneous injection morphine-induced retching (*A*, *C*) and vomiting (*B*, *D*) in ferrets. Groups of ferrets were pretreated with olanzapine (0.01 and 0.03 mg/kg, subcutaneous injection) (*A*, *B*), prochlorperazine (0.3 and 1.0 mg/kg, subcutaneous injection) (*C*, *D*), or vehicle before the administration of morphine (0.6 mg/kg, subcutaneous injection). Animals were observed for 30 min after subcutaneous injection of morphine. Each column represents the mean ± SEM of 9–10 ferrets. Statistical analyses were performed using one-way ANOVA followed by the Bonferroni multiple comparisons test: $F_{(3,39)} = 20.41$, $P < 0.0001$ (*A*); $F_{(3,39)} = 11.29$, $P < 0.0001$ (*B*); $F_{(3,37)} = 15.13$, $P < 0.0001$ (*C*); $F_{(3,37)} = 13.70$, $P < 0.0001$ (*D*). *** $P < 0.001$ *versus* vehicle-saline; ### $P < 0.001$; ## $P < 0.01$ or # $P < 0.05$ *versus* vehicle-morphine.

ligated mice with vehicle, fig. 9A; non-REM: $P = 0.001$ *vs.* nerve-ligated mice with vehicle, fig. 9C).

Discussion

The use of opioids for pain management is often associated with nausea and vomiting. Opioids induce emesis by stimulating the CTZ in the brainstem and by enhancing vestibular sensitivity.[25,26] Although several compounds are known to act on receptors in the CTZ, opioid-induced nausea and vomiting are attributable primarily to the transmission of dopamine. Many clinicians consider that typical antipsychotics such as prochlorperazine and haloperidol, which mainly act as dopamine D_2 receptor antagonists, are the drugs of choice for preventing the nausea and vomiting induced by morphine.[27–29] However, such compounds often produce extrapyramidal symptoms.[4]

Olanzapine is an atypical thienobenzodiazepine antipsychotic that is clinically indicated for schizophrenia and mania.[30] It blocks multiple neurotransmitters, including dopaminergic, serotonergic, adrenergic, histaminergic, and muscarinic receptors.[31] In the current binding study, olanzapine showed the highest affinity for muscarinic M_1 receptors. To understand its affinity in greater detail, we investigated the affinity of olanzapine toward serotonin 5-$HT_{2A/2C}$, 5-HT_3, histamine H_1, dopamine D_2, dopamine D_4, and 5-HT_4 receptors. Olanzapine also showed affinity for each of these receptors. Because of its effect on several neurotransmitters that are associated with nausea and vomiting, we expected that olanzapine would have potential as an antiemetic medication. In a behavioral study, we found that morphine-induced nausea and vomiting were decreased in a dose-dependent manner by pretreatment with olanzapine at a dose that was almost 1/200 of that at which an antipsychotic effect is observed,[32] whereas olanzapine at a dose that had antiemetic effects failed to induce catalepsy. However, although the dopamine D_2 receptor antagonist prochlorperazine suppressed morphine-induced nausea and vomiting, it did so at a dose that caused a dose-dependent increase in the expression of catalepsy. Furthermore, olanzapine had no effect on the morphine-induced release of dopamine in the nucleus accumbens. Muscarinic M_1 receptors have been suggested to be responsible for the opioid-induced stimula-

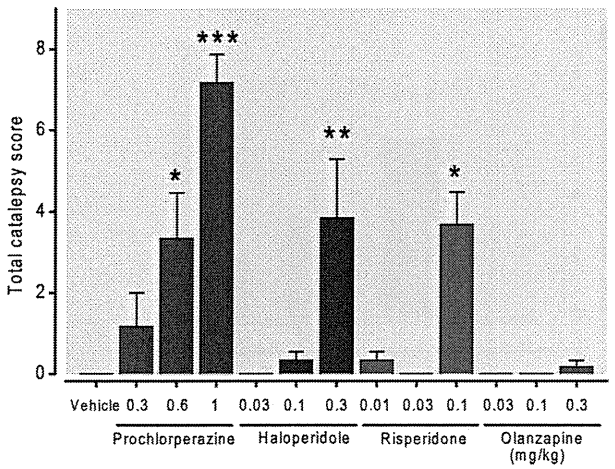


Fig. 4. Expression of catalepsy caused by antipsychotics in mice. Catalepsy values were obtained for 60 min after subcutaneous injection of antipsychotics. The time until the forepaw touched the floor or until the mouse climbed up on the bar was measured for as long as 60 s. A score was assigned to each test based on the duration of the cataleptic posture (score 1, 15 to 29 s; score 2, 30 to 59 s; score 3, 60 s or more). Each column represents the mean ± SEM of six mice. Statistical analyses were performed with one-way ANOVA followed by the Bonferroni multiple comparisons test: $F_{(12,77)} = 12.59$, $P < 0.0001$. * $P < 0.05$, ** $P < 0.01$, or *** $P < 0.001$ *versus* vehicle.

tion of the vestibular apparatus.[6] In addition, sensory input from the vestibular apparatus to the vomiting center follows muscarinic M_1 receptor pathways. Taken together with the fact that olanzapine showed the highest affinity toward muscarinic M_1 receptors, these findings suggest that, although the exact mechanism by which olanzapine suppresses morphine-induced emesis remains unclear, muscarinic M_1 receptors may be a critical target for morphine-induced emesis. To prove our hypothesis, we next investigated whether the selective muscarinic M_1 receptor antagonist trihexyphenidyl could affect morphine-induced nausea and vomiting. Trihexyphenidyl significantly suppressed morphine-induced retching and vomiting in ferrets (data not shown), which indicates that M_1 receptors play an important role in the opioid-sensitive emetic pathway. However, trihexyphenidyl significantly enhanced the morphine-induced increase in the release of dopamine in the nucleus accumbens (data not shown). If we consider the risk of the overexcitation of dopamine transmission with the use of drug combinations, a specific M_1 receptor antagonist might not be a better choice as an adjunct agent in combination with opioids. Because olanzapine acts not only on muscarinic M_1 receptors, but also partly on histamine H_1 and dopamine D_2 receptors as an antagonist,[10] it is likely that olanzapine at a dose lower than that at which it has antipsychotic effects could be useful for strongly preventing opioid-induced emesis without severe side effects.

Constipation is another adverse effect of treatment with morphine. In the current study, olanzapine at doses that had antiemetic effects had no effect on the morphine-induced

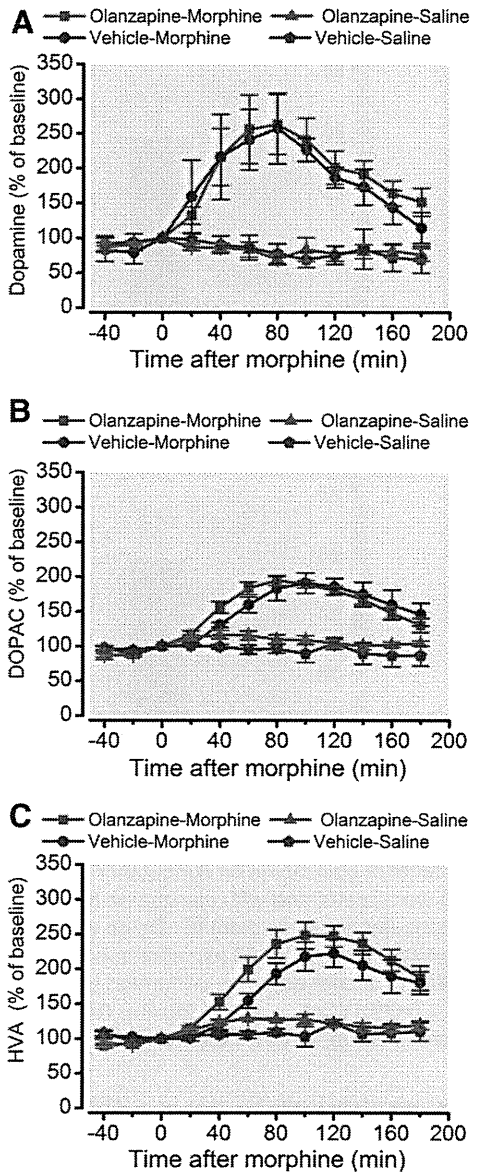


Fig. 5. Effect of olanzapine on the influence of intraperitoneal administration morphine on the dialysate concentrations of dopamine (*A*) and its metabolites (*B*, *C*) in the nucleus accumbens. After baseline fractions were collected, rats were pretreated with olanzapine (0.3 mg/kg, intraperitoneal administration) or vehicle 30 min before the injection of morphine (10 mg/kg, intraperitoneal administration) at time 0 to evoke the release of dopamine. Data are expressed as percentages of the corresponding baseline levels with SEM for three to five rats (number of rats: olanzapine-morphine, n = 5; vehicle-morphine, olanzapine-saline, n = 4; vehicle-saline, n = 3). Statistical analyses were performed with two-way ANOVA followed by the Bonferroni multiple comparisons test: vehicle-saline *versus* vehicle-morphine, $F_{(1,55)} = 19.48$, $P = 0.0069$ vehicle-saline *versus* vehicle-morphine, $F_{(1,77)} = 0.1516$, $P = 0.7086$ olanzapine-morphine *versus* vehicle-morphine (*A*), $F_{(1,55)} = 32.57$, $P = 0.0023$ vehicle-saline *versus* vehicle-morphine, $F_{(1,77)} = 0.06326$, $P = 0.8086$ olanzapine-morphine *versus* vehicle-morphine (*B*), $F_{(1,55)} = 23.42$, $P = 0.0047$ vehicle-saline *versus* vehicle-morphine, $F_{(1,77)} = 1.851$, $P = 0.2158$ olanzapine-morphine *versus* vehicle-morphine (*C*).