
Psychotropic drugs for terminally ill patients with respiratory disease

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ÖZET

Son dönem akciğer hastalığı olan hastalar için psikotropik ilaçlar

Hipnotikler, sedatifler, parenteral morfin gibi psikotropik ilaçların son dönem akciğer hastalığı olanlarda kullanımıyla ilgili yeterli bildirim yapılmamıştır. Solunum hastalığı nedeniyle ölmekte olan hastalarda bu ilaçların kullanımını daha iyi anlamak için bu hastaların hayatlarının son dönemlerini inceledik. Nisan 2000-Mart 2005 tarihleri arasında solunum hastalığı nedeniyle ölen 337 hastanın son ayındaki semptomlar ve tedaviler tarandı. Hipnotikler malign hastaların %35.8'inde, malign olmayan hastaların ise %23.2'sinde; haloperidol ve midazolam gibi sedatifler malign hastaların %34.4'ünde, malign olmayan hastaların ise %30.4'ünde kullanılmış. Malign hastaların %65'i, malign olmayan hastaların %22.4'ü parenteral morfin kullanmış. Malign hastalarda morfin kullanımının üç ana nedeni ağrı, nefes darlığı ve son dönem huzursuzluğu idi. Malign olmayan hastaların hepsinde parenteral morfin kullanım nedeni dispne idi. Sonuçlarımız son dönem akciğer hastalığı olanların bir kısmında psikotropik ilaçlar ve parenteral morfin kullanımının gerektiğini göstermektedir. Her ne kadar dikkatli seçilmiş hastalarda uygulanması yeterli olsa da, bu hasta grubunda psikotropik ilaçların kullanımıyla ilgili rehberler gerekmektedir.

Anahtar Kelimeler: Semptomlar, tedavi, psikotropik ilaçlar, son dönem hastalar, solunum hastalıkları.

SUMMARY

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Utilization of psychotropic drugs including hypnotics, sedatives, and parenteral morphine for terminally ill patients with respiratory disease has not been reported precisely. To better understand these drugs for dying patients with respiratory disease, we focused on the last month of life of them. A chart review, which was focused on symptoms and managements, in the last month of life of 337 patients who died of respiratory disease between April 2000 and March 2005 were performed. Hypnotics were prescribed in 35.8% and 23.2% of patients with malignant and non-malignant disease, respectively. Sedatives such as haloperidol and midazolam were utilized in 34.4% of patients with malignant disease, and 30.4% of those with non-malignant disease. Sixty-seven percent of patients with malignant and 22.4% of those with non-malignant disease had parenteral morphine. In patients with malignant disease, three of the main reasons for administration of morphine were pain, dyspnea, or terminal restlessness. In all of the patients with non-malignant disease, however, parenteral morphine was prescribed for the treatment of dyspnea. Our results showed that psychotropic drugs and parenteral morphine are required in some of terminally ill patients with respiratory disease. Although careful individualization of medication is appropriate, guideline for the prescribing psychotropic drugs for these patients will be required.

Key Words: Symptoms, management, psychotropic drugs, terminally ill, respiratory diseases.

The physiologic, psychologic symptoms and medical interventions of terminal phase of illness have been documented repeatedly in the clinical literature (1-5). As death approached, not only intractable pain and severe dyspnea but also psychologic symptoms such as agitation, insomnia, anxiety, fear, and mental distress were seen in many patients (1-5). Psychotropic drugs including hypnotics, sedatives, and parenteral morphine were sometimes prescribed in these terminally ill patients, but these drugs would not be used in some patients because of its respiratory depressant actions. In patients with terminally ill lung cancer and chronic obstructive pulmonary disease (COPD), symptoms and medical interventions have been documented in many previous reports (6-8). We also studied symptoms and treatments in the last two days of patients with respiratory disease (9). However, previous reports including our own, utilization of psychotropic drugs for terminally ill patients with respiratory disease other than lung cancer and COPD has not been reported precisely (6-9). In order to better understand symptoms and managements, especially medication such as hypnotics, sedatives and parenteral morphine for dying patients with respiratory disease, we focused on the last month of life of them. In the present study, reasons for prescription of these drugs were also studied.

MATERIALS and METHODS

We performed a retrospective chart review of hospitalized patients who died of respiratory di-

sease in Respiratory Divisions of University of Tsukuba Hospital and Tsukuba Medical Center Hospital between April 2000 and March 2005. All the patients who died of both acute and chronic respiratory diseases were included in this study. The search for medical charts was performed in the patient administrative system in each hospital. The review was focused on symptoms and managements in the last month of life of patients with respiratory disease. We used an assessment form, which included demographic data, symptoms such as pain, dyspnea and treatment for these patients. Especially, the form recorded the medication including hypnotics, sedatives, and parenteral morphine, which might cause respiratory depression. Reasons for prescription of these drugs were also studied.

All the patients with malignant respiratory disease diagnosed pathologically. Patients with both lung cancer and non-malignant respiratory disease such as COPD were classified as having lung cancer. The diagnosis of idiopathic interstitial pneumonia (IIP) and collagen disease-related pulmonary fibrosis (CDPF) was based on its diagnostic criteria, respectively. Pneumonia was diagnosed clinically by the presence of radiographic appearance of new or progressive infiltrates, fever, peripheral blood leukocytosis, and purulent tracheal secretions. Patients with both pneumonia and underlining chronic non-malignant respiratory disease such as COPD or IIP were classified as having the latter disease.

Four chest physicians reviewed and discussed all of the medical charts. Inter-reviewer reliability of abstraction was ensured by duplicate abstraction of all the charts review. Documentation of symptoms was found in interdisciplinary progress notes and in daily nursing flow sheets. In some charts, symptoms were also documented on medical administration records, particularly when medications were given "as required".

The Mann-Whitney U test was applied to elucidate the difference between two independent groups, and proportion was compared by chi-square test. Only results with p less than 0.05 were regarded as significant.

RESULTS

Demographic Data

During the study period, 337 patients died of respiratory disease. Demographic data of these patients were shown in Table 1. Of them, 249 (73.9%) were men, and a total of 75.7% of the patients aged 65 years and older. Patients with malignant respiratory disease (median: 71, range: 22-89 years) were significantly younger than those with non-malignant respiratory disease (median: 75, range: 22-96 years) ($p= 0.0002$). Of the 212 patients with malignant respiratory disease, 206 patients had primary lung cancer. Of the 125 patients with non-malignant respiratory disease, 47 (37.6%), 41 (32.8%), and 22 (17.6%) patients were those with IIP and CDPF, pneumonia, and COPD, respectively.

Clinical Symptoms

Table 2 lists symptoms documented in the last month of life of the 337 patients studied.

Table 1. Characteristics of malignant and non-malignant respiratory diseases.

	Malignant	Non-malignant
Number of patients	212	125
Age [median (range)], years	71 (22-89)	75 (22-96)
Male/female	163/49	86/39
Diagnosis		
Primary lung cancer	206	
Metastatic lung cancer	4	
Malignant lymphoma	1	
Mediastinal germ cell tumor	1	
IIP, CDPF		47
Pneumonia		41
COPD		22
Bronchiectasis		7
Tuberculosis		3
Pyothorax		2
Pulmonary hypertension		1
Thromboembolism		1
Pneumoconiosis		1

IIP: Idiopathic interstitial pneumonia, CDPF: Collagen disease-related pulmonary fibrosis, COPD: Chronic obstructive pulmonary disease.

Dyspnea was documented in 86.8% and 89.6% of patients with malignant and non-malignant disease, respectively. Cough and sputum were also present in two thirds of patients of both groups. However, pain was documented in 66% of the patients with malignant disease, but it was observed in only 11.2% of patients with non-malignant respiratory disease. There was a statisti-

Table 2. Symptoms in the last month of life of 337 patients with respiratory disease.

Symptoms	Malignant (%)	Non-malignant (%)	p
Dyspnea	184 (86.8)	112 (89.6)	0.4941
Cough	143 (67.5)	96 (76.8)	0.0820
Sputum	154 (72.6)	101 (80.8)	0.1145
Pain	140 (66)	14 (11.2)	0.0001
Sleep disturbance	88 (41.5)	35 (28)	0.0140
Restlessness	149 (70.3)	66 (52.8)	0.0015

cal difference ($p= 0.0001$). With regard to sleep disturbance and restlessness, statistical significant difference was observed between malignant and non-malignant diseases ($p= 0.0140$, 0.0015 , respectively).

Medical Interventions

Interventions performed in the last month of life are shown in Table 3. Between malignant and non-malignant groups of patients, there were no significant differences in rates of oxygen therapy, foley catheter. Patients with malignant respiratory disease had significantly lesser rates of central venous lines ($p= 0.0001$) and ventilation ($p= 0.0001$) (Table 3). However, patients with malignant disease had significantly higher rates of prescribing hypnotics ($p= 0.0204$) and parenteral morphine ($p= 0.0001$).

Among the patients with sleep disturbance, hypnotics were prescribed in 35.8% of patients with malignant respiratory disease and 23.2% of those with non-malignant respiratory disease. However, hypnotics were not prescribed in 18 patients because of their poor respiratory condition. Brotizolam, zolpidem tartrate, and rilmazofone hydrochloride were three of the most frequently prescribed hypnotics.

Sedatives were prescribed in 73 (34.4%) of 212 patients with malignant and 38 (30.4%) of 125 patients with non-malignant respiratory disease.

All of them were administered intravenously or subcutaneously. Among the drugs, haloperidol, hydroxyzine pamoate, midazolam, and chlorpromazine were four of the most prescribed drugs for symptomatic relief. These sedatives were transiently prescribed before initiating parenteral morphine therapy.

Parenteral morphine were used in 142 (67%) of 212 patients with malignant and 28 (22.4%) of 125 patients with non-malignant respiratory disease. In 87, 64, and 5 of the 142 patients with malignant respiratory disease, parenteral morphine was prescribed for pain, dyspnea, and terminal restlessness, respectively. On the other hand, all of the 28 patients with non-malignant respiratory disease had morphine for the treatment of dyspnea.

There was no documentation on CO_2 narcosis and other critical complications in our patients who were prescribed hypnotics, sedatives, and parenteral morphine.

DISCUSSION

In the present study, we showed that prevalence of dyspnea was very high in end of life patients with malignant as well as non-malignant respiratory disease. The prevalence of cough and sputum were also high in both groups of patients. Added to these, in patients with malignant respiratory disease, not only pain but also psycholo-

Table 3. Medical interventions and medication that might cause respiratory depression prescribed in the last month of life of 337 patients with respiratory disease.

Interventions and medication	No. of patients (%)		p
	Malignant	Non-malignant	
Medical interventions			
Oxygen	210 (99.1)	124 (99.2)	0.9999
Foley catheter	176 (83)	108 (86.4)	0.4425
Central venous line	90 (42.5)	86 (68.8)	0.0001
Ventilation	9 (4.2)	33 (26.4)	0.0001
Medication			
Hypnotics	76 (35.8)	29 (23.2)	0.0204
Sedatives	73 (34.4)	38 (30.4)	0.4734
Morphine	142 (67)	28 (22.4)	0.0001

gical symptoms such as restlessness and sleep disturbance were more prevalent than those with non-malignant. Jaeger, et al. reported that patients with malignant disease spent longer in hospital than those with non-malignant disease, and patients who had a longer hospital stay, meaning a longer terminal phase of their illnesses, had more psychological distress and received more psychotropic agents than those with a relative short stay (10). We agree with this opinion and this was one of the reasons for higher prevalence of psychological symptoms in our patients with malignant respiratory disease than those with non-malignant. Additionally, we suppose that psychological symptoms might strongly be influenced by some physiological symptoms such as severe cough and pain in these patients. We previously reported that 36.1% of patients with lung cancer, and 33.9% of patients with stable state COPD had hypnotics. And hypnotics were prescribed only for the patients with both $\text{PaO}_2 > 60$ torr and $\text{PaCO}_2 < 60$ torr (11,12). In these patients, we found no episodes of CO_2 narcosis. In the present study, sleep disturbance was observed in 88 (41.5%) of 212 and 35 (28%) of 125 patients with terminally ill malignant and non-malignant respiratory disease, respectively. However, 12 and 6 patients with malignant and non-malignant respiratory disease were not prescribed hypnotics because they had $\text{PaO}_2 < 60$ torr and/or $\text{PaCO}_2 > 60$ torr in their blood gas analysis.

In patients with severely illness, it can be difficult to decide when the switch from curative treatment to a palliative approach should be made. Conversely, it is sometimes clear that an individual is dying. In many cases, this terminal stage is often accompanied by physical symptoms as well as psychologic distress such as terminal restlessness. Under these circumstances, sedatives are prescribed. The benzodiazepine midazolam, an anxiolytic sedative with amnesic and anticonvulsant properties, is the agent most frequently used in this context (12-15). In this study, we showed that more than 80% of our patients with malignant and non-malignant respiratory disease had dyspnea in the last month of

life. These results were consistent with that of Edmonds, et al. (8). In their report, dyspnea was observed in 78% of lung cancer patients and 94% of patients with chronic respiratory disease (8). Other previous reports showed that 51-94% of non-malignant and 28-78% of malignant patients had dyspnea in their terminal phase of life (7,8,16-19). Although dyspnea was the second commonest symptom needing parenteral morphine in patients with malignant respiratory disease in our patients, it was the most frequent symptom requiring parenteral morphine in those with non-malignant respiratory disease. Despite the management of dyspnea by providing oxygen to relieve discomfort, 30.2% of patients with malignant and 22.4% of those with non-malignant respiratory disease used parenteral morphine for dyspnea in the last month of life in our study. Parenteral morphine has been found to be effective in the management of dyspnea in cancer patients as well as in those with non-malignant respiratory disease, but some ethical concerns and cultural adaptations usually arise due to its depressant action on the respiratory center (20-22). In some patients, parenteral morphine is not prescribed because of its respiratory depressant actions. Both the family and the medical staff always worry that if parenteral morphine is used for pain and/or dyspnea control in terminally ill patients, this may shorten the patient's life (22,23).

Most individuals in our country die in hospitals. Terminal hospital stay is apparently longer than those in Western countries. Therefore, improvement in the care given at the end of life is an essential issue. We do believe that psychotropic drugs and parenteral morphine are required in some of them and that respiratory depressant actions of such drugs must be taken into much consideration. Results of blood gas analysis will provide important information about the risk of respiratory depression. Although careful individualization of medication is appropriate, clinical guideline for the prescribing psychotropic drugs for terminally ill patients with respiratory disease will also be required.

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REFERENCES

1. Muers MF, Round CE. Palliation of symptoms in non-small cell lung cancer: A study by the Yorkshire Regional Cancer Organisation Thoracic Group. *Thorax* 1993; 48: 339-43.
2. Dudgeon DJ, Lertzman M. Dyspnea in the advanced cancer patient. *J Pain Symptom Manage* 1998; 16: 212-9.
3. Thorns A, Sykes N. Opioid use in last week of life and implications for end-of-life decision-making. *Lancet* 2000; 356: 398-9.
4. Hall P, Schroder C, Weaver L. The last 48 hours in long-term care: A focused chart review. *J Am Geriatr Soc* 2002; 50: 501-6.
5. Saydain G, Islam A, Afessa B, et al. Outcome of patients with idiopathic pulmonary fibrosis admitted to the intensive care unit. *Am J Respir Crit Care Med* 2002; 166: 839-42.
6. Gore JM, Brophy CJ, Greenstone MA. How well do we care for patients with end stage chronic obstructive pulmonary disease (COPD)? A comparison of palliative care and quality of life in COPD and lung cancer. *Thorax* 2000; 55: 1000-6.
7. Claessens MT, Lynn J, Zhong Z, et al. Dying with lung cancer or chronic obstructive pulmonary disease: Insights from SUPPORT. *J Am Geriatr Soc* 2000; 48: 146-53.
8. Edmonds P, Karson S, Khan S, Addington-Hall J. A comparison of the palliative care needs of patients dying from chronic respiratory diseases and lung cancer. *Palliat Med* 2001; 15: 287-95.
9. Sumi M, Satoh H, Ishikawa H, et al. Dying with respiratory disease. *Chest* 2001; 120: 1043-4.
10. Jaeger H, Morrow GR, Carpenter PJ. A survey of psychotropic drug utilization by patients with advanced neoplastic disease. *General Hospital Psychiatry* 1985; 7: 353-60.
11. Sumi M, Satoh H, Sekizawa K. Use of hypnotics in patients with chronic obstructive pulmonary disease. *Chr Respir Dis* 2004; 1: 62.
12. Sumi M, Satoh H, Nakayama M, et al. Hypnotics for patients with lung cancer. *Arch Oncol* 2003; 11: 282.
13. Stone P, Rees E, Hardy JR. End of life care in patients with malignant disease. *Eur J Cancer* 2001; 37: 1070-5.
14. Cowen JD, Walsh D. Terminal sedation in palliative medicine-definition and review of the literature. *Support Care Cancer* 2001; 9: 403-7.
15. Sykes N, Thorns A. The use of opioids and sedatives at the end of life. *Lancet Oncol* 2003; 4: 312-8.
16. Coyle N, Adelhardt J, Foley KM, Portenoy RK. Character of terminal illness in the advanced cancer patient: Pain and other symptoms during the last four weeks of life. *J Pain Symptom Manage* 1990; 5: 83-93.
17. Goodlin S, Winzelberg GS, Teno JM, et al. Death in the hospital. *Arch Intern Med* 1998; 158: 1570-2.
18. Bauduer F, Capdupuy C, Renoux M. Characteristics of deaths in a department of oncohaematology within a general hospital. A study of 81 cases. *Support Care Cancer* 2000; 8: 302-6.
19. Tranmer JE, Heyland D, Dudgeon D, et al. Measuring the symptom experience of seriously ill cancer and noncancer hospitalized patients near the end of life with the Memorial Symptom Assessment Scale. *J Pain Symptom Manage* 2003; 25: 420-9.
20. Bruera E, Macmillan K, Pither J, MacDonalod RN. The effects of morphine on the dyspnea of terminal cancer patients. *J Pain Symptom Manage* 1990; 5: 341-4.
21. Cohen MH, Anderson AJ, Krasnow SH, et al. Continuous intravenous infusion of morphine doe severe dyspnea. *South Med J* 1991; 84: 229-34.
22. Lane DJ. The clinical presentation of chest disease. In: Weatherall DJ, Ledingham JGG, Warrel DA (eds). *The Oxford Textbook of Medicine*. Oxford: Oxford University Press, 1983: 1539-52.
23. Dudgeon D. Dyspnea: Ethical concerns. *J Palliat Care* 1994; 10: 48-51.