Single-Dose Subcutaneous Benzodiazepines for Insomnia in Patients With Advanced Cancer

To the Editor:

Insomnia is one of the most common complications affecting patients with advanced cancer. Severe insomnia has a highly negative impact on quality of life. Sleeplessness exacerbates pain, causing physical and mental discomfort (e.g., fatigue, daytime drowsiness, and day-night reversal). As with other symptoms, insomnia is distressing to patients, families, and caregivers. Furthermore, with the progression of disease, many patients with advanced cancer face difficulties taking oral medication, eventually requiring parenteral drug administration. The placement of an intravenous catheter is often uncomfortable and difficult for patients with advanced cancer. In such patients, single-dose subcutaneous administration is easier and less stressful as compared with intravenous administration.

Benzodiazepines are commonly used hypnotic medications for inducing sleep in palliative care. Midazolam and flunitrazepam as injectable solutions can be used in Japan. Midazolam is a short-acting and flunitrazepam an intermediate-acting benzodiazepine. For the last eight years, we have successfully used midazolam and flunitrazepam for treating insomnia via single-dose subcutaneous administration. Single-dose administration is advantageous because it does not need specialized equipment, being simple and useful for patients and medical institutions, including patients receiving home care. However, to the best of our knowledge, single-dose subcutaneous administration of midazolam and flunitrazepam for treating insomnia has not been reported thus far.

This retrospective analysis was carried out at the palliative care unit of JCHO Tokyo Shinjuku Medical Center (formerly Tokyo Kosei Nenkin Hospital). We reviewed the electronic medical records of patients admitted from January 2012 to December 2012 who fulfilled the following inclusion criteria: 1) diagnosis of advanced cancer and hospitalized in the palliative care unit, 2) difficulty taking medications orally, 3) complaining of poor sleep, and 4) agreeing to receive a benzodiazepine via single-dose subcutaneous injection. The approximate total sleep time, number of awakenings, and occurrence of adverse effects during the night were measured by the palliative care nursing staff. The study was approved by the Institutional Review Board of Tokyo Kosei Nenkin Hospital.

During the study period, 151 patients were admitted to the palliative care unit of our hospital. There were 22 women and 39 men, with an average age of 73.3 years (range 53–95 years) who received midazolam and 13 women and 15 men, with an average age of 71.3 years (range 53–91 years) who received flunitrazepam. Primary tumor sites included lung (n = 22); esophagus, breast and colon/rectum (n = 5); pharynx (n = 4); pancreas, stomach/duodenum, liver/bile duct, ovary/uterus and kidney (n = 3); brain, peritoneum and renal pelvis (n = 2); and liposarcoma and adrenal (n = 1). The average duration of hospitalization in the palliative care unit was 35.9 days (median 16.0 days). Administration of midazolam and flunitrazepam is shown in Table 1.

The rate of patients who could sleep more than six hours in total was 57% (midazolam) and 75% (flunitrazepam). Three patients complained of mild and transient pain at the time of the subcutaneous injection. No incidents of falling or critical events occurred among any of the patients.

Benzodiazepines are one of the most commonly used hypnotic agents for treating insomnia; however, they cause various side effects. In the palliative care population, where life expectancy is limited and

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<td>Administration of Midazolam and Flunitrazepam</td>
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<table>
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<tr>
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<th>Midazolam (n = 61)</th>
<th>Flunitrazepam (n = 28)</th>
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<tr>
<td>Mean (SD)</td>
<td>Median (Range)</td>
<td>Mean (SD)</td>
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<tr>
<td>One dose (mg)</td>
<td>2.2 (.28) 2 (1.5–2.5)</td>
<td>0.88 (.12) 0.8 (0.6–1)</td>
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<tr>
<td>Total dosing days</td>
<td>2.7 (2.1) 2 (1–10)</td>
<td>3.4 (3.5) 2 (1–17)</td>
</tr>
<tr>
<td>Dose frequency/day</td>
<td>1.1 (.28) 1 (1–2)</td>
<td>1.1 (.22) 1 (1–2)</td>
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patients experience severe pain and other problems, the goal of symptomatic relief possibly overrides the concerns of side effects. Previous reports have discussed the lack of an ideal hypnotic drug for patients with advanced cancer, and an appropriate drug needs to be chosen for each patient based on individual medical status. The dosing period of the benzodiazepine was very short. The treatment with a single dose of benzodiazepine was intended to improve insomnia. Most of the patients faced difficulty in taking medications orally and had poor prognoses.

We realize that our data are clearly tentative and preliminary; nonetheless, we consider that the high percentage of patients who could sleep more than six hours in total (57% and 75%) demonstrates the potential of single-dose subcutaneous administration of midazolam and flunitrazepam as a helpful method in patients with advanced cancer with insomnia. Further trials, including randomized placebo-controlled trials, are required for validating our results.

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http://dx.doi.org/10.1016/j.jpainsymman.2015.02.018

Disclosures and Acknowledgments
The authors express their gratitude to Dr. Asao Ogawa from the Research Center for Innovative Oncology of the National Cancer Center Hospital East for his contribution to this study. Special thanks also are given to the patients and hospice professionals who took part in the study.

References

Do-Not-Resuscitate (DNR) Orders and Consultants’ Willingness to Perform Invasive Procedures

To the Editor:
As disease progresses and palliation becomes the goal of care, treatment ideally maximizes symptom control and empowers patients and families to make important end-of-life decisions. Most patients with terminal illness prefer to die in their own homes, usually under hospice care, and the quality of home death is rated higher than hospital death. Do-not-resuscitate (DNR) orders are frequently discussed with patients and/or their family members to avoid invasive interventions such as cardiopulmonary resuscitation or intubation, which usually result in poor outcomes for patients with advanced cancer. However, sometimes invasive procedures are required to manage severe symptoms. We report the case of a woman with advanced cancer who needed a chest tube insertion to relieve severe dyspnea from a pneumothorax; the consultant was hesitant to perform this procedure because the patient had a DNR order.

Case
A woman in her mid-40s with metastatic breast carcinoma to the pleura, mediastinum, lymph nodes, and bone was admitted to our hospital with shortness of breath. She was first diagnosed 11 years earlier, and after initial response to several therapies (surgery, radiation, and chemotherapy), her disease recurred. She then received several different chemotherapy regimens. The last cycle of chemotherapy was completed two weeks before she was admitted to the breast medical oncology service of our hospital for shortness of breath.

The palliative care service was consulted to help with symptom management and end-of-life care. At the time of initial evaluation, the patient reported being very short of breath and anxious; she also said that