Sedative Use in the Last Week of Life and the Implications for End-of-Life Decision Making

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Background: The use of sedation at the end of life has aroused ethical controversy, attracting accusations of hastening death by gradually increasing sedative doses. The doctrine of double effect has been introduced as an ethical defense. This study aimed to determine how sedative doses change at the end of life and how often the doctrine of double effect might be relevant.

Methods: Case note review was performed of 237 consecutive patients who died in a specialist palliative care unit. Sedative dose changes during the last week of life were noted and survival from admission was compared between groups of patients receiving no sedation, sedation for 7 days, or a commencement of sedation in the last 48 hours of life. There was detailed review of notes from patients who received a marked increase in sedative dose to explore the applicability of the doctrine of double effect.

Results: Sedation was given to 48% of patients. Of these, 13% received sedatives for 7 days or more, while 56% commenced sedative use only in the last 48 hours of life. The groups receiving no sedation or sedation for less than 48 hours had the shortest survival from admission (mean, 14.3 and 14.2 days), whereas the 7-day sedation group survived for a mean of 36.6 days ($P<.001$). Sedative use and dose increased toward the end of life, but the detailed case note review disclosed only 2 cases where the doctrine of double effect may have been implicated.

Conclusion: Sedative dose increases in the last hours of life were not associated with shortened survival overall, suggesting that the doctrine of double effect rarely has to be invoked to excuse sedative prescribing in end-stage care.

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Sedation may be used in more than 50% of patients at the end of life.1 The reasons for use vary between reports and include difficulties in controlling such symptoms as pain and breathlessness, but probably the most common indication for sedation in palliative care is delirium in an extremely ill patient.2,3 The use of sedation near the end of life has aroused ethical controversy, and physicians adopting the practice have been accused of slow euthanasia, ie, shortening the patient’s life by gradually increasing the dose of sedation.4

Although in principle it is, of course, possible to hasten death by the use of sedation, it is unclear whether life shortening does in fact occur with any frequency when sedation is adopted in the context of specialist symptom control for the terminally ill. That is the starting point for the study reported herein. Even if some life shortening were to occur, it has been held that this is justifiable under what is known as the doctrine of double effect (DDE).4 This states that a harmful effect of treatment, even resulting in death, is permissible if it is not intended and occurs as a side effect of a beneficial action.5 The legitimacy of such a justification has been criticized,6 and this article attempts to examine how often the DDE is relevant in the area of sedation in palliative care. The hypothesis of the study was that sedative drugs used to provide symptom control do not shorten life, and hence can be used safely in palliative care; and, therefore, the DDE is rarely, if ever, relevant in this context.

METHODS

We reviewed the notes of 237 consecutive patients who died in our 62-bed hospice inpatient unit between January 1 and April 30, 1999. Careful consideration was given to whether a prospective study should be performed, but this was rejected because of the possibility of introducing unacceptable bias into the results. The objective was to examine the prescribing habits of the hospice medical staff with a view to determining whether they used sedatives ap-
propriately with regard to the potential risks of shortening life. It was not practicable to keep the review activity secret, and hence during a prospective study it would have been possible for physicians to modify their approach to prescribing sedatives. This possibility was avoided by selecting a recent period from which all the case notes and medication charts of patients who died in the hospice were scrutinized. The physicians who wrote these records did not know their prescribing would be examined and, therefore, would have been pursuing what would have been their normal practice. Thus, a retrospective design was chosen not out of convenience but as the best way of uncovering the true use of sedatives in this specialist palliative care unit. However, this approach meant that it was not possible to use an objective measure of the depth of sedation achieved. Instead, a judgment was made of the dose beyond which significant sedation was likely to have resulted.

The principal potentially sedative drugs used in this group of patients were midazolam hydrochloride, haloperidol, and methotrimeprazine. Phenobarbital was given to 4 patients and propofol to one. Opioids are not used for sedation in our setting, and an investigation of opioid doses at the end of life in this unit has been published elsewhere. Haloperidol and methotrimeprazine are both also used extensively for the control of nausea and vomiting, and therefore their presence on a drug chart is not an indication of intent to sedate. Doses of these 3 drugs were recorded during the last week of life, and from this the daily change in dose was calculated.

Although good comparisons exist of the relative sedative potency of different benzodiazepines, albeit not in a palliative care setting, the same cannot be said of corresponding comparisons between benzodiazepines and antipsychotic drugs. Neither is there information about the degree to which the presence of one potentially sedating drug enhances the sedative effect of another used in combination with it. This made interpretation difficult when patients were receiving more than one sedative. On the basis of the limited evidence available and clinical impression in our patient group, cutoff points were agreed on and only total daily doses of each drug above this were considered. The doses were haloperidol, 20 mg; methotrimeprazine, 25 mg; and midazolam hydrochloride, 10 mg. The mean dose per 24-hour period was calculated and changes during the last week of life were recorded.

For estimation of survival, patients were divided into 4 groups: (1) those receiving little or no sedation, ie, patients in whom the sedative dose did not increase above the agreed cutoff point; (2) those who received significant levels of sedation for all 7 days; (3) those who received significant amounts of sedative drug only in the last 48 hours of life; and (4) those who underwent a marked increase of sedative drug dose in the last 48 hours of life, as defined by a 50% increase resulting in a dose of greater than or equal to 20 mg of midazolam or greater than or equal to 50 mg of methotrimeprazine. A case note review was conducted of the increase group to assess whether the DDE was considered in the decision-making process and whether, even if it was not considered, the course of clinical events suggested that it should have been.

For all patients, note was made of any verbal descriptors of the mode of death, whether peaceful or disturbed by restlessness, respiratory distress, or signs of pain.

Of the 237 patients whose cases were analyzed, 127 (54%) were female. The mean age of the group was 69.7 years. Diagnoses are shown in Table 1.

The most common potentially sedative drugs used were midazolam (194 patients; 82% of the total group) and methotrimeprazine (51; 22% of the total). However, in a total of only 114 patients (48%) were these drugs used in doses above the sedative threshold. Haloperidol (82; 35% of the total) was also used, but in low and stable doses generally as an antiemetic rather than a sedative. In only 1 case was a dose used above the sedative threshold.

Of the 237 patients, 123 (52%) received no significant sedation, as we defined it, at any stage during their last week of life. Of the 114 patients in whom sedation was used, 15 (13%) received sedation for at least 7 days, but 64 (56%) received sedation only within the last 48 hours of life. Of the latter, 36 experienced sedative use only within the final 24 hours of life. The remaining 35 patients received sedation intermittently for the period between 48 hours and 7 days. There were no clear differences in the demographic features of these groups, although those not receiving sedation tended to be older than the other groups.

The number of peaceful deaths was similar in all groups. The 48-hour group tended to be restless at the time of death, although this did not reach statistical significance. The group who received minimal sedation were significantly more likely to die without staff perceiving any warning sign of imminent death.

There was no difference in survival from admission (Table 2) between the group who had received no sedation in their last week and those who had received sedation in the final 48 hours (P = .23, 2-sample t test). However, the patients who had received sedation throughout their last week of life had a significantly longer survival than the other 2 groups (P < .001, 2-sample t test). This was despite their midazolam hydrochloride dose being considerably greater (mean, 54.5 mg/24 h; median, 52.5 mg/24 h) than that of all other patients receiving sedation on the last day of life (mean, 25.7 mg/24 h; median, 23.0 mg/24 h) (P < .001). Only 3 patients re-

**Table 1. Primary Sites of Disease in the Patient Group**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>66 (28)</td>
</tr>
<tr>
<td>Lung</td>
<td>53 (22)</td>
</tr>
<tr>
<td>Breast</td>
<td>25 (11)</td>
</tr>
<tr>
<td>Unknown primary</td>
<td>17 (7)</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>14 (6)</td>
</tr>
<tr>
<td>Head and neck</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Others</td>
<td>55 (23)</td>
</tr>
</tbody>
</table>

**Table 2. Survival of Patients According to the Pattern of Sedative Use**

<table>
<thead>
<tr>
<th>Pattern of Sedative Use</th>
<th>Mean Survival From Admission (95% Confidence Interval), d</th>
<th>Median Survival From Admission, d</th>
<th>Survival Range, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>No sedation (n = 123)</td>
<td>14.2 (12.7-15.7)</td>
<td>7.0</td>
<td>1-80</td>
</tr>
<tr>
<td>Last 48 h only (n = 64)</td>
<td>14.3 (11.2-17.4)</td>
<td>7.0</td>
<td>1.182</td>
</tr>
<tr>
<td>7-d sedation (n = 16)</td>
<td>36.6 (31.5-41.7)</td>
<td>34.5</td>
<td>7.86</td>
</tr>
</tbody>
</table>
ceived sedative doses of methotrimeprazine throughout their last week of life.

The likelihood of a patient receiving a sedative increased during the last week of life. This is illustrated in the Figure, which is based on the subset of patients who spent the whole of the last week of life in the hospice and displays the percentages receiving sedative doses of midazolam or methotrimeprazine on each day of that week. Fourteen of the 22 patients in this category who received methotrimeprazine also received potentially sedative doses of midazolam.

The dose of sedative drug tended to increase during the last week of life. For the 91 patients receiving sedation with midazolam on their final day (excluding the 7-day sedation group), the median midazolam hydrochloride dose of 23.0 mg/24 h compares with a median of 10 mg/24 h on the penultimate day (P<.001, Mann-Whitney test). However, 11 patients had a decrease of sedation between the penultimate and last days, and 3 patients who had sedation on the penultimate day had none at all on their final day. Thirteen of the 30 patients receiving sedative doses of methotrimeprazine on the last day of life had a higher dose than on the previous day, 4 received less, and 1 person who had sedation on the penultimate day had none on the final day. Overall, the median methotrimeprazine dose (50 mg/24 h) was the same on each of the days.

Four of the 5 patients who were given phenobarbital received it for the final 2 to 4 days of life as a supplement to midazolam. Their mean stay in the hospice was 37.5 days (range, 15-50 days). The phenobarbital dose was generally between 200 and 500 mg/24 h, except in 1 patient who received 700 mg on the penultimate day of life and 1200 mg on the last day. This drug was used in severely ill patients displaying an agitation delirium who remained in distress despite the use of increasing doses of midazolam or methotrimeprazine (or both). In each case the person was already too unwell to swallow oral medication before the initiation of sedation and had been explicitly recognized as dying by nursing and medical staff. Two patients in this group had a history of confusion (and in 1 case the onset of grand mal epilepsy) extending over several weeks, suggestive of cerebral metastases secondaries, although in neither case was the diagnosis demonstrated radiologically. A third had a primary malignant cerebral tumor. The fourth developed agitation and respiratory distress associated with hypercalkemia and an infected malignant pleural effusion. Both of these conditions had been treated repeatedly before, and the patient had announced that he did not wish to have further intervention for them. In none of these cases was it apparent that the sedation had further shortened what was already an extremely brief prognosis. The fifth patient who received phenobarbital did so only once, and her case is reviewed in the last paragraph of this section.

The 1 patient who was given propofol was a 22-year-old man with widely disseminated leiomyosarcoma who was admitted to the hospice in status epilepticus. The propofol infusion rate was kept at a level (550 mg/h) that just controlled the seizures, leaving persistent minor muscle twitching. Attempted reductions in infusion rate precipitated the onset of myoclonus and agitation. Although the patient was noted at admission to have a degree of dehydration, intravenous fluids resulted in the accumulation of peripheral edema but no improvement in his condition. He died about 48 hours after arrival, and it was not clear whether the sedation had significantly shortened what was already a terminal situation. Arguably, given the persistence and violence of his grand mal seizures, the pharmacologic restraint might have lengthened survival through avoidance of injury and respiratory obstruction.

Detailed review of the notes of patients receiving a marked increase in sedation (as we defined it) in the last 48 hours disclosed 2 cases where the DDE could have been necessary to justify the use of sedatives.

The first case was in a 58-year-old man with an astrocytoma. His general condition had been noted to be deteriorating before an acute onset of violent agitation and paranoia. Midazolam hydrochloride, 20 mg, was given intramuscularly immediately and 50 mg/24 h thereafter subcutaneously. He died 55 hours later. At the start of this episode, the physician involved considered that sedation might shorten an already short prognosis.

The second case involved a 70-year-old woman with lung carcinoma and a history of schizophrenia. Admitted to the hospice because of a generally deteriorating condition, she developed delusions and progressive agitation unresponsive to doses of haloperidol of up to 12 mg/d. During 24 hours she received 125 mg of methotrimeprazine and 60 mg of midazolam hydrochloride by subcutaneous infusion, but also another 60 mg of midazolam hydrochloride and 200 mg of methotrimeprazine in subcutaneous immediate doses for continuing agitation. At the end of this period her breathing was noted to be noisy. Phenobarbital, 200 mg, was given subcutaneously, and the patient died 6 hours later. From the history, it is possible that sedation may have allowed development of pneumonia in the presence of lung disease.

There is a widespread public and, to a lesser extent, professional concern that any doses of drugs sufficient to con-
control symptoms of terminal illness inevitably, or at least frequently, hasten the patient's death. In particular, it is supposed that this can occur with opioids and with sedatives. The use of the DDE as an ethical defense in this context has, however accurate morally, acted as a tacit admission that good symptom control is lethal. However, the applicability of the DDE to symptom control in the final stages of life has not been examined objectively. We have published elsewhere an evaluation of the pattern of opioid use at the end of life,7 and herein we present a similar evaluation of the use of sedatives in a specialist palliative care unit.

The present study confirms that sedative medication is frequently used in a palliative care setting, being received by nearly half of the patients at some point in the last week of life. The reasons for the use of sedatives in end-of-life care have been reported extensively,3,10 and prominent among them are agitation and restlessness associated with the final stages of terminal illness. It appears that these were important reasons for sedative use in our population, as 56% of those given these drugs had them only in the last 48 hours of their life, and most of these only in the final 24 hours of life. It seems unlikely that the introduction of sedatives precipitated the fatal event because the overall length of admission of this group closely resembled that of patients who did not receive any sedation.

Conversely, patients who received sedation throughout the final week of life had a markedly longer admission than did those who received shorter sedation. This is consistent with the findings of Ventafridda et al,1 Stone et al,2 and Chiu et al.11 A potential reason for this apparently paradoxical result is that the onset of delirium is a potent reason for admission to an inpatient unit. Although delirium is associated with a poor prognosis,12 patients in whom this is a prominent feature are still likely to be fitter than those whose indication for sedation is “terminal restlessness.” Thus, it is probable that people with delirium will enter the hospice at an earlier stage of their illness than those who are admitted to cope with the nursing burden entailed by physical frailty. The former may well require early sedative use for management of their mental state; the latter, only for assistance with restlessness in the last hours of life.

It is, of course, possible to hasten death by heavy sedation. On the other hand, the aim for the patients studied herein was not unconsciousness but relief of their symptoms, and the doses of medication used were proportionate to that aim. The implication of our results is that, just as opioids are safe in the terminally ill when their doses are titrated against the symptom response, the same is true of sedatives. It was possible to identify 2 cases in which, because of the severity of the patients’ delirium, the rate of increase of sedative dose was high enough to raise concern that life might have been shortened, and in one of these cases the attending physician clearly foresaw this risk. One of these patients had a history of mental illness, and in both of them their agitation had the severity described by Sirois in his account of “terminal agitation.”13 A characteristic of this clinical picture is that the patient usually dies within 24 to 72 hours. How much this outcome is shaped by the use of sedation is impracticable to investigate, as the severity of distress and the risk of harm to self and others do not permit an ethical option of refraining from sedative use.

These cases serve to emphasize that any requirement to invoke the DDE in end-of-life care is uncommon. Most episodes of sedative use are brief, and there is no evidence that they precipitate death. Rather, they are a response to features of a dying process that has already begun. For those who need such treatment, it is entirely possible to provide ongoing sedation at a level that is both therapeutically effective and safe.

CONCLUSIONS

This study helps to demonstrate that it is possible to use sedatives appropriately and safely at the end of life. Regardless of its validity as a moral philosophical concept, the DDE is almost completely irrelevant. The result and intention of the use of sedative drugs appears to be relief of symptoms and not shortening of life.

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