Opioid treatment for agitation in patients with advanced dementia

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SUMMARY

Background Some patients with advanced dementia cannot convey the experience of pain verbally and may react to pain with aggressive and agitated behaviors. We hypothesized that unrecognized pain could contribute to agitation and that low dose opioid therapy might reduce agitation by reducing pain. We therefore attempted to determine the effect of opioids on agitation in demented patients.

Methods We administered placebo for 4 weeks and a long-acting opioid for another 4 weeks to nursing home patients with advanced dementia and severe agitation despite treatment with psychotropic drugs. Patients and study nurses did not know if the medication administered was placebo or opioid. We measured the Cohen-Mansfield Agitation Inventory (CMAI) score at baseline and every two weeks.

Results Among 47 patients who entered the study, 25 completed the two phases. The median age for the 25 patients was 85.5 years. Analyses of the data of these 25 patients and of the patients <85 years-old showed no significant differences in agitation level between the placebo and opioid phases. However, among the 13 patients who completed the study and were ≥85 years old, the agitation level at the end of the opioid phase was significantly lower than at the end of the placebo phase (mean change in CMAI score: −6.4; 95% confidence interval (CI): −10.96, −1.8). The decrease in agitation in the patients ≥85 years old persisted after adjusting for sedation. The results remained unchanged when we expanded the analyses to include four ≥85 patients who dropped out of the study after the second week of the opioid phase.

Conclusion Low dose, long-acting opioids can lessen agitation that is difficult to control in very old (≥85) patients with advanced dementia. Copyright © 2003 John Wiley & Sons, Ltd.

KEY WORDS — agitation; CMAI; dementia; nursing home; opioid; pain

INTRODUCTION

In nursing homes the prevalence of dementia ranges from 40 to 78% (Rovner et al., 1986; Magaziner et al., 1996). Agitation affects over 40% of elderly demented nursing home patients (Chandler and Chandler, 1988) and its triggering factors often remain unknown. Agitated behaviors increase as dementia progresses (Cohen-Mansfield et al., 1990) and agitation frequently persists despite treatment with psychotropic drugs (Daniel, 2000; Ballard and Burns, 2001). The prevalence of pain in nursing homes is high, ranging from 45 to 84% (Parmelee, 1996; Stein and Ferrell, 1996). Some patients with advanced dementia cannot convey the experience of pain verbally and may react to pain with aggressive and agitated behaviors (Geda and Rummans, 1999; Buffum et al., 2001). Despite the evidence that some

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patients with difficult to control agitation may have unrecognized pain, opioids have not been studied as a treatment of agitation in severely demented patients unable to reliably answer questions about pain. We hypothesized that in this vulnerable patient population, at high risk for both pain and under-treatment of pain (Parmelee, 1996), unrecognized pain could contribute to agitation and low dose opioid therapy might reduce agitation by reducing pain. We therefore designed this study to attempt to determine the effect of opioids on agitation in demented patients unable to report pain. In an attempt to increase the homogeneity of the study population we chose to limit enrollment to patients unable to report pain.

METHODS

Design

We administered placebo for 4 weeks and a long-acting opioid for another 4 weeks. Patients and study nurses were not told if the medication administered was placebo or opioid. In order to avoid the risk of increased agitation in the placebo phase resulting from opioid withdrawal, all patients received placebo during the first four weeks of the trial and opioid during the second four weeks. In order to avoid constipation in the patients treated with opioids, a stool softener (docusate sodium) combined with a bowel stimulant (senna) was added during the opioid phase; an additional matching placebo was therefore administered to patients during the placebo phase. To verify blindness, at the end of the study, the two study nurses were asked to guess the drug sequence for the last three patients.

Setting and participants

This study was conducted from January 1999 to January 2001 in a nursing home with 1427 long-term beds and 202 sub-acute care beds. The study was approved by the IRB of the nursing home and by the IRB of the affiliated university hospital. Informed consent was obtained from the patients’ surrogates. We recruited nursing home patients with advanced dementia, defined as a Mini-Mental Status Examination score (MMSE) <21 (Cockrell and Folstein, 1988) and persistent agitation documented on the hospital chart for a period of at least three months despite treatment with at least two psychotropic medications. These patients were eligible for the study if they had a Cohen-Mansfield Agitation Inventory (CMAI) score ≥40, with at least one agitated behavior displayed more than once daily (Koss et al., 1997). The CMAI measures the frequency of 29 agitated behaviors over the prior week. These behaviors describe verbally aggressive behavior, verbally non-aggressive behavior, physically aggressive behavior, or physically non-aggressive behavior. The specific items that are scored are: pacing, inappropriately robing/disrobing, spitting, cursing, constant unwarranted requests for attention, repeating sentences, hitting, kicking, grabbing onto people or things inappropriately, pushing, throwing things, making strange noises, screaming, biting, scratching, trying to get to a different place, intentional falling, complaining, expressing negativism, eating/drinking inappropriate substances, hurting self or others, picking up things that do not belong to them, hiding, hoarding, tearing, performing repetitious mannerisms, making verbal sexual advances, making physical sexual advances, and general restlessness. Each behavior is scored on a 0–6 scale: ‘never’, ‘less than once a week, but still occurring’, ‘once or twice a week’, ‘several times a week’, ‘once or twice a day’, ‘several times a day’ or ‘several times an hour’, respectively. The CMAI is a validated instrument with good inter-rater reliability (Koss et al., 1997). All patients had to have serum creatinine levels <1.2 mg/dl and bilirubin <1.2 mg/dl and SGOT less than twice the upper limit of normal. In addition, all patients had to be clinically stable, with systolic blood pressure >90 mmHg, oxygen saturation >90% on room air, respiratory rate >8/minute, pulse rate between 50 and 120 per min, temperature <37°C during the week before study entry, and had a bowel movement within three days from study entry. We excluded patients with known hypersensitivity or allergy to opioids and patients already receiving opioids. We obtained a complete history and physical examination. We excluded patients who were able to complain of pain and patients with an obviously painful condition and referred these patients back to the physician of record. In order to determine the patients’ ability to reliably answer questions about pain we administered to all patients a standardized questionnaire (Table 1). This questionnaire was previously used for the same purpose in another study (Manfredi et al., 2003).

Table 1. Questionnaire to screen for eligibility

<table>
<thead>
<tr>
<th>Question</th>
<th>Eligible?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you have pain now?</td>
<td>Yes</td>
</tr>
<tr>
<td>2. Are you free of pain now?</td>
<td>Yes</td>
</tr>
<tr>
<td>3. Are you hurting now?</td>
<td>Yes</td>
</tr>
<tr>
<td>4. Is there any part of your body that hurts now?</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Patients whose answers to questions 2, 3 and 4 were consistent with the answer for question 1 were not eligible for the study.
**Intervention**

We first administered placebo to all patients for 4 weeks and, after a one-day interval, a long-acting opioid (long acting oxycodone 10 mg every 12 h or, for patients who could not swallow pills, long acting morphine 20 mg once a day) for the next 4 weeks. The study was started with long acting oxycodone; long acting morphine was introduced as we encountered a number of patients who could not swallow pills: the long acting morphine formulation can be sprinkled onto soft food (e.g. apple sauce) and administered via a feeding tube. Patients continued to receive the psychotropic drugs they were taking when they entered the study. Necessary psychotropic medications were permitted during the study and their use was recorded. According to the study design, no new psychotropic medications could be prescribed during the eight-week study period.

**Measurements**

During the first three days of treatment with placebo and opioid the two study nurses evaluated the patients at 9 am, 1 pm and 4 pm and recorded the Ramsay Sedation Scale (RSS) scores (Hansen-Flaschen and Polomano, 1994), the respiratory rate and the oxygen saturation. In addition the same two study nurses, trained in the use of the CMAI by the investigators, recorded all of the above parameters and the CMAI scores every two weeks.

**Statistical analysis**

We used the ‘t’ test for matched samples and the Wilcoxon Signed Rank Test to evaluate changes between CMAI scores at baseline, at the end of the placebo phase (week 4) and at and the end of the opioid phase (week 8). Because of the preponderance of white females, we did not adjust for gender and ethnicity. We did, however, stratify our results by age; those 85 or older (the median age for the study group) were classified as the older group, and those younger than 85 were classified as the younger group. Multivariate regression analysis via the SAS GLM procedure was used to adjust for possible concomitant changes in sedation. In order to perform intention-to-treat analysis we applied the SAS Mixed procedure for analysis of variance for repeated measures. This analysis permits evaluation of all the data, including the data for subjects who dropped out of the study before the end of the trial. In order to avoid the possible effects of sedation, which may have been present during the first two weeks of opioid treatment, the primary analysis was based on the 25 patients who completed the study and not on intention-to-treat. We used the ‘t’ test to compare the two age groups with respect to the number of psychotropic medications administered during the study period. Lastly, we used the ‘t’ test for matched samples to evaluate changes from the end of the placebo phase (week 4) to the end of the opioid phase (week 8) for the following CMAI domains: *physically nonaggressive behaviors*, i.e. general restlessness, pacing, picking up things that belong to others, inappropriate robing/disrobing, performing repetitious mannerisms, and trying to get to a different place; *physically aggressive behaviors*, i.e. hitting, pushing, scratching, grabbing onto people or things inappropriately, kicking, and throwing things; *verbally nonaggressive behavior*, i.e. expressing negativism, complaining, and constant unwarranted requests for attention; *verbally aggressive behavior*, i.e. screaming and cursing (Cohen-Mansfield et al., 1995; Cohen-Mansfield and Werner, 1998).

**RESULTS**

A total of 47 patients were entered and 25 completed the eight-week study. Among these 25 patients, 13 received long acting oxycodone and 12 received long acting morphine. Age, gender, MMSE scores, number of diagnoses of diseases and conditions associated with pain are presented in Table 2. The psychotropic medications tried in the 25 completed patients prior to enrollment in the study were: buspirone (three patients), clonazepam (two patients), fluoxetine (2 patients), haloperidol (12 patients), lithium (three patients), lorazepam (10 patients), nortriptyline (two patients), olanzapine (three patients), paroxetine (one patient), perphenazine (one patient),

<table>
<thead>
<tr>
<th>Table 2. Demographic and clinical data</th>
<th>All subjects recruited (n = 47)</th>
<th>Subjects completing study (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (standard deviation)</td>
<td>86.7 (7.0)*</td>
<td>84.6 (6.8)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, number (%)</td>
<td>5 (10.4)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Female, number (%)</td>
<td>42 (89.6)</td>
<td>22 (88)</td>
</tr>
<tr>
<td>Mini-Mental Status Examination score, mean (standard deviation)</td>
<td>6.0 (7.2)</td>
<td>7.3 (7.8)</td>
</tr>
<tr>
<td>Number of painful conditions, median (range)</td>
<td>5 (0–10)</td>
<td>5 (0–10)</td>
</tr>
</tbody>
</table>

*Data missing for one subject.*
quetiapine (four patients), risperidone (17 patients), sertraline (10 patients), temazepam (four patients), thioridazine (three patients), trazodone (13 patients), and valproic acid (seven patients). The psychotropic medications administered during the study to the same 25 patients were: lorazepam (two patients), olanzapine (two patients), quetiapine (one patient), risperidone (12 patients), sertraline (six patients), trazodone (nine patients), valproic acid (five patients), and haloperidol (one patient). The mean number of scheduled psychotropic drugs was 1.5 (standard deviation = 1.2) for those younger than 85 years, and 1.6 (standard deviation = 0.8) for those 85-year of age and older (p = 0.8).

There were no significant differences in agitation between the placebo and opioid phases for the 25 patients who completed the trial (Table 3). However, among the 13 patients who were ≥85 years old, a group considered to be ‘old old’ (Van Den Noortgate et al., 2002), the agitation level at the end of the opioid phase was significantly lower than at the end of the placebo phase: mean: −6.4 CMAI points (95% confidence interval (CI): −10.96, −1.8) (Table 3). This difference persisted after adjusting for sedation level, cognitive impairment and use of PRN psychotropic medications. The improvement in the weekly agitation score was similar in magnitude and direction, and remained statistically significant, when we included data for the four elderly patients ≥85 years old who dropped out after week 6 but before week 8. Further, the significance obtained with the Wilcoxon Signed Rank Test (p = 0.023) was similar to the significance obtained with the ‘t’ test for matched pairs (p = 0.018). While stratifying by domain of agitation showed reduced agitation in the patients ≥85 in each domain, the domains with a statistically significant decrease were physical nonaggressive behavior (mean difference: −2.15; 95% CI: −3.44, −0.86), and physical aggressive behavior (mean difference: −3.00; 95% CI −4.98, −1.02).

There was no statistical difference between the two treatment phases in sedation or use of PRN psychotropic medications. PRN psychotropic medications were used on three different occasions during the opioid phase (one 70 year-old patient received one dose and one 90 year-old patient received two doses) while during the placebo phase no patients received PRN medications. Adverse events, including constipation, nausea and falls were not statistically different in the two treatment phases (Table 4).

Among the 22 patients who started but did not complete the study, 11 patients were removed from the study during the first 4 weeks (placebo phase) and 11 patients were removed during the second four weeks (opioid phase). The main reasons for discontinuation were: unsteady gait (three patients in the placebo phase and four patients in the opioid phase), increased agitation (two patients in the placebo phase and four patients in the opioid phase), and uncontrolled agitation (one patient).

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo phase (number person-days = 1202)</th>
<th>Opioid phase (number person-days = 848)</th>
<th>P_{2-tail}</th>
<th>Rate ratio(^b)(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Number per 1000 person-days</td>
<td>Number</td>
<td>Number per 1000 person-days</td>
</tr>
<tr>
<td>Sedation</td>
<td>1</td>
<td>0.83</td>
<td>3</td>
<td>3.5</td>
</tr>
<tr>
<td>Falls</td>
<td>4</td>
<td>3.3</td>
<td>6</td>
<td>7.1</td>
</tr>
<tr>
<td>Constipation</td>
<td>3</td>
<td>2.5</td>
<td>1</td>
<td>1.2</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>3.5</td>
</tr>
</tbody>
</table>

\(^b\)The placebo is the reference, except in the case of nausea, where opioid is the reference, because there were no cases of nausea reported during the placebo phase.
and two patients in the opioid phase), infection (one patient in the placebo phase and two patients in the opioid phase), fecal impaction, (two patients in the placebo phase), seizures (one patient in the placebo phase and one patients in the opioid phase) and other reasons (four patients).

There was no correlation between the number of pain diagnoses recorded at study entry and CMAI score changes.

When the two study nurses responsible for the clinical assessment of patients were asked to independently guess the sequence of treatments (placebo or active drug) for the last three patients, they were correct in two instances and wrong the other four times. These answers indicated that blindness was maintained for the duration of the study.

**DISCUSSION**

Opioids lessened agitated behaviors without causing an increase in sedation in the 13 very old (≥85) patients. Among the different domains of the CMAI, two of the most disruptive behaviors, physical non-aggressive and physical aggressive, were statistically reduced by opioids.

Two reasons may explain the lack of effect seen in the younger group: (1) There was a clinically significant decrease in agitation in 5 patients during the placebo phase in the group of patients younger than 85 years. This unexpectedly large placebo effect may have weakened the statistical power of a study with a small number of patients; (2) Because of concerns of opioid side effects in very old, frail demented patients, the opioid dose chosen was very low and the study design did not include a dose escalation paradigm. The usual therapeutic approach with opioids is based on individual titration of the dose to effect (Jacox et al., 1994). The low dose may have had a therapeutic effect only in the older group: very old patients experience a larger therapeutic effect from small doses of opioids compared to younger patients (Kaiko, 1980; Kaiko et al., 1982; Forman, 1996).

While there have been no published studies on the magnitude of a CMAI score change that would be considered clinically meaningful, a six-point change could mean that the frequency of an agitated behavior changed from ‘several times an hour’ to ‘never’, or that the frequency of more than one behavior decreased to a lesser extent. A change of six points is likely very clinically meaningful; in fact, for individual patients, a change in two points, or even one point, could be meaningful. As statistical power is directly associated with the magnitude of the outcome variable (change in agitation as measured by the CMAI) and the sample size, attaining statistical significance with our small sample of very old patients strongly suggests that the observed improvement is real, and the studied treatment would have a similar effect in patients whose profiles are similar to our study participants.

Sedation was not present in the last two weeks of the study and, therefore, the decrease in agitation, seen in the last week of the opioid phase, cannot be attributed to opioid-related sedative effects.

There was no statistical difference in side effects between the two phases of the study. No patients discontinued the opioid because of excessive sedation or respiratory depression. Although three patients had sedation during the opioid phase and only one patient was sedated on placebo, the sedation in the patients receiving opioids was mild and limited to the initial two weeks of opioid treatment and was not present in the last two weeks. It is common to see transient sedation after starting opioid treatment: this generally improves as tolerance to this opioid side effect develops (Jacox et al., 1994). The nausea seen in three patients during the opioid phase was transitory and did not require discontinuation from the study; in two of the three cases it was deemed ‘not related’ to the study drug. Our results suggest that treatment with low-dose, long-acting opioids is safe in agitated elderly demented patients. This confirms previous studies of opioid therapy in elderly, non-demented patients, although the patients in those studies were over a decade younger than the patients in our study (Watson and Babul, 1988; Caldwell et al., 1999; Roth et al., 2000). However, the side effect data are difficult to interpret because of the small number of patients.

The use of PRN psychotropic medications was very low in both phases probably reflecting the internal policy regulating their use in our nursing home: PRN psychotropic medications are used only if alternatives are not available and the orders are limited to seven days after which they must be re-evaluated for continued use.

In conclusion, the very old patients in our study experienced a significant decrease in agitated behaviors while receiving low dose long acting opioid therapy. This decrease in agitation may be a direct opioid effect on the patients’ behavior, an analgesic action that decreases the agitated behaviors by making patients more comfortable, or a combination of these two effects.
ACKNOWLEDGMENTS

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