Analyses of Respiratory Depression Associated with Opioids in Cancer Patients Based on the Japanese Adverse Drug Event Report Database

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Opioid-induced respiratory depression is a potentially life-threatening adverse drug event. The purpose of this study was to evaluate the incidence of respiratory depression using the Japanese Adverse Drug Event Report (JADER) Database to obtain data to promote proper use of opioids. The JADER database from April 2004 to March 2017 was obtained from the Pharmaceuticals and Medical Devices Agency. We calculated the reporting odds ratios (RORs) of suspected opioids (morphine, fentanyl, oxycodone, tapentadol, methadone, tramadol, pentazocine, buprenorphine, and codeine phosphate hydrate), analyzed the daily dose at first appearance and the time-to-onset profile, and assessed the hazard type using the Weibull shape parameter. ROR analysis detected adverse event signals for all opioids. Morphine showed a large ROR value with statistical significance in elderly (=70 years old) patients. The median daily doses of oral morphine and oxycodone for inducing respiratory depression were comparably low (30 mg/d as oral morphine equivalent dose), while that of transdermal fentanyl was 120 mg/d (oral morphine equivalent dose). On time-to-onset analysis using the Weibull distribution, those opioids were classified as the early failure type. The median time-to-onset of oral morphine, oral oxycodone and transdermal fentanyl was 5.5, 11 and 12.5 d, respectively, and almost 50% of cases were reported within 30 d. Taken together, our results suggest that it is important to monitor patients carefully for at least the first one week to one month, even if opioids are administered at a relatively low dose, especially in elderly patients administered morphine.

Key words opioid; cancer patient; respiratory depression; spontaneous reporting system; Japanese Adverse Drug Event Report database; time-to-onset analysis

INTRODUCTION

Opioids are potent analgesics used for the treatment of moderate to severe acute and chronic cancer and non-cancer pain. Consumption of opioids is often used as an indicator of access to pain treatment and palliative care. However, in Japan, consumption of opioids is still at a low level compared with other advanced countries, and is less than the estimated requirement for pain relief.1) Also, management of adverse drug events (ADEs) and medical errors due to opioids is essential for the proper use of controlled medicines.

Opioid analgesics have a number of side effects, of which respiratory depression is a potentially life-threatening ADE. In some guidelines for opioids, respiratory depression is defined as (1) reduced respiratory rate (e.g., to less than 10 breath/min), (2) reduced oxygen saturation (e.g., arterial oxygen saturation less than 90%), or (3) hypercapnia/hypercarbia (e.g., arterial carbon dioxide tension more than 50 mmHg).2) Previous studies demonstrated that risk factors for opioid-induced respiratory depression include opioid overdose, advanced age, sleep apnoea, chronic obstructive pulmonary disease, congestive heart failure, renal failure, and hemodialysis/ peritoneal dialysis.3–10) However, to date, there are no nationwide data for opioid-induced respiratory depression in palliative care in Japan. Because respiratory depression is a rare ADE associated with opioids, the implementation phase of epidemiologic research is difficult. The Japanese Adverse Drug Event Report (JADER) released by the Pharmaceutical and Medical Devices Agency (PMDA) is a large spontaneous reporting system (SRS) that reflects the realities of clinical practice in Japan. JADER has been used for pharmacovigilance assessments for rare ADEs using reporting odds ratio (ROR).11–14) Therefore, we used the JADER database to analyze the factors associated with opioid-related respiratory depression in terms of medications and patient characteristics. In this study, the research committee of the Japanese Society for Pharmaceutical Palliative Care and Sciences analyzed risk factors and time-to-onset of respiratory depression related with opioids in cancer patients based on the JADER to obtain the data to promote proper use of opioids.

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METHODS

Data Source Data recorded in JADER between April 2004 and March 2017 were obtained from the PMDA website (http://www.pmda.go.jp). The database consists of four data tables: patient demographic information (demo), drug information (drug), ADEs (reac), and primary disease (hist). The "demo" table included 464259 cases, the "drug" table included 2952019 cases, the "reac" table included 734603 cases, and the "hist" table included 929291 cases. We removed duplicated data from the "drug" and "reac" tables. The "demo" table was then linked to the "drug" and "reac" tables using the ID number of each case. In each case, the contribution to the ADEs of medications given was classified into three categories: "suspected medicine," "concomitant medicine," and "interaction." We only extracted cases that were classified as "suspected medicine," which included 1191142 cases.

The "demo" table stored background parameters such as sex and age. In the analysis of the associations with sex, unknown data were excluded from the analysis. In the analysis of the associations with age classified in 10-year intervals, we defined "younger patients" to be "under 10s," "10s," "20s," "30s," "40s," "50s," "60s," and "elderly patients" to be "70s," "80s," "90s," and "100s." The data from other codes for age classification, such as "newborn," "infant," "pediatric," "youth," "adult," and "unknown," were excluded from the analysis because the actual age ranges were unclear.

The drugs selected for this investigation were nine opioids approved in Japan (morphine, fentanyl, oxycodone, tapentadol, methadone, tramadol, pentazocine, buprenorphine, and codeine phosphate hydrate).

Definition of Cancer Patients The primary diseases in the "hist" table are based on the medical terminology, as preferred terms (PTs), in the Medical Dictionary for Regulatory Activities (MedDRA). The Standardized MedDRA Queries (SMQ) index consists of groupings of MedDRA terms, ordinarily at the PT level, that relate to a defined medical condition or area of interest. From the following ten SMQs, 1633 PTs were determined after removing duplicated data to detect cancer patients in MedDRA: malignancy-related conditions (SMQ 20000092), tumour markers (SMQ 20000094), malignant tumours including gastric, colorectal, lung and hepatic cancers (SMQ 20000194), breast malignant tumours (SMQ 20000198), ovarian malignant tumours (SMQ 20000200), prostate malignant tumours (SMQ 20000202), prostate tumours of unspecified malignancy (SMQ 20000203), skin malignant tumours (SMQ 20000204), uterine and fallopian tube malignant tumours (SMQ 20000206), and malignant lymphomas (SMQ 20000215).

Definition of Respiratory Depression The ADEs in the "reac" table are also coded according to the PTs in the MedDRA. The following seventeen PTs were determined from acute central respiratory depression (coded SMQ 20000116) in SMQ to detect respiratory depression in MedDRA: acute respiratory failure (PT 10001053), apnoea (PT 10002974), apnoeic attack (PT 10002977), bradypnoea (PT 10006102), cardio-respiratory arrest (PT 10007617), dyspnoea (PT 10013968), hypopnoea (PT 10021079), respiration abnormal (PT 10038647), respiratory arrest (PT 10038669), respiratory depression (PT 10038678), respiratory disorder (PT 10038683), respiratory distress (PT 10038687), respiratory failure (PT 10038695), respiratory paralysis (PT 10038708), respiratory rate decreased (PT 10038710), cardio-respiratory distress (PT 10049874), and cardiopulmonary failure (PT 10051093).

Dose and Time-to-Onset For daily dose and time-to-onset analysis, different from the adverse event signal analysis, we extracted the respiratory depression cases and cancer patient cases from the "reac" and "hist" tables, respectively. Those tables were linked to the "drug" table using the ID number, and the cases classified as "suspected medicine" were extracted. Cases with an unknown date of administration initiation or development of ADEs were excluded. Cases were also excluded when the year and month were indicated, but the day was not, and for cases with a description of only the year. Furthermore, in the daily dose analysis when respiratory depression occurred, cases with unknown dosages were excluded. Dosages of oral oxycodone and transdermal fentanyl were converted to the oral morphine equivalent dose. Briefly, oral oxycodone 40 mg/d and transdermal fentanyl 0.6 mg/d are equivalent to oral morphine 60 mg/d. Equivalent dosages were calculated according to established and widely accepted guidelines and suggestions by pharmaceutical companies.

Statistical Analysis The adverse event signal index, ROR, is the ratio of the odds of reporting of one specific ADE versus all other ADEs for a suspected medicine compared to this reporting odds for all other medicines in the database. The ROR was calculated from the following equations, with a, b, c, and d defined by cross-tabulation as; a: number of cases with an ADE after using the suspected medicine, b: number of cases with an ADE after using all other medicines, c: number of cases with all other ADEs after using the suspected medicine, d: number of cases with all other ADEs after using all other medicines (Table 1). Additionally, we performed the Haldane-Anscombe 1/2 correction to correct for bias, since it is not possible to calculate the ROR values from a cross-tabulation that contains zero in the columns.

\[ \text{ROR} = \frac{a}{b} \times \frac{c}{d} = \frac{ad}{bc} \]

Adverse event signals are considered significant when ROR estimates and the lower limits of the corresponding 95% confidence interval (CI) exceed 1. At least two cases are required to define a signal. Furthermore, we compiled a scatter-plot (volcano plot) (Fig. 1). A volcano plot was constructed by plotting the negative log of the p-value from Fisher’s exact test on the Y-axis, while the X-axis is the log of ROR (lnOR). In this way, we identified medicines that influenced the onset of respiratory depression.

Time-to-onset duration of the data from the JADER data-

Table 1. Cross-Tabulation for the Calculation of RORs

<table>
<thead>
<tr>
<th>Respiratory depression</th>
<th>Other adverse drug events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reports with the suspected medicine</td>
<td>a</td>
</tr>
<tr>
<td>All other reports</td>
<td>b</td>
</tr>
</tbody>
</table>

The cross-tabulation is structured with reports for the suspected medicine, all other reports, reports with respiratory depression, and other adverse drug events (a-d indicate the number of cases).
base was calculated from the time of the patient’s first prescription to the occurrence of the ADEs. The median duration, quartiles, and Weibull shape parameters were used to evaluate the dates from administration to development of respiratory depression. The Weibull shape parameter test is used for the statistical analysis of time-to-onset data and can describe the non-constant rate of ADE incidence. 11,12) The scale parameter $\alpha$ of the Weibull distribution determines the scale of the distribution function. A larger scale value stretches the distribution. A smaller scale value shrinks the data distribution. The shape parameter $\beta$ of the Weibull distribution indicates the hazard without a reference population. When $\beta$ is equal to 1, the hazard is estimated to be constant over time. When $\beta$ is greater than 1 and the 95% CI of $\beta$ excludes 1, the hazard is considered to increase over time. When $\beta$ is smaller than 1 and the 95% CI of $\beta$ excludes 1, the hazard is considered to decrease over time. The data analyses were performed using JMP® Pro 13.2.1 (SAS Institute Inc., Cary, NC, U.S.A).

The daily doses at the first appearance of the ADE were compared using nonparametric Kruskal–Wallis analysis with a Steel–Dwass post hoc test between opioids. A $p$-value of $<0.05$ was considered significant.

**RESULTS**

**Number of Reports and ROR for Respiratory Depression Associated with Opioids in Cancer Patients**

Among 119,142 cases, a total of 1227 suspected medicines were reported for respiratory depression. Nine opioids used in cancer patients were included for reporting two or more cases, and a signal calculated using the ROR method was detected for each opioid (Table 2). We cyclopedically produced a scatter plot on the relationship between respiratory depression and the medicines suspected to have caused it. The $X$-axis represents ROR in the lnOR scale, and the $Y$-axis represents the negative log of the $p$-value. The dotted transverse line shows the baseline of $-\log (p\text{ value}) = 1.3$ ($p = 0.05$). (a) The odds ratios were calculated through cross-tabulation, as shown in Table 1. Blue-to-red colors show differences in the number of all reports ($a + c$) with the medicine from 0 to 22,869. (b) $\text{ROR} = (a: \text{number of reports with the medicine in males}) (d: \text{number of reports with all other medicines in females})/(b: \text{number of reports with the medicine in females}) (c: \text{number of reports with all other medicines in males})$. Blue-to-red colors show differences in the number of respiratory depression cases with the medicine in both sexes ($a + b$) from 0 to 603. (c) $\text{ROR} = (c: \text{number of reports with the medicines in elderly patients}) (d: \text{number of reports with all other medicines in younger patients})/(b: \text{number of reports with the medicines in younger patients}) (c: \text{number of reports with all other medicines in elderly patients})$. Blue-to-red colors show differences in the number of respiratory depression cases with the medicine in all ages ($a + b$) from 0 to 602. (Color figure can be accessed in the online version.)
significance for the risk of respiratory depression [RORs (95% CI); fentanyl (95%), morphine: 8.01 (5.95 to 10.78), oxycodone: 4.03 (2.99 to 5.43), pentazocine: 12.09 (6.98 to 20.92), buprenorphine: 15.30 (7.05 to 33.21), tapentadol: 4.19 (1.91 to 9.21), tramadol: 3.21 (1.47 to 7.03), methadone: 7.90 (3.01 to 20.73) and codeine phosphate hydrate: 5.34 (1.49 to 19.15)] (Table 2). Although the pentazocine and buprenorphine showed a large ROR, the estimate would be unstable because of the influence of small sample size when calculating the odds ratio.

Respiratory Depression Associated with Opioids in Cancer Patients and Patient Background In order to examine the relationships between respiratory depression and patient background when administering each opioid, we analyzed the suspected medicine data table for sex, which included 13022 cases (6817 male and 6205 female cases) and excluded 260 unknown cases. We cyclopedically produced a scatter plot on the relationship between ROR and significant differences (Fig. 1b). The X-axis represents the lnOR, and the suspected medicines in the positive direction indicate more frequent cases of respiratory depression reported in males than females. The Y-axis represents the negative log of p-value of Fisher’s exact test and the positive direction represents a significant difference and −log (p value) of >1.3 (p < 0.05) was considered significant. Among nine opioids, RORs of fentanyl, morphine, and significant differences (Fig. 1c). The peaks of reports for any opioids were within 10 d and all cases shows the number of cases that reported a suspected medicine for respiratory depression. ROR: reporting odds ratio. 95% CI: 95% confidence interval. *: p < 0.05, **: p < 0.0001.

Table 2. Number of Reports and RORs of Respiratory Depression Associated with Opioids in Cancer Patients

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Cases</th>
<th>ROR</th>
<th>95% CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>115</td>
<td>8.96</td>
<td>7.40–10.86</td>
<td>&lt;0.0001**</td>
</tr>
<tr>
<td>Morphine</td>
<td>47</td>
<td>8.01</td>
<td>5.95–10.78</td>
<td>&lt;0.0001**</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>45</td>
<td>4.03</td>
<td>2.99–5.43</td>
<td>&lt;0.0001**</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>14</td>
<td>12.09</td>
<td>6.98–20.92</td>
<td>&lt;0.0001**</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>7</td>
<td>15.30</td>
<td>7.05–33.21</td>
<td>&lt;0.0001**</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>6</td>
<td>4.19</td>
<td>1.91–9.21</td>
<td>0.005*</td>
</tr>
<tr>
<td>Tramadol</td>
<td>6</td>
<td>3.21</td>
<td>1.47–7.03</td>
<td>0.018*</td>
</tr>
<tr>
<td>Methadone</td>
<td>4</td>
<td>7.90</td>
<td>3.01–20.73</td>
<td>0.003*</td>
</tr>
<tr>
<td>Codeine phosphate hydrate</td>
<td>2</td>
<td>5.34</td>
<td>1.49–19.15</td>
<td>0.0832</td>
</tr>
</tbody>
</table>

Cases shows the number of cases that reported a suspected medicine for respiratory depression. ROR: reporting odds ratio. 95% CI: 95% confidence interval. *: p < 0.05, **: p < 0.0001.

Fig. 2. Box-Chart of Daily Dose for Each Opioid
Oral morphine (n = 15), oral oxycodone (n = 16), transdermal fentanyl (n = 16). The Y-axis represents the daily dose for each opioid as the oral morphine equivalent dose. Box plots represent the median (the horizontal line within the box), 25th, and 75th quartiles. The whiskers extend to the outermost data point that falls within the distances of 1.5 times the length of the inner quartiles. *: p < 0.05, **: p < 0.0001. Kruskal–Wallis/Steel–Dwass tests were used.
most 50% of cases were reported within 30 d.

DISCUSSION

Our results suggest that adverse event signals of respiratory depression were detected for all opioids selected for this investigation in the JADER databases, as per the risk stated in their package inserts in Japan. Morphine, oxycodone and fentanyl are recommended to manage cancer pain in step three of the WHO analgesic ladder. Among selected opioids, these three were reported more frequently for respiratory depression in the JADER databases (fentanyl, morphine and oxycodone accounted for 115, 47 and 45 cases, respectively, in order of larger number). According to the CANCER STATISTICS IN JAPAN 2017, there was more consumption of fentanyl than morphine and oxycodone from 2013 to 2015 (17.8 and 5.1 times more than that of morphine and oxycodone, respectively). The reporting frequency of ADEs in the SRS may have been influenced by the above rates.

In general, sex affects clearance of drugs, most likely because of physiologic and genetic factors. However, in a systematic review and meta-analysis, Gupta et al. reported there was no significant association between postoperative opioid-induced respiratory depression and sex. In the present study, the ROR trend for each opioid for sex varied. RORs of six opioids exceeded 1, suggesting respiratory depression related with these opioids may occur preferentially in males compared with females, while three opioids showed the opposite tendency. However, a significant association was observed only for fentanyl, and its ROR (1.60) was not so high. In contrast, Ishida et al. reported that female cancer patients had higher plasma concentrations of transdermal fentanyl probably due to a difference in the absorption rate, rather than drug metabolism. Taken together, in this study we could not conclude a clinically relevant sex difference in the risk of respiratory depression related with opioids.

In general, the risk of ADEs is higher in elderly patients compared with younger patients, and this is a common clinical problem, irrespective of the drug type. Previous studies showed that ADEs are frequent in patients ≥65 years old. Physiologically, elderly patients have an age-related reduction in the hepatic and renal ability to metabolize and excrete drugs and have chronic disease comorbidity, which is associated with potentially interacting concomitant medications. Such individuals are biologically vulnerable to opioid accumulation and to experiencing toxicity, even when using an opioid within its recommended dosing range. In the present study, the RORs of five opioids exceeded 1, suggesting respiratory depression related with these opioids may occur preferentially in elderly patients. Among them, fentanyl and morphine showed statistical significance in elderly patients defined as 70 years or older, although the ROR of fentanyl was relatively low (1.57). Consistent with the present findings,

![Fig. 3. Histogram and Weibull Shape Parameter of Respiratory Depression for Opioids](image-url)

(a) Oral morphine ($n=16$, $\beta=0.75$, 95% CI: 0.49–1.07), (b) oral oxycodone ($n=17$, $\beta=0.66$, 95% CI: 0.45–0.89), (c) transdermal fentanyl ($n=46$, $\beta=0.78$, 95% CI: 0.61–0.97). Upper panel shows box plots, which represent the median (the horizontal line within the box), 25th, and 75th quantiles. The whiskers extend to the outermost data point that falls within the distances of 1.5 times the length of the inner quartiles. The confidence diamond contains the mean and the upper and lower 95% of the mean. The bracket outside of the box identifies the shortest half, which is the densest 50% of all data.

### Table 3. Median, Quartile and Parameters of the Weibull Distribution and Failure Pattern for Each Opioid

<table>
<thead>
<tr>
<th>Drug</th>
<th>Case reports</th>
<th>Median (d)</th>
<th>Lower quartile (d)</th>
<th>Upper quartile (d)</th>
<th>Minimum (d)</th>
<th>Maximum (d)</th>
<th>Scale parameter</th>
<th>Shape parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral morphine</td>
<td>16</td>
<td>5.5</td>
<td>2.0</td>
<td>12.0</td>
<td>1.0</td>
<td>73.0</td>
<td>11.36</td>
<td>0.75</td>
</tr>
<tr>
<td>Oral oxycodone</td>
<td>17</td>
<td>11.0</td>
<td>6.0</td>
<td>28.5</td>
<td>2.0</td>
<td>327.0</td>
<td>23.27</td>
<td>0.66</td>
</tr>
<tr>
<td>Transdermal fentanyl</td>
<td>46</td>
<td>12.5</td>
<td>4.8</td>
<td>32.3</td>
<td>1.0</td>
<td>220.0</td>
<td>24.79</td>
<td>0.78</td>
</tr>
</tbody>
</table>

95% CI: 95% confidence interval.
several studies reported that the risk of opioid-related respiratory depression increased with age.\textsuperscript{5,27} Cepeda \textit{et al.} reported that the risk of respiratory depression increased substantially after 60 years of age in patients receiving parenteral meperidine, morphine, or fentanyl.\textsuperscript{39} Zedler \textit{et al.} reported that most patients with life-threatening opioid-related respiratory or central nervous system (CNS) depression were aged 55 years or older.\textsuperscript{27} In elderly patients, the half-lives of opioids and their metabolites are increased due to an age-related reduction in renal function or relative dehydration.\textsuperscript{28} Especially, the inactive and active metabolites of morphine, morphine-3-glucuronide and morphine-6-glucuronide, respectively, can accumulate at higher levels in elderly patients, which may increase the risk of the ADE occurrence, including respiratory depression. As the consequences of ADEs in elderly patients can be serious, opioids should be appropriately dosed under a good safety and tolerability profile; lower starting doses, longer dose intervals, and slow dose titration help to reduce the incidence of ADEs in elderly patients.

Bohnert \textit{et al.} reported that among patients receiving opioid prescriptions for pain, a higher morphine equivalent dose of $\geq 100 \text{mg/d}$ was associated with an increased risk of opioid overdose-related death.\textsuperscript{29} As shown in Fig. 2, the median daily dose of transdermal fentanyl was $120 \text{mg}$ of oral morphine equivalent, whereas the oral morphine and oxycodone doses were comparably low (30 mg of oral morphine equivalents). In our study, oral morphine and oxycodone contained both sustained- and immediate-release opioids. In comparison with transdermal fentanyl, oral administration of opioids shows “bolus” effects associated with peak and trough variations in blood concentrations. Such pharmacokinetic differences may contribute to the difference in the median daily dose that causes respiratory depression between oral morphine/oxycodone and transdermal fentanyl. Furthermore, several studies reported that patients using opioids with a daily morphine equivalent dose as low as 20 to 50 mg can also experience life-threatening respiratory or CNS depression under impairment of hepatic or renal function, or concomitant use of CNS depressants such as benzodiazepines, antidepressants, and alcohol.\textsuperscript{27,29}

The usefulness of the Weibull distribution for profiling the time-to-onset of ADEs has been reported.\textsuperscript{31,12,30–32} To the best of our knowledge, no time-to-onset analysis of respiratory depression for opioids in cancer patients has been done using SRSs. The aim of the time-to-onset analysis was to obtain new information and compare the risks and onset profiles of respiratory depression for opioids in the real world. The present results based on time-to-onset for oral morphine, oral oxycodone and transdermal fentanyl showed that they are the early failure type. Opioids depress ventilation through their direct actions on $\mu$-opioid receptors expressed on respiratory neurons in the brainstem.\textsuperscript{33,34} Opioid overdose causes respiratory depression immediately following administration, and such a mechanism may be related to the early failure type profile. Additionally, Young \textit{et al.} reported that patients without prior opioid tolerance were at 37% increased risk of clinically recognized opioid poisoning in the subsequent seven days.\textsuperscript{35} Our results suggest that it is particularly important to pay attention early after initiation of administration, and careful observation is recommended for at least the first one week to one month.

There are some limitations to this study. SRS, such as the JADER database, is subject to various biases, including over-reporting, under-reporting, missing data, the exclusion of healthy individuals, the lack of a denominator, and confounding factors.\textsuperscript{31–14,30–32} Because of these limitations, disproportionality measures (ROR) do not allow for risk quantification. Rather, RORs provides a rough indication of signal strength and are only relevant to the hypothesis. In absolute terms, the ROR indicates an increased risk of ADE reporting, and not a risk of ADE occurrence. Therefore, careful attention must be paid to the interpretation of the results from the JADER database.

In summary, this study was the first to evaluate the association between opioids and respiratory depression in cancer patients using the JADER database, and to apply the time-to-onset analysis technique to opioid-induced respiratory depression using the SRS. In the present study, adverse event signals of respiratory depression were detected for all opioids selected for this investigation. In the analysis of relationship between patient information and respiratory depression, we found an age, but not sex, difference in the risk of respiratory depression. The ROR of some opioids, especially morphine, was high in elderly patients. In the daily dose analysis, the doses of oral morphine and oxycodone that caused respiratory depression were relatively low. Furthermore, the Weibull distribution analysis indicated that oral morphine, oral oxycodone and transdermal fentanyl can be classified as the early failure type. Our results suggest that it is important to monitor patients carefully for at least the first one week to one month, even if opioids are administered at a relatively low dose, especially in elderly patients administered morphine.

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\textbf{Conflict of Interest} The authors declare no conflict of interest.

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