Oxycodone overdose causes naloxone responsive coma and QT prolongation

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Summary

Background: Although there are limited data on oxycodone overdose, it has been suggested that, in addition to central nervous system (CNS) depression, oxycodone may cause QT prolongation. Given the high prescription rate and increasing use of oxycodone, an understanding of its effects and treatment in overdose is necessary.

Aim: To investigate the clinical features, electrocardiogram (ECG) parameters and treatment of oxycodone overdose.

Design: Retrospective review of a clinical database.

Methods: One hundred and thirty-seven oxycodone overdoses were identified from admissions to a toxicology unit between January 2001 and May 2011. Demographic information, details of ingestion, clinical effects, ECG parameters [heart rate (HR), QT and QRS], naloxone use and length of stay (LOS) were extracted from a clinical database. QT was measured manually and plotted on a QT nomogram. LOS was extracted for all overdoses over the same period.

Results: From 137 oxycodone overdoses, 79 (58%) ingested immediate release (IR) and 58 (42%) ingested sustained release (SR) or a combination of IR and SR. The median age was 40 years [interquartile range (IQR): 33–49 years], and 87 were female (64%). The median ingested dose of IR oxycodone was 70 mg (IQR: 40–100, range: 5–200), compared to 240 mg (IQR: 80–530, range: 30–1600) for SR oxycodone. Benzodiazepines were the most frequent co-ingested drug in 52 (38%) cases. No arrhythmias were recorded. Twenty-four patients (18%) had bradycardia of which five had a HR < 50 beats/min. From 116 available ECGs, the median QRS was 95 ms (IQR: 90–102 ms), and there were 20 (17%) abnormal QT–HR pairs. Naloxone boluses were required in 65 admissions (47%), and 34 (25%) required a naloxone infusion. There was higher overall naloxone use with SR and IR+SR (32/58, 55%) compared to IR oxycodone (33/79, 42%). The median LOS was 18 h (IQR: 12–35), which was greater than the median LOS for all toxicology admissions at 15 h (IQR: 8–24) over the same period. Patients requiring a naloxone infusion had an even greater LOS of 36 h (IQR: 20–62 h).

Conclusion: In addition to the expected CNS depression, the opioid oxycodone can cause bradycardia and QT prolongation in overdose. The SR formulation is associated with the use of naloxone infusions and a longer LOS.

Introduction

Oxycodone hydrochloride is a μ-opioid receptor agonist commonly used for moderate-to-severe pain and available in immediate-release (IR) and sustained-release (SR) forms.1 It is a semi-synthetic form of morphine with similar properties causing analgesia and euphoria and thus also has abuse potential.2 Unlike morphine, it has a high oral bioavailability and a longer half-life of around 2–5.5 h,
There are limited data on oxycodone’s effects in overdose, isolated to a few case studies and post-mortem analyses. As with other opioid overdoses, effects in overdose include central nervous system (CNS) depression, respiratory depression, coma and death. In Australia, oxycodone is only available under prescription with restricted benefit. SR oxycodone (OxyContin®) has been available in Australia since 1999, under the same restriction. Evidence supports the use of oxycodone over codeine and oral morphine in the context of chronic pain, and it is becoming increasingly recommended in a number of pain control guidelines. Reports show increased prescribing and increased black market demand for oxycodone with increasing intravenous use and overdose presentations within Australia and other countries.

Given the high prescription rate and increasing use of oxycodone, an understanding of its effects and treatment in overdose is necessary. In addition, a recent report from poison centres in seven countries showed an increasing number of oxycodone exposures in all countries, including the USA, Australia and Europe.

It has been suggested that oxycodone may cause QT prolongation and, therefore, increase the risk of torsades des pointes (TdP). The availability of a SR formulation of oxycodone means that there will be delayed and prolonged opioid effects in overdose potentially requiring a longer length of stay (LOS) and increased use of critical care resources.

This study aimed to investigate the clinical features, electrocardiogram (ECG) parameters, particularly QT interval and the treatment requirements for oxycodone in overdose.

**Methods**

The study was a retrospective review of oxycodone overdoses taken from clinical database, which prospectively records information on all patients admitted to a toxicology service. The use of the database and patient information has previously been granted exemption as an audit by the Institutional Ethics Committee.

The study was undertaken in a large regional toxicology unit, which is the primary referral centre for over 500,000 people. All presentations are either seen and reviewed in the emergency department (ED) or admitted as in-patients under the toxicology service. Clinical information for all toxicology presentations is collected prospectively on a clinical data collection form at the time of presentation and entered into a relational database by two trained personnel blinded to any study hypotheses.

All presentations to the toxicology service between January 2001 and May 2011 were reviewed, and admissions that included IR and/or SR oxycodone were extracted. Oxycodone ingestion was based on patient history taken at multiple time points and collateral history from other sources such as family and ambulance services.

Information was extracted from the clinical database and patient medical records. The following data were extracted: patient demographic information (age and sex), details of ingestion (time of ingestion, estimated ingested dose (mg) and co-ingestants), clinical effects (heart rate (HR), blood pressure (BP), pupil size and Glasgow Coma Score (GCS)), ECG characteristics (HR, QRS and QT), admission disposition (ED, ward, intensive care unit (ICU) including LOS) and treatment given (naloxone use, respiratory and cardiovascular support). Detailed information on the dose and type of administration of naloxone, as well as adverse effects, was obtained from the patient medical record. The QT interval was measured manually by a single investigator, which was reviewed by another investigator for 20% of ECGs. The HR for each QT interval was taken from the automatic reading on the same ECG tracing, and the QT–HR pair was plotted on the QT nomogram. Hypotension was defined as a systolic BP < 90 mmHg, and bradycardia was defined as a HR < 60 beats/min. LOS for all toxicity presentations over the same period was also extracted from the database. For comparison, the number of cases of morphine (IR and SR), methadone and codeine each year for the same period was extracted from the database (Figure 1).

Patients qualified for ICU admission if they required ongoing airway support (intubation and ventilation), a decreased level of consciousness (GCS < 9), inotropic support (haemodynamic monitoring) or multi-organ failure. Discharge was determined by criteria pre-defined by the toxicology service, in conjunction with the psychiatry team and could occur 24 h a day.

The following outcomes were used to assess the severity of overdose: a decreased level of consciousness defined as a GCS < 9, an abnormal QT defined as the QT–HR pair being above the abnormal line on the QT nomogram, the requirement for naloxone and the use of a naloxone infusion and the hospital LOS.

Medians and interquartile ranges (IQRs) are reported for all continuous variables, and 95% confidence intervals (CIs) are reported for major dichotomous outcomes. The 95% CIs are calculated using the Wilson’s procedure with a continuity
correction. Statistical and graphical analyses were done in GraphPad Prism version 5.03 for Windows (GraphPad Software, San Diego, California, USA, www.graphpad.com).

Results

There were 140 oxycodone overdose presentations in 121 patients, of which three presentations were excluded as they were per rectum or intravenous recreational overdoses, leaving a total of 137 presentations. Sixteen patients presented on multiple occasions. Characteristics are listed in Table 1, along with clinical findings. Presentation numbers per year are shown in Figure 1, including a comparison to morphine, methadone and codeine overdoses. There were no deaths.

There were 79 (58%) patients who ingested IR oxycodone and 58 (42%) who ingested either SR (44, 32%) or a combination of IR and SR (14, 10%) tablets. One hundred and twenty-two (89%) admissions were intentional overdoses, 8 (6%) were recreational use and 7 (5%) were unintentional overdoses, such as medication errors. The median age at presentation was 40 years [IQR: 33–49 years, range: 16–90 years] and 87 presentations were female (64%). The median dose of IR oxycodone was 70 mg (IQR: 40–100 mg, range: 5–200 mg). Of these, 63 (80%) had previously been prescribed oxycodone. The median dose of SR oxycodone was 240 mg (IQR: 80–530 mg, range: 30–1600 mg) and 34 (77%) had previously been prescribed oxycodone SR. The median dose of combination IR and SR ingestions was 275 mg (IQR: 123–787 mg; range: 50–2000 mg). All 14 patients in this group had previously been prescribed oxycodone IR or SR or both. Ninety-nine (72%) patients ingested other tablets, of which benzodiazepines were the most frequent drug in 52 (38%) cases.

Neurological effects

Sixty-five (47%) patients had a GCS of <15 at first contact with emergency medical services, of which 33 had ingested IR oxycodone, 22 had ingested SR oxycodone and 10 had ingested a combination of IR and SR oxycodone. Of these patients, 36 had a GCS between 14 and 9 and 29 had a GCS < 9. Figure 2 shows the relationship between increasing oxycodone dose and reduced GCS on initial contact.

Cardiovascular effects

One hundred and thirty-six presentations had a documented BP and HR. The median minimum systolic BP was 104 mmHg (IQR: 96–118, mmHg; range: 60–160 mmHg) and 11 (8%) patients had an episode of hypotension. Only three had a systolic BP < 80 mmHg (60, 69 and 74 mmHg). The first was a beta-blocker overdose requiring intubation and high dose insulin and glucose as an inotrope, the second had ingested 60 mg oxycodone IR and the third had taken a large overdose including 1600 mg IR oxycodone, 100 mg diazepam, 2400 mg ibuprofen and 5000 mg doxylamine.

The median maximum HR was 90 beats/min (IQR: 80–109, range: 61–150), and the median minimum HR was 72 beats/min (IQR: 62–80, range 31–120). Twenty-four patients (18%) had bradycardia of which five had a HR < 50 beats/min. The lowest HR was 31 beats/minute, in the beta-blocker overdose.

ECGs were available for 116 of the 137 presentations. No arrhythmias were recorded. The median

Figure 1. The number of cases presenting each year for oxycodone (IR and SR) is compared to other major ingested opioids [methadone, morphine (IR and SR) and codeine]. *Number of cases for 2011 has been estimated based on 5 months of data for that year.
QRS was 95 ms (IQR: 90–102 ms). The median QT was 400 ms (IQR 375–420 ms, range: 320–520 ms). The QT–HR pairs for the 116 patients with an ECG are shown in Figure 3. There were 20 (17%) abnormal QT–HR pairs. Eighteen of these presentations had co-ingested other agents, including quetiapine, venlafaxine and other selective serotonin re-uptake inhibitors, which are not known to cause QT prolongation or TdP. Four patients had a prolonged QRS > 120 ms. One patient had ingested a tricyclic antidepressant (QRS = 160 ms) and a prolonged QT of 520 ms (Figure 3). Two others had previously existing conduction delays. Median ingested dose for patients with an abnormal QT–HR pair was 100 mg (IQR: 58–190 mg), which was the same as patients with a normal QT–HR pair (100 mg, IQR: 50–300 mg). Sixteen of the 20 patients with an abnormal QT had an ECG done before discharge (n=2) or on a previous or subsequent admission (n=14), which was normal in all cases.

Naloxone

Naloxone boluses were administered in 65 admissions (47%), and 33 (24%) of these were then continued on a naloxone infusion. Nine patients were treated with intramuscular (IM) naloxone pre-hospital, 38 received intravenous (IV) naloxone pre-hospital, with a total of 45 (35%) presentations receiving either IM and/or IV naloxone pre-hospital. Thirty-five presentations required either additional or initial naloxone boluses within in ED. There was a higher overall naloxone use in patients ingesting SR formulations (24/44, 55%; 95% CI: 39–69%) and combination IR+SR formulations (8/14, 57%; 95% CI: 30–81%) compared to IR formulations (33/79, 42%; 95% CI: 31–53%). A greater proportion of patients ingesting SR formulations (16/44, 36%; 95% CI: 23–52%) required naloxone infusions.

### Table 1  Characteristics, dose and co-ingestants of patients taking oxycodone overdoses

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total group (n=137)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), M (IQR)</td>
<td>40 (33–49)</td>
</tr>
<tr>
<td>Sex (female), n (%)</td>
<td>87 (64)</td>
</tr>
<tr>
<td>Dose ingested (mg), M (IQR)</td>
<td></td>
</tr>
<tr>
<td>IR (n=79)</td>
<td>70 (40–100)</td>
</tr>
<tr>
<td>SR (n=44)</td>
<td>240 (80–530)</td>
</tr>
<tr>
<td>IR + SR (n=14)</td>
<td>275 (123–787)</td>
</tr>
<tr>
<td>Prescribed medication, n (%)</td>
<td></td>
</tr>
<tr>
<td>IR (n=79)</td>
<td>63 (80)</td>
</tr>
<tr>
<td>SR (n=44)</td>
<td>34 (77)</td>
</tr>
<tr>
<td>IR + SR (n=14)</td>
<td>14 (100)</td>
</tr>
<tr>
<td>Co-ingestants, n (%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>65 (82)</td>
</tr>
<tr>
<td>Benzodiazepines and zolpidem</td>
<td>23 (58)</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>11 (7)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>6 (43)</td>
</tr>
<tr>
<td>Antidepressants (SSRI/MAOI/TCA)</td>
<td>3 (7)</td>
</tr>
</tbody>
</table>

SSRI, selective serotonin re-uptake inhibitor; MAOI, monoamine oxidase inhibitor; TCA, tricyclic antidepressant.
compared to IR formulations (13/79, 16%; 95% CI: 9–27%) or combination IR + SR ingestions (4/14, 29%; 95% CI: 10–58%) (Table 2). Naloxone infusion doses varied from 100 to 800 mg/h for 2–48 h and were commenced after discussion with the toxicologist. Adverse effects to the initial naloxone bolus occurred in nine patients. One patient had acute withdrawal and required sedation with droperidol. Eight patients had mild-to-moderate agitation not requiring pharmacological intervention. There were no complications in patients receiving naloxone infusions.

The median LOS for the entire group was 18 h (IQR: 12–35 h, range: 2–654 h), which was greater than the median LOS for all other toxicology admissions at 15 h (IQR: 8–24 h) over the same period. Patients requiring a naloxone infusion had a median LOS of 36 h (IQR: 20–62 h) with one case developing a hypoxic brain injury having a LOS of 27 days in ICU. This patient was intubated and ventilated on arrival to hospital. Median LOS for patients who received a bolus of either IM or IV naloxone at any point was 21 h (IQR: 15–38 h). The median LOS for patients not receiving naloxone was 14 h (IQR: 7–19 h) (Figure 4). Patients who required intubation had a median LOS of 39 h (IQR: 28–66 h).

Seven patients required intubation, of which only one patient did not receive a bolus of naloxone before intubation. This patient had co-ingested amitriptyline. Activated charcoal was only administered in four patients.

Discussion
This study shows that oxycodone overdose results in significant CNS depression in the majority of patients. Bradycardia appeared to be a feature of oxycodone overdose with almost a fifth of patients having a HR < 60 beats/min. An abnormal QT interval occurred in a similar number of patients where an ECG was available, suggesting that oxycodone may be a risk factor for TdP. In this study, only a small proportion of patients were intubated and ventilated, which is most likely due to the use of bolus naloxone and naloxone infusions. Patients requiring naloxone had a longer LOS but could be managed in a high dependency setting rather than requiring mechanical ventilation.

The majority of patients who presented had taken an overdose of their own prescribed oxycodone with suicidal intent. One-third had taken a slow-release preparation, and since regular use confers a level of tolerance to oxycodone, this may explain why only half had an altered GCS on first presentation to emergency services. Nevertheless, initial GCS was associated with the dose ingested, with higher doses resulting in a lower GCS (Figure 2). Almost half the presentations required naloxone at some point during their presentation, usually pre-hospital, and a quarter required a naloxone infusion, matching the pattern of initially altered GCS and SR overdose presentation numbers. Ingestions of SR oxycodone were associated with greater reductions in GCS and increased naloxone use, in keeping with its longer duration of action.

The requirement for naloxone is an important clinical indicator, due to the increased LOS and resource burden it entails. Although naloxone is highly effective at reversing opioid toxicity, it is ineffective at reversing other CNS depressants such as benzodiazepines, which were commonly co-ingested. It is also difficult to manage naloxone infusions in patients with chronic pain. Patients on infusions require higher level nursing care and a high dependency setting. However, mechanical ventilation and ICU admission are a greater burden on resources. Less than 10% of presentations

### Table 2
Details of naloxone use in patients with oxycodone overdoses

<table>
<thead>
<tr>
<th>Naloxone treatment</th>
<th>Total group (n = 137)</th>
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<tbody>
<tr>
<td></td>
<td>IR (n = 79)</td>
</tr>
<tr>
<td></td>
<td>SR (n = 44)</td>
</tr>
<tr>
<td></td>
<td>IR + SR (n = 14)</td>
</tr>
<tr>
<td>Naloxone bolus, n (%)</td>
<td>33 (42)</td>
</tr>
<tr>
<td>Pre-hospital IM bolus</td>
<td>6</td>
</tr>
<tr>
<td>Pre-hospital IV bolus</td>
<td>20</td>
</tr>
<tr>
<td>ED IV bolus</td>
<td>15</td>
</tr>
<tr>
<td>Naloxone infusion, n (%)</td>
<td>13 (16)</td>
</tr>
<tr>
<td>Ventilation required, n (%)</td>
<td>4 (5)</td>
</tr>
</tbody>
</table>

Figure 4. Box plot of hospital LOS comparing patients not given naloxone (nil), to patients only given a bolus dose of naloxone and patients given a naloxone infusion.
in our study required intubation and mechanical ventilation. The LOS of oxycodone presentations is not significantly different to the general LOS of all toxicology patients, unless associated with the need for naloxone either as a bolus or infusion (Figure 4).

Recent literature had suggested a relationship between oxycodone and prolonged QT. Fanoe et al. found a relationship between prolonged QTc and increasing oxycodone doses in a study of 27 patients and showed that oxycodone inhibited human ether-a-go-go related gene (HERG) channels expressed in HEK293 cells. Using the QT nomogram and manually measured QT intervals, we found 20 (17%) QT–HR pairs above the nomogram line. The majority of these patients had a HR > 100 beats/min, whereas we found overall a greater association with bradycardia in oxycodone overdoses. This may suggest it is a combination of medications, e.g. oxycodone and quetiapine (with its anticholinergic effect producing a tachycardia) that places the patient at risk of an abnormal QT–HR pair. This association with a prolonged QT in therapeutic doses and now in overdose supports oxycodone as an agent that prolongs the QT. However, the risk of TdP and other arrhythmias remains unclear. These have not been reported in the literature, and it is well recognized that some drugs can prolong the QT without an associated risk of TdP.

Recently, there has been heightened awareness regarding the prescription of IR and SR oxycodone by general practitioners, particularly within Australia. Roxburgh et al. showed an increase of 152% in the number of oxycodone prescriptions between 2002–2003 and 2007–2008. This is similar to the increase in the number of oxycodone overdose presentations in our study from 10 in 2002–2003 to 35 in 2007–2008 (Figure 1). Roxburgh audited oxycodone-related deaths in Australia between 2002 and 2008 showing the largest number of deaths (n=94) in 2007. This increase in both prescribing and overdose presentations suggests that oxycodone is an increasingly important public health issue. Figure 1 also demonstrates that at least in this study there has been a reduction in overdoses of morphine and methadone, and oxycodone is the predominant opioid overdose.

There are a number of limitations with this study, including the method of data collection and the non-randomized retrospective nature of the sample. However, all the data collected from toxicology patients and entered into the database is done prospectively and independent of any study hypothesis. Detailed information on naloxone treatment was obtained from the medical record using a clinical research form but was not blinded. This is unlikely to have introduced any bias because the use, dose and frequency of naloxone are recorded on the medication chart for all patients.

Oxycodone overdose was not confirmed with drug concentrations and dose was estimated based on patient history. However, further collateral history was collected from ambulance and relatives when available, including empty ingested drug packets. Previous studies in this population of patients have shown that a combination of patient history and collateral information are a good estimate of the true ingested dose. There may be an element of selection bias because patients presented to a single tertiary referral toxicology unit. However, the unit services a large surrounding area and is the only admitting hospital for all toxicology patients. A limitation of the ECG analysis was the timing of the ECG, which was not the same for every patient. The large catchment area and distances involved meant that patients presenting may have been stabilized in other centres or presented some hours after their ingestion, delaying the recording of an ECG.

In the majority of presentations, co-ingestants had been taken, which may confound the study, especially with QT prolongation. However, none of the co-ingestants in the patients with prolonged QT have been shown to cause QT prolongation. In one patient who ingested a tricyclic antidepressant, there was a prolonged QT because the QRS was widened (Figure 3).

Another potential bias was the assessment of the requirement for naloxone. There are no definitive criteria for the selection of patients who received naloxone, and the use of an initial bolus of naloxone was dictated by either the pre-hospital emergency services or the ED doctor. The use of naloxone infusions was always discussed with the attending toxicologist. Although there was always a preference for the use of naloxone rather than intubation and mechanical ventilation, some patients were intubated before establishing the diagnosis of opioid overdose. Intubation and mechanical ventilation is likely to be associated with a longer LOS than a naloxone infusion and was associated with a longer LOS in this study.

This study has shown that in addition to the expected CNS depression, the opioid oxycodone can cause bradycardia and QT prolongation in overdose. The SR formulation is associated with an increased use of naloxone infusions and a longer LOS. Although TdP has not been reported with oxycodone, a 12-lead ECG should be done in all overdoses and patients with QT prolongation should be monitored if they have a prolonged QT, until the QT normalizes. Further prospective studies are required to determine the relationship between dose and QT prolongation and the duration of the effect.
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References