Respiratory arrest and oversedation in an adolescent given intramuscular clonazepam for rapid tranquillization

Jonathan Channing, Simon Hill, Marion Wetherill and Oliver White

Abstract: Many young people in forensic adolescent units require intramuscular medication for rapid tranquillization. The efficacy and safety of the medications used is not well reported in this age group. Here we report a case of a 14-year-old girl experiencing severe oversedation and respiratory compromise on two occasions following intramuscular clonazepam.

Keywords: adolescent, clonazepam, deep sedation, forensic psychiatry, respiratory depression

Introduction

In recent months many inpatient units have had to find alternatives to intramuscular lorazepam for rapid tranquillization due to a national shortage of the licensed product since 2010 with no expectation of further licensed supplies until 2013 [Monteverde-Robb *et al.* 2011; Phillips, 2011].

The other benzodiazepines most commonly used worldwide for rapid tranquillization are clonazepam and midazolam. Midazolam has a faster onset than lorazepam but requires more frequent re-administration and has an increased risk of respiratory depression [Bak *et al.* 2011]. Many units have been using intramuscular clonazepam as an alternative benzodiazepine although the intramuscular route of administration is unlicensed in the UK (Marion Wetherill, Personal communication, Medical Information Department, Roche Products Ltd, 2010). Clonazepam has been reported to be used in doses up to 6 mg for rapid tranquillization in adults since the early 1990s with few side effects to produce similar tranquillization to haloperidol in a similar time-frame [Chouinard *et al.* 1993]. However, there are no reports about its use in adolescent patients.

Compared with lorazepam, clonazepam is associated with pharmacokinetic differences that have the potential to cause concern. Clonazepam has a slower time to peak concentration of 3 hours [Crevoisier *et al.* 2003] compared with a time of

1.5 hours for lorazepam [Wyeth Pharmaceuticals, 2005]. In terms of dose equivalence, 1 mg lorazepam is reported to be equivalent to 0.25–0.5 mg clonazepam [Curtin and Schulz, 2004]; however, the Maudsley guidelines [Taylor *et al.* 2009] state that 1 mg lorazepam is equivalent to 1–2 mg clonazepam. Information obtained from the manufacturer in 2005 gave a dose equivalence of 1–2 mg lorazepam being equivalent to 4 mg clonazepam. These differences illustrate the uncertainty of actual dose equivalence. The elimination half-life of clonazepam is relatively long with estimates varying between 20 and 80 hours [Greenblatt *et al.* 1987; Berlin and Dahlstrom, 2010]. Another source reports clonazepam's half-life to be 39 hours with that of lorazepam being 11 hours [Davies *et al.* 2010]. This gives the potential for dose accumulation when doses are repeated in succession. In addition, it is reported that there are secondary peaks observed following intravenous or intramuscular clonazepam, thought to be due to enterohepatic recycling, because the glucuronide of clonazepam may be deconjugated by intestinal flora and reabsorbed from the intestine in the form of the parent drug [Davies *et al.* 2010]. In terms of brain uptake and benzodiazepine receptor occupancy, clonazepam has been found to be similar to lorazepam [Greenblatt *et al.* 1987].

Respiratory depression is a well-recognized but rare side effect of benzodiazepine's, although this is increased if the benzodiazepine is taken with

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Correspondence to:
Jonathan Channing, BM
Specialty Registrar [CT2]
in Forensic Adolescent
Psychiatry, Bluebird
House, Tatchbury Mount,
Calmore, Southampton
SO40 2RZ, UK
[jonathan.channing@
southernhealth.nhs.uk](mailto:jonathan.channing@southernhealth.nhs.uk)

Simon Hill, MA (OXON),
B.M.B.Ch, MRCPsych
Consultant Adolescent
Forensic Psychiatrist,
Bluebird House, Tatchbury
Mount, Calmore,
Southampton, UK

Marion Wetherill, MR
PharmS, MSc, MCMHP
Locality Lead Pharmacist,
Bluebird House,
Tatchbury Mount, Calmore,
Southampton, UK

Oliver White, B med Sci
(honours), BMBS, Dip Med
Sci, MRCPsych
Consultant Child and
Adolescent Forensic
Psychiatrist, Bluebird
House, Tatchbury Mount,
Calmore, Southampton, UK

alcohol or is given to someone who has underlying pulmonary problems [McNaught *et al.* 1989].

In an adolescent forensic secure hospital it is not uncommon to require the use of intramuscular rapid tranquillization medication in the management of severe aggression and agitation for patients as young as 13 years [Hill *et al.* 2012]. Here we report a case of severe respiratory depression and oversedation in a 14-year-old girl.

Case history

Written informed consent was given by the patient for the articles production and publication. Oral lorazepam medication was offered to the patient each time before intramuscular clonazepam was given.

Miss Z is a 14-year-old girl with a background of severe neglect and abuse admitted to our hospital due to significant agitation and distress when on remand in a secure children's home. She presented with a high risk of harm to herself and to others. Her weight was approximately 45 kg on admission. Miss Z was on no regular medication on admission and had not previously been exposed to any psychotropic medication. Three weeks following admission Miss Z continued to exhibit significant self-harm behaviours, particularly in the form of head banging. She was also physically aggressive towards staff including attempting to kick and bite them during periods of control and restraint. This prompted the administration of 0.5 mg clonazepam intramuscularly (day 1, 22:20). Little effect was seen and arm holds or full restraint had to continue for 3 hours after the administration of the medication. The following day Miss Z was secluded due to ongoing aggressive behaviour to staff during a further period of control and restraint. Whilst secluded she began to harm herself with a zipper and refused to hand it to staff, instead placing it in her mouth. Owing to the lack of efficacy of the 0.5 mg clonazepam that was administered the previous day, 1 mg clonazepam intramuscular was given (day 2, 17:15). This had a more significant effect, with Miss Z beginning to stagger soon after administration and after less than 1 hour following the administration of the medication she fell asleep. Miss Z was awake soon afterwards and no respiratory difficulties were noted, although she was observed to remain drowsy.

The following day Miss Z needed to be secluded again due to further aggression to staff. Whilst in

seclusion she proceeded to bang her head on the Perspex window with varying force for just over 1 hour. She was given further medication with the aim of helping her calm down and reducing her self-harming behaviour. At this time 1 mg clonazepam was administered intramuscularly (day 3, 14:20). This resulted in her again becoming sedated but no impairment in her physical observations (heart rate, blood pressure and respiratory rate) were noted. During that evening Miss Z was again agitated and required some physical restraint via arm holds. However, she accepted oral medication and was administered 1 mg lorazepam orally (day 3, 21:15). Miss Z was noted to be sedated and had a staggering gait for the remainder of the evening, but was observed to have regular respirations. Her respiratory rate was regularly monitored overnight and noted to range from 13 to 18 breaths per minute.

On the evening of day 4, Miss Z required a further period of seclusion due to ongoing agitated and self-harming behaviours in the form of head banging. At this time 1 mg intramuscular clonazepam was therefore administered (day 4, 21:30). After some time she became calm and returned to the ward. She appeared very sedated and had to be carried to her room. Regular physical observations were conducted throughout the night.

At 04:10 on day 5, noises were heard coming from Miss Z's room and she appeared to be struggling to breathe. She was reported to have swollen and blistered lips and her colour was noted to be very pale. She was unresponsive to painful stimuli but all other observations were noted to be within normal limits. Nursing staff contacted emergency services, during which time Miss Z was noted to have stopped breathing for a short period of time. She gasped for air when she was turned over. An ambulance attended and she was taken to the accident and emergency department.

On arrival at the local accident and emergency department (travel time approximately 15 minutes) Miss Z was observed to be becoming less sedated. Blood and urine samples were taken but no medication was given. Miss Z had no memory of getting to the hospital. No apparent cause was found and Miss Z returned to the unit in the morning with observations being monitored. Miss Z was noted to have an ataxic gait and was tired during the day. When seen by the ward doctor at approximately 10:30 on day 5 she refused examination but no lip swelling or blisters were seen.

Figure 1. Estimated clonazepam plasma level with repeated doses.

It was decided that if she required further intramuscular rapid tranquillization 0.5 mg clonazepam would be given, with the contingency that intramuscular olanzapine would be used if clonazepam was not sufficiently effective. In addition, Miss Z was encouraged to accept oral rapid tranquillization medication such as lorazepam on the basis of its shorter half-life.

During the early evening of day 5 Miss Z was again being aggressive to staff. Her behaviour at this time included climbing on top of furniture, head banging and spitting at staff. There was again significant concern about the immediate risks that she presented to herself and others. She was therefore administered 0.5 mg clonazepam intramuscularly (day 5, 19:25). Miss Z was reviewed by the duty doctor 30 minutes following administration of the medication, at which time she presented as drowsy but she was able to talk, had a normal respiratory pattern and normal physical observations. It was noted that the medication had a good tranquilizing and sedating effect, and Miss Z went to her room and fell asleep. Physical observations were regularly performed. At 22:35 she was observed to be making whimpering noises. Physical observations were taken and noted to be within normal limits. At 23:15 Miss Z appeared to be hyperventilating with a respiratory rate of 65 breaths per minute, which then rapidly reduced to 14 breaths per minute with a shallow breathing pattern. At 00:15 on day 6, Miss Z's lips were noted to be swelling and she failed to respond to gentle shaking or pain. She was noted to have blue lips and oxygen

saturations were recorded at 80%. A Guedel airway was inserted (to which Miss Z did not respond) and oxygen was administered via a face-mask. This resulted in an improvement in her oxygen saturations. She was again taken by ambulance to the accident and emergency department. On arrival at the accident and emergency department intravenous flumazenil was administered, and it was noted that she almost immediately regained consciousness. She remained in hospital for a period of observation for 4 hours but no further deterioration was noted.

Following these reactions Miss Z has not received any further benzodiazepines.

Discussion

This case demonstrates the potential hazard of using a drug with a long half-life for rapid tranquillization, particularly if multiple doses are needed over a short period of time. Figure 1 illustrates an estimation of plasma levels in our patient assuming a half-life of 39 hours to generate the gradient of the line and assuming that plasma level rise is directly proportional to the dose given. It can be seen that as the next dose of medication is given before the first half-life has been reached, the maximum plasma drug level is continuing to rise. The last dose of clonazepam was only 0.5 mg, but as indicated in Figure 1 it is likely that the plasma level increased to the same level as the previous night. If Miss Z's metabolism of clonazepam resulted in an increased half-life of the medication longer than

39 hours, then the rise in plasma levels would have been more dramatic.

As well as the long half-life, a further factor which may have contributed to Miss Z's delay in onset of severe respiratory depression/respiratory arrest is the enterohepatic recycling associated with clonazepam. This can result in multiple peaks in plasma concentration [Davies *et al.* 2010].

The other possible cause of the symptoms in this case which was considered was the possibility of an allergic reaction in view of the reported lip swelling and blistering. However, in view of the fact that the symptoms occurred several hours after the medication was given and the patient recovered without any treatment for allergy makes this unlikely. No swelling or blistering was reported by the accident and emergency staff. The other fact that points against it being an allergic cause was the rapid response and recovery after intravenous flumazenil was administered.

An additional issue raised by this case is the fact that there is an effective reversing agent for the effects of benzodiazepines, i.e. flumazenil [Thompson *et al.* 2006; Heard *et al.* 2009]. However, it is only licensed for intravenous use, which is not a route available to nursing staff in most mental health hospitals. There are reports of flumazenil being used successfully sublingually, intramuscularly, rectally and intranasally [Weaver, 2011; Haret, 2008], but these routes are unlicensed and not approved for use in our hospital. This increases the concern about using benzodiazepines within a psychiatric setting where no reversing agent can practicably be given. The risk of respiratory depression appears to be significantly increased when particular benzodiazepines such as clonazepam are prescribed.

In view of this incident, our trust changed the maximum dose of clonazepam given and obtained unlicensed lorazepam injection from the USA for adolescent patients.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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