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Potentially fatal overdose of methadone in a child known to have learning difficulties

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We report the case of a 33 kg, 8 year old child with Down's syndrome who ingested 70 ml of methadone elixir (1 mg/ml), a dose equivalent to approximately 2.1 mg/kg. Following a respiratory arrest, he was successfully resuscitated and subsequently required prolonged treatment with an infusion of naloxone in a high dependency setting. The medication belonged to an adult older sibling who was a rehabilitating addict, and had stored it on the top shelf of a kitchen cupboard. We discuss the pharmacology of methadone in paediatric overdoses and the social issues regarding the danger of poisoning for older children with learning disabilities.

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Introduction

Methadone is a synthetic opioid analgesic used in the management of severe pain and in the detoxification or maintenance of opioid addicts. Methadone use has increased in recent years, as the endemic spread of HIV has driven the need to wean addicts off intravenous drugs of abuse. This increased use has in turn led to a rise in accidental poisonings. While most cases occur in recovering drug addicts, a significant number involve accidental ingestion by opioid-naive children[1].

Methadone is a weak opioid agonist acting principally at the mu receptor, as well as being an antagonist at NMDA receptors. Methadone is usually administered as a racemic mixture with the R-enantiomer being responsible for activity at mu opioid receptors, and the S-enantiomer lacking opioid activity but having equal NMDA activity[2]. Methadone has complex pharmacokinetics with a biphasic half-life, attributable to the differences in metabolism between these two enantiomers. Absorption after oral administration is fast and almost complete, producing peak plasma concentrations after 2–4 hours and peak clinical effect within 1–2 hours[2]. Oral bioavailability is high, with reported values of 0.67 to 0.95[2]. Methadone is lipophilic and has a high volume of distribution. It is around 86% plasma protein bound, although variations in binding between the two enantiomers play a part in the differences in their plasma clearance. Methadone undergoes hepatic metabolism mainly by CYP3A4, with some contribution from CYP2C9 and CYP2D6. Pharmacogenetic differences in these enzymes are thought to be one cause of the wide inter-individual variation in the plasma half lives reported (15–55 hours). Pharmacogenetic typing of methadone fatalities shows genotypes

associated with slow metabolism to be over-represented[3]. Following hepatic metabolism, methadone is renally excreted as an inactive metabolite.

Methadone – pharmacokinetics and toxicity

Opioid-naive children are particularly susceptible to the effects of methadone in overdose, and numerous deaths have been reported. Although most methadone overdoses occur in addicts, 69% of fatalities involve opioid-naive patients (both children and the elderly)[4]. A study of the kinetics of methadone in opioid-naive children (aged 1–18 years) reported considerable inter-individual variation in the half-life from 3.8 to 62 hours[5]. The authors hypothesise that the variations may be accounted for by age related differences in body fat composition, liver enzyme maturity and plasma protein levels. Previous exposure to methadone is also likely to be a factor in kinetic differences. In a study of neonates aged 34–43 weeks, who were on long term methadone treatment for opioid withdrawal, the plasma half-lives were recorded as 16–25 hours, significantly shorter than those seen in opioid-naive children[5]. Several studies have suggested that methadone induces its own metabolism, with plasma levels after 30 days treatment on a fixed dose being up to 3 times lower, thus justifying the requests of many addicts to increase their dose in order to remain withdrawal free[6].

A case series of 42 paediatric methadone ingestions in Merseyside (UK), over a four-year period, found that the number of reported incidents doubled between 1990 and 1992[7]. Of 42 children studied, 2 died, 21 were significantly drowsy on admission, 10 had respiratory depression, 17 had pinpoint pupils, 4 were hypotensive and 2 had convulsions. The authors did not attempt to correlate the amount ingested with the outcomes. However, the data suggest that methadone overdose in children is a significant and unpredictable problem in to which further research would be helpful.

Case report

An 8 year old, 33 kg child with Down's syndrome presented to our Accident and Emergency department an hour after ingestion of methadone elixir (1 mg/ml). An estimated dose of 2.1 mg/kg had been ingested. He was noted to be responsive to gentle stimulation during transport to hospital, but suffered a respiratory arrest on admission. Initial management consisted of airway support and positive pressure ventilation using an ambu-bag. Intravenous naloxone 100 mcg/kg induced spontaneous ventilation. An infusion of 50 mcg/kg/h was used to maintain a Glasgow Coma Score (GCS) of 13–14 in a high care facility over the following 36 hours. Naloxone is an opioid antagonist, whose action is principally at mu opioid receptors, with some activity at kappa and delta receptors. It has a therapeutic half-life of only 30–80 minutes, much shorter than many of the commonly ingested opioids. The bolus dose which gives an adequate response is used to calculate the subsequent infusion rate. In most cases, two thirds of the dose required as an intravenous bolus corresponds approximately to the hourly rate needed[8]. Myosis, level of consciousness, and respiratory effort are as useful as blood levels in titrating the infusion, and making decisions about its cessation. As the length of treatment required is highly unpredictable, and the child's respiratory effort is effectively dependent on the infusion, an HDU/PICU setting is desirable. In this case, recovery was complicated by an aspiration pneumonia, initial hypothermia (35°C) and mild hypotension.

The child's 35-year old sibling is a recovering drug addict and the child ingested the methadone elixir at his sibling's home during a Christmas luncheon. The medicine was stored on the top shelf of a cupboard, but the child had managed to climb on to a stool in the kitchen to retrieve it. Almost a year later, the child is fully recovered. He attends a school for children with moderate to severe learning difficulties, where the staff feel that there has been no deterioration in his level of functioning.

Discussion

This case raises several interesting issues, both social and pharmacological. There is a vast difference in half-lives between methadone and naloxone. The good initial response to bolus doses of naloxone may make it difficult for families to understand why a child needs to be admitted at all, let alone spend a long and unpredictable period of time on an intensive care unit. There are several cases in the literature of medical staff being caught out by the long and variable half-lives of certain opioids, with patients relapsing after cessation of naloxone treatment[9]. Although there have been reports linking it to pulmonary oedema, there are few dangers to using relatively high doses of naloxone in opioid-naive patients[10].

A study of the domestic situation of rehabilitating drug addicts in the UK found that 36% of methadone prescriptions were dispensed in weekly instalments, thus providing a dose sufficient for significant toxicity. 46% of the methadone maintenance patients had current

parental responsibility for a child under the age of 12 years, and only 49% were considered to be storing their methadone safely. Importantly, only 29% remembered anyone having discussed with them the dangers of methadone to children[11]. Accidental poisonings in childhood commonly occur in environments outside the child's own usual domestic setting. A typical example is the home of a grandparent[12], where many medicines may be present and not necessarily stored in a child friendly fashion. Most significant poisonings occur in the toddler age group, with a peak age of 30 months. Children with learning difficulties will remain at an inquisitive stage with little sense of personal danger for much longer than the average child. Thus an older child, who is able to reach higher and probably has better motor skills, remains vulnerable to poisoning in an unpredictable and less outwardly obvious way.

Our case also raises issues relating to '*safety in the home*'. Health visitors and school nurses are often best placed to offer advice in these matters, as they have frequent contact with parents and a good understanding of child development. This family initially failed to realise the serious nature of the overdose, accounting for the slight delay in presentation. There are proven benefits for the administration of activated charcoal (1 g/kg), orally or nasogastrically, in reducing absorption if a case is seen within the first hour. It follows that better education about the dangers of methadone poisoning, and the importance of seeking help immediately are needed in the counselling of rehabilitating addicts. Dissemination of information to the extended family is often unreliable, as written information is rarely provided[12]. Following a study of the role of the grandparent in accidental poisoning, it has been recommended that health visitors include the extended family in accident prevention programs[13]. Older children with learning difficulties may easily give a falsely optimistic impression of their level of functioning to occasional/informal carers. Information on 'developmental stage appropriate' accident prevention should be a part of the hand over of any child with special needs whether to a respite centre or extended family member.

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