Sudden death in an adult taking methadone: lessons for general practice

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Introducton

A 39-year-old man (PV) had been registered with his current general practice for 20 months. He had a long-standing history of heroin and alcohol problems dating back to early adulthood, when a knee injury prematurely ended his professional sporting career. He also had an extensive history of benzodiazepine use. He was hepatitis C-positive and had recently been hospitalised because of a buttock ulcer, but he had discharged himself against medical advice after two weeks. His buttock ulcer had not healed and was being treated by the district nursing staff. In the month after discharge from hospital his requests for methadone scripts were not following a regular pattern and he had failed to attend the drug addiction counsellor at the practice. At the time of his death he was being treated with methadone mixture 60 mg daily and temazepam tablets 20 mg twice daily, and was receiving no other drugs on prescription. In the four months prior to his death he had had three urine tests that confirmed benzodiazepine and methadone metabolites, but no morphine or other drugs, except on one occasion when he also had cocaine metabolites present. Because of his limited mobility he was not prescribed daily, supervised consumption methadone, but was dispensed methadone weekly.

On the day of his death a friend had called at 8.30 am, spoken to him for half an hour and had then left, returning at 11.00 am. On this occasion PV was asleep on the sofa. He was woken but appeared 'a bit dopey or sleepy'. The friend returned at 2.30 pm to find PV dead on the floor in his bathroom, with a considerable amount of flooding because a radiator had been pulled from its fixture. His friend reported that PV had not seemed any different from normal, and he had no reason to think that PV's death had been intentional.

Subsequent toxicological analysis revealed a methadone level of 0.51 mg/l, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP, a metabolite of methadone) 0.10 mg/l, temazepam 1080 mcg/l, oxazepam (metabolite of temazepam) not detected, amitriptyline 0.5 mg/l, nortriptyline (metabolite of amitriptyline) 0.08 mg/l. Ethanol was not detected.

While the degree of tolerance to a drug will affect the blood levels associated with toxicity, in regular users of the drug, blood methadone levels of 1.0 mg/l or more are associated with serious toxicity. Blood temazepam levels of 1000 mcg/l or less are considered within the therapeutic range, while levels of 5000 mcg/l or more may be associated with serious toxicity.[1] Blood levels of amitriptyline and nortriptyline of 0.3 mg/l or less are within the therapeutic range, while levels of 1.0 mg/l or more are associated with serious toxicity.[1] The other main finding of note on post mortem examination was the presence of liver cirrhosis attributed to hepatitis C infection. The relatively low levels of the major metabolite of temazepam (oxazepam) and amitriptyline (nortriptyline) indicate that these drugs had probably not been used in the days preceding death, and that death had probably occurred relatively shortly after their subsequent ingestion. His EDDP levels also indicate that death occurred soon after methadone ingestion. The coroner's verdict was of accidental death owing to methadone toxicity, enhanced by temazepam and amitriptyline.

Discussion

Drug misusers have an annual mortality rate six times higher than that for a general, age-matched population, with over two-thirds owing to drug overdoses.[2] In such cases it is incorrect to attribute the cause of death to an 'overdose' of a single drug.[3] Between 50% and 75% of deaths are associated with multiple drug usage, usually an opiate with a benzodiazepine or alcohol.[4] There is an overlap between quoted therapeutic concentrations and methadone concentrations seen in fatalities, partially because of the development of tolerance. Methadone is generally thought to have a 'narrow window of safety': the dose needed for effective maintenance may be very close to the dose that will kill an individual.[5,6] To further complicate interpretation of toxicological analysis when attributing a concentration of methadone to death, caution is required, as multiple sampling has shown a 100% discrepancy between methadone concentrations in samples collected from different sites of the same body.[7] The recommended procedure is for blood to be taken from a peripheral site. Femoral vein samples were taken in this case.

A confidential audit was conducted following the death of PV and established several associated risks for sudden death in the patient. He was a known user of other drugs, having been prescribed benzodiazepines since joining the practice. Although his previous urine tests had shown he was using benzodiazepines, the toxicology report suggests he was not taking these regularly prior to his death. He was

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also known to abuse alcohol, although no alcohol was detected at post mortem. He was not prescribed amitriptyline and presumably obtained these illicitly. Sedative-hypnotic drugs act synergistically on the central nervous system, making a 'normal' or usual dose of opiate potentially fatal.[8] He was infected with hepatitis C and post mortem revealed cirrhosis. Metabolism and clearance of methadone and other drugs can be reduced in the presence of liver disease and has been reported in methadone-related fatalities in the past.[2] He had failed to engage properly with both the primary care team and drug support services after his discharge from hospital and had missed several appointments, yet he remained on a weekly methadone script. Fatal heroin overdose has been reported to be higher in those who were not currently enrolled in a treatment programme,[3] and organisational failure to maintain regular contact and follow-up of patients taking methadone has been reported in a recent confidential enquiry into methadone-related deaths.[9]

There are five major benefits of methadone maintenance programmes: a decrease in illicit drug use; a reduction of injecting behaviour leading to a decrease in viral transmission; a reduction in the risk of opioid overdose death of those in treatment; an improvement in physical and mental health; and a decrease in criminal activity.[5,10] In order to avoid methadone-related deaths, guidelines have been produced that requires a structured delivery of service with clear roles and responsibilities, particularly for the prescribing doctor.[5,10] This case highlights additional risk factors that put a patient at increased risk of a methadone-related death. Concomitant prescription of benzodiazepines increases the likelihood of central nervous system depression, particularly in those who are known to abuse alcohol. Liver disease diminishes methadone metabolism and prescribing should be adjusted to take this into account. More rarely, sudden cardiac arrhythmia in the form of torsade des pointes has been reported to be associated with very high-dose methadone treatment.[11] Lastly, regular review of methadone prescribing requires a willingness on the part of the general practitioner to alter their prescribing regimen in the face of changing circumstances. This is particularly true when an individual is failing to engage with support services and is not being prescribed methadone by daily supervised consumption.

In conclusion, we agree with other commentators that attributing death to methadone 'overdose' is too simple.[8] Multifactorial contributions are critically important in methadone-related deaths. It appears that polypharmacy, the co-prescribing of benzodiazepines, tricyclic antidepressants, and other opiates, will have contributory effects on the risk of sudden death in patients on a methadone treatment programme, particularly in patients with comorbidities that affect drug metabolism. Prevention also requires adherence to a prescribing regimen, with a willingness to modify prescribing practice when faced with changing patient behaviour.

References

1. Flanagan R. Guidelines for the interpretation of analytical toxicology results and unit of measurement conversion factors. *Ann Clin Biochem* 1998; **35:** 261-267.
2. Drummer O, Syrjanen M, Opeskin K, Cordner S. Deaths of heroin addicts starting on a methadone maintenance programme. *Lancet* 1990; **336:** 108.
3. Darke S, Ross J. Fatal heroin overdoses resulting from non- injecting routes of administration, NSW, Australia, 1992-1996. *Addiction* 2000; **95:** 569-573.
4. Gossop M, Stewart D, Treacy S, Marsden J. A prospective study of mortality among drug misusers during a 4-year period after seeking treatment. *Addiction* 2001; **97:** 39-47.
5. The Advisory Council on the Misuse of Drugs. *Reducing drug-related deaths*. London: Department of Health Office, 2000.
6. Harding-Pink D. Methadone: one person's maintenance dose is another's poison. *Lancet* 1993; **341:** 665-666.
7. Milroy CM. Methadone deaths: a toxicological analysis. *J Clin Pathol* 2000; **53:** 277-281.
8. Darke S, Zador D. Fatal heroin 'overdose': a review. *Addiction* 1996; **91:** 1765-1772.
9. Scott R, Jay M, Keith R, *et al*. A confidential inquiry into methadone-related deaths. *Addiction* 1999; **94:** 1789-1794.
10. National Prescribing Centre. The management of opioid dependence. *MeReC Bull* 2002; **12:** 13-16.
11. Krantz M, Lewkowiez L, Hays H, *et al*. Torsades de Pointes associated with very high-dose methadone. *Ann Intern Med* 2002; **137:** 501-504.

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