Methadone dose and post-mortem blood concentration

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Abstract

The relationship of methadone dose with post-mortem blood concentration was investigated using data collected from 1994 coronial cases in the Australian state of New South Wales. Data on 31 subjects were summarized using linear regression. The weight-adjusted methadone dose, gender, methadone maintenance treatment status and its interaction with adjusted-dose were all significant predictors of post-mortem blood methadone concentration. Data on the death of a young man from the toxic effects of three daily doses of 30 mg methadone are used to give an example of a pair of observed (0.74 mg/l) and predicted (0.48 mg/l) post-mortem blood concentrations. The estimated post-mortem blood concentration for male maintenance patients is at least twice the trough plasma levels estimated from previously published studies of living maintenance patients. The estimated post-mortem blood concentration for female maintenance patients is at least three times the estimated trough level of living subjects. We conclude that post-mortem methadone redistribution is probably the principal cause of the observed differences between males and females in post-mortem blood concentrations and the differences between estimated concentrations for living and deceased subjects. [Caplehorn JRM, Drummer OH. Methadone dose and post-mortem blood concentration. Drug Alcohol Rev 2002;21:329–333]

Key words: forensic science, human, methadone, substance abuse treatment, toxicology.

Introduction

Methadone toxicity is an increasingly common cause of death among young people in Australia [1–5]. As methadone maintenance programmes have expanded, there has been an increase in the numbers of deaths from prescribed and diverted methadone syrup [5]. While the overall effect of methadone maintenance is to reduce addicts’ risk of death from accidental overdose by 75% [6], in 1994 in New South Wales (NSW) addicts’ risk of fatal drug toxicity in the first days of maintenance was seven times their risk on the streets [4].

The marked increase in risk was caused by a cluster of 10 deaths from methadone toxicity in the first 2 weeks of maintenance [3]. However, as maintenance patients develop a tolerance to the respiratory depressant effects of methadone (and, thereby, heroin), their risk of fatal drug toxicity falls dramatically [4,6]. This why the risk of fatal drug toxicity in later maintenance in NSW in 1994 was one-hundredth the risk in the first 2 weeks of treatment [4].

While there are no similar risk estimates available for comparison, similar clusters of death from fatal methadone toxicity in the first 2 weeks of maintenance have been identified: in 1989–90 in Victoria [1]; in 1987–92 in Harris County, Texas [7]; in 1996–99 in South Australia [8]; in 1991–96 in the Strathclyde region of Scotland [9]; in 1991–94 in Sheffield, England [10]; and in 1994–98 in Aachen, Germany [11]. While some deaths were caused by clearly inappropriate use of methadone, most were due to the difficulty in determining a starting methadone dose that is both safe and adequate to prevent withdrawals.

The difficulty in determining starting doses is due primarily to the overlap of potentially fatal with clinically effective doses, e.g. daily doses of 30 mg methadone can be both potentially fatal and inadequate to prevent discomfort. This overlap is due to wide variation in individuals’ response to methadone [12–14] and the marked differences in new patients’ recent exposure and, hence, tolerance to opioids. The problem
is compounded by new patients’ tendency to exaggerate their physical dependence [4].

Given these difficulties, deaths from methadone toxicity in the first days of maintenance are to be expected; yet the risk was not described until 1990 [15]. The 20-year delay was due, in part, to confusion caused by the frequent involvement of benzodiazepines [1,3–5,16]. Other deaths were attributed incorrectly to the consumption of illicit opioids, including illicit methadone. Doctors attributed one of the 10 1994 NSW methadone deaths early in maintenance to the consumption of heroin and another to illicit methadone (cases 2 and 8, respectively) [3].

The latter case was the only one of the 10 deaths to come to inquest. The State Coroner accepted the advice of a senior Sydney drug and alcohol specialist and concluded the deceased had most probably taken additional, non-prescribed methadone (case 8) [3]. The specialist reached this conclusion after assuming the association of methadone dose with post-mortem concentration was the same as the association of methadone dose with trough plasma concentrations in living subjects (the specialist cited Wolff et al., 1991 [17]). Unfortunately, the drug and alcohol specialist did not take into account the significant variation in the pharmacokinetics of methadone in living subjects [1,14] and the post-mortem redistribution of basic drugs such as methadone [18,19]. The little available evidence suggests post-mortem redistribution causes the concentration of methadone in the blood to increase over twofold [20,21]. As this redistribution process takes time, it is not surprising there is also evidence that the post-mortem blood concentration increases with the time taken to collect specimens [20].

The specialist also failed to take into account the variability introduced by the site-dependence of post-mortem blood methadone concentrations. The concentration of methadone in a specimen of blood taken from one site may be up to twice the concentration in a specimen taken at the same time from a different site in the same individual, e.g. femoral vein vs. brachial vein [22], or subclavian vein vs. heart [23]. Moreover, these differences seem to be unpredictable [22,23].

While the specialist was most unwise to have used the post-mortem methadone blood concentration to estimate the probable dose of methadone, there is a lack of good evidence on the question. Indeed, there are no published reports summarizing the relationship of methadone dose with post-mortem blood concentration. We investigated this relationship by summarizing data from 1994 NSW coronial cases in a linear regression.

Methods

Coronial cases involving methadone were identified from data held by the NSW Attorney General’s Department. The toxicological reports and statements regarding methadone dose were extracted from coronial files. Post-mortem blood methadone concentrations were determined by gas chromatography–mass spectrometry at the NSW Division of Analytical Laboratories. The laboratories are the State’s sole provider of forensic toxicology services.

The methadone treatment histories of the deceased were obtained from the NSW Health Department’s Pharmaceutical Services Branch and the Drugs of Dependence Unit of the Queensland Health Department.

As the error introduced by interindividual, site and temporal variability would tend to obscure the expected linear relationship of methadone dose with post-mortem blood concentration, we maximized the number of cases by including deaths involving diverted as well as prescribed methadone syrup (i.e. methadone used as maintenance treatment for heroin addiction). We also intended to include cases involving methadone tablets prescribed as analgesia.

Methadone doses were standardized for a 70-kg person—adjusted dose = dose × 70/(weight in kg). The relationship between weight-adjusted methadone doses and post-mortem blood methadone concentrations (mg/l) was summarized using a linear regression with no constant (SPIDA, Statistical Computing Laboratory, Sydney, Australia) [24]. Allowance was made initially for the effect of being in maintenance treatment, its interaction with adjusted dose, gender, its interaction with adjusted dose, age and the presence of either cirrhosis or advanced chronic active hepatitis.

The conformity of the linear regression models to the underlying assumptions was assessed by plotting the studentized residuals against the predicted values and using the Shapiro–Wilk statistic to test the distribution of the residuals [25,26]. Models were constructed so as to conform to the hierarchy principle and were tested for collinearity and influential observations [24,25,27].

The original study of 1994 NSW methadone-related deaths was approved by the Human Research Ethics Committee of the Western Sydney Area Health Service and the NSW State Coroner.

Results

Methadone was detected in post-mortem material taken during coronial investigations of the deaths of 87 adults in NSW in 1994 [4,16]. The quality of available methadone dose information allowed 33 observations, 26 maintenance and seven diversion cases to be included in the linear regression analysis of post-mortem blood methadone concentration. (As there were no reliable dosage data available for deaths due to
methadone tablets (‘Physeptone’) prescribed for pain relief, no cases involving methadone tablets are included in the analysis.) Twenty-six of the 33 cases included were men. The methadone dose was adjusted for weight. The post-mortem blood concentrations and weight-adjusted methadone doses are summarized in Table 1.

Two cases were excluded as influential observations [25: 368]. One was the mother of a 6-week-old baby and recent admission to methadone maintenance—dose 40 mg, weight 80 kg, post-mortem blood methadone concentration 1.1 mg/l. The other was an established maintenance patient who died after injecting heroin at least a day after his last dose of methadone—dose 80 mg, weight 66 kg, methadone concentration 0.22 mg/l.

The weight-adjusted dose of methadone, gender, being a methadone maintenance patient and its interaction with adjusted dose were all significant predictors of post-mortem blood methadone concentration (Table 2). While the interaction term (maintenance status × weight-adjusted dose) is not easy to interpret, it was needed to remove an apparent association between the studentised residuals and the predicted values. Age and the presence of advanced liver disease were eliminated as non-confounders. The final model accounted for 26.7% of the variability in post-mortem blood methadone concentration.

The post-mortem blood methadone concentration can be estimated by inserting values into the regression equation: post-mortem concentration = methadone dose × 0.0081 + gender × 0.33 + treatment status × 0.31 – dose × treatment status × 0.0048 (where methadone dose is in mg and adjusted for a 70-kg person; male = 0, female = 1; in maintenance = 1, not in maintenance = 0). For instance, the estimated post-mortem blood methadone concentration for the case in which the drug and alcohol specialist gave his advice—a 69-kg male maintenance patient given 30 mg methadone [3: 14]—is given by

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(70/69 \times 30) \times 0.0081 + 0 \times 0.285 + 1 \times 0.399 - (70/69 \times 30) \times 1 \times 0.0053 = 0.483 \text{ mg/l.}
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**Discussion**

The results of the present study show that, despite the error introduced by the wide variation in the pharmacokinetics of methadone [13,14,28] and inconsistent but significant post-mortem changes [20–23], there is an identifiable linear relationship between weight-adjusted methadone dose and post-mortem blood concentration. Women given the same dose per kilogram had significantly higher post-mortem blood methadone concentrations than men. This has not been reported previously. As expected [13], maintenance patients had higher post-mortem blood methadone concentrations than those who took only a single dose of methadone.

The observed post-mortem blood concentration in the 1994 case referred to in the Introduction was 0.74 mg/l while the predicted is 0.48 mg/l [3: 14]. These data are consistent with our earlier conclusion that the young man died from the effects of three daily doses of 30 mg methadone prescribed as maintenance treatment for heroin dependence [3:14]. The relatively large difference between predicted and observed values is not surprising because the linear regression model only explained a quarter of the variability in post-mortem blood methadone concentration.

The regression model fails at extreme values. For instance, the model predicts that a female given a zero dose would have a post-mortem blood methadone concentration of 0.29 mg/l. Indeed, the finding of an association of gender with post-mortem blood methadone concentration should be treated with some caution as data from only six women were included in the

| Table 1. Weight-adjusted methadone doses and post-mortem blood concentrations (n = 33) |
|-------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Weight-adjusted methadone dose (mg)* | 61.4 | 26.8 | 39.8 | 60 | 88.0 |
| Post-mortem blood methadone concentration (mg/l) | 0.60 | 0.26 | 0.40 | 0.60 | 0.74 |

* Methadone dose standardized for a 70-kg person = dose × 70/(weight in kg).

| Table 2. Linear regression model of post-mortem blood methadone concentrations (mg/ml) (n = 31) |
|-------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Methadone dose* (mg) | 0.0081 | 0.0011 | 0.000 |
| Gender (male = 0, female = 1) | 0.285 | 0.087 | 0.001 |
| Maintenance patient (no = 0, yes = 1) | 0.399 | 0.084 | 0.000 |
| Dose × maintenance patient | −0.0053 | 0.0017 | 0.004 |

* Methadone dose standardized for a 70-kg person = dose × 70/(weight in kg).
final analysis. More research is needed into the effect of gender on the relationship of methadone dose with post-mortem blood concentration.

The negative interaction term of weight-adjusted methadone dose with maintenance treatment status seems to indicate that the effect of being in maintenance on post-mortem blood methadone concentration diminished with increasing dose (Table 2). However, as the daily dose of methadone usually increases during the first months of maintenance, the interaction term is interpreted as indicating methadone metabolism and excretion increases with chronically elevated blood and tissue concentrations. This is consistent with evidence from living subjects. A study of methadone maintenance patients found the trough plasma concentration diminished after some months on the same daily dose of methadone [13]. The failure of either age or the presence of advanced liver disease to be associated significantly with blood methadone concentration is also consistent with the evidence from living subjects [29].

While we could not find a previous report summarizing the association of methadone dose with post-mortem concentration, at least two groups have used linear regression to summarize the relationship of daily methadone dose with trough, plasma concentration in living maintenance patients [17,28]. Using data from 29 stable maintenance patients, Wolff et al. [17] found the trough plasma methadone concentration increased by 0.263 mg/l for every mg/kg of methadone (0.0038 mg/l for every mg of methadone given a 70-kg person) while Horns et al. [28] found the plasma concentration (mg/l) in II stabilized maintenance patients was approximately 0.003 times the daily dose (mg).

While Wolff et al.’s [17] and Horn et al.’s [28] estimates are similar to each other, they are considerably smaller than the regression coefficient for weight-adjusted methadone dose found in the current study, 0.0081 (Table 2). When doses of methadone in the range 30–100 mg, inclusive, are inserted into the regression equations, the estimated post-mortem blood methadone concentrations in male maintenance patients are at least twice the predicted trough plasma concentrations in living maintenance patients [17,28]. For women maintenance patients, the predicted post-mortem blood methadone concentrations are at least three times the predicted trough plasma concentrations in living maintenance patients [17,28]. As whole blood methadone concentrations are approximately 75% plasma concentrations [30], the differences in concentrations between living and dead subjects are even greater than these estimates suggest.

The differences in predicted blood methadone concentrations between living and dead subjects are very similar to the ratios of post- and ante-mortem (2.8 : 1) [20] and post- and peri-mortem blood concentrations (2.6 : 1) [21] reported previously on single cases. We take this as evidence that the difference between predicted blood methadone concentrations between living and dead subjects is due primarily to post-mortem redistribution of methadone.

If post-mortem methadone blood concentrations are indeed higher in women, this is probably not due to their having higher blood concentrations before death [28]. Rather, women are likely to have greater post-mortem redistribution as they tend to have more fat in the areas from which peripheral blood specimens are usually collected—the brachial, subclavian and femoral veins.

The findings of the present study again serve to highlight the difficulties involved in interpreting post-mortem blood methadone concentrations. While there seems to be a linear relationship between dose and post-mortem blood concentration, there is great inter-individual variation and, perhaps, a significant difference between males and females. However, it can be confidently concluded that, given the same dose of methadone per kilogram, the post-mortem blood concentration is likely to be two or three times greater than the trough plasma concentration in a living subject.

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