22th October 2022

[redacted]

Ms Caitlin Healey-Nash
NSW Crown Solicitor's Office

Special Commission of Inquiry into LGBTIQ hate crimes Special Commission re death of Andrew Currie

I have been asked to review the files and produce a toxicology report.

Background

I qualified in 1989 from the University of Edinburgh, Scotland as a medical practitioner (MB ChB). I have been a specialist general physician and clinical toxicologist since 1998, working previously as the Director of the National Poisons Information Service Guy's and St Thomas's Hospitals, UK and on call for Australia giving expert toxicology advice through the NSW Poisons Information Centre. I am a Fellow of three Royal Colleges of Physicians, Fellow of the American College of Medical Toxicology, Fellow of the American Academy of Clinical Toxicology and Regional Adviser to NSW, Queensland and the ACT for the Royal College of Physicians of Edinburgh. I remain clinically active in the care of both general medical and clinical toxicology patients.

I am currently Director of Medical Education and consultant physician and toxicologist at Fiona Stanley Hospital, Western Australia. I have diagnosed and treated many patients with toxicity from drugs, including opioids such as morphine, methadone and codeine. In the early part of my clinical training in Edinburgh I also saw patients with barbiturate poisoning, though it has become considerably less common now.

The case

This is articulated in the letter of instruction of 26th September 2022 by Ms Caitlin Healey-Nash

Statements and reports examined in making this report

- Post-mortem report into the death of Mr Andrew Currie
- Post-mortem toxicology report Mr Andrew Currie
- Police report into death of Andrew Currie

- Statement of Mr Currie's stated friend GB

Post-mortem blood toxicology results in Mr Andrew Currie;

The toxicology results recorded a combination of the following drugs:

• **In the blood:** 12 mg/L pentobarbitone, 3.4 mg/L Codeine, 0.12 mg/L Methadone and 0.07 mg/kg Morphine. No alcohol was detected.

In the liver: 43mg/kg Pentobarbitone, 11 mg/kg Codeine, 0.36 mg/kg Methadone and 0.26 mg/kg Morphine. Paracetamol was also detected but not quantified.

• **In the stomach**: 42 mg Pentobarbitone, 47 mg Codeine and 0.1 mg Methadone.

• **In the urine:** 5.8 mg/kg Morphine.

• **In the bile:** 17 mg/kg Morphine.

• 91 mmol of chloride ion per litre was detected in blood from the left side of the heart and 77 mmol from the right side.

Questions posed by Ms Healy-Nash in her letter of instruction of 26th September 2022;

1. Was the level of Pentobarbitone, Codeine, Methadone, Morphine and/or Paracetamol detected in Mr Currie's blood and organs likely to have been lethal, either alone or in combination with each other?

Opioid toxicity- broad observations in this case

Codeine, morphine and methadone belong to a class of drugs called opioids, which bind to the same receptors in the central nervous system (CNS) and gut.

In my clinical experience and in the evidence from the medical literature, the timing of death within a few hours of receiving a lethal dose of opioid(s) and finding a post-mortem blood concentration of an opioid in blood in the toxic-fatal range are typical of deaths resultant from opioid toxicity (Baselt). I do accept that there can be overlap of toxic and fatal ranges of opioids for example in post-mortem blood, and that the blood concentration alone helps guide interpretation but is seldom definitive alone, unless extremely high blood concentrations are found.

The evidence I have examined indicates that Mr Currie was not opioid naïve (e.g. taking codeine at times according to friend's statements and police statements (e.g. 14/10/1988). As such he would have some physiological "tolerance" to the effects of opioid drugs.

In examining Mr Currie's potential susceptibility factors for opioid toxicity I note;

1. ***Mr Currie had no underlying respiratory disease***

Mr Currie had no underlying chronic obstructive pulmonary disease (bronchial obstruction or emphysema) [post-mortem report] – such conditions can render someone increasingly susceptible to the toxic effects of opioid drugs (AMH, 2022)

2. ***Body weight***

I note Mr Currie's body weight was 65 kg (post-mortem report). Body length 163 cm. Body Mass Index: 24.5 kg/m2 i.e. a healthy weight range. People with high BMI e.g. over 35 are more susceptible to the respiratory depressant effects of opioids.

3. ***Mr Currie had no established hepatic (liver) disease***

Mr Currie's liver showed mild bridging fibrosis on histology (PM report) but no pathological evidence of hepatic cirrhosis. As morphine is metabolised by the liver, patients with cirrhosis have longer half-lives of morphine in blood.

4. ***Mr Currie was not opioid naïve***

Mr Currie would have expected to develop pharmacological tolerance to the opioid drugs following regular use over weeks and months. This would make him relatively more tolerant to opioid drug effects than de novo users but not immune to toxic/ fatal doses.

Naloxone is a specific antidote for opioid toxicity. It is the allyl analogue of oxymorphone, a potent narcotic analgesic but is without agonist activity of its own. It is supplied as the hydrochloride salt in a 0.4mg/ml solution for parenteral injection; the usual adult intravenous dose is 0.4mg, repeated at frequent intervals as needed. Naloxone has been incorporated in oral tablets of certain opioids in amounts of 0.5-20 mg to discourage abuse (Baselt). A single oral extended-release dose of 20 mg in 24 healthy volunteers resulted in average peak concentrations of 0.07ng/L at 4 hours, with an elimination half-life of 9.9 hours (Smith et al, 2008). I note in this case that had there been earlier recognition of central nervous system or respiratory decline as a result of the opioid/ barbiturate abuse in Mr Currie, then an opioid antidote (naloxone may have been administered intravenously) and medical supportive care (e.g. respiratory support) would have been expected to be life-saving in this case.

Opioids and their mechanism of toxicity:

Morphine

Morphine sulphate pentahydrate is a water soluble salt of morphine that may be orally or parenterally administered (TGA.GOV.AU, AMH 2022). The oral dose forms are presented as immediate-release or modified-release formulations (AMH, 2022).

Morphine, when administered as morphine sulphate is about two-thirds absorbed from the gastrointestinal tract with the maximum analgesic effect occurring 60 minutes post-administration for the immediate-release oral formulations. Following oral administration of morphine, the extent of absorption is essentially the same for immediate or extended-release formulations, although the time to peak blood level (T

max) will be longer and the maximum concentration (C max) will be lower for formulations that delay the release of morphine in the gastrointestinal tract. Once into the blood stream the morphine is eliminated with an assumed half-life of 2-4 hours. The terminal half-life of morphine is 2-4 hours, however a longer term half-life of about 15 hours has also been reported in studies where blood has been sampled up to 48 hours (accessdata.fda.gov). Morphine pharmacokinetics are altered in patients with cirrhosis. Clearance was found to decrease with a corresponding increase in half-life.

Morphine remains a popular drug for treatment of moderate to severe pain, often by subcutaneous, intramuscular, intravenous routes of administration.

Therapeutic blood concentrations of morphine
A single 0.125 mg/Kg (8.75 mg for a 70 kg man) intravenous dose in 11 healthy adults gave an average serum concentration of 437 µg/L (i.e. 0.4 mg/L) at 0.5 minutes, with a rapid early decline to 23 µg/L by 2 hours (Aitkenhead et al, 1984).

8 opium-dependent men given a single 13 mg morphine dose developed peak plasma morphine concentrations that average 19 µg/L (range 9-28) at 1 hour (Somogyi et al, 2008). A single oral dose of 30 mg immediate-release morphine given to healthy adults resulted in peak plasma concentrations averaging 24 µg/L for morphine at 0.8 hours. Volunteers given a single oral 60 mg dose of a modified-release capsule exhibited peak plasma levels averaging 16, 81 and 456 µg/L at 7.9, 9.3 and 9.7 hours (Bochner et al, 1999). The apparent morphine elimination half-life for the modified-release preparation used in this study ("Kapanol") was 15-16 hours (Broomhead et al, 1997), but other sustained-release oral preparations such as oramorph and embeda were found to exhibit half-lives as short as 3.2 hours (Drake et al, 1996) or as long as 25 hours (Johnson et al, 2010). The oral bioavailability of morphine ranges from 15-64% and averages 38%; a 20-30mg oral dose in adult terminal cancer patients was sufficient to maintain serum morphine levels above 20 µg/L (considered to be analgesic) for 4-6 hours in most patients (Sawe et al, 1981). In adult cancer patients receiving 15 mg immediate-release morphine oral doses eery 6 hours (60 mg/day) for 5 days, steady-state plasma concentrations averaged 14 µg/L morphine (Hasselstrom et al, 1991). Adult cancer patients titrated to achieve pain relief with 60-180 mg daily of sustained-release morphine had trough serum concentrations averaging 19, 118 and 896 µg/L (Klepstad et al, 2000). Adult cancer patients receiving an average daily oral sustained-release morphine dose of 170 mg (range 10-1400) had average plasma levels at 1-2 hours post-dose of 36 µg/L (range 2.9-320 µg/L) for morphine.

The plasma half-life of morphine in adult surgical patients averages 1.8 hours for women and 2.9 hours for men (Rigg et al, 1978). The half-life is not significantly increased in renal failure patients (Aitkenhead et al, 1984), but is approximately doubled in cirrhotic subjects (Mazoit et al, 1987). The elimination of the active metabolite morphine-6-glucuronide (Hanks et al, 1987; van Dorp et al, 2006) is similar to that of morphine in patients with normal function, but may be prolonged in renal disease (Peterson et al, 1990). The majority of administered morphine is inactivated by conversion to morphine-3-glucuronide, most of which is excreted in the bile and eventually in the faeces. However there is substantial enterohepatic

circulation of conjugated and intestinally-deconjugated morphine which means that up to 87% of a morphine dose is eliminated in the 72 hour urine.

Opioid analgesics such as morphine act on opioid receptors in the central nervous system and gut (AMH, 2022). Therefore the adverse effects of therapeutic doses of opioid drugs include nausea, somnolence, dizziness, sweating, constipation and urinary retention (Baselt, AMH 2022). The affinity of individual opioid analgesics for receptors varies and opioids may act as pure agonists (e.g. morphine) or partial agonist/ antagonists (e.g. buprenorphine).

Toxic blood concentrations of morphine

Large doses (55-65 mg) of morphine given by intravenous infusion to adult surgical patients produced peak plasma concentrations of 800-2600 µg/L (0.8-2.6mg/L) with concentrations of 300-500 µg/L (0.3-0.5mg/L) still detected after 1.5 hours; this amount of drug produced profound respiratory depression in all patients and assisted ventilation was required (Stanski et al, 1976).

Toxic effects of morphine use include pupillary constriction, constipation, urine retention, nausea, vomiting, drowsiness, dizziness, apathy, respiratory depression, hypotension, clammy skin, coma and pulmonary oedema (Baselt). Impairment of cognition and motor control is demonstrable in healthy volunteers at plasma morphine concentrations equal or greater than 0.040 mg/L (Kerr et al, 1991). Blood morphine averaged 0.045 mg/L (range 0.017-0.104) in 5 injured operators of motor vehicles (Van der Linden et al, 2013). The UK established a threshold of 0.08 mg/L for morphine in blood as indicative of impaired driving ability (UK GOV 2014).

Doses of morphine of greater than 30 mg parenterally and 100 mg orally are toxic to the non-tolerant adult.

A 45 year old woman who intentionally administered an oral overdose manifested coma, hypoxia, cerebral oedema and a serum morphine level of 0.19 mg/L (Friedrich et al, 2013). A 46 year old woman developed coma after ingesting at least 5 g of prolonged-release morphine tablets but survived with treatment; her plasma concentrations, first measured 60 hours post-ingestion were 0.62, 6.2 and 11 mg/L (Westerling et al, 1998).

Fatal blood concentrations of morphine

Death may occur following oral doses of 120 mg or more (Baselt).

Chan et al 1986 reported the deaths of two men involving oral or intravenous morphine administration with findings of 0.07-0.35 mg/L unconjugated morphine in blood.

Felby et al reported 10 adult fatalities after intravenous morphine with average morphine blood concentration 0.7 (range 0.2-2.3).

A woman found dead after apparent acute oral overdosage with immediate-release tablets had post-mortem blood morphine concentration of 59 mg/L (Lichtenwalner et al, 2010).

Morphine may exhibit post-mortem redistribution; heart:femoral blood concentration ratios averaged 1.2 (range 0.05-2.8) in a series of 24 deaths (Hepler et al, 2004), 2.2 (range 1.0-5.8) in a series of 10 cases (Dalpe-Scott et al, 1995) and 2.2 (range 0.2-9.2) in 30 other cases (Logan and Smirnow, 1996). Post-mortem femoral blood morphine level did not change significantly during 24 hours of cadaver storage at 4 degrees C (Hargrove and Molina, 2014).

In overdose opioids cause stupor, coma, muscle flaccidity, severe respiratory depression, hypotension and cardiac arrest. Pupillary constriction is common.

The post-mortem morphine levels in blood of Andrew Currie were 0.07 mg/L. This represents a therapeutic level of morphine in blood and was likely significantly contributory to his death. Morphine has a short half-life of elimination from blood (a few hours). As explained below under "Codeine" the most likely source of the morphine is as a metabolite of codeine, because of the ratio of its concentration to the parent drug.

In my opinion, morphine (likely secondary to codeine overdose, and produced by codeine's metabolism into morphine by the liver) found in therapeutic concentrations at post-mortem was a contributing factor to death in this case. This is because of the effects of morphine to cause sedation. Morphine also reduces the respiratory rate which cause hypoxia, making impact of the aspiration on oxygen levels in the blood more severe. The presence of methadone in therapeutic concentrations (see below), morphine in therapeutic concentrations and codeine in toxic/ fatal doses (see below) would have also added to the risk of sedation in Mr Currie.

Methadone

'Methadone has the pharmacologic properties of morphine and is approximately equipotent as an analgesic (Baselt).

Unlike morphine however, methadone produces marked sedative effects with repeated administration as a result of drug accumulation. Whereas heroin is short-acting, methadone is long-acting and effective orally. Methadone's half-life averages from 8-59 hours but it can last up to 130 hours in some people, in comparison to its analgesic effects which usually lasts only 4-8 hours (US FDA, Eap et al, 2002). This unusual pharmacokinetic profile can contribute to an unpredictable accumulation of methadone. Methadone plasma half-life, once stabilised in those on methadone maintenance programs, averages 24-36 hours with a range of 13-50 hours, making it a useful once daily medication as compared with morphine or heroin. However, up to 10 days of methadone maintenance treatment may be needed to achieve steady state and before that new patients are at risk of fatal overdose.

Doses of 30-40 mg of methadone prevent most withdrawal symptoms and craving, but are not high enough to block the reinforcing effects of high doses of potent heroin. Methadone is excreted primarily in the urine and is an agonist at li and 8 opiate

receptors. Methadone is primarily metabolised through CYP3A4 enzymes. Medications that inhibit CYP3A4, use of alcohol or severe liver disease increase the risk of overdose. Serotonin re-uptake inhibitors (e.g. fluoxetine) may increase methadone levels and sedation. Methadone should be avoided in severe liver disease (not found at post-mortem in Mr Currie).

The span of blood concentrations of victims of methadone overdosage overlaps that of methadone maintenance subjects.

Therapeutic blood concentrations of methadone

A single 10 mg oral dose given to 8 healthy younger adults produced an average peak plasma concentration of 43 µg/L (0.043 mg/L) at 2.1 hours, while the same dose administered intravenously to the same subjects resulted in an average peak level of 135 µg/L (0.135 mg/L) when first measured at 2 minutes post-injection; elimination half-lives averaged 34 hours for both routes of administration. The oral bioavailability of the drug averages 85% (Dale et al, 2022). Plasma methadone concentrations in adult cancer patients reached an average peak of 34 µg/L at 50 minutes after a 10 mg intramuscular injection (Grabinski et al, 1983).

Twelve older adult chronic pain patients receiving 10-100 mg daily oral methadone doses for 9 months had trough serum concentrations ranging from 114-551 µg/L (0.114 mg/L) for methadone (Fredheim et al, 2007). With chronic administration of 100-120 mg daily oral doses of the drug to 5 tolerant younger men, the plasma concentration again peaked at 4 hours, with an average value of 830 µg/L (range 570-1060), and declined to 460 µg/L (range 280-790) 24 hours after the last dose (average plasma half-life of 25 hours) (Inturrisi and Verebely 1972). The plasma half-life averaged 20 hours in 5 healthy subjects during conditions or acid urine and 42 hours in the same subjects when the urine was maintained alkaline (Nilsson et al 1982). Plasma methadone concentrations in patients on maintenance therapy increased by an average of 263 µg/L (0.263 mg/L) for every 1mg/Kg increase in oral dosage (Wolff et al, 1991). CYP3A4 liver enzyme activity has a modest effect on the rate of methadone metabolism (Shiran et al, 2008).

“The adverse effects of methadone therapy in therapeutic doses include sedation, dizziness, nausea, weakness, diaphoresis, anorexia, visual disturbances, headache, insomnia, constipation, bradycardia, palpitations and respiratory depression (Baselt, Els et al, 2017).

Toxic and fatal blood concentrations of methadone

A 60 mg dose given to a 37 year old former addict caused coma and severe hypotension; his blood methadone concentration was 0.25 mg/L at 10 hours (Heggs et al, 2008). Blood concentrations in 114 impaired drivers averaged 0.26 mg/L (Jones et al, 2007).

Methadone concentrations in fatalities reported in the medical literature averaged 1.0 mg/L in blood (range 0.4-1.8) (Manning et al, 1976). Blood methadone concentrations averaged 0.28 mg/L (range 0.006-3.1) in 59 adult victims of fatal methadone overdosage, compared with an average of 0.11 mg/L (range 0.03-0.56) in controls (Worm et al, 1993). Importantly, the span of blood concentrations of victims of methadone overdosage overlaps that of methadone maintenance subjects, and it's difficult if not impossible to distinguish between the two on this basis alone (Baselt). In another study, post-mortem blood methadone concentrations averaged 0.70 mg/L in 16 victims of fatal overdosage and 0.64 mg/L in 35 individuals whose deaths were not drug-related (Baker and Jenkins, 2008). Post-mortem blood methadone concentrations in 13 methadone maintenance patients who died of accidental methadone overdose averaged 1.3 mg/L (range 0.18-4.0), while 11 maintenance patients whose deaths were not drug-related had blood methadone levels averaging 1.1 mg/L (range 0.18-3.0) (Gagajewski and Apple, 2003).

Opioid-induced respiratory depression, the primary cause of opioid-induced death, is the neural depression of central respiratory drive which, together with a decreased level of consciousness, causes ventilatory insufficiency (Baldo and Rose, 2022). The risk of arrhythmias due to long QT has been raised in respect of methadone but the incidence is not currently well characterised. Ventricular arrhythmia has been reported in methadone maintenance patients receiving an average daily oral dose of 400 mg (Krantz et al, 2002).

Variability of responses to opioids and individual differences in physiological and neurological states (e.g. sleep-disordered breathing, concurrent drug administration) add to the risk.

Collapse or sudden death can occur in addicts started on a methadone maintenance program; this may be due to high methadone dose, accumulation where renal or hepatic injury is present or where an interaction may have occurred in people taking multiple illicit drugs. An overdose of methadone is characterised by;

- Stupor
- Pinpoint pupils
- Slow pulse and shallow breathing (respiratory depression)
- Low body temperature
- Low blood pressure, poor circulation
- Cold clammy skin with bluish tinge (cyanosis)
- Seizures
- Coma

Naloxone is a specific antidote and can be life-saving if given early in the course of overdose. Death in adults from methadone overdosage are common, and lack of tolerance was considered to play a major role in many (Greene et al, 1974).

Thus, it can be seen that Mr Currie's blood concentration of methadone of 0.12 mg/L (120 µg/L) was in the therapeutic range but below either the toxic or fatal ranges. Alone it would not be expected to result in clinical opioid toxicity effects (resulting in death predominantly due to respiratory depression) but would contribute to overall opioid toxicity when combined with other opioid drugs e.g. codeine and methadone.

Methadone may exhibit post-mortem redistribution; heart: femoral concentration ratios averaged 1.1 (range 0.8-1.4) in 5 cases (Prouty and Anderson, 1990)" Post-mortem redistribution occurs in vivo when the drugs move from organs of high drug concentrations down a concentration gradient into blood. The time for this to occur was about 4-5 days in the case of Mr Currie and hence, post-mortem redistribution could theoretically have occurred to some degree. This means that the blood samples results reported in the analytical toxicology report might be up to an average of 10% higher (in the case of methadone) than the concentrations in Mr Currie's blood at or around his time of death. **The recognition of possible post-mortem re-distribution effects does not change my conclusions that the concentration of methadone found in Mr Currie at post-mortem was likely in the therapeutic range.**

Post-mortem tissue concentrations of methadone in fatalities due to methadone
In a series of 10 young adult fatalities attributed to methadone, it was found that liver was the tissue with the highest concentration of those studied (Manning et al, 1976);

Drug	Blood	Brain	Liver	Bile	Kidney
Methadone average mg/L or mg/Kg	1.0	1.0	3.8	7.5	2.9
Methadone range	(0.4-1.8)	(0.5-1.4)	(1.8-7.5)	(2.9-18.0)	(1.1-6.0)

The finding of a liver methadone concentration of 0.36 mg/Kg in Mr Currie is not in the range seen in fatalities due to methadone.

Pentobarbitone
Pentobarbitone is a short-acting barbiturate used clinically as a sedating-hypnotic agent. It occurs in capsule/tablet, suppositories and parental injections forms. A normal adult dose is 15-200mg orally, rectally or by intramuscular or intravenous injection. The injectable solution contains 40% propylene glycol.

Therapeutic blood concentrations of pentobarbitone
After a 5 minute intravenous infusion of 50 mg in 5 healthy men, plasma pentobarbitone concentrations averaged 1.2 mg/L (range 1.1-1.3) at 0.08 hours,

declining to 0.54 mg/L by 1 hour and 0.27 mg/L by 24 hours (Smith et al, 1973). Plasma concentrations averaged 3 mg/L at 6 minutes after intravenous injection of 100mg of pentobarbitone in 7 healthy adults and fell to 1.6 mg/L by 1 hour, when they began to decline with a half-life of 22 hours (Ehmebo, 1974). A single oral 100 mg dose given to healthy subjects produced peak serum pentobarbitone concentrations of 1.2-3.1 mg/L at 0.5-2.0 hours after administration; these levels diminished slowly, and after 48 hours an average serum concentration of 0.3 mg/L was found (Sun and Chun, 1977). Estimates of the plasma half-life of pentobarbitone have ranged from 15-48 hours, with the average between 20 and 30 hours (Breimer, 1977). Oral administration of 600 mg of the drug to 5 healthy young men over a 3 hour period produced a maximal average blood concentration of 3.0 mg/L (range 1.8-4.7) by 0.5 hours after the last portion; this level remained unchanged by 4.5 hours and declined to 1.5 mg/L (range 1.2-1.7) after 18 hours (Parker et al, 1970). The oral bioavailability of pentobarbitone is 100% (Doluisio et al, 1978).

Repeated intravenous doses of pentobarbitone, usually 100-200 mg every 30-60 minutes have been used to reduce intracranial pressure and lower cerebral oxygen demand in patients with severe head trauma., Reye's syndrome or anoxic brain damage. The doses are adjusted to maintain the plasma drug level at 25-40 mg/L, and therapy may continue for up to several weeks (Marshall et al, 1978, 1979).

Adverse reactions to pentobarbitone include somnolence, confusion, dizziness, ataxia and headache. Continuous intravenous infusion has caused lactic acidosis due to propylene glycol (the carrier) accumulation (Miller et al, 2008).

Toxic blood concentrations of phenobarbitone

An impaired driver was found to have a blood pentobarbitone level of 7.5 mg/L (DiGregorio et al, 2001). Two comatose young adults who survived intentional overdosage with veterinary pentobarbitone solutions had pentobarbitone levels of 7.8 mg/L in serum or 26 mg/L in blood (Cantrell et al, 2010; Jang et al, 2011).

A plasma concentration of 28 mg/L was seen in a comatose patient who regained consciousness when the level fell to 13 mg/L after 24 hours (Prescott et al, 1973). In 7 other comatose adult victims of acute intentional oral overdosage, serum or plasma pentobarbitone concentrations averaged 33 mg/L (range 13-85) when first measured 2-24 hours post-admission; all patients recovered within 2-7 days (Scala-Bertola et al, 2012; Tamlihat et al, 2013; Hatali et al, 2014; Plumb et al, 2014; Arens and Mollin 2015; Crellin et al, 2015; Lasala et al, 2015).

Fatal blood concentrations

A 38 year old veterinarian who self-injected 5000 mg of the drug intravenously was found comatose and died 13 days later; on day 2 of his hospitalisation his serum pentobarbitone was 57 mg/L (Zanife et al, 2012). In 61 adult fatalities attributed to pentobarbitone, post-mortem blood concentrations averaged 40 mg/L (range 12-112)

(Rehling, 1967). In another 55 adult cases, blood concentrations averaged 30 mg/L (range 5-169) and liver concentrations averaged 130 mg/Kg (range 23-550) (Baselt and Cravey, 1977). The estimated lethal dose as established by investigation of these cases has ranged from 2-10 g (Cravey et al, 1977). In 3 adult fatal overdoses in which pentobarbitone and 3'hydroxypentobarbitone concentrations were measured by gas chromatography, the following tissue distribution was observed(mg/L or mg/Kg) (Robinson and McDowall, 1979):

Drug	Blood	Lung	Liver	Kidney	Urine	Gastric
Pentobarbitone average	29	35	77	28	25	325 mg
Pentobarbitone range	(10-51)	(16-51)	(20-165)	(18-46)	(5-62)	(74-550)
Hydroxypentobarbitone average	1.3	8	7	6	74	0
Hydroxypentobarbitone range	(0-4)	(4-10)	(5-9)	(4-7)	(65-82)	(0)

Pentobarbitone may exhibit postmortem redistribution; heart/ femoral blood concentration ratios averaged 1.3 (range 1.0-1.7) in 3 deaths (Prouty and Anderson 1990; Han et al, 2012).

Overdosage of pentobarbitone may lead to respiratory depression, hypotension, coma and death.

Mr Currie had 12 mg/L of pentobarbitone in his post-mortem blood which is in the toxic to lower end of the fatal ranges. He had 43 mg/Kg of pentobarbitone in his liver which is in the fatal range (please see table above). Mr Currie had 42 mg pentobarbitone in his stomach contents which confirms ingestion as at least one route of exposure to the drug. The source of the phenobarbitone found in Mr Currie is unknown. It is not a drug of recreational use.

Codeine

Codeine is a narcotic analgesic and is considered to be 1/10 or 1/16 as potent as morphine on a dose per Kg basis.

"Therapeutic" blood concentrations of codeine

- "An average peak serum codeine concentration of 30 µg/L was found in two subjects 2 hours after oral administration of 15 mg of codeine base (Schmerzler et al, 1966)."
- "8 healthy adults given 30mg oral codeine had peak plasma levels of 67 µg/L for codeine, 968 µg/L for codeine-6-glucuronide and 54 µg/L for morphine-3-

glucuronide; elimination half-lives for the 3 species averaged 1.5, 2.8, 1.7 hours respectively (Vree et al 1992)."

- "Codeine concentrations in 20 subjects after the oral administration of 60 mg of the drug reached an average peak of 134 µg/L at 1 hour, declining with an average half-life of 2.4 hours (Findlay et al, 1978)."
- "A single oral dose of 120 mg given to healthy adults produced peak plasma codeine and norcodeine levels averaging 470 and 30 µg/L respectively at 1.2 and 1.5 hours post-administration (Kim et al, 2002).

"Toxic" blood concentrations of codeine

- "A 62 year old developed coma and respiratory failure after 25 mg three times per day for three days codeine dosing. His initial plasma levels were 114 µg/L codeine, 361 µg/L codeine-6-glucuronide, 80 µg/L morphine, 580 µg/L morphine-3-glucuronide and 136 µg/L morphine-6-glucuronide (Gashe et al, 2004)."
- "20 impaired motor vehicle operators had blood codeine averaging 213 µg/L (range 146-279) (Bachs et al, 2003)."
- "Blood codeine concentrations of 2.6 and 7.0 mg/L were found in two men arrested for impaired driving (Cosbey 1983; Gjerde and Morland 1991)."
- "Serum concentrations exceeding 5.0 mg/L were seen in a comatose adult who had self-administered 750-900 mg codeine intravenously; consciousness returned three days later when the serum level fell below 1.3mg/L (Huffman and Ferguson, 1975)."

"Fatal" blood concentrations of codeine

"The acutely lethal dose of codeine has been estimated at 0.5-1.0g. Doses of this magnitude may cause unconsciousness and convulsions, and death from respiratory failure may result in 2-4 hours." (Baselt).

- "Post-mortem blood codeine concentrations in 8 adults succumbing to codeine overdosage ranged from 1.4-5.6 mg/L (Wright et al, 1975)."

- "Baselt summarises data from 11 cases in which codeine was implicated in death where concentrations exceeded 1mg/L and found the average codeine was 2.8 (range 1.0-8.8 mg/L) and morphine was 0.2 (range 0-0.5 mg/L). Codeine may be subject to post-mortem redistribution."

The analytical toxicology report on Mr Currie demonstrates 3.2 mg/L of codeine present. This indicates codeine in toxic to fatal ranges. Adverse effects of codeine therapy include nausea, vomiting, sedation, dizziness, and miosis (small pupils), low blood pressure on standing, urine retention and respiratory depression.

On autopsy 11 mg/Kg codeine and 0.2 mg/Kg of morphine was found in Mr Currie's liver. Nakumura et al 1976 described a series of 39 adult fatalities in which

codeine was implicated. The following table summarises the data from 11 cases in which the blood codeine concentration exceeded or equalled 1.0 mg/L;

Drug	Blood	Bile	Liver	Kidney	Urine	Units mg/l or mg/kg
Codeine average	2.8	18	6.8	12	104	
Codeine Range	(1-8.8)	(5-43)	(0.6-45)	(2.3-36)	(29-229)	
Morphine average	0.2	38	1.5	2.0	20	
Morphine range	(0-0.5)	(3.1-117)	(0-63)	(0.3-5.2)	(0-58)	

As codeine is biotransformed in man via o-demethylation to morphine, the ratios of codeine to morphine exhibited in Mr Currie's liver suggest that the source of morphine found in the deceased results from metabolism of codeine into morphine, rather than morphine from an exogenous source (i.e. unlikely to have been directly injected or ingested). The finding of morphine in post-mortem bile of 17 mg/kg and urine of 5.8 mg/Kg in Mr Currie, together with no morphine detected in the stomach at post-mortem is also in keeping with the pattern of codeine metabolism to morphine, rather than extraneous administration of morphine by or to Mr Currie. The absence of morphine in the stomach also suggests ingestion was unlikely.

Paracetamol

< 5 mg/L represents a therapeutic dose of paracetamol. No paracetamol was quantified in the post-mortem blood. Mr Currie's liver at post-mortem did not show signs of paracetamol-induced liver injury.

Summary of post-mortem toxicology findings

Pentobarbitone was found in toxic to lethal concentrations in Mr Currie's post-mortem blood and within the fatal range in his liver. Phenobarbitone would cause significant CNS and respiratory depression. Alone it would be fatal, but when combined with the codeine (in toxic to fatal ranges), methadone (in the therapeutic range) and morphine (in the therapeutic range) would have added effects on CNS and respiratory depression caused by all these opioid drugs.

In finding a post-mortem blood concentration of codeine well into the potentially toxic and fatal lethal ranges in Mr Currie, it is likely that opioid toxicity (i.e. CNS and respiratory depression) was the direct cause of his death together with a fatal dose of pentobarbitone also causing CNS and respiratory depression. One opioid (codeine) was found in the toxic to lethal ranges in Mr Currie. In combination with other opioids in this case they would likely cause opioid toxicity i.e. respiratory and CNS depression. 47 mg of codeine was found in Mr Currie's stomach contents, confirming ingestion as a likely source of the drug.

The post-mortem blood finding of 0.07 mg/L of morphine (in the therapeutic range – likely as a metabolite of codeine) and methadone 0.12 mg/L in the therapeutic range indicate it is very likely that codeine and methadone (opioid) administration significantly contributed to Mr Currie's demise from an ingested overdose of both codeine and pentobarbitone.

Mr Currie most likely died as a consequence of codeine and pentobarbitone oral overdosage, on a background of methadone use. But for the presence of the codeine and pentobarbitone in overdose Mr Currie would have been expected to survive.

2. Which, if any, of the substances found in Mr Currie's toxicology results can be accounted for by the ingestion of Nembudeine prior to his death?

As articulated under the answer to question 1 above, Nembudeine (a trade name for Codeine) ingestion would result in the codeine and its metabolite morphine found at post-mortem in the case of Mr Currie.

3. Which, if any, of the substances found in Mr Currie's toxicology results suggest separate ingestion of substances? Are you able to provide an opinion on the time period and/or manner of ingestion of these substances?

The pentobarbitone, codeine and methadone are each separate drug moieties (the latter two both being of the opioid class of drugs that bind to the same opioid drug receptors). I cannot ascertain from a single post mortem sample and the history available whether these three drugs were co-ingested or co-administered concurrently, or taken separately, or on more than one occasion. I note however that Mr Currie was alive long enough for his liver to metabolise some codeine that had been taken into morphine and that both codeine and pentobarbitone were both found in significant quantities in Mr Currie's stomach contents at post-mortem, indicating that full absorption had not yet taken place at the time of death.

4. What is the significance, if any, of the chloride ion detected in Mr Currie's blood results?

Any laboratory test can be subject to error, and normally we would expect left and right heart blood electrolyte concentrations, including chloride concentrations, to be essentially similar on both sides of the heart in a well and living person.

Intriguingly, in this case if the laboratory results were correct then the right heart blood had a low/normal sodium ion concentration of 91 mmol/ L (normal range approx. 95-105 but individual laboratory reference ranges do vary) and the left heart blood had a reported reduced chloride ion concentration of 77 mmol/L. This creates a hypothesis of whether lactic acidosis occurred or whether propylene glycol (often present as a carrier in phenobarbitone intravenous preparations) has created an anion gap

acidosis. I cannot confirm this hypothesis as I do not have full urea and electrolytes and blood gas and plasma osmolar results. The disparity between right and left heart chloride concentrations reported in this case could reflect that blood from the liver and gut drains to the right heart first (and reflects the uptake of drugs and the effects of their carrier molecules first). This is speculative on my part rather than strong clinical evidence.

5. Please provide any other comment, within the area of your expertise, regarding the likely cause of Mr Currie's death.
Nil else to note.

I wish to pass on my condolences to the family for their loss.

I, Professor Alison Jones, acknowledge for the purpose of Rule 31.23 of the Uniform Civil Procedure Rules 2005 that I have read the Expert Witness Code of Conduct in Schedule 7 to the said rules and agree to be bound by it.

Yours sincerely

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