IN THE CORONERS COURT
OF VICTORIA
AT MELBOURNE

Court Reference: COR 2012 4819

FINDING INTO DEATH WITHOUT INQUEST

Form 38 Rule 60(2)
Section 67 of the ***Coroners Act 2008***

I, AUDREY JAMIESON, Coroner having investigated the death of ERIC HORACE JULIEN

without holding an inquest:
find that the identity of the deceased was ERIC HORACE JULIEN
born on 1 January 1926
and the death occurred on 13 November 2012
at the Monash Medical Centre, 246 Clayton Road, Clayton, 3168

from:

1 (a) Acute on chronic renal failure
1 (b) Rhabdomyolysis
1 (c) Drug interaction (Simvastatin and Clarithromycin)

Pursuant to Section 67(2) of the **Coroners Act 2008**, I make these findings with respect to the following circumstances:

1. Mr Eric Horace Julien was 86 years of age at the time of his death. He was a retired engineer and lived with his wife, Mrs Freda Julien, in Springvale South. His medical history included chronic renal failure with a creatinine of 150umol/L[1] in 2011, hypercholesterolaemia,[2] type II diabetes requiring insulin, hypertension,[3] coronary artery bypass graft surgery (1975 and 2000) and a cardiac pacemaker inserted in 2009. He was prescribed Simvastatin to treat his hypercholesterolaemia.

[1] Normal creatinine ranges from 45-80umol/L.

[2] Hypercholesterolemia refers to levels of cholesterol in the blood that are higher than normal.

[3] Hypertension is a blood pressure greater than 140/90mmHg consistently.

2. On 10 October 2012, Mr Julien presented to his General Practitioner (GP) Dr Anthony Chan with a three-week history of a productive cough and flu-like symptoms. Dr Chan diagnosed Mr Julien with a chest infection and prescribed antibiotic Amoxycillin 500mg three times daily (TDS).

3. On 17 October 2012, Mr Julien represented to Dr Chan, and reported worsening flu-like symptoms with increased coughing and copious sputum production. On examination, Dr Chan found Mr Julien had worsening crepitations on his lung bases and therefore changed the antibiotics from Amoxycillin 500mg TDS to two courses of Clarithromycin[4] 250mg twice daily (BD).

4. On 7 November 2012, Mrs Julien contacted Dr Chan, as her husband was displaying flu-like symptoms and was experiencing back and leg pain, with decreased mobility. In addition, blood tests ordered by Dr Chan showed Mr Julien had severe abnormal liver function. Dr Chan accordingly advised Mrs Julien to have her husband transported to hospital by ambulance.

5. Later that day, Mr Julien was admitted to the Monash Medical Centre (MMC) Emergency Department. Mr Julien was diagnosed with acute on chronic renal failure, generalised muscle weakness and myalgia.[5] In addition, Mr Julien had word finding difficulty, dysphasia,[6] and slurred speech.

6. Mr Julien was transferred to the general ward. On the ward, Mrs Julien requested that her husband be documented as 'not for resuscitation and have no invasive procedures performed'. Mr Julien's renal function continued to deteriorate over the following days as did his neurological function.

7. On 13 November 2012 at approximately 5.17pm, staff initiated a 'medical emergency team' (MET) call, as Mr Julien was unresponsive. He was not resuscitated in accordance with his wife's wishes and was pronounced dead at 5:27pm.

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[4] Clarithromycin is in a class of medications called Macrolide antibiotics. It works by stopping the growth of bacteria.

[5] Muscle pain and is a symptom of many diseases and disorders.

[6] Dysphasia is a partial or complete impairment of the ability to communicate resulting from brain injury.

INVESTIGATION

8. Dr Heinrich Bouwer, Forensic Pathologist with the Victorian Institute of Forensic Medicine (VIFM), performed a post mortem examination on the body of Mr Julien, reviewed a post mortem CT scan and reviewed the Victorian Police Report of Death, Form 83. Anatomical findings included renal scarring and histological examination showing marked nephrosclerosis[7] together with acute tubular necrosis,[8] consistent with acute rhabdomyolysis.[9] Additional findings included gastrointestinal haemorrhage, cardiomegaly, coronary artery atherosclerosis, remote myocardial infarction, lung adhesions and a thyroid colloid nodule. No evidence of injury was identified.

9. In addition, a post mortem muscle biopsy was referred to Associate Professor Penny McKelvie for special investigation and she reported that the muscle fibres showed prominent muscle fibre necrosis and degeneration consistent with recent toxic injury and rhabdomyolysis. Dr Bouwer commented that this finding is in keeping of the clinical diagnosis of rhabdomyolysis, consistent with a drug interaction between Simvastatin and Clarithromycin.

10. Toxicological analysis of blood and other bodily fluids retrieved post mortem demonstrated results consistent with severe renal impairment. No biochemical evidence of anaphylaxis was identified. Dr Bouwer ascribed the cause of Mr Julien's death to acute on chronic renal failure, secondary to rhabdomyolysis, as a consequence of a drug interaction (Simvastatin and Clarithromycin).

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[7] Kidney disease that is usually associated with hypertension; sclerosis of the renal arterioles reduces blood flow that can lead to kidney failure and heart failure.

[8] Medical condition involving the death of tubular cells that form the tubule that transports urine to the ureters while reabsorbing 99% of the water (and highly concentrating the salts and metabolic byproducts). Tubular cells continually replace themselves and if the cause of ATN is removed then recovery is likely. ATN presents with acute kidney injury (AKI) and is one of the most common causes of AKI.

[9] Condition in which damaged skeletal muscle tissue breaks down rapidly. Breakdown products of damaged muscle cells are released into the bloodstream; some of these, such as the protein myoglobin, are harmful to the kidneys and may lead to kidney failure. The severity of the symptoms, which may include muscle pains, vomiting and confusion, depends on the extent of muscle damage and whether kidney failure develops.

CPU Review

11. The Coroners Prevention Unit (CPU)[10] reviewed the appropriateness of prescribing Clarithromycin and Simvastatin concurrently by Dr Chan on behalf of the Coroner.

12. The CPU reviewed the Medical records from MMC, the Medical Deposition form the MMC and Dr Bouwer's medical examination report.

13. The review indicated that the concurrent use of these two drugs is contraindicated. Co-administration may significantly increase the plasma concentration of Simvastatin with an increased risk of muscular skeletal toxicity. This manifests as muscle pain or weakness associated with grossly elevated levels of creatinine kinase. Rhabdomyolysis is a rare reported complication, which may cause acute renal failure secondary to myoglobulinuria[11] and may result in death.

14. An extract from the Monthly Index of Medical Specialties (MIMS)[12] in the abbreviated prescribing information for Clarithromycin issues a warning that appears in the first paragraph:

> Contraindications, Macrolide hypersensitivity; concurrent treatment with Astemizole, Cisapride, Pimozide, Terfenadine, Ergotamine, Dihydroergotamine, Lovastatin, Simvastatin; severe hepatic failure with renal impairment.

15. In the full prescribing information from MIMS, the following information is provided:

    a. Clarithromycin/Contraindications:

       Clarithromycin is contraindicated as concurrent therapy with: Astemizole, Cisapride, Pimozide, Terfenadine, as this may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Concomitant administration of Clarithromycin and Ergotamine

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[10] The Coroners Prevention Unit (CPU) was established in 2008 to strengthen the prevention role of the coroner. The unit assists the coroner with research in matters related to public health and safety and in relation to the formulation of prevention recommendations, as well as assisting in monitoring and evaluating the effectiveness of the recommendations.

[11] The presence of myoglobin in the urine, usually associated with rhabdomyolysis or muscle destruction. Myoglobin is present in muscle cells as a reserve of oxygen.

[12] MIMS online, https://www.mimsonline.com.au, accessed on 22 October 2013.

or Dihydroergotamine is contraindicated, as this may result in ergot toxicity. Concomitant administration of Clarithromycin with Lovastatin or Simvastatin is contraindicated.

b. Clarithromycin/Interactions:

Hydroxymethylglutaryl coenzyme A reductase inhibitors. Concomitant use of Clarithromycin with Lovastatin or Simvastatin is contraindicated and treatment with these agents should be discontinued during Clarithromycin treatment. As with other Macrolides, Clarithromycin has been reported to increase concentrations of HMG-CoA reductase inhibitors. Rare reports of rhabdomyolysis have been reported in patients taking these drugs concomitantly. Patients should be monitored for signs and symptoms of myopathy.

c. Clarithromycin/Impaired renal function:

Clarithromycin is principally excreted via the liver and kidney. Caution is advised in patients with severe renal insufficiency. In patients with renal impairment, appropriate adjustments should be made when prescribing Clarithromycin. Treatment should not be continued beyond 14 days in these patients.

16. In 2011, Mr Julien had a Creatinine of 150umol/L and an eGFR of 37,[13] which indicates very poor glomerular filtration, which translates into poor kidney function.

17. The general practice medical records confirmed that Mr Julien was reviewed by Dr Chan in regards to flu-like symptoms, approximately three weeks before his death and prescribed Clarithromycin. The records also reflect that Mr Julien had been previously prescribed Simvastatin 40mg daily.

Request for statement

18. To understand Dr Chan's clinical decision-making process, a statement was obtained from him, specifically asking what prescribing guidance he sought.

19. In his statement dated 18 August 2013, Dr Chan explained that when he reviewed Mr Julien on 17 October 2012, the reasons why he changed Mr Julien's antibiotics from Amoxycillin

[13] Normal eGFR is >90ml per/min.

(Amoxil) 500mg TDS to Clarithromycin (Klacid) 250mg BD was because he considered that the Amoxycillin previously prescribed was ineffective in regards to Mr Julien's bacterial infection.

20. Dr Chan stated that at the time, he believed that Clarithromycin and Simvastatin could be used together with caution, but now appreciates that the combination of these medications is contraindicated.

21. Dr Chan states that he usually uses MIMS as a reference system prior to prescribing medications to check for contraindications, but on this occasion, he did not check the MIMS as he has prescribed Clarithromycin previously to Mr Julien without any problems.

22. Review of Dr Chan's statement revealed a lack of appreciation on Dr Chan's behalf that the combination of Clarithromycin and Simvastatin was unsafe and contraindicated, as he had prescribed this for Mr Julien previously. It appeared that Dr Chan placed Mr Julien at an unnecessary risk and that he should have ideally ceased Mr Julien's Simvastatin while he was administered Clarithromycin, as recommended in MIMS.

23. Most patients who concurrently receive Clarithromycin and Simvastatin do not have a severe reaction, and it is not possible to determine ahead of time which patients will have a severe reaction with adverse outcomes.[14] While Dr Chan might have been reassured that Mr Julien had not had problems taking the drug previously, the prescribing information in MIMS is clear that the two drugs should not be prescribed concurrently.

Mention Hearing

24. A Mention Hearing was called on 5 May 2014 to address the above concerns regarding Dr Chan's prescribing methods, to provide Dr Chan with a chance to be heard in the context of my intention to make an adverse comment regarding his prescribing methods, and to ascertain whether Dr Chan had employed strategies to improve his practice. Dr Chan was represented at the Mention Hearing by Ms Erin Gardner of Counsel.

25. Ms Gardner conveyed her client's deep regret and sadness in relation to Mr Julien's death, and restated Dr Chan's frank and open acknowledgment of his prescribing error. Ms Gardner

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[14] Horn, J,R. Hansten, P. 2009, Drug Interactions decisions: Using Evidence to Weigh Risks. Published Online. http://www.pharmacytimes.com/publications/issue/2009/2009-01/2009-01-9970.

explained that Dr Chan accepts that he should have ideally ceased the Simvastatin whilst the Clarithromycin was being administered.

26. Ms Gardner explained that Dr Chan had obtained his Bachelor of Medicine and Bachelor of Surgery from Melbourne University in 1988, and attained his fellowship of the Royal Australian College of General Practitioners in 1993. He has been engaged in General Practice for 23 years, and at the Springvale Clinic for 19 years. Ms Gardner explained that the practice is a bulk billing practice, many of its patients are refugees, and that Dr Chan is one of the few GPs in the area who conduct home visits, including home visits for Transport Accident Commission and WorkCover patients. Dr Chan had never been the subject of any complaint or finding to the effect that he has provided care to a patient that was of lesser standard than that expected of a GP.

27. Ms Gardner explained that Dr Chan was Mr Julien's GP for 13 years and continues to be Mrs Julien's GP to date. All of the consultations proximate to Mr Julien's death had been home visits, and Dr Chan attended Mr Julien's home with a copy of his medical file, including his medication history.

28. Ms Gardner noted Dr Chan's usual practice when he is prescribing a new medication to a patient would be first to ask a patient whether they had taken the medication before, and if so, whether they had an allergic reaction to the medication. Dr Chan would then check MIMS to ascertain if the prescription was safe and appropriate in the circumstances.

29. Ms Gardner stated that Dr Chan had access to a hardcopy of MIMS handbook in 2012 and has a current subscription to this resource. He acknowledges that his prescribing Clarithromycin to Mr Julien in October 2012 was at odds with his usual practice, in that he did not check MIMS, and was unaware the two medications were contraindicated.

30. Ms Gardner explained how it was from Dr Chan's perspective that he came to make this error. Dr Chan first prescribed this combination of medication to Mr Julien in 2004 and in 2008 without incident. Ms Gardner highlighted the significance of these dates in that if one had consulted MIMS in 2009 and 2010, these two medications were not recorded as contraindicated at that time. Ms Gardner noted that the first such warning about the co-administration of the two medications was inserted in the 2011 edition of MIMS, and that the CPU report is couched in terms of the 2013 online MIMS version.

COMMENTS

Pursuant to section 67(3) of the **Coroners Act 2008**, I make the following comment(s) connected with the death:

31. I accept that I must evaluate Dr Chan's prescribing methods at the time of the incident and in the context of the historical development of MIMS. I accept that the circumstances of Dr Chan, having previously simultaneously prescribed Clarithromycin and Simvastatin to Mr Julien without incident at a time where doing so was not contraindicated, made it easy for Dr Chan to incorrectly assume in October 2012 that he was prescribing these medications in a safe manner.

32. While Dr Chan's mistake is in some respects understandable, it is nonetheless regrettable that, contrary to his usual practice, he failed to check MIMS in October 2012 when he prescribed Mr Julien with Clarithromycin and Simvastatin simultaneously.

33. I appreciate and commend the frankness and openness with which Dr Chan readily made concessions regarding his prescribing error, however this does not detract from the significance of this error, that I am satisfied was causal in Mr Julien's death.

34. Ms Gardner referred to an article mentioned within the CPU report that suggested that it is necessary for health professionals to be made aware of published clinical evidence about the risks of medication combinations, and that perhaps our altering systems are inadequate. I would however like to point out that this article, citing the example of prescribing these medications concomitantly, was published in 2009, and the prescribing error occurred in 2012, when the 2012 MIMS handbook clearly stated the dangers in co-administering these medications. I therefore do not consider that the prescribing error occurred in the context of Dr Chan not having ready access to this information.

35. The more preferable statement of this concept is that it is incumbent upon health professionals to check that their practice accords with known safe practice at the time, and to have easy access to (and to use) resources that guide safe prescribing methods. For those GPs engaging in home visits, such access is easily available through carrying hard copies of current MIMS (or similar) handbooks, or I believe also through applications downloaded (and regularly updated) on mobile telephones.

36. Ms Gardner informed me that Dr Chan now consults with the MIMS handbook each and every time he prescribes a medication to a patient irrespective of the patient's medication history or his knowledge of the patient. This is a practice that I consider prudent and would prevent a similar error from occurring in the future, and I am therefore satisfied that Dr Chan's commitment to this practice fulfils my statutory prevention role.

FINDINGS

I find that Dr Chan made a prescribing error in prescribing Mr Julien Clarithromycin whilst he was taking Simvastatin, and I further find that the administration of this combination of medications appears likely to have contributed to the condition that caused Mr Julien's death.

I am satisfied that Dr Chan has appropriately reflected on his prescribing methods and has committed to a practice that would prevent a similar prescribing error from occurring in the future.

I accept the medical cause of death as ascribed by Dr Heinrich Bouwer and find that Mr Eric Horace Julien died from chronic renal failure, secondary to rhabdomyolysis, as a consequence of a drug interaction (Simvastatin and Clarithromycin).

Pursuant to section 73(1) of the **Coroners Act 2008**, I order that these Findings be published on the internet.

I direct that a copy of this finding be provided to the following:

Mrs Freda Julien

Ms Lara Larking, TressCox Lawyers, on behalf of Dr Anthony Chan

Ms Erin Gardner of Counsel

Ms Susan Van Dyk, Medico Legal Officer, Monash Health

Australian Health Practitioners Regulation Agency

Police Coronial Support Unit

Signature:

AUDREY JAMIESON
CORONER
Date: **27 November 2014**