



FINDING OF INQUEST

An Inquest taken on behalf of our Sovereign Lady the Queen at Adelaide in the State of South Australia, on the 18th, 19th and 20th days of March 2013 and the 17th day of April 2014, by the Coroner's Court of the said State, constituted of Mark Frederick Johns, State Coroner, into the death of Cynthia Joy Werner.

The said Court finds that Cynthia Joy Werner aged 76 years, late of Playford Nursing Home, 1 Wilton Street, Davoren Park, South Australia died at Davoren Park, South Australia on the 19th day of December 2010 as a result of colchicine toxicity. The said Court finds that the circumstances of her death were as follows:

1. Introduction and reason for Inquest

- 1.1. Cynthia Werner was 76 years of age when she died on 19 December 2010. An autopsy was performed by Dr Jonathon Herbst under the supervision of forensic pathologist, Dr Karen Heath. The cause of death was given as colchicine toxicity, and I so find¹. Dr Heath explained in her evidence that colchicine is a naturally occurring substance derived from the plant known as the meadow crocus or Autumn Saffron. The substance colchicine can be extracted and is used in medications predominantly for the treatment of gout.
- 1.2. Ms Werner suffered from gout and it was this condition that led to the prescription of colchicine in her treatment. The evidence taken at this Inquest included that of Dr Heath, Ms Ailsa Bradfield, who is the Director of Nursing at Playford Village Nursing Home where Ms Werner was a resident, Dr Khoo who was the general practitioner who treated Ms Werner while she was at the nursing home, and two experts, Associate Professor Whitehead, specialist geriatrician, and Mr Van Den Berg,

¹ Exhibit C6

senior visiting rheumatologist. The evidence of the two experts about colchicine and its potential lethality is a matter that is not well understood within the medical community, according to those experts. The Inquest considered carefully the treatment provided by Dr Khoo and the care provided by Playford Village Nursing Home. I have no criticism of either Dr Khoo or the Playford Village Nursing Home. In my opinion this case provides an opportunity to illustrate the dangers of colchicine as an agent for the treatment of gout, and highlights certain ambiguities in some of the published medical guidelines that describe appropriate dosages for colchicine.

2. Background

- 2.1. Ms Werner had been a resident of another nursing home before Playford Village, having first been admitted to nursing home care on 8 April 2004. She became a resident of Playford Village Nursing Home in November 2009.
- 2.2. Ms Werner had an intellectual impairment since birth and her medical conditions included depression, hypertension, osteoporosis, an ankle deformity which she had had since birth, gastroesophageal reflux, hyperparathyroidism and gout.
- 2.3. On 25 March 2010 Dr Khoo attended on Ms Werner at the Playford Village Nursing Home. He noted that she had pain in her left hip and was unable to get out of bed, nor to weight bear. Ms Werner was admitted to the Lyell McEwin Hospital on that day with left hip pain for investigation. The admission note of the registrar on the following day notes extensive tophi on the left hand². The registrar arranged for an aspirate of the left knee joint to be performed and the result showed that uric acid crystals were present which confirmed the diagnosis of gout. Ms Werner was prescribed prednisolone 25mg for 5 days. She was transferred to the Modbury Hospital GEM Unit where she remained until 1 April 2010. The admission note at Modbury Hospital on 26 March 2010 recorded a plan to commence colchicine at 500mg, three times per day and if gastrointestinal symptoms occurred, the dose to be reduced to twice per day. On 30 March 2010 the records show that colchicine was ceased because of diarrhoea, a known side effect. The discharge summary, a copy of which was present in the nursing home records, states that she was initially treated with colchicine which was ceased after two days because of diarrhoea. It says that

² Tophi are subcutaneous large deposits of uric acid crystals which have a whitish appearance as they sit just below the skin. They are an indication of longstanding increasing burden of uric acid and while not always associated with acute attacks of gout, they are a strong predictive factor that this can, and might, occur – Exhibit C10

she was given prednisolone 25mg for 5 days with good effect, and was pain free on discharge and mobilising.

- 2.4. Ms Werner's next presentation to hospital was on 10 August 2010. The Playford Village Nursing Home notes showed that there had been a general deterioration in her mobility and cognitive state in the period leading up to that date. She was admitted initially under the care of the orthopaedic surgeons because it was thought that she might have septic arthritis of the right ankle. However, in the course of investigations she was found to have a urinary tract infection and, ultimately, after a repeat aspirate of the right ankle she was found to have uric acid crystals and a diagnosis of gout was made. She was transferred to a medical unit.
- 2.5. A medical registrar entry on 13 August 2010 noted that Ms Werner's renal function was not severely impaired³ and the plan was to start prednisolone as well as ibuprofen 40mg TDS. The following day colchicine was initiated at 500µg, three times per day. Prednisolone was continued as was ibuprofen. On 17 August 2010 Ms Werner was noted to be 'feeling okay' and the colchicine and ibuprofen were ceased. There was no evidence in the notes suggesting gastrointestinal upset having prompted the decision to cease colchicine.
- 2.6. In summary, on the second admission to the Lyell McEwin Hospital Ms Werner had colchicine on 14 August 2010 on two occasions, on 15 August 2010 on three occasions, on 16 August 2010 on three occasions and then it was stopped.
- 2.7. On Ms Werner's return to the nursing home on 19 August 2010 Dr Khoo prescribed allopurinol at an initial dose of 100mg per day and co-prescribed colchicine at one 500µg tablet per day. The allopurinol is a uric acid lowering therapy and was introduced to reduce the underlying problem which exposed Ms Werner to attacks of gout. I will describe the role of the colchicine and allopurinol in more detail below. It is sufficient for present purposes to note that it is common practice to introduce colchicine at a low dose to 'cover' the commencement of allopurinol in order to avoid the risk of an acute attack of gout being precipitated as a result of the introduction of allopurinol. The evidence showed that Dr Khoo's decision to use colchicine in this manner was appropriate and accepted practice.

³ Urea of 11.7 and creatinine of 79

- 2.8. Dr Khoo ceased the colchicine after two months. However, Dr Khoo did not alter the dosage of allopurinol: he maintained it at the initial dose.
- 2.9. The next matter of significance is that on 7 December 2010 Ms Werner complained of pain in her left hand. The nurses noted extreme swelling and pain and the South Australian Ambulance Service attended at the nursing home in order to assist in removing a ring from her finger. On 9 December 2010 Dr Khoo attended and noted that Ms Werner's hand remained swollen. On examination he noted chronic tophi involving both hands, worse on the left with tenderness. He diagnosed gout and commenced Ms Werner on prednisolone at a dose of 25mg daily, colchicine at 500µg three times per day and he increased the allopurinol dose from 100mg to 300mg per day.
- 2.10. On 11 December 2010 Dr Khoo contacted the nursing home to enquire about Ms Werner's response to the medication he had prescribed. He was informed that there had been some subsiding of the swelling, but that pain was continuing.
- 2.11. On 13 December 2010 Dr Khoo attended and examined Ms Werner. He noted that there was some subsiding of her right hand pain and swelling. He instructed that the prednisolone continue for seven days at 25mg and then be reduced for five days and then to cease.
- 2.12. The nursing home notes show that Ms Werner started to suffer from diarrhoea on 15 December 2010. Thereafter, she continued to suffer from diarrhoea and there are numerous entries in the notes evidencing this.
- 2.13. As I have said, Ms Werner died on 19 December 2010. The autopsy report noted that her blood contained colchicine at a level of .025mg per litre which was reported to be a potentially lethal concentration. The nursing home records showed that Ms Werner had received colchicine doses as follows: two doses on 9 December 2010, three doses on 10 December 2010, two doses on 11 and 12 December 2010 and then three doses a day from 13 December 2010 until it was discontinued on 18 December 2010 when a locum doctor was called. This doctor ordered the cessation of the colchicine and advised that Ms Werner should be transferred to hospital for review if she had not improved over the next 24 hours. Unfortunately, she died at 6am the following morning.

3. **Gout, colchicine and allopurinol**

- 3.1. Associate Professor Whitehead said that gout is a relatively common inflammatory arthritis that is caused by the deposition of uric acid crystals on the surface of joints. The uric acid crystals incite an inflammatory response in the body that leads to swelling and pain in the joints. It is considered a disorder of urate metabolism and is extremely painful⁴. Dr van den Berg elaborated. He said that neutrophils ingest the uric acid crystals in a process he described as digestive. They have digestive enzymes which normally function to clear foreign material including bacteria. Unfortunately, the uric acid crystal damages the neutrophils and the inflammatory enzymes are then leaked out. The inflammatory enzymes then attract further neutrophils into the joint. More and more neutrophils are recruited into the joint which then suffer the same fate and Dr van den Berg used the analogy of pouring petrol onto a fire. He said that colchicine's mode of action, although not completely understood, appears to impair the movement of neutrophils. It appears to paralyse the neutrophils so that they cannot get into the joint and this breaks the cycle he had described. He said that colchicine in his clinical experience is most useful if started really early in an attack⁵.
- 3.2. Associate Professor Whitehead said that in order to control the symptoms of gout and to reduce the levels of inflammation in the joints, there are three drugs that are generally used. The first are non-steroidal anti-inflammatory drugs such as brufen. The second are steroidal anti-inflammatory drugs such as prednisolone which Associate Professor Whitehead described as his drug of first choice. He said that both non-steroidal anti-inflammatory and steroidal anti-inflammatory drugs have side effects. However, it is his view that prednisolone is probably the safest of them because the non-steroidals can affect kidney function which is a problem in older people who often have compromised kidney function. He said that prednisolone if used in the long term can have a lot of side effects, but in the short term these can be managed and, usually, gout can be controlled in a relatively short period of time such as a few days⁶.
- 3.3. Associate Professor Whitehead said the third category of drug for the treatment of gout is colchicine. He said he does not use it because it produces the unacceptable side effect of diarrhoea.

⁴ Transcript, page 174

⁵ Transcript, pages 215-216

⁶ Transcript, page 175

- 3.4. In summary, Associate Professor Whitehead said that in hospital practice, prednisolone is the preferred treatment for gout and Dr van den Berg agreed⁷.
- 3.5. Associate Professor Whitehead described the strategies to reduce the risk of acute attacks of gout in a person with a history of gout. He said that a common approach is to use a class of drugs called xanthine oxidase inhibitors of which allopurinol is an example and is most widely used⁸. He said that allopurinol should be used between acute attacks. He said that it should not be started during an acute attack because, paradoxically, allopurinol can cause uric acid levels to rise transiently and may drive further crystal deposition into the joints. He said that once an acute attack has settled, a practitioner would generally start allopurinol at a low dose with the aim of reducing the uric acid level in the blood to less than .35mmol per litre. Associate Professor Whitehead confirmed that he would introduce colchicine as a preventative drug while initiating allopurinol to avoid the risk that the introduction of allopurinol might precipitate acute attacks of gout. In this instance colchicine is used at a low dose (.5mg daily) which is common practice and regarded as safe⁹. Associate Professor Whitehead said that he would continue the colchicine until the uric acid had achieved its target level¹⁰ or until symptoms of gastrointestinal upset occurred¹¹. Associate Professor Whitehead said that the allopurinol dosage should be titrated gradually to 200mg or 300mg after its initial introduction. He had no criticism of Dr Khoo's initial dosage of allopurinol, but said that it should have been increased in conjunction with monitoring blood levels of uric acid with a view to achieving the target level of .35mmol per litre. Interestingly, Dr van den Berg acknowledged in his oral evidence that it was not clear how far the learning behind the approach of titrating the allopurinol had penetrated the community of general practitioners as at 2010.

4. Unexpected deaths related to colchicine

- 4.1. Associate Professor Whitehead said that he did not believe that the relationship between excessive colchicine use and the risk of death was common medical knowledge. He said that he had canvassed some of his colleagues on this topic and that most of them were not aware of the relationship.

⁷ Transcript, pages 176 and 210-211

⁸ Transcript, page 176

⁹ Transcript, page 176

¹⁰ Transcript, page 177

¹¹ Transcript, page 177

- 4.2. Dr Heath in her evidence had noted that at autopsy, microscopic examination had revealed mitotic arrest¹². She said this is a phenomenon in which the normal process of cell division is stopped or arrested. She said that it is readily identifiable microscopically¹³. Dr Heath said that when the cells can no longer proliferate and divide, the cells most rapidly affected are those lining the mucosa or the lining of the gastrointestinal tract. She said because the gastrointestinal tract is the most susceptible to the effects of colchicine causing mitotic arrest, gastrointestinal upset, nausea, vomiting and profuse diarrhoea are early symptoms. She said the cells of the gastrointestinal tract eventually die and slough off and this is what leads to those symptoms¹⁴. Dr Heath said that colchicine toxicity goes on to cause multi organ failure as evidenced by acute renal failure, acute liver failure, respiratory failure and cardiac failure¹⁵. Dr Heath said that Forensic Science South Australia has previously seen two other cases of death due to colchicine toxicity. She produced an article 'Unrecognized fatalities related to colchicine in hospitalized patients'¹⁶.
- 4.3. Both in his extremely helpful report¹⁷ and his oral evidence, Associate Professor Whitehead acknowledged that he only had a vague awareness before seeing that article of the risk of multi organ failure from colchicine and that as a result of reading the article, he had changed his view about the matter¹⁸. He said that upon reading the paper it highlighted to him the important fact that there is a documented risk of death from using colchicine which was, in his opinion, not a well known fact amongst the medical community¹⁹. Indeed, the present case shows that colchicine was used twice in a public hospital setting with this patient. I make no criticism of that, but it demonstrates that colchicine use is, at the time of this Inquest, reasonably common in the public hospital system.
- 4.4. Associate Professor Whitehead said that in an older patient such as Ms Werner there are other factors involved. He noted that in the days prior to her death she had a blood test that revealed that she was quite low in potassium and also acidotic. He noted that normally an individual who is acidotic has elevated potassium levels, so the combination of low potassium in someone who is acidotic means there is quite a

¹² Transcript, page 11

¹³ Transcript, page 11

¹⁴ Transcript, page 11

¹⁵ Transcript, page 12

¹⁶ Clinical Toxicology (2011) 49, 648-652 by Mullins, Cannarozzi, Bailey and Ranganathan

¹⁷ Exhibit C10

¹⁸ To 178

¹⁹ Transcript, page 178

profound loss of potassium. He said this predisposes a person to cardiac arrhythmia²⁰. It was his opinion that the low potassium was attributable to the diahorrea, which in turn was attributable to the colchicine²¹.

- 4.5. Associate Professor Whitehead said colchicine is a very old drug that has been in use for many years. He said that it was well recognised for many years that if a patient developed diahorrea while on colchicine, the colchicine should be stopped²². However, this was more thought to be for the patient's comfort to alleviate the symptoms of diahorrea, than to avoid the risk of multi organ failure from colchicine²³.
- 4.6. Associate Professor Whitehead was not critical in any way of Dr Khoo. He said that it would have been preferable to have escalated the dose of allopurinol while monitoring the uric acid levels and titrating the dose to achieve the target urate levels. He also thought that for acute attacks he would have initiated prednisolone alone, but understood why Dr Khoo had acted differently, particularly bearing in mind the fact that Ms Werner had been treated with colchicine in two public hospital settings. Associate Professor Whitehead said that he thought that it is unreasonable to expect that Dr Khoo would know about the risk of death from colchicine which is not widely known in the clinical community, even amongst specialists²⁴.
- 4.7. Associate Professor Whitehead said that the allopurinol dosage should not have been increased at the time of Ms Werner's acute attack as it might exacerbate the attack²⁵. Dr van den Berg's evidence was that in his judgment it is not widely appreciated within the medical profession generally, how toxic colchicine can be²⁶. Finally, for completeness, I note that Dr van den Berg further elaborated upon the necessary allopurinol treatment in a patient such as Ms Werner. He said that the presence of tophi suggested that Ms Werner had a large whole body burden of uric acid crystals. He said that it would be unrealistic to expect to be able to reduce that body burden in anything under several years, even if the serum uric acid level came down to .36mmol per litre or below. He said that the crystals need to be dissolved and excreted by the

²⁰ Transcript, page 179

²¹ Transcript, page 180

²² Transcript, page 189

²³ Transcript, page 181

²⁴ Transcript, page 187

²⁵ Transcript, page 188

²⁶ Transcript, page 220

kidney and in his conservative estimate this would take probably two or three years, even at the desirable uric acid level of .36mmol per litre or below²⁷.

5. MIMS and Australian Medicine Handbook - Discrepancy

- 5.1. Associate Professor Whitehead noted that the recommendations in the Australian Medicine Handbook differ from the MIMS product information. He said he thought that was a considerable cause for concern in that the doses in the MIMS statement suggest a higher dose than those listed in the Australian Medicine Handbook²⁸. Indeed, Dr van den Berg noted that the colchicine dosages prescribed during both hospital admissions, as well as during Ms Werner's last illness in the nursing home, exceeded the current recommendations²⁹.

6. Summary

- 6.1. Colchicine clearly is a drug about which it would be timely to provide further information to the medical community. I do not suggest that colchicine should not be used at all. Clearly it has a place as a cover for allopurinol, and although both Associate Professor Whitehead and Dr van den Berg expressed a preference for the use of prednisolone in an acute attack, they did not it seems to me suggest that colchicine should never be used. Indeed, in his evidence Dr van den Berg said that it is his clinical experience that colchicine is most useful if started really early in an attack. He remarked as follows:

'So if I have got patients who are experienced players, they know that they are going to get an attack of gout. They can't describe to me the feeling that they get, but they know the feeling. They will take a colchicine and they will abort the attack at that point. Once an attack of gout has been really well established, the value and benefit of colchicine I feel is quite significantly reduced.'³⁰

- 6.2. Nevertheless, particularly bearing in mind the confusion that appears to exist in the published guidelines about colchicine, it is appropriate for the matter to be brought to the attention of the general medical community.

²⁷ Transcript, page 225 - I note that Dr van den Berg's target level for uric acid level is .36mmol per litre in comparison with that suggested by Associate Professor Whitehead of .35mmol per litre.

²⁸ Exhibit C9

²⁹ Exhibit C10

³⁰ Transcript, page 216

7. Recommendations

- 7.1. Pursuant to Section 25(2) of the Coroners Act 2003 I am empowered to make recommendations that in the opinion of the Court might prevent, or reduce the likelihood of, a recurrence of an event similar to the event that was the subject of the Inquest.
- 7.2. Accordingly, I recommend that the Minister for Health take appropriate steps to draw to the attention of the medical community the issues identified in this finding with respect to the potential for toxicity in the use of colchicine, and the fact that there appear to be discrepancies in some of the publications related to dosage.

Key Words: Medication; Colchicine Toxicity

In witness whereof the said Coroner has hereunto set and subscribed his hand and

Seal the 17th day of April, 2014.

State Coroner