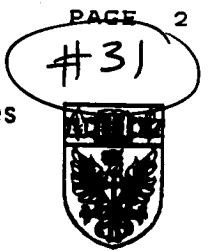




St. Joseph's Hospital
Father Sean O'Sullivan Research Centre

McMaster University
Faculty of Health Sciences



Centre for Evaluation of Medicines

November 5, 1999

Fax: (416) 314-4030

Dr. James T. Cairns
Deputy Chief Coroner for Ontario
26 Grenville Street
Toronto, ON
M7A 2G9

Dear Dr. Cairns:

Re: Lisa Shore
Deceased: October 22, 1998
Your File: R 12799/98

Thank you for asking me to complete a formal review of the information in this case. As you know, I completed a preliminary review and reported to you on April 12th. At that time I had the report of The Centre of Forensic Sciences dated March 8, 1999. I have subsequently received supplemental information from The Centre of Forensic Sciences related to morphine concentrations in the PCA syringe and in the urine of the deceased. I have also received some additional clinical information from The Hospital for Sick Children although I have not reviewed the complete medical file.

On review of all the available pharmacologic and toxicologic information, I am unable to reach any definitive conclusion on the cause of death in this case. I have sufficient information to suggest that death cannot be explained solely on the basis of a reaction to morphine as administered to the deceased. It is, however, likely that her death is in some way related to her drug therapy which included morphine and three other agents (gabapentin, carbamazepine, and amitriptyline). I also note from the post-mortem report that there was evidence of viral infection affecting the myocardium of the deceased (lymphocytic infiltrates). While such an infection, of itself, would not likely cause sudden death it may well have contributed to some interaction involving the four therapeutic drugs administered for relief of pain. Although it cannot be proven with certainty, there is a strong possibility that death may be explained by an interaction of therapeutic drugs and an underlying viral infection to cause some change in cardiac conduction.

I have performed an extensive search for literature that might help to clarify the cause of death, but so far have found no description of the kind of interaction described in the paragraph above. I will continue to search and will work with the manufacturers of the products in question to see if there is any case report which has not appeared in the published literature.

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Hamilton, Ontario, Canada L8N 4A6

There is one other critical element required for the interpretation of the forensic report and that is an accurate description of the source of blood which has been subjected to assay. It is not clear to me whether the samples that have been analyzed were obtained post-mortem or immediately before death or perhaps during the course of a resuscitation attempt. According to the records that I have reviewed, the patient was found without vital signs at 07:15 and there is a record of a blood sample taken for blood gases at 07:46. I have assumed that this blood sample may have been the source of assay material or alternatively that blood was taken at the time of post-mortem examination which commenced 5.5 hrs. after the patient was found without vital signs. The source of this sample and the timing of the assay is important because post-mortem redistribution of morphine has been reported in animal studies. It is likely that the morphine concentration reported at the time of death represents one extreme of the possible range. The true value might be lower by 50% or more. Perhaps in the course of the inquest now scheduled, information will be provided that will allow a better interpretation of the morphine blood concentration at death.

With those caveats I will attempt to answer the questions that have been posed. For the most part my analysis is restricted to my area of expertise which is paediatric pharmacology and toxicology.

- 1) According to the records that I have examined, the deceased received a total of 14.5 mgs of morphine beginning with an initial bolus dose of 2 mgs given at 23:50 on October 21, 1998. Subsequently, the patient took a total of 6 mgs by PCA infusion and was then given a further 2 mgs as an intravenous bolus followed again by three more PCA doses totaling 4.5 mgs.
- 2) It is not entirely clear to me why the emergency room physician would choose to give an additional 2 mg bolus at 00:40 although it is probable that the initial treatment had not yet proven successful in relieving pain. There is normally a 10-20 minutes lapse of time before maximum pain relief is achieved; however, the bolus dose given at 00:40 was given 50 minutes after morphine treatment had been initiated.
- 3.) There are difficulties in interpreting the morphine concentration at death which was reported as 105 ng/mL. Pharmacokinetic measurements of morphine may vary considerably from child to child and depend to some extent on the underlying condition for which morphine is being administered. Nonetheless, in the case of an otherwise healthy 40 kg 11 year old I would assume that morphine administered in the manner described leading up to 01:07 would establish a steady state concentration of approximately 100 ng/mL. Variations of 20% on either side of this figure would strike me as unremarkable. Such a figure (100 ng/mL) would be a reasonable approximation of the concentration of morphine expected at the time of the last PCA administration of morphine at 01:07.
- 4.) The morphine concentration of 105 ng/mL measured after 07:15 suggests that the concentration at 01:07 might have been considerably higher. If one assumes

conservatively a half life of 3 hours of morphine in a child of this age, then the concentration at 01:07 would have been approximately 300 ng/mL. This is a high concentration which would likely be associated with respiratory depression and hypotension and would be entirely in keeping with the drop in blood pressure and respiratory rate observed between 01:30 and 03:00.

- 5.) As noted above, I am not comfortable with extrapolating back to 01:07 to determine a concentration of morphine based on a post-mortem measurement taken after 07:15. It is quite possible that the measurement reported by The Centre of Forensic Sciences is spuriously high. The measurement of morphine concentration in the urine of the deceased was 8000 ng/mL and the volume of urine in the bladder at death was reported as 50 mLs. This indicates a total amount of morphine in the bladder at the time of death of 0.4 mgs and this figure does not suggest an extraordinarily high concentration in blood during the critical period between 01:07 and 07:15.
- 6.) The Centre of Forensic Sciences has measured the morphine concentration in the PCA infusion syringe and found that to be 0.8 ng/mL. This compares reasonably well with the prescribed concentration of 1.0 ng/mL (50 mgs. in 50 mLs). The measurement does indicate a lack of precision in the measures by The Centre of Forensic Sciences and suggests that we might expect at least a 20% error in morphine measurements.
- 7.) Based on the above considerations, I think it is more likely that the true morphine concentration before death was in the range of 40-50 ng/mL. If this is correct, it is likely that the peak concentration in the period 01:00-01:30 would have been in the range of 120-150 ng/mL. Such concentrations would be in keeping with the dose of morphine administered up to 01:07. I see no evidence that would lead to a conclusion of an inadvertent administration of an overdose of morphine either by bolus injection or by PCA infusion.

* 8.) Based on the pharmacokinetic assumptions outlined above it is reasonable to conclude that the deceased had a relatively high dose of morphine but one which is entirely in keeping with accepted therapeutic norms. According to other records which I have examined, the dose also compares relatively closely with that administered on March 19 and 20, 1998 during the course of an earlier hospital admission. At that time no untoward effects were observed that could be attributed to morphine treatment.

March 19/20
rec'd 11 mg
over
4 hrs

not 14.5 mg in
90 minutes

See pt 13.

9.) In examining the flow sheet completed after transfer to the ward, it is clear that respiratory rate declined between 01:45 and 02:50. At 02:50 respiration was recorded at a rate of 8-10. Such slowing of respiration is certainly compatible with morphine effect and in retrospect treatment with a narcotic antagonist might have been justified. A decision was made at 02:50 to stop PCA administration of morphine and a recheck of respiratory rate at 03:20 found a rate of 12. It is also noteworthy that at 02:50 in spite of the slow respiratory rate air entry was described as good and the chest was described as clear.

- 10.) At 03:20 the heart rate was recorded as 120 and subsequently it was measured at 130 at 04:00 and at 134 at 04:15. Unfortunately, corresponding blood pressures are not measured because the patient was drowsy or asleep; however, this rapid heart rate suggests a lowering of blood pressure which might also be compatible with morphine effect. It is notable that the patient was able to cooperate at 05:00 with the measurement of an oral temperature (35.7). In summary, it seems clear that there was a relatively high morphine concentration in blood in the period after 01:07 when the last dose of morphine was given. The resulting morphine concentrations apparently produced pain relief and may also have caused respiratory depression, hypotension and tachycardia.
- 11.) The dosage of gabapentin given to this patient is quite high but is in keeping with new investigational uses of this agent for the treatment of intractable pain. The official product monograph states that doses above 1200 mgs/day have not been investigated in children over 12 years of age. Studies in children aged 4 to 12 have employed doses ranging between 10 and 20 mgs/kg/day. A dose of 20 mgs/kg/day for the deceased would have been 800 mgs/day rather than the 1400 mgs/day that was prescribed. It is reasonable to assume that the dose prescribed was appropriately calculated by the experts at the Boston Children's Hospital.

The therapeutic range reported in adults is between 2.0 and 8.0 ng/mL. The concentration reported in the deceased of 11 ng/mL seems in keeping with her relatively high dosage and is unlikely in itself to have caused her demise. There are reports in the literature of overdose patients surviving concentrations as high as 60.0 ng/mL.

- 12.) The other administered drug, carbamazepine in a dose of 400 mgs daily and amitriptyline in a dose of 75 mgs nightly, yielded post-mortem concentrations within the expected range. Again, it is unlikely that either of these medications contributed directly to death although it is possible that they were part of a complex drug interaction.
- 13.) It is recognized that patients vary somewhat in their sensitivity to analgesic drugs including morphine, so it is important to know as much as possible about the previous exposure of the deceased to morphine and other opiate narcotics. As noted above, the records from The Hospital for Sick Children do suggest that she had received PCA morphine to a dose of 11 mgs over 4 hours in March, 1998 without incident. It would be useful as well to know as much as possible about the patient's reaction to morphine and to combinations of morphine with other drugs during her hospitalization in Boston. There may be significant inter-individual variation in the response to drugs such as gabapentin, carbamazepine, and amitriptyline so it would be useful to know if she had ever previously been exposed to the combination of these three drugs with morphine. *o*
- 14.) Finally, there is nothing in the clinical data available which would serve to confirm an interaction among the drugs prescribed. However, such an interaction cannot be ruled

*o morphine
in Boston*

out. Gabapentin is a relatively new therapeutic agent and, while it is reported as being exceptionally safe, it is possible that some interaction of gabapentin with the other active drugs (morphine, carbamazepine, and amitriptyline/nortriptyline) perhaps with actions amplified by hypotension and a concurrent viral infection has affected the cardiac conduction system. In the absence of an electrocardiogram taken before the resuscitation attempt, I think it will impossible to answer this question.

In summary, I believe that the cause of death in this case will not be made definitively on the basis of pharmacology or toxicology analysis. I do, however, think it is likely that death was caused by a cardiac conduction disturbance which may have resulted from a complex interaction among the therapeutic drugs, the patient's physical condition and a concurrent viral infection. *

I hope the inquest now scheduled will shed some additional light on these matters and I look forward to appearing.

Yours sincerely,



S. M. MacLeod, MD, PhD, FRCPC
Director,
Father Sean O'Sullivan Research Centre

* further tests showed viral infection
per attached

SMM:dh

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FAX

Dr. Peter Liu
Centre for Cardiovascular Research
Toronto General Hospital
University Health Network
Toronto, Ont

Dec. 17, 1999

The Office of the Coroner
Toronto, Ontario

ATTENTION: JEFF

RE: LISA SHORE BIOPSY ANALYSIS

The results of the RT-PCR show that the sample was negative for enteroviral RNA. The sample was positive for beta-actin, a control for the RNA quality. The positive control for enteroviral RNA was CVB3 cDNA (3 copies of genome), which showed a faint band.

This strongly suggests that the sample was not infected with enterovirus.



Dr. Peter Liu