

**From:** John Stephens

**Date:** 15 March 2013 07:32:01 GMT

**To:** Malcolm VandenBurg

**Subject: The Risks in Use of Naloxone with Patients dependent on Opiates for Analgesia**

Dear Dr VandenBurg, I have read with great interest your report in which you describe a fatality in a cancer patient with known coronary heart disease, dependent on opiates for pain relief, who was given a large bolus of naloxone for opiate reversal for suspected opiate related mental confusion and altered consciousness.

As a result of such rapid and complete opiate reversal (which did not alleviate the patient's symptoms) there was a re-emergence of severe pain and associated emotional stress which, you argue compellingly, caused cardiac damage through sympathetic stimulation and possible cytokine release in the presence of underlying coronary heart disease. It is well known (Brotman DJ et al, Lancet 2007 Sept 22:370(9592):1089-100) that emotional stress can cause fatal cardiac events in the presence of coronary heart disease. Further, as you point out, such stress can cause Takotsubo syndrome, an acute cardiac condition associated with heart failure and extensive left ventricular regional wall damage. The exact pathophysiology is unknown but acute sympathetic stimulation affecting the coronary microvascular bed appears to be the most likely explanation. Takotsubo syndrome is a dramatic illustration of the potentially harmful effects of sympathetic stimulation, caused by emotional stress, on the coronary arteries and heart muscle.

Against this background you point out that Summaries of Product Characteristics (SPCs) draw attention to the potential cardiovascular dangers of rapid and complete opiate reversal with naloxone, particularly in patients with coronary heart disease, and recommend that it should be given in small, incremental doses, rather than as a large iv bolus thus allowing opiate toxicity to be reversed while maintaining adequate pain relief.

You also point out that the hospital Trust concerned, while recommending that naloxone be given slowly, did not in its guidelines mention the risk of serious cardiac side effects particularly in patients with known coronary heart disease.

I fully support your arguments in relation to this case, which remind us of the potential acute harmful effects on the heart of emotional stress, and your recommendation that a warning of the risk of serious cardiac events caused by naloxone, particularly in patients with known heart disease, should be incorporated in adult palliative care guidelines. In this case, naloxone was given in a manner and dose contrary to Trust guidelines.

While some fatal cardiac events are apparent at autopsy others are not. For example, a fatal cardiac arrhythmia could not be confirmed or otherwise at autopsy and neither could Takotsubo syndrome because in vivo left ventricular regional wall motion abnormalities (apical ballooning, the hallmark of Takotsubo syndrome) cannot be seen post mortem.

I agree therefore that, in this case, the administration, contrary to guidelines, of a large bolus dose of naloxone may have contributed to cardiac dysfunction in this patient and contributed to her early demise.

yours sincerely,

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