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Title	Fatal overdoses involving hydromorphone and morphine among inpatients: a case series
Authors	Amanda Lowe, Michael Hamilton, Julie Greenhall, Jessica Ma, Irfan Dhalla, Nav Persaud
Reviewer 1	Dr. Balthasar Hug
Institution	Basel University Hospital, Internal Medicine
General comments (author response in bold)	<p>General:</p> <p>This is an interesting and impressive article for anyone prescribing drugs and all with an interest in adverse drug events (ADEs). Actually, this is of high interest for any clinician. The authors describe eight cases of deaths following opioid prescription and application and discuss them suggesting some ideas about improvement. The article is well done and timely, but could be spiced with some more clinical input and a short systematic overview over drug safety.</p> <p>Specific</p> <p>Methods:</p> <p>- P. 4, study population: here the reader wonders why the authors did not search for more drugs or drug classes than hydromorphone and morphine. Why did they not include other opioids? Their work is interesting and very helpful. Therefore, they should explain why they excluded other medications. ***We focused on morphine and hydromorphone because of the similar sounding names but different potencies.</p> <p>- Furthermore, they should provide some kind of algorithm for finding their cases, e.g. a sentence saying that they found x coroner's cases, y were in correlation with some drug intake/application and 8 were connected to morphine and hydromorphone or something similar. ***We obtained the cases by reviewing existing reports. Please see the comment above about the flow diagram.</p> <p>- P.4, ethical approval: For the international reader, the authors should provide more information about „St. Michael's Hospital“: in which town and province is it situated? ***We clarified this sentence.</p> <p>Results:</p> <p>- The case reports are very interesting to read. They are well characterized and quite homogenous in the writing except for case #8 on p. 8, which shows a lot of details not described in the other cases (exact hours of the day and enumeration of all side diagnoses even those irrelevant to the case evolution). This case should be rewritten reducing details according to the other cases. ***We have made this change.</p> <p>- One type of result is missing namely the type of institution where the incidents took place. There are just hints like „admitted to a palliative care ward“ (case #3, p. 5), „admitted to hospital“ (case #1, p. 4, #8 etc.) and the like. If the authors would not like to disclose too much information they can add a sentence saying „Of the eight cases described here two were admitted to tertiary university referral hospitals, three were hospitalized in nursing homes etc.“ or the like thereby not disclosing any information about the single cases. ***We have made this more clear in the new Table.</p> <p>- Another suggestion to spice up the case reports would be an additional interpretation by a clinician or pharmacologist. I am specially referring to case #5 with its lethal use of naloxone. This is discussed by the authors on p. 10, lines 40-46 in two sentences, but not enough in my view. Most physicians involved in clinical work are accustomed to using naloxone in regard to long acting opioids or heroin overdose in the emergency department with a dose of naloxone each intramuscularly, subcutaneously and only in the end intravenously (with the iv injection the patient wakes up and might get very dysphoric and agitated). This prevents the secondary apnea encountered in the patient in case #5 or the drug addict walking out of the emergency ward with the same result of secondary apnea. This section should get a review and be rewritten accordingly. ***In the Interpretation, we discuss the fact that a single dose of naloxone was administered to a patient who received a long acting opioid; This is part of a paragraph about detecting and reversing opioid toxicity. (The authors include clinicians already.)</p> <p>Discussion/Interpretation:</p> <p>- It would be nice to see a bit of a systematic overview of ADEs and about their preventability, since this aspect is crucial for reducing ADEs in clinical care(1). There is a seminal paper about the topic by Bates et al (1995)(2) and it seems that about every second ADE with opioids is potentially preventable. I suggest the authors write a paragraph on this topic introducing their interpretations. ***We have added this to the Interpretation and cited the seminal study by Bates et al</p> <p>Conclusions, p.11</p> <p>- The first sentence of the conclusions is not true the way it stands there now: „Fatal opioid overdoses....are preventable.“ Neither did the authors research that nor do they show evidence in the literature they cite. ADEs with narcotics seem to be preventable in about 50% of cases(3). This sentence needs to get cut out or rewritten in the above sense e.g. „Many fatal opioid overdoses...are preventable.“ or similarly. ***We have re-phrased this sentence accordingly.</p>

	<p>- The last sentences of the conclusions starting in line 25 with „System based approaches...manipulations at the bedside.“ in line 36 does not belong into the conclusions’ section but to the end of the interpretations’ section, because here the authors describe future measures to be taken to prevent ADEs and not any results of their study.</p> <p>*** We have moved this passage.</p> <p>Table 1</p> <p>- This table gives a nice overview over the type of ADEs. What is missing is the transcription error as mentioned in the abstract referring to case 5. The term „order processing“ for a transcription error is too broad and unspecific and I would suggest to introduce „transcription error“ into the table.</p> <p>*** We have added a new Table 1.</p> <p>1 Gurwitz JH, Field TS, Avorn J, et al. Incidence and preventability of adverse drug events in nursing homes. Am J Med. 2000 Aug 1;109(2):87-94.</p> <p>2 Bates DW, Cullen DJ, Laird N, et al. Incidence of adverse drug events and potential adverse drug events. Implications for prevention. ADE Prevention Study Group. Jama. 1995 Jul 5;274(1):29-34.</p> <p>3 Bates DW. Frequency, consequences and prevention of adverse drug events. J Qual Clin Pract. 1999 Mar;19(1):13-7.</p>
Reviewer 2	Dr. Domenico Motola
Institution	University Of Bologna, Department of Pharmacology, Bologna, Italy
General comments (author response in bold)	<p>The manuscript by Amanda Lowe et al is interesting and well written and it is a case-series of possible fatal medical error involving morphine o hydromorphone use.</p> <p>I have one major objections and one minor one:</p> <p>1) Acknowledging that there may also have been other unreported or unrecognized cases, 8 cases in 6 years can be defined as an uncommon event (if not rare) considering the total amount of morphine and hydromorphone prescribed to all patients during the period considered, but this information is not showed. If the authors are not able to provide the data of annual consumption of drugs in DDD, they must recognize this limit in their discussion.</p> <p>***We acknowledge in the limitations section that this case series provides no information about incidence.</p> <p>2) Another recognized method for minimize medication errors involving drugs is the “double check” system when giving high-alert drugs, such as those with low therapeutic index. Authors may list it on page 10, after line 30</p> <p>***We have added this.</p>
Reviewer 3	Dr. David G. Bailey
Institution	Lawson Health Research Institute, University Hospital, London Health Sciences Centre, London, Ontario
General comments (author response in bold)	<p>The authors summarize 8 cases reported to the Coroner of Ontario 2007 – 2012 of deaths from overdose of morphine and hydromorphone in hospitalized and institutional patients. They discuss the errors that led to this outcome and put forth potential interventions for future prevention.</p> <p>The authors state that it complements other population based studies but do not indicate what is novel about their work.</p> <p>***We have added this.</p> <p>It might be worth mentioning that hydromorphone and morphine are among the highest prescribed drugs in Canada, at least in 2012 (see attached list from Pharmacy Practice 2013)</p> <p>***We have added this.</p> <p>The presentation of the cases sometimes could be made more easily understandable. I would suggest shortening the cases and using a more standardized approach. Particularly pertinent is consistency in medication reporting, i.e. drug, dose, route and interval. The following is a possible format that might be incorporated.</p> <p>***We have addressed through the new Table 1.</p> <p>Case 1 Ordered: hydromorphone 1 mg (0.5 ml from 2 mg/ml vial) subcutaneously Administered: morphine 25 mg (0.5 ml from 50 mg/ml vial) subcutaneously Error: five – fold equivalent increase in dose</p> <p>Case 2 Ordered: initially morphine 1 to 5 mg every 2 hours Ordered: increased to morphine 5 to 10 mg intravenously every 2 hours. Ordered: increased to hydromorphone 5 to 10 mg intravenously every 4 hours. Error: five – fold equivalent increase in peak dose effect</p> <p>Case 3 Ordered: hydromorphone 0.4 mg (0.4 ml from 1 mg/ml vial) Administered: hydromorphone 4 mg (0.4 mg from a 10 mg/ml vial) Error: 10 – fold increase in dose from incorrect vial concentration</p> <p>Case 4 Ordered: hydromorphone 0.2 mg/hr infusion (0.1 mg/ml at 2 ml/hr) Administered: hydromorphone 2 mg/hr infusion (1 mg/ml at 2 ml/hr) Error: 10 – fold increase in dose above that in the computerized prescriber entry field as result of</p>

added information in the comment field

Case 5

Ordered: long acting morphine 15 mg orally twice day (30 mg /day)

Ordered: discontinue morphine and start hydromorphone 2 mg orally four times daily (8 mg / day) and 2 mg six times daily as needed (12 mg / day)

Administered: morphine continued (30 mg/day) plus hydromorphone (at least 8 mg/day)

Error: At least a 2 – fold increase in dose equivalent from order processing

Administered: naloxone 0.2 mg intravenously to reverse overdose toxicity

Error: inappropriate naloxone dosing schedule (initial dose 0.4 mg to 2 mg which may be repeated every 2 to 3 minutes until full reversal to a maximum of 10 mg)

Case 6

Ordered: morphine 2 mg intravenously every four hours as needed

Administered: as above initially but later hydromorphone 3 mg intravenously

Error: more than five – fold increase in dose equivalent

Case 7

Administered: Day 1 (total) - hydromorphone 6.5 mg and morphine 12 mg parenterally

Administered: Day 2 (total) - hydromorphone 22 mg intravenously

Administered: Day 3 (total) - hydromorphone 22.5 intravenously and codeine 120 mg orally

Administered: Day 4 (single doses) – dimenhydrinate mg(?) orally(?) and then hydromorphone 4 mg intravenously

Error: probable drug interaction

Case 8

Ordered: morphine 4 mg subcutaneously every 4 hours with morphine 2 mg subcutaneously per hour as needed

Administered: hydromorphone 4 mg

Error: five – fold equivalent increase in dose

Although the authors describe systems that been introduced to reduce errors, it would be interesting to know whether there are data on their effectiveness.

*****We have briefly described that these methods are not proven effective.**