

Hiccups exemplify the overlap between myocardial infarction and pulmonary embolism symptomatology



In paraphrase, the authors of a recent case report suggest that there should be a high index of suspicion for acute myocardial infarction (AMI) when a patient presents with hiccups in the context of old age, atypical presentation [of AMI], and multiple risk factors for acute coronary syndrome (ACS) [1]. It is also the case, however, that both ACS [2] and pulmonary embolism (PE) [3], respectively, are age related disorders [2,3]. The diagnostic difficulties generated by this phenomenon are compounded by the overlap in the clinical manifestations of the two disorders. This overlap is exemplified by the occurrence of hiccups, not only in the presence of AMI [1], but also in the presence of PE [4,5].

In all three reports [1,4,5], apart from hiccups, the most striking atypical feature was total absence of chest pain or dyspnoea. The two disorders, AMI and PE, also share other atypical presenting features such as abdominal pain, documented in 11% of 94 consecutive patients with AMI [6], and in 12% of 90 PE patients [7]. Syncope/presyncope is another atypical symptom, documented in 19.1% of 1763 patients with atypical AMI (all without chest pain) [8] vs occurrence of PE in 97(17.3%) of 560 patients hospitalised for a first episode of syncope [9]. In the latter report 24(24.7%) of the 97 PE patients “had no clinical manifestations of the diagnosis [of PE], including tachypnea, tachycardia, hypotension, or clinical signs or symptoms of deep vein thrombosis” [9].

In the emergency department context, the electrocardiogram is one of the most frequently used diagnostic modalities for expediting the distinction between AMI and PE, both in the typical and in the atypical context of the clinical presentation of either of these two disorders. This modality, however, cannot reliably distinguish between the two disorders, given the fact that AMI-related ST segment elevation [1] can also be simulated by the PE-related ST segment elevation (in anterior leads and also in inferior leads) which occurs in the total absence of coronary artery occlusion [10]. In the latter review of 34 PE cases (mean age 56.5), troponin was elevated in 15(78.9%) of the 19 patients in whom it was evaluated [1].

Given the fact that both AMI and PE are age-related, and have overlapping clinical, electrocardiographic, and laboratory stigmata, there is considerable scope for underdiagnosis as well as overdiagnosis of these two disorders in elderly patients, especially when they present atypically.

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Hypoglycemia work up when medication is not a risk factor



In the reported study, although as many as 97 patients did not have medication as a risk factor for hypoglycaemia, no mention was made of the endocrinological “work-up” of those subjects [1]. Patients who belong to that category should be managed along the lines recommended in a recent review of the approach to spontaneous hypoglycaemia [2]. In that review the recommendation was that those who are seemingly well should undergo a diagnostic work up in which blood samples are taken to evaluate parameters over and above plasma glucose before treatment with either intravenous glucose or glucagon. The rationale is that “the directions of glucose, insulin, C-peptide, and proinsulin during a hypoglycemic event facilitate diagnosis” [2]. That diagnostic advantage will be lost if pretreatment samples of blood are not obtained during the episode of spontaneous hypoglycaemia. Consequently, a subsequent, artificially-induced stress test will be necessary to reproduce hypoglycaemia [2]. Even in patients initially perceived to have medication as the sole risk factor for hypoglycemia there should be a heightened index of suspicion for coexisting undiagnosed hypoadrenalism when recurring episodes of hypoglycaemia occur despite a reduction in insulin dosage [3,4]. The reason is that type 1 diabetes may coexist with primary hypoadrenalism when the two disorders have an autoimmune basis [3,4]. Apart from being hypoglycemic such patients may otherwise be seemingly well, as was the case in a patient who presented at her routine diabetic clinic review only complaining of recurring hypoglycaemia [3]. In another patient with the association of type 1 diabetes and Addison’s disease the opportunity to make a timely diagnosis of hypoadrenalism was missed when blood levels of cortisol were not evaluated during a hospital admission for hypoglycaemic coma. The diagnosis was only made 6 months later, using the short synacthen test (intramuscular synthetic adrenocorticotrophic hormone) [4]. In conclusion, pretreatment blood samples should be taken for parameters which are indicative of insulinoma in all apparently well patients where medication-related hypoglycaemia has been ruled out. Even among insulin treated patients those with type 1 diabetes should have blood samples taken for cortisol levels if they experience recurring episodes of hypoglycaemia in spite of a reduction in insulin dose. That should be the case even though the patient is seemingly well, given the fact that clinical features of Addison’s disease can be subtle, and not all patients are pigmented [5]. Using those strategies physicians in ED can optimise

opportunities to validate the diagnosis of rare endocrine disorders which are, nevertheless, eminently treatable.

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Rapid induction onto sublingual buprenorphine after opioid overdose and successful linkage to treatment for opioid use disorder



Over 70,000 Americans died from drug overdose in 2017, a number unthinkable in 1997 when this number stood at less than 17,000. In 2016 alone, over 1.6 million years of life were lost due to overdose driving an overall decrease in US life expectancy [1,2]. Yearly over 500,000 overdosed patients present to the ED, nearly double the number of visits for ST elevation MI [3–5]. Untreated, the one year standardized mortality ratio exceeds 100 after discharge from an ED visit for non-fatal opioid overdose. That staggering mortality can be reduced by 38–59% if patients treated are treated with medications, such as buprenorphine or methadone, for opioid use disorder (MOUD) [4–7]. Buprenorphine's high-affinity, opioid agonist blockade, and ceiling effect on respiratory depression suggest opioid overdose followed by naloxone reversal and administration of buprenorphine (ODNaloxoneBup) should be safe and effective [6,7]. Our initial experience supports this.

Due caution given the many unknowns around ODNaloxoneBup suggest it should only be considered in an otherwise healthy patient with no suspected co-ingestions and no recent methadone use with a normal level of consciousness, normal mental status, and the ability to provide informed consent. Administration of buprenorphine to patients intoxicated with alcohol, benzodiazepines or other sedative can result in respiratory depression. Patients with acute illness or severe chronic illness such as infection, heart failure, liver failure, respiratory failure or acute renal failure can experience unpredictable sedation and respiratory depression. Patients with altered mental status are not able to provide a reliable history or adequately consider the risks and benefits to provide informed consent. Patients taking methadone should be supported to continue methadone

treatment; overdose is not an indication to switch to buprenorphine and may disrupt care (Fig. 1).

There are two major adverse events possible with ODNaloxoneBup: 1) additive sedation with respiratory depression and 2) precipitated withdrawal. While neither of these has been reported at this time, any ED should be prepared and willing to adequately manage these potential complications. Reversal of buprenorphine is accomplished with high-dose naloxone (2–3 mg IV push followed by 4 mg/h infusion) [8,9]. Precipitated withdrawal is treated with an empirically titrated multimodal approach that may include: benzodiazepines, alpha-2 agonists (clonidine or dexmedetomidine), high affinity full agonist opioids (hydromorphone), ketamine, and dopamine antagonists (e.g. metoclopramide or haldoperidol) [10].

Here we briefly describe three examples of how ODNaloxoneBup can be accomplished in the ED without the occurrence of serious adverse effects. In all cases, the history and clinical response to naloxone suggested that there was no additional sedative, such as alcohol or benzodiazepine, present. Later toxicologic analysis confirmed this. The first two cases (Patient A and B) are two heroin-using men who presented directly to our ED. Per patient report, at the doorstep to the ED, the two men split a previously street-obtained “orange pill with a white center” that they believed to be Suboxone™. They self-administered the pill fragments sublingually. Both men became unresponsive after presenting to ED triage; they remember walking into the ED but have no recollection of events until several hours later after naloxone reversal. After discussion of risks and benefits buprenorphine was administered. Laboratory testing confirmed the tablet contained fentanyl (see Figs. 2 and 3). The third case (Patient C), is a 42-year-old male heroin user who was found unresponsive on the street. Paramedics administered 2 mg intranasal naloxone and with immediate return to normal mental status and respiratory rate. In the ED the patient reported anxiety and discomfort with a Clinical Opioid Withdrawal Scale score of 4. After discussion of risks and benefits, buprenorphine was administered (see Fig. 2). At presentation all patients clinically displayed opioid overdose without signs or report of sedative use. At discharge all patients were comfortable and had received a 24-h-dose of sublingual buprenorphine. All patients attended their follow up appointment with our Bridge Clinic.

Once naloxone has reversed opioid overdose (regardless of whether withdrawal signs/symptoms have been precipitated), initiation of buprenorphine should yield a relative increase in mu-opioid receptor (MOR) agonism and be experienced as stabilization or withdrawal relief. *In vitro* (+NaCl), naloxone exhibits 5-fold higher MOR affinity than morphine and comparable MOR affinity as sufentanil and, under these same physiological conditions, buprenorphine exhibits 6-fold higher MOR affinity than naloxone [11]. Following naloxone displacement and reversal of opioid overdose, buprenorphine is therefore expected to displace naloxone from available MORs (and residual naloxone effect should wash out rapidly due to its pharmacokinetics; see Fig. 3). Once bound to MORs, buprenorphine's high-affinity, longer-acting MOR occupancy should effectively prevent return of full agonist toxicity (provide opioid blockade) [4] even if relatively high concentrations of full agonist remain in the circulation [7,12–14]. The positive treatment responses observed in these cases suggest the possibility that as naloxone was metabolized (Patients A and C) and/or displaced from MORs (Patient B), a mixed state of buprenorphine partial agonism and opioid agonism occurred, thereby avoiding an abrupt transition from full to partial agonism that would have been experienced as precipitated withdrawal.