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Case Study: (AHRQ) Don't Push

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Learning Objectives

At the end of this activity, you will be able to:

- Describe the delicate balance of effectiveness and safety when it comes to powerful drugs.
- Discuss the ways protocols can be helpful and whether they can at times be problematic.

Description

IV haloperidol to manage psychosis in an AIDS patient causes polymorphic ventricular tachycardia ('torsade de pointes'), necessitating a transvenous pacemaker. Was the patient's treatment appropriate? Read the Case Study and commentary, and form your own opinion.

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Key Topics

HIV/AIDS, mental health, cardiovascular care, delirium (acute), adverse event, medication safety, adverse drug event.

The Case

A 37-year-old HIV-positive woman was brought to the emergency room by her family because she had exhibited altered mentation for 3 days. The patient had been diagnosed with HIV infection 3 years earlier. Her opportunistic infections included thrush and *Pneumocystis carinii* pneumonia (PCP). She had never received highly active antiretroviral therapy (HAART). Nevertheless, her lowest CD4 count

was 560 and her viral load was low. The patient did not have any significant past surgical or psychiatric history. Medications on admission included only trimethoprim/sulfamethoxazole [Bactrim] for PCP prophylaxis.

The patient's mental status deteriorated rapidly after admission: She tossed about on her bed and had visual and auditory hallucinations. Per the hospital's safety protocol, the planned lumbar puncture was put on hold because of her agitation. Neurology and psychiatry consultations were sought. The psychiatry team recommended haloperidol administered via intravenous (IV) push 5 mg every 20 minutes until sedation was achieved, so that the neurologist and psychiatrist could evaluate the patient. However, after 3 doses of haloperidol, the patient's face turned pale and she started gasping for air. The patient was connected to a cardiac monitor on a crash cart, which showed polymorphic ventricular tachycardia ("torsade de pointes") (See below Figure).

The patient received IV magnesium sulfate immediately. In the cardiac intensive care unit, she required placement of a transvenous pacemaker. She was able to return to a regular medical floor one day later, and her mental status improved without any intervention over the subsequent week.

The Commentary

Herber Y. Meltzer, MD, Bixler Professor of Psychiatry and Professor of Pharmacology, Vanderbilt University School of Medicine

The almost fatal outcome in this case directly resulted from treatment with high and frequent doses of haloperidol, administered according to a commonly used critical care protocol that calls for multiple, sometimes escalating doses of the drug, at 15–20 minute intervals. (1,2) The issue here is whether such a protocol was appropriate and whether it provides the best balance of effectiveness and safety, given the large number of new, “atypical” antipsychotic agents now available.

Because this patient had no significant psychiatric problems prior to developing an unspecified change in mental status, hospitalization was indicated to rule out an opportunistic central nervous system (CNS) infection, metabolic derangement, or other cause of delirium. It would be helpful to know whether she was already experiencing psychotic symptoms prior to admission or whether definite signs of an organic process, such as confusion and disorientation, were evident during the evaluation. A recent onset of psychosis without organic symptoms would be much less worrisome.

The prevalence of psychosis during the course of HIV infection ranges from 0.5%-15%. (3) It may be independent of HIV encephalopathy or dementia, or may be the result of an underlying vulnerability to becoming psychotic under stress. This woman is at the upper age of risk for developing schizophrenia but well within the prime age range for a first episode of mania. The stress of being HIV

positive and attendant changes in social and work function can contribute to the emergence of vulnerability to these disorders.

Had psychotic symptoms alone been present during the evaluation or right after admission, it would have been appropriate to administer one of the atypical antipsychotic drugs (eg, aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone) orally, instead of oral, intramuscular (IM), or IV haloperidol or other older, “typical” antipsychotic drugs. Clozapine is a second-line treatment, reserved for patients who fail to respond to one or two of the other atypical antipsychotic drugs. The distinction between typical and atypical antipsychotic drugs relates to their capacity to cause extrapyramidal symptoms (EPS); the atypical drugs are much less likely to produce these adverse effects. Because patients with AIDS are more susceptible to developing EPS (4) (possibly because AIDS compromises the dopaminergic and cholinergic systems required for normal motor behavior [5]), atypical antipsychotic drugs are the treatment of choice for HIV-related psychoses (6,7), with or without dementia. Clozapine produces the least EPS of all of the agents, and has been used in HIV-positive patients, despite its ability to cause agranulocytosis in about 0.7% of individuals.(8)

Oral antipsychotic medications require days to weeks to take effect. Intramuscular medication reaches the brain within 30 minutes (intravenous injection does so within minutes), but only haloperidol and ziprasidone are currently available and FDA-approved for IM use. Three issues must be considered in choosing between them: (i) the risk of torsade de pointes; (ii) the risk of EPS; and (iii) cost. Given repeatedly, IM haloperidol, 5 mg-10 mg, and IM ziprasidone, 20 mg, produce virtually the same increases in QTc interval (2.2 ms). Intramuscular ziprasidone produced greater improvement in agitation and psychopathology with fewer EPS than IM haloperidol (9), and is therefore the preferred choice when control of agitation within 20 minutes to 2 hours is sufficient. Intramuscular olanzapine (Zyprexa®) is expected to receive FDA approval in the near future; it represents an equally preferable choice to haloperidol in this setting.(10) If sedation is required within minutes, IV lorazepam may be added.

No case of torsade de pointes from ziprasidone has been reported even though more than 450,000 people have received the oral formulation (A. Loebel, MD, oral communication, Pfizer Inc., September 2003). This suggests the risk is low. Since IM ziprasidone costs approximately 20 times more than IM haloperidol, ziprasidone will likely prove cost effective only in subgroups of patients at high risk for adverse effects from haloperidol, such as AIDS patients.

The limited mental status data provided in the case summary made the need for rapid and deep sedation difficult to determine. The patient is described as “tossing in her bed” which, unless she was restrained, suggests no more than moderate agitation, no intent to harm herself or others, and enough cognitive intactness to avoid wandering. The severity of visual and auditory hallucinations is not described, but, even when severe, these are not considered justification for IV haloperidol push

therapy. Consequently, an atypical antipsychotic (administered IM or possibly orally) would likely have been adequate here, especially since limb restraints could be added if necessary.

In my opinion, IV haloperidol push treatment (1,2,11-14) to achieve rapid sedation of agitated psychotic patients to facilitate medical work-up is generally problematic. The initial basis for this practice was small, uncontrolled studies, which indicated that massive doses of IV haloperidol were sometimes necessary and well tolerated.(11,12) This evolved into widely adopted recommendations for giving IV haloperidol at doses of 2 mg IV (range 0.5-10 mg) and doubling the dose every 20 minutes until adequate control is achieved.(1,2) Dissemination of this practice has been accompanied by numerous case reports of torsade de pointes (14-16), with an incidence of 3.6% in one series.(16) Given the clear risks, more evidence is needed before recommending high-dose IV haloperidol rather than giving lower doses a chance to work.

If high-dose IV haloperidol is to be used, or might become a possibility, baseline QTc interval and serum magnesium and potassium concentrations should be measured.(14) If the baseline QTc interval is 440 ms or longer, and patients have electrolyte disturbance or are receiving other drugs which might prolong QTc interval, IV haloperidol should be given cautiously. Continuous cardiac monitoring during the course of IV haloperidol push therapy is warranted.(1,2,14) Of note, another butyrophenone, droperidol, was withdrawn from clinical use because of the high rate of torsade de pointes in critical care patients.

Was it correct to discharge this patient without any antipsychotic treatment after her mental status improved? The rapid improvement suggests that the psychotic symptoms were not related to underlying schizophrenia or mania. There is too little information to draw firm conclusions about the basis for the mental changes that preceded hospitalization. Most likely, this was a case of HIV psychosis, not the sign of an adventitious CNS infection. In such cases, with the psychosis clearing so rapidly, prophylactic treatment with an antipsychotic drug is probably not indicated. However, education of the patient and family to watch for early signs of psychosis or other forms of psychopathology would be indicated to avoid another costly and potentially dangerous visit to an emergency room. Recurrent psychotic episodes would necessitate continuous treatment with one of the newer antipsychotic drugs.

Take-Home Points

- Obtain a detailed history of the type and temporal course of mental status changes in HIV-positive patients before initiating medical workup and treatment of the changes.
- Treat psychotic symptoms in HIV-positive patients with low oral doses of an atypical antipsychotic drug, such as aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone

(or offer IM ziprasidone), depending on the clinical status of the patient and need for rapid control.

- If sedation is truly urgent for medical or safety reasons, use IV push haloperidol but attempt to keep the dose as low as necessary.
- Pretreatment ECG, measurement of QTc, and ongoing monitoring for development of torsade de pointes throughout course of treatment with IV haloperidol and during recovery is indicated.
- Efficacy and safety of IM ziprasidone vs. IV haloperidol need to be studied in randomized clinical trials.

Disclosures

The author is a consultant to the following companies whose drugs are discussed here: Bristol Myers Squibb (aripiprazole), Janssen (haloperidol, risperidone), Eli Lilly (olanzapine), Novartis (clozapine), and Pfizer (ziprasidone). He has received grant support from these companies, as well as from Astra Zeneca (quetiapine).

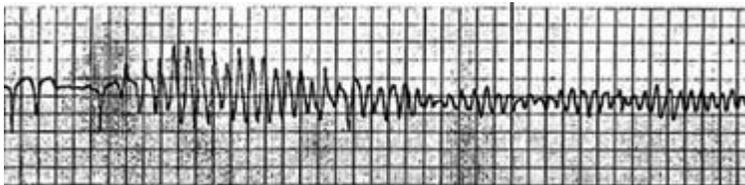
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Figure

Electrocardiogram showing torsade de pointes. Torsade de pointes, which generally occurs in patients with prolonged QT intervals, is characterized by QRS complexes that change amplitude and direction, or “twist.”



Discussion Questions

Submitted by M. Justin Coffey, MD, Psychiatry Resident, University of Michigan, Ann Arbor, Michigan, USA

1. Map the process that led to this patient being harmed, including the harm(s) itself. Where does your process map begin? Where does it end? See IHI.org for resources on process mapping.
2. This case involves communication between teams, namely the primary team and the psychiatry and neurology consultation teams. Even though the details of the communication are omitted, what aspects of teamwork impacted this patient's care? Was the impact positive? Negative? What challenges do primary teams face when seeking and deciding whether to follow management recommendations from consultant services?
3. What role does this hospital's "safety protocol" play in this case? Was harm avoided by its being in place? Discuss the ways protocols can be helpful to improving patient care? In what ways might protocols be ineffective interventions or even obstacles to improvement?
4. This patient was diagnosed as having delirium (a state of decreased level of alertness and connectedness with one's immediate environment that often comes with delusions and hallucinations). Often, delirium that arises on a general medical floor (as opposed to a psychiatric unit) is managed with medications (as in this case) but also with physical restraints (not employed in this case). While physical restraints restrict certain rights of patients, they also serve to protect them from themselves by, among other things, limiting the amount of medication needed to control agitated behavior. Should physical restraints be considered "harm"? Are they safer or less safe than using medications first to manage delirium? How would you go about teaching non-mental health care specialists how to use restraints safely and effectively?
5. Upon review of this case, an "interdisciplinary adverse event review committee" was alarmed by the fact that this patient was administered IV haloperidol without simultaneous cardiopulmonary monitoring (e.g., telemetry). The committee has asked you to chair an "improvement team" to rectify this situation. What steps would you take to ensure that the next patient administered IV haloperidol in your hospital would be connected to appropriate cardiopulmonary monitoring?
6. If you were a member of the team caring for this patient, how would you explain what happened to her? Is an apology warranted? Since polymorphic ventricular tachycardia is a known complication of using IV haloperidol, when it occurs, does it constitute an "error"?

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<http://www.webmm.ahrq.gov/case.aspx?caseID=40>

AHRQ WebM&M is produced for the Agency for Healthcare Research and Quality by a team of editors at the University of California, San Francisco. The AHRQ WebM&M site was designed and implemented by Silverchair.