Theoretical and practical issues related to the management of severe and refractory psychotic illness complicated by pulmonary embolism

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ABSTRACT

Pulmonary embolism (PE) is a potentially fatal condition. We describe the educative case of a young adult male, with a longstanding history of schizophrenia, who was receiving anticoagulant treatment because of repeated episodes of PE in the past. He presented with severe exacerbation of psychosis and did not respond to oral and parenteral antipsychotic medication during inpatient treatment. He was taken up for electroconvulsive therapy (ECT) and received a single ECT uneventfully. The ECT course had to be interrupted because of the unexpected development of a 4-day febrile illness, after which he experienced sudden onset breathlessness, which was diagnosed as acute-on-chronic PE. After the crisis resolved with 4 days of intensive care, he was managed with clozapine. We discuss concerns associated with the psychiatric management of patients with PE; special issues include the use of restraints, parenteral antipsychotic medications, anticoagulants, and ECT.

**Key words:** Anticoagulation, antipsychotic drugs, electroconvulsive therapy, intramuscular injection, pulmonary embolism, thromboembolism

INTRODUCTION

Medical comorbidity is common in patients with schizophrenia. Sometimes, the comorbidity is of an unusual nature, throwing up multiple management challenges. We present an instructive case of acute-on-chronic pulmonary embolism (PE) complicating a severe and treatment-refractory episode of schizophrenic illness.

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CASE REPORT

Mr. AP, a 25-year-old patient, was brought with a 1-month history of being abusive, aggressive, and assaultive, associated with poor sleep, and appetite. At the time of presentation, he was suspicious of people in his environment and his affect showed fear. Behavioral abnormalities such as gesticulating and talking to himself were apparent. Prominent auditory hallucinations were elicited on mental status examination.

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AP had been diagnosed with schizophrenia in 2007 and had been on maintenance oral antipsychotic treatment ever since. His course of illness was checkered by intermittent relapses due to poor adherence to medications. The most recent relapse occurred 6 months earlier, and there was a poor response to oral antipsychotic treatment because he continued to take his medications irregularly. The symptoms exacerbated during the month preceding admission, possibly because of even poorer medication adherence.

Importantly, AP had a history of 3–4 episodes of PE dating back to 2006; that is, before the onset of psychosis. He had been extensively investigated after the initial diagnosis of PE, but no cause or predisposing factors could be identified. There were no thromboembolic phenomena in other organ systems. There was no other medical comorbidity. He was receiving long-term warfarin treatment (2.5–5.0 mg/day) with regular international normalized ratio (INR) monitoring, along with sildenafil (20–40 mg/day) for pulmonary hypertension, but because of poor adherence to his medical regimen, he suffered recurrences of PE much as he had suffered relapses of psychosis.

AP was admitted for the management of severe psychosis. He was treated with oral olanzapine (up to 40 mg/day), oral haloperidol (up to 40 mg/day), and oral aripiprazole (up to 20 mg/day), separately and together, across a period of nearly 2 weeks. Haloperidol, along with promethazine, was also occasionally administered by the intravenous route. Physical restraints were intermittently applied, depending on the degree of agitation and aggression at the time. All through his admission, his PE regime (warfarin and sildenafil) was continued, maintaining his INR at 2–3; at times that he refused oral treatment, anticoagulation was maintained using parenteral heparin.

The intravenous antipsychotic treatment, the high oral antipsychotic doses, and the polypharmacy were necessitated by the severity of illness and by concerns related to the use of intramuscular (IM) depot antipsychotics and concerns related to the application of physical restraints. IM injections were considered undesirable because of the risk of hematoma formation within muscle tissue in an anticoagulated patient, and physical restraints were considered undesirable because of the risk of bruising at the restraint application sites, and the risk of deep vein thrombosis due to venous stasis in an immobile patient.

Given the severity of the psychosis, the almost complete absence of response to nearly 2 weeks of antipsychotic medication, and the practical need for rapid symptom resolution, electroconvulsive therapy (ECT) was planned. Chest X-ray, routine blood tests, and two-dimensional echocardiography results were within normal limits. Consent for high-risk ECT was taken because, with a history of PE, and ongoing treatment with anticoagulants, there was a theoretical risk of both coagulation events and bleeding events associated with ECT. Besides anesthesiological clearance, cardiological clearance for ECT was also obtained.

Bitemporal brief-pulse ECT was initiated with pentothal anesthesia (300 mg), glycopyrrolate (0.2 mg), and succinylcholine (35 mg) premedication; the delivered charge was 120 mC. The patient experienced a generalized tonic-clonic convulsion and recovered uneventfully. However, about 30 h after ECT, he unexpectedly developed a febrile illness (temperature, 38.3–39.4°C) which persisted for about 4 days. ECT was therefore discontinued after the first treatment, and the patient was managed on oral antipsychotics, as earlier.

Despite optimization of the INR and maintenance of adequate hydration, the patient experienced sudden onset breathlessness about 4 days after ECT; that is, on the day the fever subsided. The breathlessness was severe; the patient was observed to be gasping, and accessory muscles of respiration were in use. His oxygen saturation was in the region of about 80%. Because no airway-related explanation for the breathlessness was evident, an episode of PE was suspected. The revised Geneva score for PE risk was 8; this indicated an intermediate risk of current PE. Computed tomography pulmonary angiography showed a large saddle-shaped thrombus in the left pulmonary artery and a small, nonocclusive thrombus in the right pulmonary artery. Recent thrombosis was confirmed by the detection of a D-dimer level of approximately 8 times above the maximum normal value.

A diagnosis of acute-on-chronic PE was made, and the patient was oxygenated and managed in intensive care for the next 4 days. Afterwards, he was started on clozapine. There was rapid improvement within a week, and he was discharged a few days later on clozapine 250 mg/day.

DISCUSSION

There are several concerns that arise in the context of this patient. These are the risk of venous thromboembolism and PE in association with antipsychotic treatment; risks associated with the use of IM antipsychotic injections and restraints in anticoagulated patients; and risks associated with the use of ECT in anticoagulated patients with a history of PE.

Antipsychotic drugs and risk of thromboembolism
Antipsychotic drugs can decrease physical activity levels through several routes; for example, directly and acutely, such as through sedation, and indirectly and chronically, such as through weight gain. Reduced physical activity and spells of inactivity could increase the risk of thromboembolism through venous stasis; and, indeed, a recent systematic review and meta-analysis suggested that
there is a 50% increased risk of venous thromboembolism associated with antipsychotic exposure (11 studies; odds ratio [OR]: 1.54; 95% confidence interval [CI]: 1.28–1.56). Another review found that the highest risk was associated with clozapine, followed by risperidone and olanzapine; the risk appeared to be dose-dependent, and associated with second-generation antipsychotics, low potency antipsychotics, and antipsychotic polytherapy. The risk may also be highest in the initial 3 months of treatment. Besides physical inactivity, other mechanisms have been proposed for antipsychotic-associated thromboembolism; these include enhanced platelet aggregation, increased levels of antiphospholipid antibodies, hyperprolactinemia, and hyperhomocysteinemia.

Significant associations notwithstanding, thromboembolism as an antipsychotic adverse effect is very rare; so rare, in fact, that reliable estimates are not available for absolute risk (most of the studies on the subject have been case-control studies). The implication, therefore, is that a clinician does not need to hesitate with a prescription of an antipsychotic on the grounds that it may trigger thromboembolic phenomena; however, in patients at known risk of thromboembolic phenomena, antipsychotic drugs, and drug regimens that increase the risk (as discussed above) may need to be cautiously prescribed. Anticoagulant measures, if indicated, require to be optimized and monitored.

**Antipsychotic drugs and risk of pulmonary embolism**

Antipsychotic drugs have been associated with PE, as well. Whereas an earlier meta-analysis narrowly failed to find a significant association between antipsychotic use and PE (3 studies; OR: 4.90; 95% CI: 0.77–30.98), the addition of this study changed the overall estimate, indicating that antipsychotic exposure increases the PE risk. Given the rarity of the adverse event, the clinical and management implications are the same as those suggested in the previous subsection, in the context of general thromboembolism.

**Electroconvulsive therapy, thromboembolism, and pulmonary embolism**

An interesting question is whether the convulsive contractions during ECT can dislodge existing clots, or whether the hyperdynamic circulation during ECT can create vascular turbulence, leading to thromboembolic complications. In this context, ECT has been safely administered in the presence of deep vein thrombosis complicating catatonia. In fact, ECT can be lifesaving in catatonia, a condition that is associated with prolonged immobility, dehydration, and an increased risk of venous thrombosis, and PE. Thromboembolic events are rare with ECT, but reports do exist; for example, described a patient with embolic stroke following ECT.

The above notwithstanding, PE may rarely occur during an ECT course or after ECT, and fatal outcomes have also been reported. Nevertheless, there are also reports of the safe use of ECT in patients with PE, including patients with recent PE. In fact, ECT had even been safely continued (after stabilizing the patient) when PE occurred during the ECT course. It is essential that, in patients at risk of thromboembolic phenomena, anticoagulant measures are optimized before ECT is undertaken.

ECT is of special concern in patients in whom pulmonary function is compromised because of recent PE. This is because the lungs may not be able to supply enough oxygen to meet myocardial demands during the seizure. In such patients, care must be taken to attenuate the tachycardia and systolic hypertension during ECT through the use of beta-receptor blockade.

**Electroconvulsive therapy in the anticoagulated patient**

When ECT is administered to anticoagulated patients, the risk of bleeding should be considered. This is because ECT is associated with a brief hypertensive surge during which capillary bleeding or blood vessel rupture is possible at vulnerable sites. An anticoagulated status increases the risk of significant bleeds. This risk, however, seems small and theoretical, and may be of concern only in specific situations, such as in patients with aneurysms or arteriovenous malformations, and those with acid peptic disease.

In this context, Mehta conducted a retrospective review of ECT in patients receiving long-term warfarin therapy. They identified 35 consecutive patients who had received a total of 300 ECTs with data available for 284 ECTs. There were no complications associated with ECT and anticoagulation despite the expected occurrence of transient, ECT-related tachycardia and hypertension. Earlier, Petrides and Fink also reported the safe use of ECT in patients receiving anticoagulant treatment.

However, one case of intracerebral hemorrhage has been reported in the context of ECT and anticoagulation. It has been suggested that, to lower the bleeding risk, the anticoagulation dose should not be too high. Issues related to the administration of ECT in anticoagulated patients are discussed in greater detail elsewhere.

**Physical restraints in the anticoagulated patient**

For two reasons, physical restraints are undesirable in anticoagulated patients. One is that restrained patients who are disturbed often struggle, and this can result in bruising at the restraint application sites. The other is that immobilization can result in venous stasis, and hence a risk of thromboembolic phenomena if the anticoagulation is inadequate.

Patients who need to be restrained may not cooperate well with regard to oral intake. Care must be taken to ensure...
adequate hydration lest hemoconcentration predispose to intravascular coagulation. It goes without saying that anticoagulant measures require to be optimized and monitored.

**Intramuscular injection in the anticoagulated patient**

Patients on anticoagulants should ideally avoid IM injections because of the risk of hematoma formation; this risk is expressed in anticoagulation treatment guidelines.[21,22] IM injections may cause tissue injury and may also puncture small blood vessels in their way. Nevertheless, many studies have documented the relative safety of IM injections in anticoagulated patients.[23-25] It has been suggested that if IM injections are required, sufficient pressure should be applied at the site of injection for a sufficient period of time to ensure that there is no leakage of blood into muscle tissue.[22] Whereas we might have administered depot antipsychotics to our patient in this manner, it is uncertain whether a depot drug would have elicited response when oral medications did not. However, given the past history of repeated noncompliance, it is possible that our patient will default on clozapine, as well, making maintenance treatment with a depot antipsychotic a necessary consideration.

Planned IM injections in patients on oral anticoagulation treatment can be undertaken by discontinuing the anticoagulation medication for a short period, such as 3 days, and then resuming the medication after the IM injection.

**Concluding notes**

Thrombi generally do resolve, especially when thrombolytics are used in treatment, and when anticoagulants are administered, because these tilt the body mechanisms toward thrombolysis. Unfortunately, many patients continue to have thrombi that do not resolve. In the case of PE, this can be because the condition is often not diagnosed or is diagnosed too late, by which time the thrombus becomes organized and becomes “chronic.” Our patient probably had a chronic thrombus because of late help-seeking and poor adherence to anticoagulant treatment.

The nature of the prothrombotic disorder in our patient was not identified; one probably existed, because he had had several PE episodes in the absence of any apparent predisposing condition such as major illness, fracture, or surgery. Antipsychotic medication is unlikely to have been causally responsible in the patient because PE antedated the schizophrenia. It is impossible to say, however, whether antipsychotic treatment increased the subsequent risk, resulting in the several PE episodes that he had suffered. In such patients, long-term anticoagulation proves necessary. In patients, such as ours, who do not maintain the target INR, dabigatran can be considered, or a similar drug that does not require monitoring. However, the treatment will be more expensive than conventional anticoagulation measures, increasing the risk of noncompliance. Notably, the saddle thrombus that was identified in our patient is amenable to surgical endarterectomy.

Finally, anticoagulant measures do not imply drug treatment alone; also important are avoidance of immobility, maintenance of adequate hydration, efficient treatment of infection, and adequate attention to other risk factors for intravascular coagulation.

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**Conflicts of interest**

There are no conflicts of interest.

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