Acta Neuropsychiatrica
An International Journal of Translational Neuropsychiatry

Acta Neuropsychiatrica 2012: 24: 361–368

DOI: 10.1111/j.1601-5215.2012.00641.x

Risperidone and pulmonary embolism: a harmful association? Case series and review of the literature

Gallerani M, Imberti D, Mari E, Marra A, Manfredini R. Risperidone and pulmonary embolism: a harmful association? Case series and review of the literature.

Objective: Risperidone is an atypical antipsychotic drug used to treat a number of psychiatric diseases, such as schizophrenia, schizoaffective and bipolar disorders and irritability in children with autism. Moreover, it is also often administered for short-term treatment of persistent aggression in people with moderate-to-severe Alzheimer's dementia. A possible association between risperidone and venous thromboembolism (VTE) has been described. We intended to verify the dimension of the problem in our hospital setting.
Methods: We considered all consecutive patients hospitalised in our Internal Medicine Department from January 2004 to December 2010, who were treated with risperidone and presented pulmonary embolism (PE).
Results: Four cases of patients, apparently free from the well-known major risk factors for VTE (i.e. cancer, prolonged immobilisation, acute cardiac and respiratory failure, infections), who presented PE associated with risperidone therapy, were reported in details.
Conclusions: A review of the available literature, discussing the possible different pathogenic reasons for this increased risk of VTE, is provided.

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Keywords: psychosis; risperidone; venous thromboembolism

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Accepted for publication November 13, 2011

Significant Outcomes

Our study showed:

- Pulmonary embolism is not a negligible finding in a cohort of patients admitted to a medical department (0.66%).
- A possible association between risperidone and pulmonary embolism has been shown (26/494), especially in elderly patients.
- Four patients, apparently free from all the major risk factors, developed a pulmonary embolism, although they had all a favourable outcome.

Limitations

- As a result of a small series of clinical cases, any definite conclusion cannot be drawn. Further investigation on larger scale cohorts of patients will be needed to confirm this possible, and potentially harmful, association.

Introduction

Risperidone is an atypical antipsychotic, belonging to the chemical class of benzisoxazole derivatives, used to treat a number of psychiatric diseases, such as schizophrenia (including adolescent schizophrenia), schizoaffective disorder, the mixed and manic states associated with bipolar disorder, and irritability in children with autism. Moreover, risperidone is also often administered for the short-term treatment (up to 6 weeks) of persistent aggression in people with moderate-to-severe Alzheimer's dementia (1–6). Venous thromboembolism (VTE) is a relatively frequent cardiovascular disease, with a yearly incidence of about 150–220 new cases/100 000 patients (7), and pulmonary embolism (PE) ranks second among causes of out-of-hospital sudden death (8). Among a number of inherited and acquired risk factors, antipsychotic therapy is a well-known iatrogenic risk factor for VTE, and a careful search for other predisposing or favouring risk factors for VTE should be done before starting any antipsychotic treatment (9).

We report here four cases of patients with PE associated with risperidone therapy and discuss its possible role as risk factor.

Methods

We considered all consecutive patients hospitalised in our Internal Medicine Department from January 2004 to December 2010, who were treated with risperidone and presented PE.

Results

During the considered period, 49 335 patients were hospitalised in the Internal Medicine Department, and 326 (0,66%) of them suffered from PE. As many as 494 patients were assuming risperidone and 26 of them (5.2%) suffered from PE. In particular, we considered only those patients ($n = 4$) apparently free from the well-known major risk factors for VTE (i.e. cancer, prolonged immobilisation, acute cardiac and respiratory failure, infections).

Detailed informations of all four cases are provided.

Case report 1

An 81-year-old woman, with a history of hypertension and depression, and under therapy with metoprolol tartrate 50 mg/bid, telmisartan 40 mg/day, picotamide 300 mg/day, and citalopram 20 mg/day, started complaining of nausea 2 weeks prior to admission. Three days before, she presented psychomotor agitation, insomnia and auditory hallucinations. On admission, temperature, pulse, arterial blood pressure and respiration rate were 36.8 °C, 78/min regular, 130/85 mmHg and 18 breaths/min, respectively. On physical examination, cardiovascular, respiratory, abdominal and neurological findings were unremarkable. In particular, bone-tendinous reflexes, tactile, thermal and pallaesthetic sensitivity were normal. There were no limitations in personal autonomy [Barthel score: activities of daily living (ADL) 89/100; Braden score: 21/22]. Blood chemistry panel as well as instrumental examinations, such as electrocardiogram (ECG), chest X-ray, abdominal ultrasound and echocolordoppler of carotid arteries, were normal. Computed tomography of the brain showed a slight hypodensity, suggesting chronic ischaemia, at the left external capsula. An evening dose of risperidone (1 mg/day) was therefore added to home therapy. During the first days of hospitalisation, the patient experienced disappearance of hallucinations, mood improvement and normalisation of sleep-wake cycle. Two days after starting risperidone therapy, the patient presented a lipothymic episode with hypotension (70/40 mmHg). Heart rate was regular, 86/min, oxyhaemoglobin saturation was 94% on room air, the ECG was unmodified, cardiac enzymes such as myoglobin and troponin-I were normal, but D-dimer was elevated (1359 ng/ml vs. 0–370 normal range). A 99mTc-MAA lung scan showed, on the right lung, two defects of the lateral segment of the upper lobe and the upper segment of the lower lobe. No deep venous thrombosis was detected by the Doppler ultrasound of the lower limbs. The patient started an anticoagulant therapy with enoxaparin 6000 UI/bid for 6 days, combined with warfarin, and she dramatically improved, with normalisation of blood pressure within 24 h and of D-dimer on the third day. A clinically stable condition allowed hospital discharge 6 days after the occurrence of PE.

Case report 2

An 84-year-old woman, with a history of Alzheimer's disease, arterial hypertension, chronic atrial fibrillation and chronic coronary heart disease on admission, was treated with metildigoxin 0.2 mg/day and nitroglycerin transdermal 10 mg/day.

Two weeks before, she presented spatial and temporal disorientation and psychomotor agitation, and a therapy with risperidone 2 mg/day was started. The patient was hospitalised in our department for a sudden onset of dyspnoea associated with lipothymia and followed by a thoracic trauma with fractures of 6th, 7th, 8th and 9th right ribs. On admission, temperature, pulse, pressure and oxyhaemoglobin saturation were 37.1 °C, 86/min irregular for atrial fibrillation, 130/80 mmHg and 86% on room air and 98% under oxygen therapy 2 l/min, respectively.

https://doi.org/10.1111/j.1601-5215.2012.00641.x Published online by Cambridge University Press

The patient was suffering, polypnoeic (36 breaths/min), and presented spatial and temporal disorientation; respiratory sound was diffusely reduced, with the presence of basal crackles.

The patient was disorientated; bone-tendinous reflexes, tactile, thermal and pallaesthetic sensitivity were normal. An important limitation in personal autonomy was present (Barthel score: ADL 44/100; Braden score: 13/22). Laboratory tests showed that the Hb was 10.3 g/dl, fibrinogen 653 mg/dl (n.v. 150–400) and D-dimer 856 ng/ml (n.v. 0–370).

A computed tomography of the chest revealed the presence of several small defects, suggesting pulmonary bilateral PE. No deep venous thrombosis was discovered from bilateral Doppler ultrasound of the lower limbs. The patient was treated with enoxaparin (6000 UI/bid) and showed a satisfactory clinical improvement within a few days. The patient was discharged from the hospital 8 days after the occurrence of PE in a stable cardiorespiratory condition, with a prescription for secondary prophylaxis with enoxaparin (6000 UI o.d.).

Case report 3

An 87-year-old woman, with a history of chronic bronchitis, hypertension, arthrosis, bilateral glaucoma and depression, was hospitalised for a sudden onset of dyspnoea followed by syncope. Her domiciliary therapy included ramipril 2.5 mg/day, lansoprazole 30 mg/day, salbutamol-fluticasone 50/250 μg/bid, fluoxetine 20 mg/day and lorazepam 2.5 mg. Three months before hospitalisation, the patient complained of an initial and progressive reduction of her autonomy and recurrent episodes of disorientation, and a treatment with haloperidol was started. After one week, because of intolerance, the haloperidol was stopped and risperidone (1 mg/day) was started.

On admission, temperature, pulse, blood pressure, respiration rate and oxyhaemoglobin saturation were 36.7 °C , 106/min regular, 140/70 mmHg, 36 breaths/min and 92% under oxygen therapy 3 l/min, respectively.

The patient showed spatial and temporal disorientation, but neurologic clinical examination was normal. Cardiovascular, respiratory, and abdominal examinations were normal. Barthel score was 86/100 and mini mental state was 16/30. Laboratory tests showed that the D-dimer was 4355 ng/ml (n.v. 0–370), Hb 9.9 g/dl, fibrinogen 560 mg/dl (n.v. 150–400) and C-reactive protein 4 mg/dl (n.v. 0–0.50). The ECG showed sinusal tachycardia (110 bpm) and a complete right branch block with abnormalities of inferior and lateral repolarisation. Chest X-rays showed bilateral signs of heart failure, right basal effusion and enlargement of the cardiac silhouette. Chest computed tomography revealed the presence of a large embolus at the bifurcation of the main pulmonary arteries, and a pulmonary infarction of the right inferior lobe with slight pleural effusion. The abdominal ultrasound was normal, while Doppler ultrasound of the lower limbs found a calf and popliteal right thrombosis. The patient was treated with enoxaparin (6000 UI/bid) and warfarin, with rapid clinical improvement within a few days. The patient was discharged 10 days after the occurrence of PE, in good and stable cardiorespiratory clinical conditions, and with the recommendation of warfarin for at least 6 months.

Case report 4

A 61-year-old man, affected by Paget's disease, hypertension and depression with a clinical history negative for previous episodes of PE, was admitted to the hospital complaining of ingravescent dyspnoea. Home treatment included enalapril 20 mg/day, association of furosemide (25 mg/day)-spironolactone (37 mg/day), lorazepam 2.5 mg/day, and risperidone (4 mg/day) (started 3 years previously), About 3–4 weeks before, he presented general discomfort, and later marked asthenia, dyspnoea and lower limb oedema.

On admission, temperature, pulse, pressure, respiration rate and oxyhaemoglobin saturation were 36.7 °C, 86/min regular, 140/70 mmHg, 20 breaths/min and 94% in room air, respectively. Respiratory and cardiac examinations were normal, with a slight jugular turgor. The liver was palpable at 2 cm below the right costal margin, with no tenderness. There were neither clubbing nor superficial lymphadenopathies. Carotid pulses were symmetrically normal. A central nervous system examination was normal. There were no limitations in personal autonomy (Barthel score: ADL 88/100; Braden score: 20/22). Laboratory tests showed that the D-dimer was 710 ng/ml (n.v. 0–370), pro-brain natriuretic peptide (BNP) 1418 pg/ml (n.v. 0–241), plasma homocysteine levels 19.2 μmol/l (n.v. 5–15). Platelet count, fibrinogen, prothrombin time (PT), activated partial thromboplastin time (APTT), β2 microglobulin, folic acid, cholesterol level, thyroid functions, serum electrolytes, calcium, and phosphate were normal. Oncologic markers, anti-hepatitis B and C antibodies, IgG and IgM anti-phospholipids, lupus anticoagulant, anti-nuclear antibodies (ANAs), anti-DNA antibodies, anti-mitochondrial antibodies (AMA), extractable nuclear antigens (ENA) screening, anti-neutrophil cytoplasmic antibody test were negative.

An ECG showed the presence of a 'pulmonary' P wave with signs of right ventricular dysfunction,

https://doi.org/10.1111/j.1601-5215.2012.00641.x Published online by Cambridge University Press

while the cardiac silhouette was enlarged during a chest X-ray exam.

An abdominal ultrasound and echocolordoppler of the vein system of the lower limb were normal.

A computed tomography of the chest revealed the presence of several defects suggestive of pulmonary distal bilateral PE, with an enlargement of the pulmonary artery and its main branches. A transthoracic echocardiogram detected an important increase of the right heart pressure (severe pulmonary hypertension: 85 mmHg), enlargement and hypokinesia of the right ventricle, enlargement of the right atrium (27 cm^2) and moderate pulmonary valve insufficiency. A pulmonary angiogram confirmed the presence of multiple distal bilateral thromboemboli.

The patient was treated with enoxaparin (6000 UI/bid), and, after 2 days, with vitamin K antagonists. After 4 months of follow-up, the progressive and significant increase of pulmonary hypertension, distal location of the emboli and unsuitability for pulmonary thromboendoarteriectomy, the patient was scheduled to start treatment with bosentan.

Discussion

Risperidone is a selective monoaminergic antagonist with a high affinity for serotonin type 2 (5HT2), dopamine type 2 (D2), H1 histaminergic, a1 and a2-adrenergic receptors. It acts as an antagonist at other receptors, but with lower potency. It has a low-to-moderate affinity for serotonin 5HT1C, 5HT1D and 5HT1A receptors, a weak affinity for the dopamine D1 and haloperidol-sensitive sigma sites, and no affinity for cholinergic muscarinic or $\beta 1$ and $\beta 2$ adrenergic receptors.

Risperidone is indicated for acute and chronic schizophrenic psychoses and other psychotic conditions with positive and negative symptoms. It is also indicated for affective symptoms associated with schizophrenia (1–6,10–39), and it has been shown that the severity of psychotic symptoms may be associated with reduced heart rate variability (40). Moreover, paliperidone (the principal active metabolite of risperidone) has been shown to be effective, at low doses, in reducing behavioural disturbances and symptoms in patients with delirium (41).

The side effects in patients receiving risperidone are numerous (4–6,10–11,13–16,18–19,21–29,31–48) and sometimes fatal. Although the causes of death associated with the use of risperidone were different, most of them appeared to be related either to infections (e.g. pneumonia) or cardiovascular events (e.g. heart failure, sudden death, stroke or PE). A possible association between PE and the use of antipsychotic agents were first suggested in the 1950s after the introduction of phenothiazines (49). Since then, several case studies have supported the notion of an increased risk of VTE with conventional antipsychotic agents (50–52). More recently, Zornberg and Jick (53) documented a seven-fold increase in the risk of idiopathic VTE amongst users of conventional antipsychotic agents who were younger than 60 years and free of major risk factors. A similar thromboembolic effect of conventional antipsychotic agents has also been observed among individuals with risk factors for VTE (9,54–57).

Atypical antipsychotic agents represent a newer class of drugs characterised by a distinct pharmacologic and clinical profile. They are more effective for the treatment of negative symptoms and confer a lower risk of extrapyramidal adverse effects compared to conventional agents (58,59). An association between atypical antipsychotic agents and VTE has been previously suggested for clozapine among young adults with psychiatric disorders (57,60–62). This association is primarily supported by results of a large record-linkage study in which a five-fold increase of fatal PE was found (56,62). Three cases of VTE have been reported amongst elderly patients treated with olanzapine (63), and one case in a young man with a psychotic disorder (57). A possible association between risperidone and massive PE has been suggested from a review of autopsy reports in the Japanese population (64). A single study compared the effect of antipsychotic agents on the risk of VTE relative to that of thyroid replacement therapy. It found only a slightly increased risk with butyrophenones (65).

An Italian study aimed at estimating the effect of atypical and conventional antipsychotic agents on the risk of hospitalisation for VTE among elderly patients found that relative to non-users, the rate of hospitalisation for VTE was increased for users of atypical antipsychotic agents, including risperidone [adjusted hazard ratio (HR): 1.98; 95% confidence interval (CI): 1.40–2.78], olanzapine (adjusted HR: 1.87; 95% CI: 1.06–3.27), and clozapine and quetiapine fumarate (adjusted HR: 2.68; 95% CI: 1.15–6.28). On the other hand, the rate of VTE associated with phenothiazines or other conventional agents did not increase (66).

A case of a 25-year-old man with an early onset of schizoaffective disorder, without an identified risk factor for thromboembolism, who developed recurrent PE has been reported. Of interest is that one episode of PE occurred shortly after initiating treatment with olanzapine and two episodes during treatment with risperidone (67). More recently the use of risperidone has been thought to have played a contributing role in the occurrence of a PE in a 7-year-old girl treated with this drug in the last 5 months for hyperactivity and impulsive behaviour (68).

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Finally, the Italian Pharmacovigilance Network (48) has reported 2 cases of PE associated with the use of risperidone and the English Pharmacovigilance Network of MHRA (Medicines and Healthcare Products Regulatory Agency) has reported 30 cases of PE and 1 case of pulmonary artery thrombosis as adverse drug reactions related to risperidone (69), respectively.

Applying the algorithm of Naranjo (70) in our report, the relationship between risperidone and the onset of VTE is possible (score +4) for cases 1, 2 and 3, and probable (score +5) for case 4.

Several underlying mechanisms have been proposed to explain the association between antipsychotic drugs and VTE. Traditionally, conventional antipsychotic agents have been associated with enhanced aggregation of platelets (71). Conversely, *in vitro* data does not support a direct effect of risperidone on human platelet function, plasma coagulation or fibrinolysis (72). However, atypical agents show a high affinity for the serotonin receptor type 2A, and serotonin-induced platelet aggregation may be affected (73). Antispychotics, such as olanzapine, risperidone or clozapine, which have an affinity for 5HT2 receptors, can induce a release of serotonin, and the subsequent increase in plasma serotonin might provoke an enhanced aggregation of platelets, thereby increasing the risk of thrombosis (74–76).

Moreover, sedation induced by antipsychotic drugs can increase venous stasis (77). Hypercoagulability via an enhanced aggregation of platelets with conventional antipsychotics has been suggested (71,76), and a nearly three-fold increased risk of peripheral oedema associated with risperidone has been described (4).

Immobilisation is considered an important risk factor for surgical and bedridden patients but also for healthy persons during long-distance air travel or in persistent sitting positions. The conditions such as physical restraint, severe catatonia and neuroleptic malignant syndrome immobilisation, causing a slowing down of the bloodstream, are likely to be the common risk factors for the development of VTE. Additional risk factors for VTE inherent to the specific psychiatric conditions are: heavy resistance during physical restraint situations (damage to the vessel walls), lack of fluid intake in severe catatonia (hypercoagulability), fever and rhabdomyolysis in the neuroleptic malignant syndrome (hypercoagulability). The association could also be related to underlying risk factors present in patients with psychosis, such as smoking (77) and weight gain induced by antipsychotic agent (44). Another hypothesis is the increased levels of lupus anticoagulant and anticardiolipin antibodies induced by conventional antipsychotic agents and clozapine (78,79). A number of plausible underlying mechanisms have also been described: hyperhomocysteinaemia, which is probably more related to the psychiatric disorder itself (80,81). Other metabolic abnormalities (dyslipidaemia, increased plasma levels of leptin and glucose) have been observed among users of atypical antipsychotic agents (42,82) known to be associated with decreased fibrinolytic activity (72); hyperprolactinaemia in an indirect pathway (17), which is perhaps unlikely to be an etiologic factor in the early thromboembolic occurrence.

In our series, none of the patients suffered from catatonia, neuroleptic malignant syndrome immobilisation, rhabdomyolysis or autoimmune disease.

Only patient 4 was chronically treated with furosemide and risperidone. In patients treated with both furosemide and risperidone a higher mortality rate was reported when compared with the patients treated with risperidone or furosemide only. It has been thought that this association could be related to an increased risk of dehydration.

Moreover, it should be noted that the prescription of risperidone was debatable and even not indicated in patients 2 and 3 (1,5,6,23,30,47). Risperidone has been administered in patients with Alzheimer's disease for reducing psychomotor agitation.

It is well known that a large percentage (about 80%) of patients with dementia can present behavioural changes or psychological symptoms in the course of the illness. This clinical situation causes a lower quality of life for both patients and carers, and often results in transfer to residential care and higher costs. Currently, no drugs are licensed for behavioural changes and psychological symptoms in patients with dementia. Nevertheless, antipsychotic medications are currently used for people with dementia, for both psychotic symptoms and for less specific problems such as agitation and aggression. There have also been long-standing concerns about the inappropriate use of these drugs in such situations.

In conclusion, our report suggests that risperidone may increase the risk of PE. Thus, it is advisable to be cautious when prescribing risperidone, particularly for elderly patients.

Acknowledgement

This paper has been supported, in part, by a scientific grant (FAR - Fondo Ateneo Ricerca) from the University of Ferrara, Italy.

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