

Fatal Venous Thromboembolism Associated with Antipsychotic Therapy

Raymond E Farah, Nicola M Makhoul, Rola E Farah, and Moshe D Shai

OBJECTIVE: To describe the occurrence of pulmonary embolism (PE) as a rare adverse effect of clozapine that is treatable, but sometimes fatal, and survey the literature on the subject in the hope of increasing awareness of the potential danger that may result from drug interactions.

CASE SUMMARY: A 47-year-old woman treated with clozapine and paroxetine was admitted to the hospital with dyspnea and swelling of the leg. The patient was diagnosed as having PE and was treated with intravenous heparin. On hospital day 7, sudden acute respiratory failure developed and the patient died. Postmortem examination confirmed the existence of massive PE.

DISCUSSION: The woman had no identifiable risk factors other than receiving a combination of clozapine and paroxetine, with a demonstrated elevated clozapine blood concentration. Use of the Naranjo probability scale revealed a probable likelihood that the adverse reaction was drug related.

CONCLUSIONS: The association of antipsychotic drugs and venous thromboembolism has been previously described, but is still a rare finding. This case highlights the importance of monitoring and possibly discontinuing treatment when venous thrombosis is suspected. There should be careful monitoring, especially in patients with risk factors for thrombosis. Finally, antidepressant-antipsychotic drug combinations can increase the risk of rare adverse effects, such as venous thromboembolism, even in the absence of other risk factors.

KEY WORDS: clozapine, paroxetine, pulmonary embolism, venous thromboembolism.

Ann Pharmacother 2004;38:1435-8.

Published Online, 27 Jul 2004, www.theannals.com, DOI 10.1345/aph.1E021

Pulmonary embolism (PE) and deep vein thrombosis (DVT) are common causes of illness and death in all age groups. Prompt diagnosis and treatment can reduce the morbidity and mortality rate of the disease. Unfortunately, the diagnosis is missed more often than it is made because PE frequently causes only vague and nonspecific symptoms. In >90% of the episodes of PE, the thrombi originate from leg veins; however, PE can arise from DVT anywhere in the body. Some studies show that the overall mortality rate of PE in untreated patients is 25–30% and 5–8% in patients who received treatment. Thrombosis in the veins is triggered by venostasis, hypercoagulability, and vessel wall inflammation (Virchow triad).^{1,2} All known clinical risk factors for DVT and PE have their basis in one or more of the triad, such as gynecologic (pelvic) surgery, major trauma, indwelling venous catheter, immobilization, pregnancy, malignancy, drugs such as oral contraceptives, and genetic factors.³

We report a rare case of PE and DVT associated with the use of an antipsychotic drug and antidepressant that was diagnosed and treated appropriately, but the patient deteriorated and died. Psychiatric disorders themselves and treatment with conventional antipsychotic drugs have, in a number of early studies, been associated with venous thromboembolism. In addition, recent epidemiologic data support this association, especially between the atypical antipsychotic agent clozapine and venous thromboembolism. We presumed that the antidepressant increased the blood concentration of the antipsychotic.

Case Report

A 47-year-old woman had been hospitalized for many years in a psychiatric institution and treated with clozapine 300 mg/day and paroxetine 20 mg/day over a period of 2 years (these were the only medications that she was receiving). She was admitted to our hospital due to swelling of her right leg and breathlessness that had developed several days prior to admission. Chest X-ray was normal, but a ventilation/perfusion scan confirmed a mismatch defect involving most of the lateral segment of the right middle lobe of the lung (high probability of PE). Doppler ultra-

Author information provided at the end of the text.

sonography of the lower extremities was unremarkable. Physical examination showed a dyspneic patient with respiratory rate of 30 breaths/min, blood pressure 130/90 mm Hg, pulse 110 beats/min, temperature 35 °C, and weight 60 kg. The patient was alert without any evidence of catatonia. Lung examination revealed mild wheezing on auscultation over both lung fields, and cardiac examination revealed normal S1 and S2, with no S3, S4, murmur, or rub. The abdomen was soft and not tender, and there was no organomegaly. The lower extremities revealed swelling of the right leg.

The initial laboratory results demonstrated hemoglobin (Hb) 11 g/dL, hematocrit 32%, total white blood cell count $11 \times 10^3/\text{mm}^3$ with normal differential count, platelet count 132 000, and mean corpuscular volume $90 \mu\text{m}^3$. Blood urea, serum creatinine, blood glucose, and serum electrolytes were normal. Liver function tests showed aspartate aminotransferase 208 IU/L (normal 15–50), alanine aminotransferase 566 IU/L (10–35), and lactic dehydrogenase 1100 IU/L (230–460). The remaining liver function tests and enzymes were normal, as were blood lipids. Arterial blood gas analysis showed pH 7.43, PO_2 50 mm Hg, PCO_2 25 mm Hg, oxygen saturation 82%, and bicarbonate 21 mEq/L. Prothrombin time and activated partial thromboplastin time were normal. The lupus anticoagulant was negative and anticardiolipin antibody immunoglobulin M and G were normal. Protein C and S activity was normal.

The clozapine blood concentration at admission was 600 ng/mL. The antigenic antithrombin concentration was normal. An electrocardiogram showed sinus tachycardia with T-wave inversion in leads VI–V4. The patient was diagnosed as having acute PE due to chronic antipsychotic drug treatment. She was treated with intravenous heparin 1200 units/h, which stabilized her condition for several days. On day 7, acute respiratory failure developed and the patient needed mechanical ventilation. Several hours later, she died. A postmortem examination showed a very large thrombus in the right pulmonary artery and another thrombus in the right popliteal vein.

Discussion

Drugs that cause PE most frequently are oral contraceptives, tamoxifen, raloxifene, cancer chemotherapy agents, Chinese herbal remedies, and specific cyclooxygenase 2 inhibitors.^{4–8} The use of these drugs must be considered in the differential diagnosis of every case with thromboembolic event.

After discovery of the neuroleptic qualities of chlorpromazine and its analogs in the early 1950s and their widespread application, a higher incidence of venous thromboembolism was described in the German^{9,10} and French¹¹ literature between 1953 and 1977. Several of these reports were case series, but some contained control groups.^{9–11} A comprehensive study compared 2 groups of patients between 1953 and 1963 (1172 schizophrenic or depressive patients on chlorpromazine, amitriptyline, or imipramine vs 1172 psychiatric patients who did not use neuroleptic or antidepressant medication).¹² The frequency of thromboembolic complications was 2.9% and 0.6%, respectively. The report contains multiple references to the literature, among others, a 1959 study that found 11 cases of venous thrombosis among 338 phenothiazine users versus only one case in a non-phenothiazine control group.¹⁰ In the last 4 years, further data were published on the thromboembolic complications of antipsychotic drugs. A Swedish study reported 6 cases of PE and 6 of venous thrombosis during clozapine treatment.¹³ Two other studies were from the Netherlands¹⁴ and US.¹⁵

Thromboembolic complications have been associated with psychiatric disease and psychotropic drug therapy and are more common than other complications such as agran-

ulocytosis, congestive heart failure, and liver damage. Thromboembolic complications are difficult to diagnose in the psychiatric patient; the majority are discovered on post-mortem examination.^{14,16} Venous thrombosis seems to be associated with the use of neuroleptic drugs in psychiatric patients. However, it cannot be excluded that the findings are an expression of some other underlying factor that could predispose to thrombosis. Nevertheless, we conclude that the association between venous thrombosis and psychiatric medications is worthy of renewed investigation, with an emphasis on the effect of neuroleptic drugs.¹³ Hagg et al.¹³ concluded that the assumed risk of thromboembolism in clozapine-treated patients is at least one per 2000–6000, especially in the initial 3 months of treatment. Men are more prone to develop this reaction — 77% of affected patients were men.¹³ In our case, the patient was a woman with no known risk factors or other medications suspected to increase the risk for thrombosis. The biological mechanisms responsible for this possible adverse reaction are unknown, but a number of hypotheses have been suggested. The increased risk may be the result of drug-induced sedation, obesity, hyperleptinemia, antiphospholipid antibodies, or increased activity in the coagulation system. Strong affinity for the 5-HT_{2A} receptor of the novel antipsychotic may increase coagulability and the risk of thrombosis.¹⁷ The association could also be related to underlying risk factors present in patients with psychosis, such as smoking.^{2,11} Zornberg and Jick¹⁵ reported that the group most at risk for venous thrombosis was using a mild antipsychotic for a short time and that the link was not dose dependent.

Combination drug therapy may lead to unpredictably high antipsychotic blood concentrations that, in turn, can increase the risk of thromboembolism. Clozapine represents an important pharmacologic advance for many patients with treatment-resistant schizophrenia. Indeed, the overall mortality rate in this population has been shown to be lower, perhaps because of a significantly reduced risk of suicide.¹⁸ Good medical practice dictates that optimal therapy is provided when these benefits are balanced with the safety of clozapine. Despite the limitations of present knowledge, clinicians should be aware of this possible adverse reaction and should consider interrupting or changing the antipsychotic regimen in patients with other risk factors.¹⁹ Use of the Naranjo probability scale indicated a probable relationship between venous thromboembolism and antipsychotic drug therapy in our patient.²⁰ If the increased risk of thromboembolism is true in such patients, further questions need to be addressed, such as Would thrombophilia testing be useful for patients using long-term antipsychotic drugs for psychiatric reasons? If the mechanism of action in some cases is via stimulation of anticardiolipin antibodies, would testing before treatment be beneficial and justified, especially in pregnant women? Should patients using these drugs for any reason be offered antithrombotic prophylactic treatment? Is it justified to combine 2 drugs, as in our case, known to cause thrombotic events and drug interaction?²¹ In such cases, close moni-

toring and possible discontinuation of treatment after a diagnosis of venous thrombosis are recommended. More studies are needed to further elucidate this adverse effect, particularly to determine the incidence rate, possible predisposing factors, and biological mechanisms involved.¹⁹

Summary

The increased risk of venous thromboembolism with the use of antipsychotic drugs is rare and should not discourage their use when indicated. Nevertheless, healthcare providers must be aware of this treatable, although potentially fatal, adverse reaction when starting treatment, especially in patients who have other risk factors for venous thromboembolism.

Raymond E Farah MD, Specialist in Internal Medicine, Department of Emergency, Western Galilee Hospital–Nahariya, B Rappaport Faculty of Medicine, Technion, Nahariya, Israel

Nicola M Makhoul MD, Director of Respiratory Intensive Care, Western Galilee Hospital–Nahariya

Rola E Farah MD, Specialist in Obstetrics and Gynecology, Department of Obstetrics and Gynecology, HaEmek Medical Center, Afula, Israel

Moshe D Shai MD, Director of Internal Medicine, Department F, Western Galilee Hospital–Nahariya

Reprints: Raymond E Farah MD, Emergency Department, Nahariya Hospital, Western Galilee Hospital–Nahariya, POB 21, Nahariya 22100–Israel, fax 972(4) 9107482, raymondfarah@hotmail.com

We thank Ms. Tobie Kuritsky for grammatical correction of the article.

References

- Encke A. [Pathophysiology of venous thrombosis] German. *Langenbecks Arch Chir* 1977;345:323-9.
- Thornycroft IH, Goldzicher JW. Venous thromboembolism. A review. *J Reprod Med* 2003;48(11 suppl):911-20.
- Harrington DJ, Malefora A, Schmelova V, Kapustin S, Papayan L, Blinov M, et al. Genetic variations observed in arterial and venous thromboembolism — relevance for therapy, risk prevention and prognosis. *Clin Chem Lab Med* 2003;41:496-500.
- Dhingra K. Selective estrogen receptor modulation: the search for an ideal hormonal therapy for breast cancer. *Cancer Invest* 2001;19:649-59.
- Clemett D, Spencer CM. Raloxifene: a review of its use in postmenopausal osteoporosis. *Drugs* 2000;60:379-411.
- Falanga A, Donati MB. Pathogenesis of thrombosis in patients with malignancy. *Int J Hematol* 2001;73:137-44.
- Gorey JD, Wahlqvist ML, Boyce NW. Adverse reaction to a Chinese herbal remedy. *Med J Aust* 1992;157:484-6.
- Crofford LJ, Oates JC, McCunc WJ, Gupta S, Kaplan MJ, Catella-Lawson F, et al. Thrombosis in patients with connective tissue diseases treated with specific cyclooxygenase 2 inhibitors. A report of four cases. *Arthritis Rheum* 2000;43:1891-6.
- Brehmer G, Ruckdeschel KT. [Technic of the hibernation therapy.] German. *Dtsch Med Wochenschr* 1953;78:1724-5.
- Grahmann H, Suchenwirth R. [Thrombosis hazard in chlorpromazine and reserpine therapy of endogenous psychoses.] German. *Nervenarzt* 1959;30:224-5.
- Singer L, Finance MF, Ruh MD. [Pulmonary embolisms occurring in 1 month in 3 aged women with manic-depressive psychoses. Discussion. Etiopathogenic role or psychiatric treatment] French. *Ann Med Psychol (Paris)* 1975;1:256-63.
- Meier-Ewert K, Baumgart HH, Friedenberg P. [Thromboembolism complications in neuro- and thymoleptic therapy] German. *Dtsch Med Wochenschr* 1967;92:2174-8.
- Hagg S, Spigset O, Soderstrom TG. Association of venous thromboembolism and clozapine. *Lancet* 2000;355:1155-6.
- Thomassen R, Vandenbroucke JP, Rosendaal FR. Antipsychotic medication and venous thrombosis. *Br J Psychiatry* 2001;179:63-6.
- Zornberg GL, Jick H. Antipsychotic drug use and risk of first-time idiopathic venous thromboembolism: a case-control study. *Lancet* 2000;356:1219-23.
- Hafner H, Brehan I. Thromboembolic complications in neuroleptic treatment. *Compr Psychiatry* 1965;6:25-34.
- Kamijo Y, Soma K, Nagai T, Kurihara K, Ohwada T. Acute massive pulmonary thromboembolism associated with risperidone and conventional phenothiazines. *Circ J* 2003;67:46-8.
- Walker AM, Lanza LL, Arellano F, Rothman KJ. Mortality in current and former users of clozapine. *Epidemiology* 1997;8:671-7.
- Hagg S, Spigset O. Antipsychotic-induced venous thromboembolism: a review of the evidence. *CNS Drugs* 2002;16:765-76.
- Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30:239-45.
- Joos AA, Konig F, Frank UG, Kaschka WP, Morik KE, Ewald R. Dose-dependent pharmacokinetic interaction of clozapine and paroxetine in an extensive metabolizer. *Pharmacopsychiatry* 1997;30:266-70.

EXTRACTO

OBJETIVO: Clozapina, un antipsicótico, y paroxetina, un antidepresivo, son muy utilizados en el tratamiento psiquiátrico. Los efectos adversos de ambos medicamentos se han descrito ampliamente. En este reporte, se describe la embolia pulmonar como un efecto adverso poco frecuente relacionado con clozapina. Este efecto adverso puede tratarse, aunque a veces es mortal.

RESUMEN: Una mujer de 47 años tratada con clozapina y paroxetina fue ingresada en el hospital con disnea e hinchazón de la pierna. A la paciente se le diagnosticó una embolia pulmonar y fue tratada con heparina intravenosa. Al día 7, la paciente desarrolló abruptamente un fallo respiratorio agudo y murió. El estudio "post mortem" confirmó la embolia pulmonar masiva.

DISCUSIÓN: La embolia pulmonar mortal presentada en este artículo no tenía ningún otro factor de riesgo identificable excepto el hecho de recibir una combinación de clozapina y paroxetina. El nivel sanguíneo de clozapina estaba elevado. La aplicación del algoritmo de Naranjo demostró que la relación entre la reacción adversa y los medicamentos era probable.

CONCLUSIONES: Aunque la asociación entre el uso de medicamentos antipsicóticos y el tromboembolismo venoso ya se ha descrito, continua siendo un hallazgo raro. En este artículo, los autores presentan la trombosis venosa como un efecto adverso de los antipsicóticos. Esta descripción de un caso confirma la importancia de hacer un seguimiento y, posiblemente, suspender el tratamiento cuando se sospecha el tromboembolismo venoso. Debe hacerse un seguimiento cuidadoso, especialmente en los pacientes con riesgo de trombosis. Finalmente, la combinación de antidepresivos y antipsicóticos puede aumentar el riesgo de efectos adversos raros como el tromboembolismo venoso, aún en la ausencia de otros factores de riesgo.

Lydia González

RÉSUMÉ

OBJECTIF: La clozapine, un agent antipsychotique, et la paroxétine, un antidépresseur, sont tous les 2 largement utilisés lors de traitement pharmacologique psychiatrique. Les effets indésirables de ces 2 médicaments sont bien connus. Dans ce rapport de cas, les auteurs décrivent la survenue d'une embolie pulmonaire, effet indésirable rare attribué à la clozapine, traitable mais quelquefois léthal. Les auteurs ont revu la littérature sur le sujet dans l'espoir d'attirer l'attention sur les dangers potentiels pouvant résulter d'interactions médicamenteuses.

SOMMAIRE DU CAS: Une femme de 47 ans traitée par la clozapine à raison de 300 mg par jour et par la paroxétine à raison de 20 mg par jour depuis plusieurs années, a été admise à l'hôpital, souffrant de dyspnée depuis plusieurs jours et d'œdème à la jambe droite. La patiente ne recevait aucun autre médicament. Le niveau sanguin de clozapine à

l'admission était de 600 ng/mL. Un diagnostic d'embolie pulmonaire a alors été posé et la patiente a reçu de l'héparine par la voie intraveineuse à raison de 1200 unités par heure, ce qui a stabilisé sa condition pour plusieurs jours. Le septième jour de traitement, une insuffisance respiratoire aiguë est apparue soudainement et une ventilation mécanique a été requise. Plusieurs heures après le début de la ventilation mécanique, la patiente est décédée. Une autopsie a confirmé l'existence d'une embolie pulmonaire massive.

DISCUSSION: Les contraceptifs oraux, le tamoxifène, le raloxifène, les agents de chimiothérapie, les herbes chinoises, et les inhibiteurs de la cyclo-oxygénase 2 sont les médicaments causant le plus souvent des embolies pulmonaires. L'utilisation de ces médicaments doit être prise en considération lors du diagnostic différentiel de chaque cas d'évènement thromboembolique. Des complications thromboemboliques sont associées aux maladies psychiatriques et aux agents antipsychotropes et sont plus fréquentes que d'autres complications comme l'agranulocytose, l'insuffisance cardiaque congestive, et l'hépatotoxicité. Les complications thromboemboliques sont difficiles à diagnostiquer chez le patient psychiatrique, et la majorité le sont post-mortem. Certains auteurs (Hagg, *Lancet* 2000) rapportent un risque de thromboembolie de 1 sur 2000-6000 chez les patients recevant de la clozapine, surtout durant les 3 premiers mois de traitement. Les hommes sont plus sujets à cette complication, 77% des cas rapportés l'étant chez des hommes. Les mécanismes biologiques impliqués sont inconnus mais plusieurs hypothèses sont avancées dont la forte affinité pour les récepteurs 5-HT_{2A} des nouveaux agents

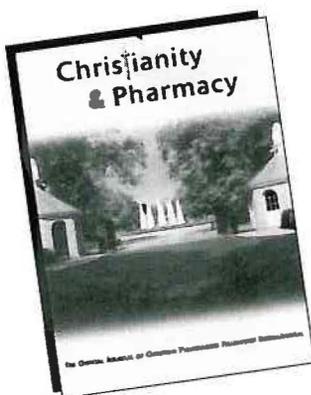
antipsychotiques. Les associations médicamenteuses peuvent hausser les niveaux sanguins d'un des médicaments et peuvent ainsi augmenter le risque de complications thromboemboliques. Ce cas d'embolie pulmonaire massive létale ne présentait aucun facteur de risque identifiable sauf la prise concomitante de clozapine et de paroxétine, avec un niveau sanguin élevé de clozapine. L'application de l'échelle de probabilité de Naranjo a révélé une probabilité que cet effet indésirable soit dû à la clozapine.

CONCLUSIONS: L'association d'agents antipsychotiques et de thromboembolie veineuse a déjà été décrite mais est très rare. Dans cet article, les auteurs démontrent que la thrombose veineuse est un effet lié au médicament clozapine et que la paroxétine a pu augmenté le risque en raison d'une interaction médicamenteuse. Ce cas illustre l'importance du suivi étroit de la thérapie médicamenteuse et de l'arrêt du traitement lorsque l'on suspecte une thrombose veineuse. Un suivi étroit doit donc être effectué, surtout en présence de facteurs de risque de thrombose. Enfin, les associations d'agents antidépresseurs et antipsychotiques peuvent augmenter le risque d'effets indésirables rares comme la thromboembolie veineuse, même en l'absence d'autres facteurs de risque. D'autres études sont nécessaires pour élucider les mécanismes des effets indésirables thromboemboliques associés aux agents antipsychotiques.

Dcnysc Demers

Christianity and Pharmacy

a journal for pharmacy professionals committed to Jesus Christ



Highlights from past issues:

- What if Your Conscience Costs You Your Job?
by Norma Robinson
- Balancing Science and Faith in Pharmacy Practice
by Joe Rogowski
- Serving the Lost Through the Indian Health Service
by James Bresette
- A New Concept of Divinity
by Young Hee Abramson
- Safari of a Lifetime
by Kevin Wilson

For membership and subscription information, contact:

Christian Pharmacists Fellowship International • PO Box 449 • Blountville, TN 37617-0449

Phone 423/323-1328 • Toll-Free 888/253-6885 • FAX 423/323-7215

www.cphi.org

Christian Pharmacists Fellowship International (CPFI) is a worldwide, nondenominational ministry of individuals working in all areas of pharmaceutical service and practice. CPFI's mission is to help pharmacy professionals grow spiritually and to promote fellowship among pharmacists. In fulfillment of these goals, many members serve as missionaries, demonstrating Jesus Christ's love through medical care to the disadvantaged of the world.