Noncardiogenic pulmonary edema associated with clopidogrel: A serious but unexpected side effect of clopidogrel

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Clopidogrel has a favourable side effect profile, in which the most serious complications are related to bleeding diathesis. Drug reactions represent frequently encountered clinical problems that can also be life-threatening. In the present case, serious noncardiogenic pulmonary edema was observed as an idiosyncratic reaction after clopidogrel use. Using the Naranjo adverse drug reactions probability scale, a possible likelihood of this putative interaction between clopidogrel and pulmonary edema was calculated. Such an adverse effect of clopidogrel has never been reported before. The present report shows the importance of recognizing rare adverse reactions of newer drugs, such as clopidogrel, in clinical practice.

Key Words: *Clopidogrel; Coronary intervention; Hypersensitivity reaction*

Clopidogrel is a commonly used medication with a favourable side effect profile; most of the reported adverse effects relate to abnormal bleeding. We report a patient who experienced a life-threatening event associated with the use of this medication.

CASE PRESENTATION

A 71-year-old man was admitted to the Dr Siyami Ersek Thoracic and Cardiovascular Surgery Center (Istanbul, Turkey) due to dizziness. His medical history was unremarkable except for hypercholesterolemia, for which he had been taking atorvastatin 20 mg daily and acetylsalicylic acid 100 mg daily for the past five years. The patient did not report any history of chest pain or shortness of breath. The physical examination revealed no major abnormalities except for a systolic murmur in the right carotid artery region. The Doppler examination of the carotid arteries demonstrated turbulent flow and high velocity signals localized to the right common carotid artery. Subsequently performed magnetic resonance angiography revealed 95% stenosis of the distal common carotid artery up to the proximal portion of the internal carotid artery. Normal exercise thallium-201 scintigraphy ruled out undiagnosed coronary artery disease. On echocardiographic evaluation, only a trace of mitral regurgitation and grade 1 diastolic dysfunction were observed. The patient's ejection fraction was 60%, with a normal left atrial diameter (Table 1). Thereafter, he was prepared for an angioplasty procedure to the carotid artery stenosis. Clopidogrel 75 mg daily was initiated, and three days later, the patient underwent an uncomplicated angioplasty and stenting procedure through a femoral artery; 200 mg prilocaine hydrochloride was used as a local anesthetic. He was discharged

Un œdème pulmonaire non cardiogène associé au clopidogrel : Un effet grave mais inattendu du clopidogrel

Le clopidogrel a un profil d'effets secondaires favorable, les complications les plus graves étant reliées à une diathèse hémorragique. Les réactions indésirables aux médicaments sont des troubles cliniques fréquents qui peuvent mettre la vie en danger. On a observé une réaction idiosyncrasique, sous forme de grave œdème pulmonaire non cardiogène, après l'utilisation de clopidogrel. Au moyen de l'échelle de probabilité des réactions indésirables de Naranjo, on a calculé la possibilité de cette interaction putative entre le clopidogrel et l'œdème pulmonaire. On n'a jamais déclaré un tel effet secondaire du clopidogrel auparavant. Le présent rapport de cas démontre l'importance de dépister les réactions indésirables rares de nouveaux médicaments comme le clopidogrel en pratique clinique.

the next day with the following medications: clopidogrel 75 mg/day, atorvastatin 20 mg/day and acetylsalicylic acid 100 mg/day. Two days later, he was admitted to the Center's emergency service for shortness of breath. He was dyspneic and tachypneic, and widely distributed pulmonary rales could be heard on auscultation. Arterial blood gas analysis showed a normal blood pH, with a normal partial pressure of carbon dioxide (30 mmHg), but a lower partial pressure of oxygen (57 mmHg), with an oxygen saturation of 91%. A chest radiograph demonstrated diffuse, bilateral interstitial and alveolar infiltrates with bilateral pleural effusion and a localized homogenous collection on the right lung, which looked like with a phantom tumour on first impression (Figure 1). The patient's blood pressure was 120/70 mmHg, his heart rate was 99 beats/min and his body temperature was 36.9°C. The only abnormal laboratory findings, compared with the results before the carotid intervention, were an elevated C-reactive protein (CRP) level (11 mg/L, normal values range between 0 mg/L and 5 mg/L) and an elevated erythrocyte sedimentation rate (ESR) (88 mm/h) (Table 1). The electrocardiogram showed a normal sinus rhythm, and normal levels of cardiac markers ruled out an acute coronary syndrome. A repeat echocardiogram revealed a normally contracting myocardium without any wall motion abnormality. The only difference from the previous echocardiogram, performed five days earlier, was the emergence of minimal pericardial effusion surrounding the heart. The effusion was 1 cm thick and did not compromise the diastolic filling of the cardiac chambers. Thereafter, nasal oxygen therapy (4 L/min) was initiated, which resulted in a significant increase in the partial pressure of oxygen. On the basis

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TABLE 1
Laboratory findings

Parameter	Hospital day						
	-3	-1	1	3	5	7	30
Clopidogrel exposure, mg	75	75	75	—	—	—	—
Leukocytes, $\times 10^9/L$	6	NA	7	5	7	6	5
Hemoglobin, g/L	14.99	NA	10.99	11.98	11.98	13.99	12.99
Platelets, $\times 10^9/L$	204	NA	170	270	346	344	295
AST, U/L	20	NA	24	35	24	40	25
ALT, U/L	25	NA	33	35	29	35	30
Creatine kinase (muscle-brain), U/L	16	NA	28	20	20	15	13
C-reactive protein, g/L	0.8	NA	12	NA	9	4	1.2
ESR, mm/h	24	NA	83	NA	63	55	29
Creatinine, $\mu\text{mol/L}$	110	NA	110	110	120	NA	100
Blood urea nitrogen, mmol/L	1.17	NA	1.50	1.33	1.17	NA	1.33
Total protein, g/L	78	NA	79	77	NA	NA	74
Albumin, g/L	39	NA	40	36	NA	NA	35
Lipase, U/mL	NA	NA	0.7	NA	NA	NA	NA
Amylase, U/L	NA	NA	910	NA	NA	NA	NA

ALT Alkaline aminotransferase; AST Aspartate aminotransferase; ESR Erythrocyte sedimentation rate; NA Not available

of the radiological and physical findings, and with the suspicion of acute heart failure as the cause, one dose of intravenous furosemide 40 mg was given. The preserved cardiac function on echocardiography was not compatible with a heart failure syndrome. Consequently, invasive hemodynamic monitoring with a Swan-Ganz catheter was performed and yielded the following values: a central venous pressure of 4 mmHg (normal range 0 mmHg to 5 mmHg), a pulmonary capillary wedge pressure of 12 mmHg (normal range 8 mmHg to 12 mmHg), normal systemic and pulmonary resistances, and a normal cardiac index. The normal value of the pulmonary capillary wedge pressure and the normal cardiac index virtually ruled out heart failure as the cause of the pulmonary edema. A pulmonary infection due to bacteria was unlikely, because the patient had no fever, his white blood cell count was normal, and the throat and blood cultures were negative. Nevertheless, empirical antibiotic therapy with ciprofloxacin 200 mg/day was started intravenously. Despite the evidence against heart failure as the etiology, intravenous furosemide was administered again on the second day, but the dyspnea did not improve. With the knowledge that massive pulmonary embolism may infrequently cause pulmonary edema, high resolution computed tomography was performed on the second day of hospitalization. This ruled out pulmonary embolism; however, it demonstrated a localized fluid collection in the right major pulmonary fissure, with a ground-glass appearance of the lungs, bilateral pleural effusion and minimal pericardial effusion, but no thrombi in the pulmonary vasculature. On the third day of the hospitalization, the patient was still dependent on nasal oxygen. Other medications included enoxaparin 0.4 cc subcutaneously, inhalation therapy with salbutamol, acetylsalicylic acid, clopidogrel, N-acetylcysteine and atorvastatin 20 mg/day. There was no response to ciprofloxacin. Clopidogrel has rarely been associated with inducing spontaneous massive pulmonary hemorrhage, but the mildly hemorrhagic sputum and the steady hemoglobin levels during the hospitalization period without signs of hypovolemia made pulmonary hemorrhage unlikely. Because the patient's condition was not stabilized and no clinical cause for the noncardiogenic alveolar edema had been found, a drug reaction was suspected as the underlying etiology. As his medications were reviewed, it was found that the only change was clopidogrel 75 mg, having been added to his drug therapy before the

Figure 1 Chest radiograph demonstrating diffuse, bilateral interstitial and alveolar infiltrates with bilateral pleural effusion and a localized homogenous collection on the right lung

development of symptoms. With the knowledge of hypersensitivity reactions induced by clopidogrel, it was decided that the patient discontinue this drug. The day after the discontinuation of clopidogrel, the symptoms of dyspnea resolved; the alveolar infiltrations on chest radiograph regressed over 48 h and fully disappeared on the fifth day of clopidogrel withdrawal (Figure 2). CRP levels and ESR, as acute phase reactants, began to decrease. On the ninth day of hospitalization, the patient was fully symptom-free and discharged with dipyridamole, in addition to acetylsalicylic acid and a statin. Repeat echocardiography revealed only minimal pericardial effusion. At the follow-up examinations on the first and third months, the patient was totally symptom-free and all laboratory values were in the normal range.

DISCUSSION

Clopidogrel is a widely used adjunctive antiplatelet therapy in patients undergoing coronary and peripheral artery stenting. It is generally well tolerated and its efficacy in preventing ischemic events is in some aspects better than acetylsalicylic acid, as shown in clinical trials (1,2). Some severe adverse effects of clopidogrel therapy have been reported, including aplastic anemia (3), thrombotic thrombocytopenic purpura (4) and hemolytic uremic syndrome (5). Although such reactions are very rare, the treating clinician must be aware that clopidogrel may induce such idiosyncratic reactions. It is also known that clopidogrel may be associated with dyspnea and cardiac failure, which occurred in 4.5% and 1% to 2.5% of clopidogrel-receiving patients, respectively, in the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial (1). However, these same reactions also occurred in the acetylsalicylic acid-treated group in that trial, and indeed, fewer than 1% of patients discontinued clopidogrel therapy.

We do not believe that the findings in our patient can be attributed to these potential side effects of clopidogrel, but we do believe that the dyspnea developed in our patient was, in fact, the clinical end point of a more severe and systemic reaction to clopidogrel. It seems likely that our patient experienced a severe idiosyncratic reaction to clopidogrel, which expressed itself as alveolar exudation and serositis. Sarrot-Reynaud et al (6) reported a case of severe hypersensitivity to clopidogrel, consisting of an acalculous cholecystitis, mediastinal lymphadenopathy and testicular swelling, in addition to pulmonary infiltrates and bilateral pleural effusion. Similar to our case, the patient in that report also developed these symptoms after five days of

Figure 2) Chest radiograph taken on the fifth day of clopidogrel withdrawal. Note the full disappearance of interstitial and alveolar infiltrates and pleural effusion

clopidogrel therapy, and the discontinuation of clopidogrel resulted in complete resolution in the next seven days. On the other hand, the reaction in our patient was more limited and localized only to the respiratory and cardiovascular systems, causing respiratory distress, probably through alveolocapillary membrane damage, resulting in increased membrane permeability.

According to the Gell and Coombs classification system, drug hypersensitivity reactions include four different types (7,8). Of these, hypersensitivity reaction type 3 demonstrates an immune complex reaction, the prototype of which is the well-known serum sickness (8). Although serum sickness results from the injection of heterologous or foreign protein, or serum, reactions secondary to the administration of nonprotein drugs are clinically similar to serum sickness reactions (9). The classical clinical findings may include cutaneous symptoms, fever, lymphadenopathy, arthritis or arthralgias, edema, and renal and/or neurological manifestations. Although rare, pulmonary and cardiovascular involvement may also occur in serum sickness, presenting as myocardial and pericardial inflammation, and as pericardial and pleural effusions. In fact, dyspnea and cyanosis are not uncommon in patients with this type of hypersensitivity (9). It is also important to mention that type 3 hypersensitivity reaction is associated with a high level of CRP and a high ESR, which were the only abnormal findings in our patient's laboratory results. The elevated values of these inflammatory markers cannot be explained with an active infection or another inflammatory disorder, and their regression on cessation of clopidogrel suggests a possible drug reaction. In the light of the patient's clinical presentation, we speculate that our patient experienced a type 3 hypersensitivity reaction due to clopidogrel.

Such pulmonary and cardiovascular involvement in type 3 hypersensitivity associated with clopidogrel use has not been reported before; however, the ability of clopidogrel to induce serum sickness-like reactions was reported by Phillips et al (10). The four cases in their report demonstrated mostly skin lesions and arthritic symptoms, which clearly differs from our patient's condition. However, these manifestations may represent part of a wide clinical spectrum.

To represent a more objective assessment of the likelihood that our patient had experienced a clopidogrel-induced drug reaction, we applied the Naranjo adverse drug reactions probability scale (11). This is a tool used to determine the likelihood that an adverse drug reaction is caused by the implicated medication. By answering the questions proposed for this probability

TABLE 2
Naranjo adverse drug reactions (ADR) probability scale criteria

Questions	Yes	No	Do not know
Are there previous conclusive reports on this reaction? (0)	+1	0	0
Did the ADR appear after the suspected drug was administered? (+2)	+2	-1	0
Did the ADR improve when the drug was discontinued? (+1)	+1	0	0
Did the ADR appear with rechallenge? (0)	+2	-1	0
Are there alternative causes for the ADR? (-1)	-1	+2	0
Did the reaction appear when placebo was given? (+1)	-1	+1	0
Was the drug detected in blood at toxic levels? (0)	+1	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased? (0)	+1	0	0
Did the patient have a similar reaction to the same or similar drug in any previous exposure? (0)	+1	0	0
Was the ADR confirmed by any objective evidence? (+1)	+1	0	0

According to the criteria set by Naranjo et al (10), the likelihood of causing the ADR by the implicated drug ranges from being doubtful (score <0) to possible (score 1–4), probable (score 5–8) and highly probable (score ≥9). The numbers in parentheses represent the scores applied to the patient in the present report, resulting in a total score of +4

analysis, a score of 4 is obtained for our case, which places the likelihood of our putative drug reaction due to clopidogrel into a 'possible likelihood' range (Table 2). We mention that some important points in this probability scale were not possible to assess in our case; clearly a rechallenge test would not be appropriate. However, a positive response to this test would move the score into the probable range.

We believe that our case demonstrates a very rare, idiosyncratic side effect of clopidogrel, which clinicians must be aware of given the widespread use of this medication.

REFERENCES

- Harker LA, Boissel JP, Pilgrim AJ, Gent M. Comparative safety and tolerability of clopidogrel and aspirin: Results from CAPRIE. CAPRIE Steering Committee and Investigators. Clopidogrel versus aspirin in patients at risk of ischaemic events. *Drug Saf* 1999;21:325-35.
- Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494-502. (Errata in 2001;345:1716, 2001;345:1506).
- Trivier JM, Caron J, Mahieu M, Cambier N, Rose C. Fatal aplastic anemia with clopidogrel. *Lancet* 2001;357:446. (Lett)
- Bennet CL, Connors JM, Carwile JM, et al. Thrombotic thrombocytopenic purpura associated with clopidogrel. *N Engl J Med* 2000;342:1773-7.
- Oomen PH, Tulleken JE, Zijlstra JG. Hemolytic uremic syndrome in a patient treated with clopidogrel. *Ann Intern Med* 2000;132:1006. (Lett)
- Sarrot-Reynaud F, Bouillet L, Bourrain JL. Severe hypersensitivity associated with clopidogrel. *Ann Intern Med* 2001;135:305-6.
- Coombs RRA, Gell PGH. The classification of allergic reactions underlying disease. In: Gell PGH, Coombs RRA, eds. *Clinical Aspects of Immunology*. Philadelphia: Blackwell Science, 1963:317-20.
- Riedl MA, Casilla AM. Adverse drug reactions: Types and treatment options. *Am Fam Physician* 2003;68:1781-90.
- Chen SM. Serum Sickness. <www.emedicine.com/emerg/topic526.htm> (Version current at March 16, 2007).
- Phillips EJ, Knowles SR, Shear NH. Serum sickness-like reaction associated with clopidogrel. *Br J Clin Pharmacol* 2003;56:583.
- Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30:239-45.