Clinical Kidney Journal, 2016, vol. 9, no. 4, 580–582

doi: 10.1093/ckj/sfw039
Advance Access Publication Date: 30 May 2016
Exceptional Case

EXCEPTIONAL CASE

Relapsing thrombotic microangiopathy and intravenous sustained-release oxycodone

Melissa Nataatmadja and Dakshinamurthy Divi

Department of Nephrology, Gold Coast University Hospital, Southport, QLD, Australia

Correspondence and offprint requests to: Melissa Nataatmadja; E-mail: melissa.nataatmadja@gmail.com

Abstract

Thrombotic microangiopathy (TMA) associated with injecting sustained-release oxymorphone, an opioid intended for oral use, has previously been reported. We report a case of TMA secondary to intravenous use of sustained-release oxycodone, and the first case to demonstrate relapsing disease due to persistent intravenous opioid use. In cases such as these, TMA is suspected to be due to a polyethylene oxide (PEO) coating found on these drugs, and the disease is likely due to a directly toxic effect of PEO to endothelial cells. We hypothesize that there are unidentified genetic predispositions causing some persons to be susceptible to developing this disease.

Key words: oxycodone, Oxycontin, plasma exchange, polyethylene oxide, thrombotic microangiopathy

Background

Recently, thrombotic microangiopathy (TMA) resembling thrombotic thrombocytopenic purpura (TTP) with normal ADAMTS13 activity has been observed in persons injecting Opana ER (oxymorphone), an opioid intended for oral use. This phenomenon has so far been reported only in the USA, and the mechanism by which TMA is induced is not yet known.

Case report

A 29-year-old female presented to a regional hospital with headache and feeling generally unwell. She was treated for migraine and discharged, but re-presented 3 days later. Blood tests revealed a haemoglobin of 70 g/L and platelets of 17×10^9/L (Table 1). She was given packed red blood cells (PRBCs) and fresh frozen plasma (FFP) and was transferred to our hospital, the nearest tertiary centre. She had no significant past medical history other than depression, for which she was taking desvenlafaxine 100 mg daily.

Her creatinine was 90 mmol/L and she had no neurological abnormalities, fever or diarrhoea. On arrival at our hospital, a diagnosis of TMA was confirmed by the presence of elevated lactate dehydrogenase (LDH) and bilirubin, reduced haptoglobin and the presence of fragments on blood film. She was commenced on therapeutic plasma exchange (TPE) for a presumed diagnosis of TTP. Her blood tests rapidly normalized with TPE after eight sessions and she was discharged with outpatient follow-up. ADAMTS13 activity had been requested prior to her receiving blood products and showed a normal result of 94%.

She did not attend outpatient follow-up as planned, but re-presented to hospital 2 weeks later with recurrence of haemolytic anaemia and thrombocytopenia, as well as renal impairment with a creatinine of 118 mmol/L (Table 1). Urine showed mild haematuria of 20×10^6/L and an albumin:creatinine ratio of 6.4 g/mol. She also reported new visual disturbances, and ophthalmologic examination revealed retinal ischaemia. She again was commenced on TPE and additionally 1 mg/kg of prednisolone. Repeat ADAMTS13 testing was requested, again returning a normal result. As a result, atypical haemolytic-uremic syndrome (aHUS) was considered and genetic testing was ordered.

The patient had initially denied illicit drug use, but during her second admission she admitted that she and her husband had

Received: December 28, 2015. **Accepted:** April 14, 2016

Table 1. Investigation results

Test (reference range)	Initial hospital presentation	Admission to our hospital	First discharge	Second hospital presentation	Second discharge
Haemoglobin (115–160 g/L)	70	72	103	81	109
Platelets (150–400 × 10^9/L)	17	30	351	8	314
Film	Not performed	Moderate polychromasia, fragmented red cells and spherocytes	Occasional spherocyte and fragmented red cell noted	Moderate numbers of fragmented red cells and spherocytes, large platelets	Occasional red cell fragment
Direct Coombs test	Not performed	Negative	Negative	Negative	Not performed
LDH (150–280 U/L)	839	970	206	1630	328
Bilirubin (<20 µmol/L)	35	34	6	51	9
Haptoglobin (0.36–1.95 g/L)	Not performed	0.02	2.06	0.03	0.82
Creatinine (46–90 mmol/L)	90	95	61	118	77
eGFR (>90 mL/min/1.73 m^2)	75	70	>90	54	>90
ADAMTS13 activity	>94%	102% (after 2 units PRBC and 2 units FFP)	Not performed	146%	N/A

been injecting oxycodone (Endone) and sustained-release oxycodone (Oxycontin) tablets for the past year. They had been obtaining Oxycontin by prescription for her husband's chronic back pain, and each injected 120 mg daily. For the past 2 months they had been using reformulated Oxycontin, which had replaced original Oxycontin in Australia at that time. This new formulation had a tamper-resistant polyethylene oxide (PEO) coating that was difficult to crush and formed a gel-like substance when immersed in water, making it much more difficult to inject [1, 2]. Our patient stated that she used kitchen shears to break the tablets into smaller parts, so when she subsequently soaked and heated them in water, it was easier to remove the coating.

TPE was ceased and the patient was discharged with arrangements for outpatient follow-up. Unfortunately, she did not attend her appointments and was subsequently lost to follow-up. The results of genetic testing took several months to return, but massively parallel sequencing was negative for known aHUS-associated mutations.

Discussion

TTP, an occlusive thrombotic microangiopathy, is characterized by thrombocytopenia and erythrocyte fragmentation due to endothelial cell injury [3]. The complete pentad of TTP (haemolytic anaemia, thrombocytopenia, renal impairment, neurological impairment and fever) is often not seen, and is not required for diagnosis. In clinical practice, the diagnosis of TTP is strongly supported by the presence of thrombocytopenia, schistocytosis, elevated lactate dehydrogenase (LDH) and low haptoglobin [4, 5]. TTP may be hereditary, due to a deficiency of ADAMTS13, or may be acquired, due to an autoantibody to ADAMTS13, which is the more common form in adults [6]. Treatment in hereditary TTP involves replacement of ADAMTS13 by infusion of fresh-frozen plasma (FFP), cryoprecipitate-poor plasma, detergent-treated plasma or intermediate purity factor VIII concentrate [5, 7]. Treatment of TTP due to the presence of autoantibodies, however, requires TPE to both remove the antibodies and replace ADAMTS13 [7, 8]. Immunosuppression using prednisolone is used in patients with unresponsive or recurrent illness, and other agents including rituximab, cyclophosphamide, cyclosporine and vincristine have also been used [8]. HUS is most commonly caused by shiga-like toxin-producing *Escherichia coli* (STEC-HUS). Atypical HUS, however, is due to complement regulation abnormalities and may be treated with eculizumab, a terminal complement inhibitor [4].

TMA has been associated with the use of certain medications, particularly chemotherapeutic agents, including vascular endothelial growth factor inhibitors, calcineurin inhibitors, interferon, gemcitabine and quinine [6]. TMA secondary to intravenous (IV) opioid use is a relatively recent occurrence in the literature. In the USA, reformulated Oxycontin and Opana ER with a PEO coating were approved by the FDA in 2010 [9]. Original Oxycontin was discontinued, however, both Opana formulations remained available. Following a report by a Tennessee nephrologist of three cases of TTP-like illness from an unexplained cause in 2012, the FDA issued a warning regarding the possibility of developing TMA secondary to injecting Opana ER [10]. Subsequent investigation and case identification by the Centers for Disease Control (CDC) identified a total of 15 cases by the end of that year and a strong association between injecting Opana ER and the development of TMA [odds ratio 35 (95% confidence interval 3.9–312.1)] [11].

Since then, there have been only a few reports published of TMA following injection of Opana ER [12–16]. All patients had anaemia, thrombocytopenia and evidence of haemolysis, with a negative direct Coombs test and normal ADAMTS13 activity. Most patients received TPE and achieved remission. While renal biopsy was not performed in our patient, a case series of three patients using IV Opana ER found thrombotic microangiopathy on renal biopsy, involving mainly the interlobular arteries, and severe endothelial cell swelling and intimal mucoid oedema [13].

Previous authors have speculated that this syndrome may be due to the PEO coating on the reformulated tablets, the active medication component itself or a substance or solvent used by the patients to prepare the tablets for IV use. Our case report supports the reformulated tamper-proof coating as the likely cause, given that TMA has been observed in patients taking two different types of opioids, both with the same PEO coating. A study performed in rats also demonstrated dose-dependent haemolytic anaemia and thrombocytopenia following IV and intraperitoneal injection of a high-molecular-weight PEO, further supporting PEO as a causative substance [17]. Lastly, our patient used only mechanical methods to prepare the medication for injection and used no additional solvents or substances.

To our knowledge, until reformulated Oxycontin became available in Australia in May 2014, this syndrome had not been

reported outside of the USA and had not been reported with any oral opioid other than Opana ER. A single case report has been published of TMA secondary to IV Oxycontin use, although it is likely that there have been more cases that have not been reported [18]. In that case, the patient was forthcoming with his IV drug use and haematologic derangement was less severe than in our patient, with a haemoglobin of 87 g/L and platelets of 53×10^9/L. The patient recovered with cessation of IV opioid use and no treatment with TPE. A case series of American patients using Opana ER also reported that TPE may not be necessary, as all 15 of their patients recovered with only supportive care and cessation of IV drug use [16]. However, given the difficulties in clinically differentiating PEO-related TMA from TTP, we recommend that where a history of IV opioid use is not initially evident, or where there is severe haematological or biochemical derangement, TPE ought not be delayed in order to either observe clinical course or to await ADAMTS13 results. Due to the life-threatening nature of TTP and the difference in clinical outcome that even a 24-h delay in treatment can make, we suggest that where the diagnosis is in question, at least FFP infusion should be performed.

We believe this is the first reported case to demonstrate a relapse of PEO-associated TMA due to recommencement of IV opioid use after achieving initial remission. This syndrome has been observed to resolve with no treatment other than withdrawal of IV opioid use and, as in our case, is seen to reoccur with resumption of IV opioid use. This is supportive of PEO being directly toxic to endothelial cells rather than mediating TMA through an antibody response. In the case of our patient, her partner was also using Oxycontin intravenously but did not develop any known illness. Given that IV misuse of oral medication is far more common than this rare disorder, it is possible that it is a small but predisposed subset of the population who go on to develop this syndrome. While our patient did undergo genetic testing for aHUS, which was negative, we also hypothesize that there are unidentified genetic predispositions that cause some people to develop TMA following IV opioid use. We recommend that clinicians consider this syndrome and acquire a thorough history of both licit and illicit drug use in all patients presenting with TMA.

Acknowledgements

We would like to thank haematologist Dr Tara Cochrane and nephrology trainee Dr Pooja Sanghi for their input in the diagnosis and clinical management of this patient. We would also like to thank haematologists Dr Sunelle Englebrecht and Dr Jeremy Wellwood and nephrologist Dr Balaji Hiremagalur for their advice and insights when reviewing this case.

Conflict of interest statement

None declared.

References

1. NPS MedicineWise. *Opioid abuse: will tamper-proof oxycodone help?* http://www.nps.org.au/publications/health-professional/health-news-evidence/2014/tamper-proof-oxycodone
2. Mundipharma. Product information: Oxycontin modified release tablets. http://secure.healthlinks.net.au/content/mf/pi.cfm?product=mfpoxycr
3. Goldberg RJ, Nakagawa T, Johnson RJ *et al*. The role of endothelial cell injury in thrombotic microangiopathy. *Am J Kidney Dis* 2010; 56: 1168–1174
4. Moake JL. Thrombotic microangiopathies. *N Engl J Med* 2002; 347: 589–600
5. Moake J. Thrombotic thrombocytopenia purpura (TTP) and other thrombotic microangiopathies. *Best Pract Res Clin Haematol* 2009; 22: 567–576
6. George JN, Nester CM. Syndromes of thrombotic microangiopathy. *N Engl J Med* 2014; 371: 654–666
7. Scully M, Goodship T. How I treat thrombotic thrombocytopenic purpura and atypical haemolytic uraemic syndrome. *Br J Haematol* 2014; 164: 759–766
8. George JN. Clinical practice. Thrombotic thrombocytopenic purpura. *N Engl J Med* 2006; 354: 1927–1935
9. U.S. Food and Drug Administration. FDA approves abuse-deterrant labelling for reformulated OxyContin. FDA News Release 2013. http://fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm348252.htm (15 February 2015, date last accessed)
10. U.S. Food and Drug Administration. FDA warns about serious blood disorder resulting from misuse of Opana ER. Drug safety and availability 2012. http://www.fda.gov/drugs/drugsafety/ucm322432.htm (15 February 2015, date last accessed)
11. Centers for Disease Control and Prevention. Thrombotic thrombocytopenic purpura (TTP)-like illness associated with intravenous Opana ER abuse—Tennessee, 2012. *MMWR Morb Mortal Wkly Rep* 2013; 62: 1–4
12. Amjad AI, Parikh RA. Opana-ER used the wrong way: intravenous abuse leading to microangiopathic hemolysis and a TTP-like syndrome. *Blood* 2013; 122: 3403
13. Ambruzs JM, Serrell PB, Rahim N *et al*. Thrombotic microangiopathy and acute kidney injury associated with intravenous abuse of an oral extended-release formulation of oxymorphone hydrochloride: kidney biopsy findings and report of 3 cases. *Am J Kidney Dis* 2014; 63: 1022–1026
14. Kapila A, Chhabra L, Chaubey VK *et al*. Opana ER abuse and thrombotic thrombocytopenic purpura (TTP)-like illness: a rising risk factor in illicit drug users. *BMJ Case Rep* 2014. pii: bcr2013203122. doi: 10.1136/bcr-2013-203122.
15. Rane M, Aggarwal A, Banas E *et al*. Resurgence of intravenous Opana as a cause of secondary thrombotic thrombocytopenic purpura. *Am J Emerg Med* 2014; 32: 951.e3–951.e4
16. Miller PJ, Farland AM, Knovich MA *et al*. Successful treatment of intravenously abused oral Opana ER-induced thrombotic microangiopathy without plasma exchange. *Am J Hematol* 2014; 89: 695–697
17. Karpova GV, Abramova EV, Lamzina T *et al*. Myelotoxicity of high-molecular-weight poly(ethylene oxide) [in Russian]. *Eksp Klin Farmakol* 2004; 67: 61–65
18. Tate C, Mollee P. Intravenous OxyContin-associated thrombotic microangiopathy treated successfully without plasma exchange. *Med J Aust* 2015; 202: 330–331