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Thrombotic Microangiopathy Associated with Intravenous Injection of Opana ER®: University Medical Center Case Series

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Abstract

In response to the rapidly rising intravenous opioid abuse epidemic, the United States Food and Drug Administration is currently promoting the development of prescription opioid tablets that are specifically formulated to deter abuse. Opana ER® (Endo Pharmaceuticals) recently underwent reformulation to include a crush-resistant coating. Only recently described, illicit intravenous injection of reformulated Opana ER® is associated with a distinctive clinical syndrome of thrombotic microangiopathy. Ten patients with the appropriate history and presenting symptoms were identified within an 8 month interval (July 2012 through February 2013) at the University of Tennessee Medical Center (UTMC) Knoxville with ICD-9 code of 446.6 (thrombotic microangiopathy) by electronic search. Review of laboratory data, electronic medical records, blood product usage, and total hospital admission charges were compiled for these individual patients. We report the clinicopathologic findings and correlating laboratory data for a group of patients presenting with thrombotic microangiopathy and documented recent history of intravenous Opana ER® injection. We also report the economic impact and effect on blood product utilization by this study group.

Keywords: 2-Thrombotic microangiopathy; opioid; therapeutic plasma exchange; plasma cryoprecipitate reduced

Introduction

Opioid analgesics are a group of widely prescribed medications for post-operative, non-cancer and cancer-related pain. This class of medications is notable for the widely recognized potential for abuse, addiction and as an impetus for criminal behavior [1]. The United States Food and Drug Administration (FDA) recently reported an estimated 15,500 people died due to inappropriate use of prescription opioid drugs in 2009. The high number of deaths due to misuse of opioid drugs has increased 313 percent over the previous two decades. For each death, the FDA reports an additional 10 treatment-related hospital admissions, 32 emergency department visits and 825 illicit (non-medical) opioid drug users [2].

Opana ER® (Endo Pharmaceuticals) is an extended-release form of oxymorphone, a potent opioid pain reliever. Opana ER® rapidly rose in popularity following the reformulation of OxyContin® (Purdue Pharma). The reformulated version of OxyContin ® was designed to prevent crushing, dissolving and subsequent intravenous (IV) injection [1]. The immediate-release and extended-release versions of Opana® were initially released onto the market in 2006 [3]. Opana ER® manufacturer developed a crush-resistant pill which was FDA-approved in late 2011. In 2012, the production of Opana ER®'s original formulation ceased in lieu of the new crush-resistant formulation [1]. Many websites and chat rooms have since emerged detailing methods to circumvent the new tamper-resistant coating of Opana ER®. The illicit IV use of opioid prescription medications has become a nationwide epidemic [1,2,4]. The choice illicit drug of abuse has progressively gone through a transition to the current favorite: opioids [1,4]. While acknowledging this rise to popularity, one must recognize the socioeconomic burden on society. In an effort to deter illicit opioid abuse, the FDA has advocated reformulated, tamper-resistant opioids, made changes in labeling to include risk for abuse, and increased prescriber education through outreach with key members of the prescribing community. Namely, the FDA mandated a Risk Evaluation and Mitigation Strategy for extended-release and long-acting opioids. This program requires the manufacturers to make educational materials about the safe use of opioids available to patients as well as having training programs available to prescribers [2].

Only recently described by the Centers for Disease Control and Prevention (CDC) in January 2013 is a distinctive clinical syndrome of TTP-like symptoms associated with illicit IV injection of reformulated Opana ER® [3]. We present a University-based hospital's experience of a series of ten patients with characteristic clinical and laboratory findings of Thrombotic Microangiopathy (TMA) and documented recent history of illicit IV Opana ER® use. This article describes the clinical and laboratory findings of each patient, as well as the utilization of blood products, and the economic impact by our case series.

Results

We identified a total of 18 patients in an 8 month time frame (July 2012 through February 2013) at the University of Tennessee Medical Center (UTMC) Knoxville with ICD-9 code of 446.6 (thrombotic microangiopathy) by search of hospital electronic medical records. Chronic TMA was noted in the electronic medical record of 6 patients who presented for routine clinical follow-up with no treatment during our study time frame. An additional 2 patients were treated with Therapeutic Plasma Exchange (TPE) for TMA unrelated to Opana ER® use (one pregnant patient with placenta accreta; one patient with Wegener's granulomatosis, end-stage renal disease and pneumonia). One patient with history of end-stage cirrhosis was treated with TPE for TMA and had positive toxicology screen for opiates at admission; however, there is no documentation of IV Opana ER® use. This is the only patient who expired during this time frame.

Documentation of IV Opana ER® use was identified in 10 patients with TMA, by their own verbal report and noted in the electronic medical record. This patient population was selected as our study group and further investigated. The patient age ranged from 20 to 41 years (mean 28.2) with 40% male and 60% female. All patients were Caucasian. The listed home county address for 9 of the patients is within Eastern Tennessee and one from Central Tennessee, but all within a 170 mile radius. The Tennessee counties include: Fentress (1), Hamblen (2), Hawkins (2), Knox (1), Scott (2), and Sevier (2). The average length of stay for the initial admissions ranged from 6 to 28 days (average 15.2). The final inpatient fees determined by UTMC billing department generated for these patients during the 8 month time period (initial and readmissions) totaled $1,025,382. The individual fees for the initial admission ranged from $29,021 (no apheresis patient) to $149,270 per admission. The initial admission fees for all 10 patients totals $851,714 with 3 patients having re-admission fees totaling $173,688 [Table 1].

Patient Number	1	2	3	4	5	6	7	8	9	10
Age (years)	31	35	21	26	41	21	21	21	21	21
Sex	F	F	F	M	F	M	F	M	F	M
Race	C	C	C	C	C	C	C	C	C	C
TN County	Haw	Haw	Haw	Knox	Se	Se	Haw	Sc	Fe	Sc
Number of Hospital Admissions	2	1	1	1	3	1	1	2	2	1
Length of Stay (initial admission/ readmission)	20 19	14	23	28	10 7	12	11	6	20 4	8
Total Fees (US dollars) Initial Admission Readmission	 72,322 139,655	149,270	141,180	113,093	 55,258 18,464	72,038	73,081	45,007	 101,357 15,549	29,021

F = Female, M = Male, C = Caucasian, Fe = Fentress, Haw = Hawkins, Ham = Hamblen, Sc = Scott, Se = Sevier

Table 1:

An additional 10 month follow-up revealed 3 of the 10 patients were re-admitted. Patient # 8 was re-admitted within 1 week of this study period with a length of stay of 76 days and additional final bill of $457,059. This patient was also re-admitted 5 additional times within 8 months of our study period. Patient # 5 was re-admitted 2 additional times. Patient # 6 was re-admitted two additional times and expired due to complications of sepsis and endocarditis.

All patients were negative for HIV antibodies; however, 7 patients were positive for hepatitis C antibodies and 1 positive for hepatitis B core IgM antibody while being negative for hepatitis B surface antigen (patient # 1). Likely sepsis was reported in 6 patients. D-Dimer was reported positive in 4 patients. Only 1 of the 6 female patients was recently pregnant. This female patient was transferred to our facility following recent intrauterine demise in addition to symptoms of TMA (patient # 3). Urine toxicology screens at admission were positive in all patients (5 opiates only, 1 opiates and benzodiazepines, 2 benzodiazepines, 1 opiates and cannabinoids, 1 benzodiazepines and cannabinoids). The ADAMTS13 activity levels ranged from 33 to 77% (average 61%, normal ref. range > 66%). The platelet count at admission ranged from 18 to 150 (average 54.3, ref. range 130 – 400 x 10^9/L). The platelet count at discharge ranged from 113 to 381 (average 221). Lactate Dehydrogenase (LDH) levels at admission were elevated in 9 of 10 patients (average 791.3, ref. range 110-250 IU/L). All patients were anemic at admission with average hematocrit of 23.83% (range 15.3% - 31.6%, ref. range 37.0 – 47.0%). Schistocytes were documented on the peripheral blood smear of 6 patients. Elevated serum creatinine levels were noted in 8 patients (range 1.6 to 11.22, average 3.19, ref. range 0.60 - 1.30 mg/dL). Fever was reported at admission in 2 patients and 5 had reported neurologic symptoms [Table 2].

Patient Number	1	2	3	4	5	6	7	8	9	10
ADAMTS13 RR: >66% (Percent Activity)	55%	77%	77%	70%	33%	73%	45%	54%	51%	75%
Platelet Count Admit/ Discharge RR: 130-400 (Plt Ct x 109/L)	41/149	18/378	19/250	60/236	31/166	62/202	51/113	66/145	150/381	45/181
LDH Admit/Discharge RR: 110-250 (IU/L)	363/218	217/199	1382/160	1890/205	1685/231	397/168	794/308	338/232	430/120	417/178
Hemoglobin, Admission RR: M= 14-18 F= 12-16 (g/dL)	9.2	6.7	4.7	8.9	8.1	8.6	7.3	6.8	10.2	8.2
Schistocytes (PB)	No	NP†	NP†	NP†	Yes	Yes	Yes	Yes	Yes	Yes
Serum Creatinine, Admission RR: 0.60-1.30 (mg/dL)	1.7	1.55	3.2	1.6	1.02	1.19	11.22	3.08	5.74	1.55
Neurologic Sx.	No	No	No	Yes	Yes	Yes	No	Yes	No	Yes
Fever	No	No	No	Yes	No	Yes	No	No	No	No
Likely Sepsis	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes	No
HIV AB Screen	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
Hepatitis C AB Screen	Pos.	Neg.	Neg.	Neg.	Pos.	Pos.	Pos.	Pos.	Pos.	Pos.

RR = Reference Range, (PB) = Peripheral Blood, Sx. = Symptoms,
AB = Antibodies, Neg. = Negative, Pos. = Positive
† Not performed; Peripheral blood smear not reviewed

Table 2:

TPE was utilized in 9 patients and 1 patient was treated with serial thawed plasma transfusions. Only 2 of the 10 patients required dialysis treatments (patients # 7 and 8). During initial admissions, a total of 77 TPE procedures were performed with total overall volume of apheresis of 272,757 mL. TPE performed during re-admissions in this time frame totaled 36 procedures with a total overall volume of apheresis of 60,895 mL. No significant complications of TPE were reported in the electronic medical record. The total blood products utilized during this time frame included: 47 red blood cell units, 3 apheresis platelet units, 120 thawed plasma units, and 653 units (189,068 mL) of plasma cryoprecipitate reduced [Table 3].

Patient Number	Number of Therapeutic ApheresisProcedures	Volume of Apheresis Procedures (mL)	Number of CPP Units (mL)	Number Thawed Plasma Units	Number of RBC Units	Number of Apheresis Platelet Units
1 Readmit	16 9	76,488 60,895	166 (47,145) 113 (31,878)	2 0	2 0	0 0
2	10	28,935	56 (16,189)	0	8	1
3	18	61,840	109 (32,525)	0	9	2
4	7	21,404	40 (11,761)	0	5	0
5 Readmit	7 0	16,537 0	51 (14,670) 0	1 18	4 1	0 0
6	5	21,511	33 (9,828)	4	4	0
7	8	23,608	41 (12,217)	4	5	0
8	4	17,630	32 (9,381)	5	2	0
9 Readmit	2 0	4,804 0	12 (3,474) 0	0 0	3 0	0 0
10	0	0	0	35	4	0
Totals Initial Readmit Overall	 77 36 T = 113	 272,757 60,895 T = 333,652	 540 113 T = 653	 51 69 T = 120	 46 1 T = 47	 3 0 T = 3

CPP = Cryo-poor plasma (plasma cryoprecipitate reduced), RBC = red blood cell

Table 3:

Discussion and Conclusion

Tamper-resistant tablets to prevent crushing and dissolving were developed in an attempt to reduce misuse of prescription drugs. Despite this, there are numerous websites and chat rooms with information about ways to circumvent these efforts. Some techniques

suggested in web-based chat rooms include: use of nail file to remove outer layer, microwaving, use of acid base extraction, and use of a solvent with filtration [5,6]. The new formulation of Opana ER® was FDA approved in late 2011 and released in February 2012. The CDC first reported cases of "TTP-like illness associated with IV Opana ER® abuse" in August 2012. The CDC report notes 15 patients in Tennessee reported through October 2012 [3]. We found 10 cases at our institution from July 2012 through February 2013, which extends beyond the time frame of the CDC report, but we are unsure if any of our patient population was included in the cases reported by the CDC. The tamper-resistant tablets are coated with inactive ingredients including Polyethylene Oxide (PEO); a compound similar to Polyethylene Glycol (PEG) with a higher molecular weight [3,7]. Used as an inactive ingredient in many other drug formulations, PEO confers tablet hardness and aids in controlling the release of the active ingredient, oxymorphone. PEO is a polymer and the molecular weight is highly variable [7]. However, PEG has been used in certain IV medications with very few studies on toxicity. It does appear the major target organ for toxicity was the kidney when high doses of PEG were given to laboratory animals [8]. The disparity in molecular weights between the PEG used in this study of toxicokinetics and the PEO used in Opana ER® could possibly contribute to systemic manifestations [7,8]. To our knowledge, studies involving the IV injection of PEO have not been performed. Therefore, it is difficult to predict the pharmacokinetics as well as toxicity and organ damage for this route of administration. It is interesting to note that re-formulated OxyContin® contains PEO; however, no cases of TMA associated with the IV use of re-formulated OxyContin® have been reported [3]. These drugs are produced by different manufacturers; therefore, there may be variation in the ingredients and/or manufacturing process of the tamper-resistant forms. In addition, this may represent a shift in the prescription practice from re-formulated OxyContin® to Opana ER®. In April 2010, re-formulated OxyContin® was FDA approved. An alert issued by Nassau County Department of Social Services, Long Island, New York reported that between August 2010 and February 2011, there was a 43% decrease in Medicaid prescriptions for OxyContin® with a 45% increase in Opana ER® [9].

There is overlap in our patient population, as well as in the CDC case-control study group, with some of the known associations with TMA, such as Hepatitis C infection and clinical features of sepsis. The CDC case-control study reports a strong association between injection of re-formulated Opana ER® and "TTP-like illness" (OR=35.0; CI=3.9-312.1) [3]. The exact underlying cause for this association is unknown and is likely multifactoral. Decreased levels of ADAMTS13 is a proposed etiologic mechanism for TMA and patients with Hepatitis C infection and IV drug abusers are known to have decreased levels [10]. The interaction and relationship of the re-formulated PEO coating and ADAMTS13 activity is unknown. One possible mechanism is formation of an inhibitor and/or autoantibody to ADAMTS13 contributing to the clinical symptoms of TMA as the tablets are altered for injection. Unfortunately, our patient population was not tested for ADAMTS13 autoantibodies and the method of altering the tablets is unknown. It would be of interest to know exactly how the drugs were altered by the abusers in our population since the mechanism utilized to alter the tablets may be a contributing factor. Since our patient population was concentrated in a relatively small geographic region, and some are immediate family members, it is likely that our patient population may be using a similar technique to alter the tablets for injection.

In addition to the clinical novelty, the impact of this method of drug abuse on the health care system is quite significant. At our institution, we saw 2 cases of TMA requiring TPE that were unrelated to IV Opana® abuse and 1 patient with an undocumented drug history. In contrast, we had 10 patients within this time frame with TMA and documented IV Opana ER® abuse, which is 77% of TMA patients requiring treatment during this time frame. Four of our ten patients were re-admitted during this study time frame. Two patients had similar findings of the initial presentation of TMA and reported continued use of IV Opana ER®. One patient received additional TPE and one received serial thawed plasma transfusions. The other two admissions were for reasons other than TMA. During this time frame, these 10 patients generated over 1 million dollars in fees. IV Opana ER® abuse is not only a social issue, but greatly impacts the available medical resources in our community, including availability of staffing and equipment.

In addition to the financial impact, there is a potential impact on the available blood supply which at times can already be limited. During our 8-month study period, a significant number of blood products were utilized. Our local blood supplier could not meet the demand for plasma cryoprecipitate reduced units for these apheresis treatments and many units had to be acquired and shipped from outside blood donor centers. Within 10 months following our study period, 3 of the 10 patients were re-admitted. One patient was re-admitted within 1 week of this study period requiring 27 TPE procedures and utilizing 12 red blood cell units, 11 units thawed plasma and 198 units plasma cryoprecipitate reduced (55,511 mL). Only 1 of 10 patients is known to have expired with cause of death listed as complications of sepsis and endocarditis.

This case report illustrates at least some aspects of the growing epidemic of prescription drug abuse and its potential impact on the medical community and society at large. The exact cause for TMA in this patient population is unknown and will require further investigation. We did not identify any unique clinical symptom or laboratory findings in our patient population that would alert clinicians of possible IV Opana ER® use when patients present with TMA. Questioning patients who present with TMA about their illicit drug use may reveal more reports and associations with IV Opana ER®. Due to the novel nature of our report, long-term sequalae have not been clearly defined at this time. Long-term patient follow-up may be needed to fully characterize the emphasized aspects of this report.

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