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Massive Ingestion of Clopidogrel in a Suicidal Attempt: A Case Report and Review of Literature

İntihar Amaçlı Aşırı Doz Clopidogrel Alımı: Olgu Sunumu ve Literatürün Gözden Geçirilmesi

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Abstract

Clopidogrel is an antiplatelet agent mainly used in coronary artery disease. It has a rare toxicity due to low side effect profile. In this paper we present a 55-year-old male patient presenting to the emergency department due to a clopidogrel overdose of 4200 mg in a suicidal attempt. He had no major or life-threatening hemorrhage, but hematuria that regressed spontaneously without a significant hemoglobin drop. He was monitored at the emergency department for 48 hours and discharged after an uneventful clinical course. There are limited reports about clopidogrel overdose in the literature. Although major systemic side effects such as major bleeding, purpura, heart failure, and other effects are known to occur with clopidogrel overdose, our patient did not experience such effects. *(JAEM 2013; 12: 167-9)*

Key words: Clopidogrel, bleeding, overdose, suicide

Özet

Klopidogrel özellikle koroner arter hastalığında kullanılan bir antiagregandır. Düşük yan etki profili nedeniyle nadiren toksisiteye yol açar. Bu olguda intihar amaçlı 4200 mg klopidogrel doz aşımı ile acil servise başvuran 55 yaşındaki erkek hastayı sunduk. Hastanın önemli veya yaşamı tehdit eden kanaması yoktu ancak hematürisi önemli hemoglobin düşüşü olmadan kendiliğinden geriledi. Acil serviste 48 saat gözlenen hasta klinik seyrinin stabl olması üzerine taburcu edildi. Literatürde klopidogrel doz aşımı hakkında sınırlı raporlar vardır. Klopidogrel doz aşımına bağlı majör kanama, purpura, kalp yetmezliği gibi önemli sistemik yan etkileri bilinmesine rağmen bizim hastamızda bu tür etkiler yoktu. Bunun sonucunda klopidogrel'in geniş bir terapötik pencereye sahip olduğu söylenebilir. *(JAEM 2013; 12: 167-9)*

Anahtar kelimeler: Klopidogrel, kanama, aşırı doz, özkıyım

Introduction

Clopidogrel, a second-generation thienopyridine, is used to inhibit platelet aggregation in a variety of disease states, primarily coronary artery disease (1). Despite its relatively wide spectrum of clinical applications, clopidogrel overdose have been very rarely reported in the literature (2). As a powerful and widely employed antiplatelet therapy, it is imperative for clinicians to become familiar with overdose of clopidogrel. We report in this paper a case of clinically silent massive clopidogrel ingestion in a suicidal attempt.

Case Report

A 55-year-old previously healthy male presented to the emergency service 5 hours after ingesting 56 tablets of 75 mg clopidogrel (4200 mg total) for suicidal purposes. He admitted that he had taken the tablets on purpose and two of his close relatives living in the same house who had seen the empty bottle confirmed the incident. The patient did not recall if he had vomited at all after ingestion of the drug. He subsequently noted no rectal, nasal, gingival bleeding, or hemoptysis. However, he noted that his urine turned pinkish-red when he urinated. He felt no rapid heart beat, respiratory difficulty, lightheadedness, or altered consciousness. At presentation he was asymptomatic. On physical examination, he was well appearing, conscious, fully cooperative, and oriented. His blood pressure was 130/70 mmHg, pulse rate was 60 bpm, respiratory rate was 22/min, and the body temperature was 37ºC. Laboratory examinations were as follows: Hb: 13.9 g/dL, Htc: 42.8%, WBC: 11.15, MCV: 88.4 fl, MCH: 28.7 pg/mL, MCHC: 32.5 g/dL, RDW: 14%, PT: 13.3 sn, APTT: 35.7 s, INR: 0.99, Fibrinogen: 350 mg/dL, AST: 47 U/L, ALT: 20 U/L, LDH: 330 U/L, CK: 125U/L, CK-MB: 20 U/L, Myoglobin: 2.1 ng/mL, and troponin: 0.001. Iron, transferrin, ferritin, renal function tests, and electrolytes were all normal. Blood gas analysis revealed a PO_2 of 73.4 mmHg, PCO_2 of 31.2 mmHg, pH of 7.36, HCO_3 of 15.8 mmol/L. The control arterial blood gas

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levels were normal. His electrocardiogram and chest X-Ray were not remarkable for any pathology. His oropharyngeal, nasal, auditory examinations were negative for a focus of bleeding. He had no sign of hematoma in any part of the body. Abdominal examination revealed no tenderness, guarding, or flank tenderness. His rectal examination did not reveal fresh (hematochezia) or digested blood (melena). His stool sample was negative for occult blood. His urinalysis revealed 400/hpf (normal range 0-3/hpf) erythrocytes and 8/hpf (normal range 0-3.5/hpf) leucocytes with no bacteria or casts.

As the patient presented 5 hours after ingestion, we did not perform detoxification with active charcoal. In addition, no active charcoal has been available onthe market or in hospitals since 1 year. Therefore, we did not administer active charcoal. A 16-F foley urinary catheter was placed. His urine outflow was adequate and urine color was initially pinkish-red and lightened upon vigorous flushing and irrigation of the urinary bladder with isotonic saline 500 cc. No further urine color darkening was observed for the remainder of the observation period. His hemoglobin level did not drop significantly (to 13.5 g/dL and 13.4 g/dL in the next 2 measurements in 24 hours). His vital signs and neurologic status as assessed every 4 hours did not deteriorate. He was monitored at the emergency department for 48 hours and discharged without any complications.

Discussion

Clopidogrel is a prodrug that is converted to its active metabolite in the liver, which binds selectively and noncompetitively to the platelet surface low-affinity platelet P2Y12 ADP-receptor binding site (3). It irreversibly inhibits ADP binding to the receptor and subsequent receptor activation of the platelet glycoprotein (GP IIb/IIIa) complex necessary for fibrinogen-platelet binding (1, 3). The effect of clopidogrel lasts for the life span of the platelets (about 7-10 days).

In the CAPRIE trial (4) the clinically important adverse events were gastrointestinal hemorrhagic complications occurring at a rate of 2.0% that required hospitalization in 0.7%. In the same study the incidence of intracranial hemorrhage was 0.4% for clopidogrel. In the CURE trial clopidogrel combined with aspirin was associated with an increase in bleeding, primarily gastrointestinal and at puncture sites (5). The incidence of intracranial hemorrhage was 0.1% and rate of fatal bleeding was 0.2%.

Information about clopidogrel overdose is limited. The Texas Department of State Health Services reported 582 clopidogrel exposures between 1998 and 2004, as collected by the Texas Poison Center Network (TPCN) (6). The mean exposed dose was 249 mg (range 25-7500 mg, SD±643 mg). The most frequently reported dose among reported doses was 150 mg (48.3%), Seventy-three percent of these exposures had no clinical effect. The rate of any adverse clinical effect was 11.2%, gastrointestinal side effects being the most common (4.7%) followed by neurological (3.0%) cardiovascular (0.6%), and ocular (0.6%) side effects. The most common side effects were vomiting (2.4%) and dizziness (2.4%). Blood in the rectum and haematemesis each occurred in 0.6% of exposures whereas other sources of bleeding, including fatal intracranial hemorrhages were not observed, and no deaths occurred. Although the majority of exposures were seen with doses equal to or less than 150 mg, the rate of any effect was 27%, with the rate of major effects of only 3.2%. Our case, although having ingested a massive dose of Clopidogrel, did not experience any major side effect. In the CAPRIE trial (4) a 34-year-old female ingested a single dose of 1,050 mg. In another study (2), a 49-year-old male committed a suicide attempt with 1,650 mg of clopidogrel. These cases experienced no side effects and recovered spontaneously without any sequel . In one study, a dose of 1875 mg of clopidogrel ingested in a suicidal attempt while on chronic clopidogrel 75 mg/day and aspirin 100 mg/day, caused pulmonary hemorrhage and hemothorax that resolved with conservative treatment (7).

As far as we know, our case ingested the highest clopidogrel dose at one time so far, without any major bleeding or life-threatening complication. Our patient only developed hematuria that resolved upon irrigation of the urinary bladder. In addition, his hemoglobin levels did not decrease significantly, which suggested that the urinary bleeding was mild and temporary.

As for the treatment, supportive therapy is the logical first step. Platelet transfusion may be reasonable to reverse the pharmacological effects of clopidogrel if quick reversal is required, particularly in the case of bleeding (2). The most commonly employed treatment modalities in a report were decontamination by dilution (30.2%), food (12.4%), and activated charcoal (7.1%) although less than half of all cases in that report received no type of therapy. In a recent report desmopressin was used in rats, with partial reversal of clopidogrel-induced platelet inhibition (6, 8). One phase I trial assessed the safety and effects of recombinant FVIIa in reversing clopidogrel-enhanced bleeding in an experimentally induced punch biopsy in healthy subjects. Recombinant FVIIa at doses of 10 and 20 µg/kg significantly mitigated the clopidogrel-induced effects on blood loss volume (BV). A significant reduction of clopidogrel-induced bleed duration (BD) was observed with 20 µg/kg rFVIIa (p=0.048). No higher dose was tested due to early termination of the study. The authors concluded that rFVIIa (10 and 20 µg/kg) reversed the effect of clopidogrel on blood loss (9).

We did not employ any specific therapy because the patient remained clinically stable and asymptomatic. In addition, our patient's hemoglobin levels remained stable for 24 hours. No study so far has demonstrated beneficial effects with specific therapies in asymptomatic patients with normal or near-normal laboratory results. Therefore it is prudent to monitor asymptomatic patients with watchful waiting and frequent checks of vital signs, neurologic status, and hemoglobin levels as potentially devastating side effects, particularly bleeding, may occur later.

Conclusion

We presented a patient who, to our best knowledge, intentionally ingested the largest amount of clopidogrel in the literature with only mild complication. Clinical effects of clopidogrel overdose seem to be relatively rare and mild, as indicated by our case and others as well as a large registry, although such a conclusion cannot be drawn with a limited number of cases and more studies are needed.

Conflict of Interest
No conflict of interest was declared by the authors.

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Informed Consent: Written informed consent was obtained from the patient who participated in this case.

Author Contributions

Concept - F.Y., O.Ç.; Design - F.Y.; Supervision - C.K.; Funding - M.E.K.; Materials - E.D.A.; Data Collection and/or Processing - O.Ç., C.K.; Analysis and/or Interpretation - M.E.K.; Literature Review - F.Y., B.T.; Writer - F.Y., O.Ç.; Critical Review - C.K., M.E.K.

Çıkar Çatışması

Yazarlar herhangi bir çıkar çatışması bildirmemişlerdir.

Hakem değerlendirmesi: Dış bağımsız.

Hasta Onamı: Yazılı hasta onamı bu olguya katılan hastadan alınmıştır.

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References

1. Huber K. Clopidogrel in coronary artery disease: update 2012. Adv Cardiol 2012; 47: 31-8. [CrossRef]
2. Kocabay G, Okçular I, Akkaya V, Güler K. Suicide attempt with clopidogrel. Hum Exp Toxicol 2006; 25: 731-4.[CrossRef]
3. Coukell AJ, Markham A. Clopidogrel. Drugs 1997; 54: 745- 50.[CrossRef]
4. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996; 348: 1329-39. [CrossRef]
5. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK, et al. 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. [CrossRef]
6. Forrester MB. Pattern of clopidogrel exposures reported to Texas poison centers during 1998-2004. Clinical Toxicology 2007; 45: 950-5.[CrossRef]
7. Borderías Clau L, Garrapiz López J, Caballero G. Pulmonary Haemorrhage and Haemothorax After Massive Ingestion of Clopidogrel as a Suicide Attempt. Arch Bronconeumol 2009; 45: 570-4.[CrossRef]
8. Levine M, Swenson S, McCormick T, Henderson SO, Thomas SH, Markland FS. Reversal of thienopyridine-induced platelet dysfunction following desmopressin administration. J Med Toxicol 2013; 9: 139-43.[CrossRef]
9. Skolnick BE, Shenouda M, Khutoryansky NM, Pusateri AE, Gabriel D, Carr ME. Reversal of clopidogrel-induced bleeding with rFVIIa in healthy subjects: a randomized, placebo-controlled, double-blind, exploratory study. Anesth Analg 2011; 113: 703-10.