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Original Article

Intravenous Methylprednisolone, a Possible Cause of the Atrial Fibrillation

Afsaneh Vazin[a,*], Gholamreza Rouzitalab[a], Mohammad Firoozifar[b], Farid Zand[b]

[a]*Department of Clinical Pharmacy, Faculty of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran*
[b]*Anesthesiology and Critical Care Department, Faculty of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran*

Abstract

We are presenting a case illustrating atrial fibrillation (AF) following the use of methylprednisolone in a patient with pelvic and femur fracture. A 48- year- old man with no significant past medical history, was admitted to the emergency department after injury in a car accident. He suffered a multiple bone fracture with chief complaints of pain and shortness of breath. He was transferred to the ICU. To prevent fat embolism syndrome, he was treated with methylprednisolone 500 mg every 6 h. About 4 h after the second dose, his normal sinus rhythm changed to a sinus tachycardia and then to AF. The methylprednisolone therapy was discontinued. After about 8 h of methylprednisolone discontinuation, the patient's normal sinus rhythm returned. Corticosteroids have been utilized for prevention and treatment of fat embolism syndrome, although there is uncertainty about their effectiveness. Cardiac dysrhythmias have been reported following the use of methylprednisolone. One possible mechanism of methylprednisolone induced AF is the direct effect on cell membrane, resulting in potassium efflux, which in turn, may initiate cardiac dysrhythmias. Previous methylprednisolone-associated AF case reports suggest a higher chance of AF occurrence with higher dose of methylprednisolone. Corticosteroids should be used with caution, especially when high doses are indicated and in patients with high risk for arrhythmias.

Keywords: Arrhythmia; Atrial fibrillation; Fat embolism; Methylprednisolone.
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1. Introduction

Fat embolism syndrome (FES) was first recognized and clinically described in the nineteenth century by Zenker (1862), Czerny (1875), and Scriba (1880). The syndrome has been associated with traumatic and non-traumatic disorders which contributes to the development of acute respiratory distress syndrome [1]. FES rarely occurs due to the nonorthopedic causes [2].

Fat embolism is the release/formation of fat globules into the circulation and is usually

*Corresponding authors: A. Vazin, Assistant Professor of Pharmacy Practice, Shiraz University of Medical Sciences, School of Pharmacy, Shiraz, Iran
Tel: (+98)711-2424128, Fax: (+98)711-2424126
E-mail: Vazeena@sums.ac.ir

lodged in respiratory venous capillary beds that may cause FES, which is associated with a series of respiratory symptoms, hypoxia and even death. The formation and consequences of fat emboli is highly unpredictable and it seems to have high morbidity and mortality (10-20%) rate, especially in elderly and in patients with multiple underlying medical problems [3].

The treatment of manifestations of FES is mainly supportive care. Different modalities such as early fracture fixation and general ICU management have been proposed for treatment and prevention of fat embolism [4-6]. The role of corticosteroids is controversial in reducing morbidity and complications. While one study by Lindeque, *et al*. has supported the use of methylprednisolone in patients with FES after long bone fractures, another report by Richards does not recommend routine use of corticosteroids to prevent fat embolism [1, 3-5].

Despite several case reports of cardiac arrhythmias in association with methylprednisolone [8-11], serious cardiovascular side effects are very rare and high dose methylprednisolone pulse therapy is generally considered safe [7]. In our institution, methylprednisolone is routinely used in patients with long bone fractures for prevention of fat emboli.

Several cases of atrial fibrillation have been reported with IV methylprednisolone pulse therapy, however, none have been utilizing this medication for treatment or prevention of FES. This report is trying to discuss the use of methylprednisolone in patients with, or at high risk for, fat emboli and reports a possible sequel, AF, with its use.

2. Case presentation

A 48 year-old male was brought to the emergency department after an injury in a car accident with the chief complaint of shortness of breath and pelvic pain and was admitted to the ICU. The patient was intubated due to bilateral pneumothorax, which was the result of chest injury. Mechanical ventilation was initiated and a chest tube was inserted. He had no relevant past medical history for any disease. He had never smoked and had no other risk factors for cardiovascular disease. Initially, his cardiac monitor showed normal sinus rhythm.

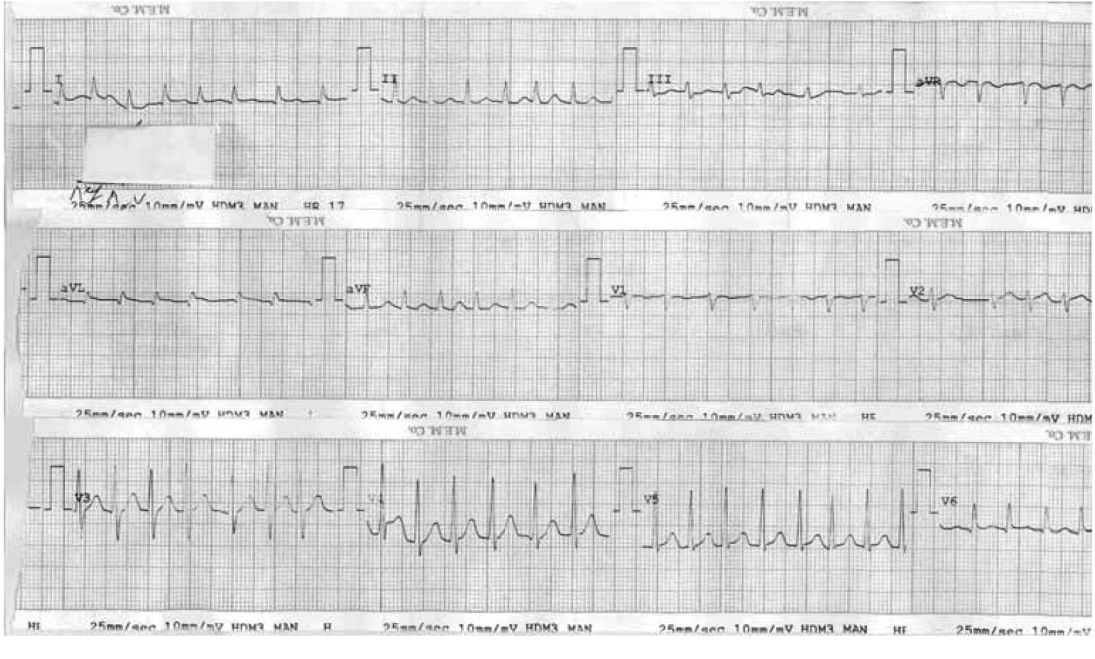

Figure 1. The electrocardiogram indicating atrial fibrillation in a patient receiving high dose of methylprednisolone.

Table1. Characteristics of patients experiencing atrial fibrillation associated with methylprednisolone therapy.

Author	Age (years)	Gender	Dose	Infusion time	Onset of atrial fibrillation after methylprednisolone initiation	Disease	Previous cardiovascular disease
Ueda *et al.*, 1988	12	F	1 g IV daily	2 h	After 24 h	Systemic lupus erytheomatosus	No
Ueda *et al.*, 1988	16	M	1 g IV daily	4 h	After 24 h	Idiopathic nephrotic syndrome	No
Aslam *et al.*, 2001	37	F	40 mg every 8 h	Not stated	At day 3	Systemic lupus erytheomatosus	Yes
McLuckie *et al*., 1993	22	M	1 g IV daily	2 h	At day 3	Multiple sclerosis	No
Moretti *et al.*, 1999	59	M	1 g IV, daily 125 mg IM	2 h, bolus	7 h after the third dose, after the ninth dose	Multiple sclerosis	No

On admission to the ICU, he was afebrile, with pulse rate 95 beats/min., respiratory rate 24 breaths/min. and blood pressure (BP)115/70 mmHg. Arterial blood gas showed PaO_2 92.6 mmHg, $PaCO_2$ 35.6 mmHg, HCO_3^- 24.8 mEq/ml, O_2 saturation 97.7% and pH 7.46. Laboratory tests were done on admission to ICU, Hgb 10.6gm/dl; white cell count 8500 cells/L; platelet 158000 cells/L; Na^+ 138 meq/L; K^+: 4.1 meq/L; BUN 22 mg/dl; Cr 0.9 mg/dl. X rays showed pelvic, mid and distal port right femur fractures. Traction splint was applied.

His medications on admission to the ICU were as follows: Enoxaparin 60 mg subcoetaneous everyday, ranitidine 50 mg IV every 8 h, cefazolin 1 g IV every 6 h, gentamycin 60 mg IV every 8 h.

On second day of admission, to prevent the occurrence of FES, methylprednisolone was initiated at 500 mg, administered IV over 2 h and repeated every 6 h. About 4 h after the second dose, his normal sinus rhythm changed to a sinus tachycardia and then to AF (Figure 1). His vital signs prior to the AF episode were stable: Respiratory rate 16 beats/min., BP 125/75 mmHg, Temp 37.2 °C. Serum electrolytes and atrial blood gases at the time of AF revealed: K^+ 3.7 mEq/L, Mg^{++} 2.69 mEq/L, Ca^{++} 8.6 mEq/L, PaO_2 80.4 mmHg, $PaCO_2$ 39.4 mmHg, HCO_3^- 27.1 mEq/ml, O_2 saturation 93.6% and pH 7.45.

The methylprednisolone therapy was discontinued and to control his heart rate, verapamil 5 mg was administered intravenously. After about 8 h of methylprednisolone discontinuation, the patient's normal sinus rhythm returned (Figure 2).

3. Discussion

Corticosteroids have been used to prevent or treat fat embolism syndrome, although there is uncertainty about their effectiveness. The proposed mechanism by which corticosteroids exert their therapeutic effects in treatment of FES is stabilization of membranes, inhibition of complement mediated leukocyte aggregation and limitation of rising the level of free fatty acids. Among corticosteroids, methylprednisolone is the preferred agent for prevention or treatment of FES [11].

Our case was a middle-aged man who developed AF after second dose of methylprednisolone. Other concurrent drug treatments were continued after the resolution of observed arrhythmia (enoxaparin, ranitidine, cefazolin, gentamycin). Furthermore, lack of evidence to suggest that those drug therapies can cause AF suggests that there is very low possibility that these drugs caused AF in our patient. His previous ECG had shown normal heart rhythm and

his history was negative for cardiac abnormalities or hyperthyroidism, thereby making a preexisting cardiac problem less likely. Moreover, after 8 h of cessation of methylprednisolone the patient sinus rhythm returned to normal. To further determine and establish causality a validated nomogram, Naranjo Algorithm, was utilized [12]. Total score on the Naranjo Algorithm determined the probability of causality to be probable (score: 5).

A literature search of Medline (1966-January 2008) revealed five case reports of AF associated with methylprednisolone that had been used for treatment of different underlying diseases (Table 1) [7-10]. In the case reported by Aslam *et al.*, although a relatively smaller dose of methylprednisolone was utilized, prior history of cardiovascular disease could have contributed to occurrence of AF. In other four cases substantially larger doses were used and in four cases presence of an autoimmune disease have been reported (Table 1).

Recently, van der Hoof *et al.* performed a case controlled study on 385 patients to test the hypothesis that the use of corticosteroids increases the risk of new onset AF [13]. In that study, it was reported that high dose corticosteroids ($\geqslant$7.5mg prednisolone equivalent) is associated with an increased risk of new onset AF.

In previous case reports, daily doses of methylprednisolone that caused AF varied,

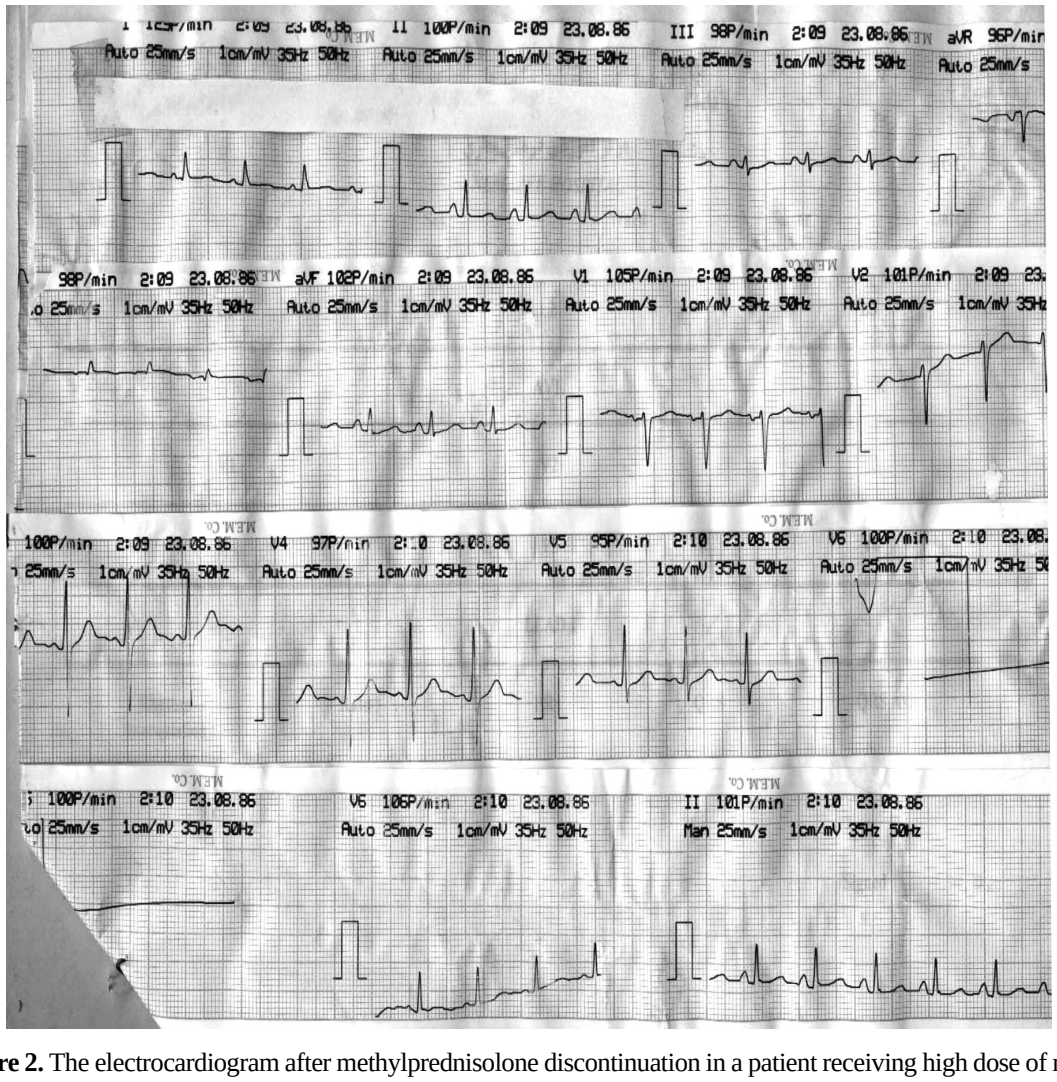

Figure 2. The electrocardiogram after methylprednisolone discontinuation in a patient receiving high dose of methylprednisolone.

ranging from 120 mg to 1000 mg and all five cases reported AF within 72 h after beginning pulse methylprednisolone therapy [7-10]. This wide dose range suggests that AF is not a dose related event when high doses are utilized. In our case, high dose methylprednisolone (500 mg q6h) was associated with development of AF within 10 h of initial dose.

Concerning the route of administration, AF occurred in two cases of IV methylprednisolone pulse therapy. AF is reported with intramuscular administration of methylprednisolone in one case [10]. In Huerta *et al*. study, an increased risk of AF is reported with oral steroids, especially with short-term use [14]. Therefore, it is probable that development of arrhythmia is not dependent on the corticosteroids route of administration.

The reason for corticosteroids induced AF is not clearly understood, however, several mechanisms have been proposed to explain why methylprednisolone has this potential effect. One possible mechanism is the direct effect of methylprednisolone on the cell membrane, which causes potassium efflux [15]. This local effect may influence arrhythmogenesis. Fujimoto *et al*. measured serum potassium in 20 patients before and during methylprednisolone therapy. A small but significant increase in urinary potassium has been observed which explains the potassium efflux theory [16]. Other proposed mechanisms are late potential development, anaphylactic reaction and peripheral vasodilation [16-17]. In our patient, besides high dose methylprednisolone, low-normal serum potassium (3.7 mg/dl) might have contributed to the arrhythmia.

4. Conclusion

The patient described here experienced AF probably induced by methylprednisolone as validated by the Naranjo probability scale. Corticosteroids should be used with caution, especially in high dose especially in elderly patients and patients with previous cardiovascular disease. Before and during the administration of high dose methylprednisolone, close monitoring of ECG and electrolyte status of patients even without known cardiovascular disease, is recommended. The effect of corticosteroids in fat embolism syndrome is under debate. Further investigations about methylprednisolone indication and its appropriate dose in treatment and prevention of fat embolism syndrome are necessary.

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