CASE REPORT

Coma Blisters in the Setting of Quetiapine Overdose: Case Report and Review of Literature

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Abstract

Background: Skin lesions and blistering in the overdose patient, most notably associated with barbiturate overdoses, are commonly referred to as coma blisters, 'barb blisters', or 'barb burns'. We present a patient who was noted to have skin lesions including bullae and blistering following a prolonged coma after quetiapine overdose.
Case report: A 27 year old male presented to our institution with the history of having ingested 7,200 mg of quetiapine in a suicide attempt up to 35 hours prior to being discovered. The patient was found comatose, and was noted to have multiple vesicles on his right ankle and a firm, erythematous plaque and bullae on his right thigh.
Discussion: Sequelae related to prolonged immobility of any cause may include injury to muscle, vascular, microvascular and cutaneous structures. Coma blisters differ from pressure ulcers in many ways and cannot be graded using the typical staging system. Histopathologic analysis suggests an array of microvascular injuries which are secondary to direct pressure injury as well as specific drug effect.
Conclusion: This is the first description of a dermatologic manifestation attributed to coma from isolated quetiapine overdose. Blister formation can be considered as a possible complication of quetiapine overdose.

Keywords: Blister; Coma; Quetiapine; Overdose

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INTRODUCTION

Coma blisters are skin lesions associated with coma in patients with drug overdose (1). These blisters are classically attributed to barbiturate toxicity, with one report described bullous lesions in 6.5% of 290 patients hospitalized with confirmed barbiturate overdoses (2). Due to the historical association and reference to barbiturates, coma blisters have also been colloquially referred to as "barb burns" or "barb blisters". Since the decline of barbiturate use, reports of blisters in the setting of a toxic exposure have become uncommon. However, multiple other drug classes have subsequently been associated with the development of these bullous eruptions including tricyclic antidepressants, anticonvulsants, benzodiazepines, as well as opioids and phenothiazines (3-6).

We present a patient who suffered a prolonged coma after quetiapine overdose and was noted to have bullae and blistering of the lower extremities. We discuss the role of pressure injury and subsequent impairment in tissue oxygenation versus specific drug effects such as endothelial disruption and microvascular thrombus formation in the evolution of these skin manifestations.

CASE REPORT

A 27 year old man was transferred to a tertiary care center with a history of ingesting 7,200 mg of quetiapine in a suicide attempt. He had been found comatose, having ingested the quetiapine up to 35 hours prior to being discovered. Shortly after being found he awoke and subsequently became mildly agitated requiring several 1 mg intravenous doses of lorazepam. He was also placed in soft restraints in order to keep him from falling out of the bed and otherwise safe. The agitation and confusion improved over 24 hours. At this point, he complained of diffuse myalgias and weakness. The initial vital signs were normal except a slight tachycardia (Table 1). There were no signs of muscle rigidity or hyperthermia and the patient was without myoclonus, clonus or hyperreflexia. The patient was, however, dry and with diminished bowel sounds. He required an indwelling catheter due to urinary retention. The patient had multiple vesicles on his right ankle (Figure 1), and a firm erythematous plaque and bullae on his right thigh (Figure 2). Marked unilateral swelling was noted on his right leg, although distal pulses were intact. Initial laboratory abnormalities included a creatine kinase of

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Table 1. Clinical and laboratory findings of the patient at presentation

Examination	Result
Systolic blood pressure (mmHg)	122
Diastolic blood pressure (mmHg)	69
Pulse rate (beats/min)	87
Respiratory rate (breaths/min)	16
Body temperature* (centigrade)	37.1
Oxygen saturation (percent)	100
Creatine kinase (U/L)	33,000
Creatinine (mg/dL)	1.2

* Oral measurement

33,000 U/L and creatinine of 1.2 mg/dL. The patient had a negative urine illicit drug screen. The ECG upon admission was normal sinus rhythm without abnormality. The patient's course was complicated by methicillin-sensitive staphylococcus cellulitis and bacteremia which had likely originated from an open area at the edge of his hip bullae (Figure 2). His treatment regimen included hydration, local wound care and systemic antibiotics. The specific overdose was confirmed by the patient as well as family and corroborated by pill counts.

DISCUSSION

Quetiapine is a second generation antipsychotic often used to treat schizophrenia and bipolar disorder. Overdose manifestations commonly include CNS depression, delirium, anticholinergic features, hypotension, and QTc prolongation (7). Our patient was brought to the hospital over 35 hours after the reported time of ingestion. He had prolonged coma and pressure injury including rhabdomyolysis as well as confusion and agitation and other features of anticholinergic toxicity seen with quetiapine overdose (7); however, his hemodynamic was normal by the time he was brought to the hospital. Other classic features including hypotension, QT prolongation and arrhythmia may have occurred in the time elapsed prior to hospitalization.

Coma blisters have been reported in the setting of overdose with various drugs including barbiturates, amitriptyline, benzodiazepines, carbamazepine, glutethimide, opioids, theophylline (Table 2), as well as carbon monoxide poisoning (1-6,8-18). Basu et al. reported these skin lesions following combined regimens of anticonvulsants in two epileptic children (clobazam, lamotrigine ethosuximide, sodium valproate in one case and clobazam, levetiracetam in other case) that the clobazam was in common in both regimens (4). Branco et al. described coma blisters in a patient after overdose of various antidepressants, phenobarbital and quetiapine (12). Ours is the first reported case of the development of coma blisters after overdose with quetiapine alone.

Prolonged immobility may lead to pressure induced skin injury including subcutaneous tissue and deeper underlying structures (19). This is due to injury to the vasculature and other subcutaneous structures which can be seen on microscopy (19). In a case series of cutaneous biopsy specimens in patients with drug-induced coma due to numerous agents including benzodiazepines, opiates, barbiturates, tissue changes included necrosis of eccrine sweat ducts, hair follicles, sebaceous glands with neutrophilic infiltration of blood vessels as well as endothelial damage and loss of tight junction integrity (19). Similarly, our patient had evidence of prolonged immobility including being found unconscious and having a remarkably elevated creatine kinase. Several factors contributing to the development of pressure ulcers include direct compression

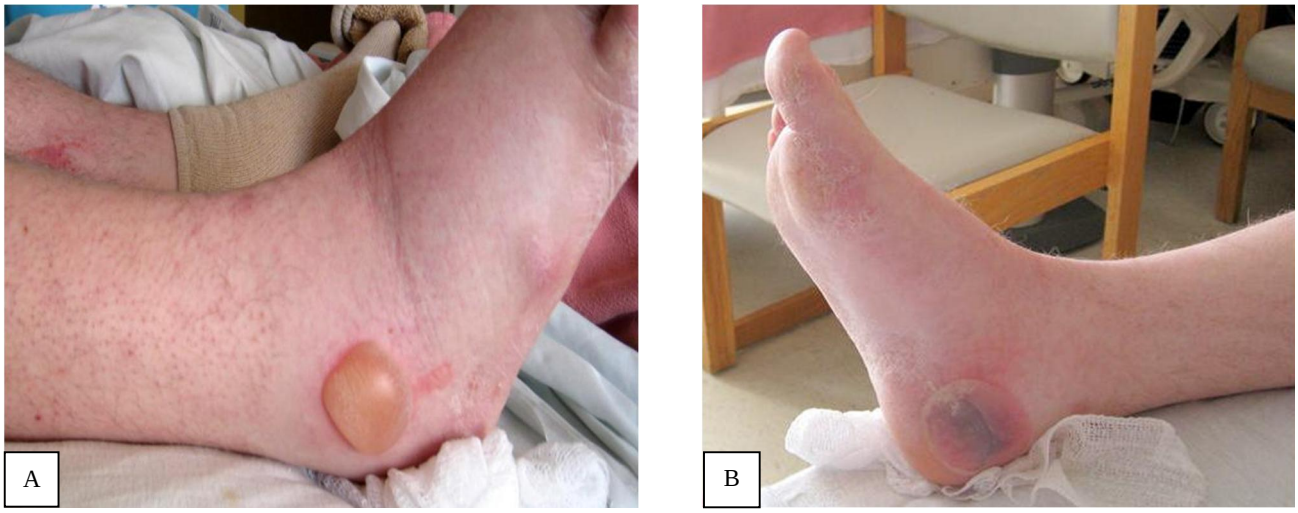

Figure 1. Development of large blisters and ulceration following quetiapine overdose: (A) on the right ankle (B) on the interior right heal.

in the affected part from the weight of the body, tangential sheering forces, frictional heat, and trapped moisture (20). The typical staging system for pressure ulcers is based on determining sequential layers of dermis and subcutaneous injury in a grade I to IV scoring system. Coma blisters associated with drug overdose differ from traditional pressure ulcers and cannot be graded using the typical staging system because injury may extend beyond relatively intact overlying areas (21). This may lead to an under appreciation of the severity of illness.

Although pressure may be one contributing factor in coma blisters, non-dependent areas may also be affected. Direct drug tissue toxicity perhaps exacerbated by relative hypoperfusion and anoxia can potentially be the underlying mechanism. In this regard, development of coma blisters on both pressure bearing and non-pressure bearing areas in a patient with hypoxemic respiratory failure unrelated to overdose was reported by Agarwal et al., though the patient was on medications capable of inducing coma blisters (22). Correspondingly, Keng et al. reported blister formations in non-pressure bearing areas of the body after ingestion of high amount of phenobarbital (23). Additionally, coma blisters most often manifest within twenty-four hours, while pressure ulcers typically occur three to five days following immobility (24). Besides, Kashiwagi et al. discussed an immunologic mechanism in the development of coma blisters related to inflammatory mediators (25).

LIMITATIONS

The primary limitation of this report is the lack of laboratory confirmation of the overdose. However, the history of quetiapine overdose was provided by the patient as well as the family and was supported by a pill count. The clinical presentation was also consistent with quetiapine overdose.

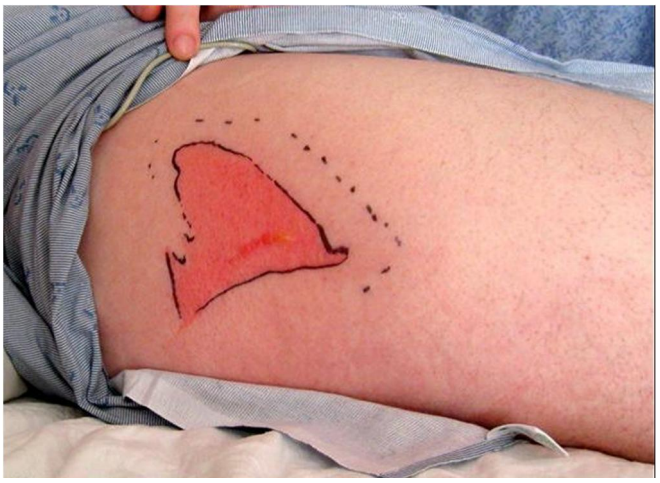

Figure 2. Plaque and bullae on upper right thigh of the patient. Cellulitis later developed at the outer edge of this lesion and was the likely source of this patient's subsequent bacteremia. Margins marked in black.

Table 2. Drug-induced coma blister

Drug	Reference
Barbiturates	1,2
Amitriptyline	3,8
Benzodiazepines	4,5,9-12
Carbamazepine	13
Glutethimide	14
Opioids	6,15
Quetiapine	Present case,12
Theophylline	16

CONCLUSION

This is the first description of a dermatologic manifestation from isolated quetiapine overdose, and the first description of coma blisters resulting from isolated quetiapine exposure. Our patient had evidence of prolonged immobility, one of the primary causes of coma blisters; however, hypoxia or hypotension, sheer forces, moisture and direct drug toxicity may have contributed as well. The exact mechanism of these rapidly developing blisters is unclear but may be related to pressure augmented by direct cytotoxicity in relatively hypoperfused tissues. Heightened awareness is needed to exclude complications that may develop in these superficial-appearing bullae.

Conflict of interest: None to be declared

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