

# Furosemide-induced eruption of haemorrhagic bullae on the fingers

## Introduction

This article describes a man who developed severe haemorrhagic necrotizing blisters within 1 week of being started on regular furosemide. The lesions were confined to the fingers bilaterally and accompanied by severe swelling and loss of function. There were no associated features. All investigations were negative and an adverse drug reaction to furosemide was diagnosed. The drug was stopped and the lesions resolved fully. This form of cutaneous drug reaction is one of the rarest forms of reactions to furosemide especially when confined only to the fingers. One must be aware of such complications and be prepared to withdraw the diuretic to confirm the diagnosis and achieve resolution of the lesions.

## Discussion

Furosemide is a commonly used loop diuretic in the management of pulmonary oedema and oedema associated with congestive heart failure, renal disease and hepatic cirrhosis. Loop diuretics are also gaining ground in the treatment of resistant hypertension (Leto et al, 2014).

Furosemide is not significantly metabolized before urinary excretion, has a half-life of 2 hours and is 95% protein-bound. Loop diuretics work by inhibiting the sodium-potassium-dichloride pump in the thick ascending limb of the loop

of Henle, resulting in the metabolic dose-related and long-term side effects including hypokalaemia, hypomagnesaemia, dehydration, hypocalcaemia, metabolic alkalosis, hypochloraemia, hyponatraemia, hypotension (Davies and Wilson, 1975).

Several dermatological reactions have

been reported (Moore, 2002), including acute generalized exanthematic pustulosis or bullous pemphigoid (Noce et al, 2000), erythema multiforme, acquired epidermolysis bullosa, cutaneous necrotizing vasculitis, Sweet's syndrome and acute febrile neutrophilic dermatosis (Hendricks and

Figure 1. Dorsum of right hand showing the lesions at presentation.



Figure 2. Dorsum of left hand showing lesion on little finger at presentation.



## CASE REPORT

A 79-year-old man was admitted for elective coronary artery bypass surgery and aortic valve replacement. Preoperatively he was taking aspirin, digoxin, perindopril, simvastatin, carvedilol and warfarin for chronic atrial fibrillation. Postoperative recovery was uneventful, with discharge after 6 days.

The patient presented 1 week later with lethargy, orthopnoea, chest discomfort, haemoglobin 8 g/dl and was transfused two units of red cell concentrate. After transfusion, the patient was still orthopnoeic. Echocardiography excluded pericardial effusion or regional wall motion abnormalities. Owing to lower limb pitting oedema and a 3 kg weight gain over 1 week, furosemide was started, the patient improved and was discharged.

The following week the patient re-presented with haemorrhagic bullous lesions on the second to fifth digits on the dorsum of the right hand (Figure 1) and on the dorsum of the left little finger (Figure 2). The lesions were painless, non-pruritic, and developed over the course of 3–4 days after which they began to ulcerate and

bleed on contact. The patient remained afebrile but was unable to grasp objects because of the swelling.

Anti-neutrophil cytoplasmic antibody, anti-nuclear antibody, extractable nuclear antibodies, erythrocyte sedimentation rate, C-reactive protein, complement C3 and C4, creatine kinase, cryoglobulins, hand and chest X-rays, and culture from fluid from lesions were requested following rheumatological review. All investigations were normal. Bactigras and Tubifast dressings were applied.

After initial treatment with ciprofloxacin and topical steroid by dermatologists, the lesions worsened over the next 3 days. The diagnosis of a vasculitic drug reaction to furosemide was considered, and an excision skin biopsy was performed, which revealed necrotic skin cells, eosinophil infiltration and thrombosed dermal vessels with negative immunofluorescence. This suggested a drug reaction. Furosemide was stopped and after 4 days the lesions dried up. Spironolactone was added to his treatment and soon after his hands were back to normal.

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Ader, 1977). Some dermatological reactions may be a result of the chlorine in the chemical structure exhibiting photochemical activity which causes free radical reactions with lipids, DNA and proteins, leading to photosensitive skin eruptions.

The diagnosis of a furosemide-induced reaction is based on exclusion, histological findings and improvement on cessation. The normal blood investigations argue against a drug-induced vasculitis; the histological result was not typical of vasculitis but of drug-induced bullous reaction, and patients with vasculitis tend to be on long-term furosemide (Hendricks and Ader, 1977). This case scored 7 points on the Naranjo adverse drug reaction probability scale (Naranjo et al, 1979).

The lesions in this patient were not typical of erythema multiforme in their appearance and were non-pruritic. Furosemide-induced bullous pemphigoid causes lesions over the body requiring systemic steroids (Noce et al, 2000). Epidermolysis bullosa is unlikely as the lesions are pruritic following long-term furosemide use (Hendricks and Ader, 1977). The lesions described were similar to Sweet's syndrome, but this is normally associated with fever. With all the above conditions excluded the only condition remaining from the differential diagnosis is the very rare bullous haemorrhagic eruptions (Actavis UK Ltd, 2016).

Bullous haemorrhagic eruptions secondary to furosemide follow a similar distribution as this patient's case (Ebringer et al, 1969). They have also been described in other members of the sulfonamide class of drugs, including antibacterial sulfonamides, thiazide and loop diuretics, acetazolamide, sulfonylurea hypoglycaemic agents, some COX-2 inhibitors and sulfasalazine, although distribution of lesions may vary.

The dermatological side effects of sulphonamides like furosemide are estimated at 2.5–3.5%. Although rare, recognition is important as these drugs are used frequently. Withholding the drug treats and confirms the diagnosis. There is little evidence about alternative diuretic therapy should the patient be diuretic-dependent. Other loop diuretics should be avoided, as should thiazide diuretics because of a crossover effect (Guin, 1980). Spirinolactone or ethacrynic acid, a loop diuretic without a sulphur group, may be an alternative (Molnar and Somberg, 2009). **BJHM**

Actavis UK Ltd (2016) Summary of Product Characteristics: Furosemide Tablets BP 20mg. [www.medicines.org.uk/emc/medicine/24100](http://www.medicines.org.uk/emc/medicine/24100) (accessed 22 June 2016)

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## LEARNING POINTS

- The different skin reactions to furosemide can be differentiated by appearance and histopathology.
- Bullous haemorrhagic eruptions are very rare, difficult to diagnose and can have devastating effects if left untreated.
- A high index of suspicion is required since furosemide is commonly used, making an encounter with this side effect likely.
- Drug withdrawal is usually sufficient treatment for resolution.

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