Case Report

Critical illness and multi-organ failure following topical application of skin-lightening preparation

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Summary

Topical application of skin-lightening cream is increasingly undertaken in many non-Caucasian populations for cultural and social reasons. It is a rare cause of poisoning that has potential to lead to significant harm due to skin damage and systemic absorption of cream following application over prolonged periods of time. This case report describes the development of multi-organ failure in an adult due to salicylate toxicity after whole-body application of a skin-lightening cream for 24 h. It highlights the need for vigilance and awareness of the toxic potential of topical salicylates.

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Accepted: 15 May 2019

Keywords: aspirin toxicity; treatment; burns; fluid management; renal failure; electrolytes

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Introduction

Skin lightening is practiced in many non-Caucasian cultures and may be undertaken through topical application of salicylate-containing creams. In the event of topical absorption of the salicylate-containing cream, the plasma salicylate concentration in isolation is a poor predictor of severity of poisoning. However, plasma salicylate concentrations greater than 700 mg.l⁻¹ often cause severe symptoms and are potentially fatal. Toxicity may be graded clinically as mild (nausea, vomiting and tinnitus), moderate (hyperventilation and confusion) or severe (coma, seizures, cerebral and pulmonary oedema). Mortality risk factors include pulmonary oedema, focal neurology, hyperpyrexia and metabolic acidosis. Management of salicylate poisoning is generally supportive. Specific treatments, which may need to be delivered on the intensive care unit (ICU), include urinary alkalinisation, haemodialysis and haemofiltration, central electrolyte replacement and mechanical lung ventilation [1]. Despite its widespread practice, we believe that salicylate poisoning in an adult secondary to topical application of a skin-lightening preparation has not been described previously.

Report

A previously well 44-year-old Afro-Caribbean woman presented to the emergency department with a one day history of worsening respiratory distress associated with lethargy, pyrexia and confusion. Before admission, she had applied a salicylate-containing topical skin-lightening preparation to her body, sparing the hands, feet and face. Treated areas were wrapped in transparent plastic film for approximately 24 h before being removed due to development of widespread superficial burns and worsening symptoms.

Initial assessment identified respiratory distress and tachypnoea, bilateral basal crepitations and type I respiratory failure. Cardiovascular assessment demonstrated sinus tachycardia and hypotension. Neurologically, the patient was confused with a Glasgow coma scale score of 14/15. Skin assessment revealed superficial burns affecting 90% of the body surface area (BSA), with small, intact blistering to 4% BSA but no mucosal involvement. There was a persistent pyrexia above 38 °C.

Initial investigations demonstrated raised inflammatory markers, acute kidney injury, rhabdomyolysis with markedly elevated creatine kinase, and a deranged clotting profile with elevated international normalised ratio and activated partial thromboplastin time. Arterial blood gas analysis confirmed type I respiratory failure and there was a compensatory metabolic acidosis with hypocapnia and hypokalaemia. Urinalysis was positive for protein, blood and ketones. Chest radiography demonstrated bilateral basal consolidation.

She was transferred to the ICU with an initial working diagnosis of chemical burns secondary to application of topical skin-lightening preparation. Immediate management included siting a central venous catheter for electrolyte replacement and fluid resuscitation. An arterial cannula was inserted for regular blood gas analysis and continuous blood pressure measurement. Urinary alkalisation using sodium bicarbonate was commenced due to rhabdomyolysis. Additional support included enteral nutrition, patient-controlled opioid analgesia and antibiotics for a possible chest infection. Mechanical lung ventilation and continuous veno-venous haemofiltration were anticipated but ultimately not required. A multidisciplinary team referral included the regional tertiary burns centre and local dermatology team. Subsequent dermatology review recommended two-hourly topical emollients and skin wash for chemical burns. Skin biopsy and fresh frozen samples were analysed to exclude toxic epidermal necrolysis.

After 24 h, her clinical condition stabilised, however, she continued to demonstrate respiratory failure and a persistent metabolic acidosis. The topical cream used by the patient was made available to the clinical team and noted to contain salicylate. Subsequent retrospective serum analysis revealed an admission plasma salicylate level of 844 mg.l^{-1} , decreasing to 434 mg.l^{-1} after 24 h treatment in the ICU. Escalation of care to include dialysis was considered, however, due to decreasing plasma salicylate levels, supportive care continued until symptom resolution and normalisation of blood parameters, including renal function, plasma salicylate levels and acid–base balance. It is likely that urinary alkalisation provided additional but unintended benefit in promoting urinary elimination of plasma salicylate.

The patient was transferred to the ward after five days in the ICU and discharged home after nine days. On discharge, patient education was provided regarding use of topical skin-lightening preparations and salicylate poisoning. Community follow-up was arranged under the dermatology team. An adverse drug reaction yellow form was submitted to the Medicines and Healthcare products Regulatory Agency.

Discussion

This case demonstrates the unique presentation of salicylate toxicity in the context of topical skin-lightening use. Although salicylates themselves are not the active agent causing skin-lightening in such preparations, they are utilised to promote absorption through the skin by means of epithelial cell breakdown. The potential of these preparations to cause toxicity is related to the large surface area to which they are applied and the prolonged duration of application. Additionally, the widespread availability of these over-the-counter preparations and lack of pharmaceutical regulation, in combination with the erroneous presumption of safety, further contributes to the risk of adverse events and harm.

Salicylate-containing topical preparations are most commonly used as analgesics. However, salicylates are contained in many other topical preparations, including those intended for dermatological and cosmetic use. Many of these agents are available as non-prescription, over-the-counter products and can be purchased from sources providing no qualified medical advice in their use. Moreover, topical preparations are available in a wide range of concentrations and formulations, including gels, ointments, lotions, sprays and transdermal patches [2, 3]. Prolonged, repeated or inappropriate administration can lead to adverse events and non-efficacious use, resulting in harm [4]. Formulations typically contain a single active drug entity but may contain combinations of agents to provide analgesic, antipruritic, anaesthetic or counter-irritant action, thus increasing their potential to cause cutaneous reactions and drug interactions [1]. Taken together, the above factors increase the likelihood for accidental and intentional misuse.

The potential of topical salicylates to cause systemic toxicity is dependent upon the ability of these agents to penetrate the skin and reach the vascular dermis. As keratolytic agents, salicylates dissolve the intercellular binding of epithelial cells, resulting in skin peeling, erythema and discomfort [5]. Moreover, as lipophilic compounds, salicylates are readily absorbed across the skin before being hydrolysed in the tissues [3]. The plasma half-life of salicylates is dose-dependent, being two to three hours in low doses, 12 h at typical anti-inflammatory doses, and as much as 15–20 h at toxic doses [3]. At therapeutic doses, metabolites are conjugated with glycine and glucuronic acid before being eliminated in the urine. However, these pathways demonstrate saturation kinetics at higher doses and contribute to the prolonged half-life observed [3]. Furthermore, the rate of elimination in the urine and relative proportion of metabolites and free salicylate is highly dependent upon other factors, including the dose

administered and pH; hence the potential efficacy of urinary alkalinisation. Systemic features of toxicity may occur, including tachypnoea, nausea, vomiting, aural symptoms, hypoglycaemia, renal failure, pulmonary and cerebral oedema. Additionally, a pseudo-allergic reaction may occur as a consequence of dysfunctional leukotriene metabolites and prostaglandin synthesis [6].

Accidental and intentional misuse of salicylates has historically been associated in part with the ubiquity of salicylates in over-the-counter analgesic medications [6, 7]. In the USA, 77% of reported cases of salicylate poisoning occurs in children under 6 years of age [8]. Despite this, the incidence of salicylate-related toxicity has been declining in recent years, in part related to the increase in numbers of alternative analgesic preparations containing the non-steroidal anti-inflammatory agents diclofenac and ibuprofen [1]. This finding is in contrast to the incidence of toxicity associated with non-pharmaceutical salicylate preparations, including herbal, cosmetic and dermatological agents, which has increased steadily over the same time period [1]. This may in part be explained by the generally upheld, but nonetheless incorrect, assumption that these agents are inherently safe, resulting in unintentional poisoning [9, 10].

This case has highlighted the potential of topical skin-lightening preparations to cause critical illness. It demonstrates the ability of these preparations to cause widespread cutaneous burns and systemic absorption of potentially toxic compounds, including salicylates. Awareness of this possibility is particularly relevant in the context of intensive care medicine as this case represents the first documented example of such a presentation. In this instance, although the patient believed she had used the same preparation several times previously, on close inspection it was apparent that the most recent preparation, despite near-identical packaging, had subtle differences in the ingredients that may have contributed to her critical illness. Furthermore, the application of such a preparation for extended periods of time, in some instances several days, is widespread in many cultures and increases the likelihood of further cases occurring. This case highlights the need for vigilance and awareness of the toxic potential from topical salicylates.

Acknowledgements

Published with the written consent of the patient. No external funding or competing interests declared.

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