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CASE REPORTS

Salicylism from Topical Salicylates: Review of the Literature

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ABSTRACT

Background: Although topical salicylates are widely used, toxicity from this route is rare. Case Report: We present an unusual case of salicylism from a topical salicylate preparation in an 80-year-old woman. The patient was admitted to the dermatology service with a diagnosis of erythroderma and was treated with salicylate containing ointments. After six days of treatment the patient became confused and paranoid. A serum salicylate was 3.36 mmol/L (46 mg/dL). The patient was admitted to the intensive care unit were she was rehydrated and treated with bicarbonate and activated charcoal. Results: Her serum salicylate fell to 1.90 mmol/L (26 mg/dL) over a two day period and she regained a normal mental status.

INTRODUCTION

Topical salicylic acid is commonly used as a keratolytic to treat skin conditions such as psoriasis,[1] eczema,[2] and icthyosis.[3] Liniments containing methyl salicylate are also applied topically to relieve muscle or joint pain.[4,5] Many authors believe that topical salicylates act locally and have little systemic toxicity.[4,6] Percutaneous absorption of salicylates occurs slowly and serum levels following topical application are usually inconsequential.[2,7,8] Hence, toxicity from topical salicylates is rare. We report a case of salicylism following topical application of salicylic acid that presented with metabolic acidosis and altered mental status in an elderly women. Previously reported cases of salicylate toxicity from this route are reviewed.

Case Presentation

An 80-year-old woman was admitted to hospital for severe erythroderma of unknown etiology. The differential diagnosis included psoriasis, seborrheic dermatitis, scabies, lymphoma, infectious causes and idiopathic causes. On admission, the patient was

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alert and oriented with normal vital signs and the following electrolytes: Na 139 mmol/L, K 4.3 mmol/L, Cl 109 mmol/L, HCO_3 22 mmol/L, BUN 21.1 mmol/L (59 mg/dL), Cr 159 μmol/L (1.8 mg/dL), glucose 5.5 mmol/L (99 mg/dL) and anion gap 8. She was taking Captopril for hypertension and had been prescribed Doxepin, accutaine, and Acyclovir as empiric treatment for erythroderma. In hospital the following salicylate containing ointments were applied: salicylic acid 5% in petrolatum to body 4x/d, salicylic acid 10% in petrolatum to hands and feet 4x/d, salicylic acid 2% in olive oil to scalp nightly. She was not taking oral salicylates and was never witnessed to put her hands to her mouth.

On the evening of the sixth hospital day the patient developed an altered mental status. On examination she was found to be confused, drowsy, and paranoid with deep respirations. Her vital signs were blood pressure 120/80 mm Hg, respiratory rate 22/min, heart rate 80 BPM, temperature 99°F. The respiratory examination was remarkable only for coarse crackles which cleared with coughing. The cardiovascular examination revealed normal heart sounds and no jugular venous distention. The neurologic examination was without focality. Her skin was diffusely erythematous. The remainder of the physical examination was normal.

Repeat electrolytes were: Na 153 mmol/L, K 4.6 mmol/L, Cl 125 mmol/L, HCO_3 14 mmol/L, BUN 19.3 mmol/L (54 mg/dL), Cr 256.7 μmol/L (2.9 mg/dL), glucose 6.2 mmol/L (111 mg/dL), anion gap 14, and arterial blood gas pH 7.54, $PaCO_2$ 17.5 mm Hg, Po_2 80 mm Hg. Salicylate toxicity was suspected based on the clinical presentation and mixed acid base disturbance. A serum salicylate was 3.36 mmol/L (46 mg/dL). The chest radiograph was normal for age without pulmonary edema.

The patient was transferred to intensive care for IV hydration and urine alkalinization. Excess ointment was removed and the skin was washed with soap and water. Hemodialysis was not performed. Serum salicylate fell to 1.90 mmol/L (26 mg/dL) over a two day period and blood gases normalized. The patient regained a normal mental status.

DISCUSSION

Many compounds may cause systemic toxicity after cutaneous application. Table 1 lists some of these. The stratum corneum is the principal barrier against percutaneous absorption. For a substance to be absorbed after cutaneous application a sequence of steps must occur. The substance must first diffuse through the carrier to the skin surface and partition into the intercellular lipid of the stratum corneum. From there, it must diffuse across the stratum corneum and partition into the aqueous viable epidermis. Next, it must diffuse through the viable epidermis and dermis before gaining systemic access via the cutaneous vasculature. Lipid soluble substances are generally better absorbed than highly ionic compounds.[9] Because substances become partitioned into the transcellular lipid of the stratum corneum before systemic absorption, the stratum corneum acts not only as a barrier but also as a reservoir for ongoing absorption. The amount of material present in the stratum corneum after a thirty minute application is proportional to the amount ultimately absorbed over a four day period.[10] This factor becomes important in skin decontamination. Although removing free drug from the skin surface will decrease its subsequent absorption, many compounds are rapidly nonspecifically adsorbed to the skin. These compounds are not well removed by simply washing the skin with soap and water. Rarely, washing will hydrate the skin and allow increased absorption of certain substances but, in general, washing will slightly decrease cutaneous absorption.[11] Washing agents with greater affinity for a specific compound may remove more of the agent but data on this are limited and washing the skin with soap and water remains the decontamination method of choice for cutaneous exposures.[11]

Chronic salicylism is an important cause of morbidity and mortality in the elderly. Affected patients are frequently misdiagnosed as having cardiopulmonary disease, encephalopathy, alcohol withdrawal, and metabolic acidosis.[12,13] Mortality rate is higher in patients with delayed diagnosis.[13] Management of patients with salicylate toxicity involves supportive care, decontamination, and urine and blood alkalinization to enhance elimination and prevent the shift of salicylates from blood into tissues. Hemodialysis corrects acid-base and fluid and electrolyte abnormalities and effectively removes salicylates.

As is often the case,[13] salicylism was not initially considered in this patient. Initial investigations after

Table 1

Selected Substances Causing Systemic Toxicity After Dermal Application

Compound	Systemic Toxicity
Acrylamide	Polyneuropathy
Aniline	Methemoglobinemia, hemolysis
Boric acid	Renal toxicity (chronic use in infants)
Camphor	Delirium, seizures, respiratory depression
Carbamates	Muscarinic symptoms
Carbon tetrachloride	Hepatotoxicity
Chlorinated hydrocarbons	Coma, seizures
Corticosteroids	Adrenal downregulation/ Cushingold features (especially in infants and with large applications)
Cyanide	Uncoupling of oxidative phosphorylation
Formaldehyde	Metabolic acidosis
Hexachlorophene	Altered mental status, coma, seizures
Hydrazine	Seizures, hepatotoxicity, hemolysis
Mercury compounds	Acrodynia, neuropsychiatric symptoms (erethism), renal dysfunction
Organic solvents	Headache, ataxia, CNS depression
Organophosphates	Muscarinic symptoms
Phenols	Seizures, coma, respiratory arrest, hypotension, cardiac arrhythmias
Podophyllum	Coma, vomiting, peripheral neuropathy, muscle weakness, hypotension, hyperthermia
Toluidine	Methemoglobinemia

the patient's condition deteriorated focused on the worsening renal function. Blood salicylate was requested only after the classic arterial blood gas findings were recognized. Electrolytes on the third day in hospital showed a widened anion gap.

Salicylates are slowly absorbed through normal skin.[7,8] Only 1.5% to 2% of a dose of topical salicylic acid is absorbed after 30 min contact time.[8] The elderly have even lower cutaneous absorption of salicylates.[14] Methyl salicylate may be better absorbed, with 12% - 20% of a topical dose absorbed after ten hours.[4] Heat and exertion increase percutaneous absorption of salicylates. Topical absorption of methyl salicylate increased more than three-fold in subjects exercising in the heat.[15] Other factors that increase absorption of topical drugs include use of occlusive dressings, application in skin folds, infancy, and skin inflammation.[16] Children are at increased risk for systemic toxicity from topical salicylates because of an increased body surface to weight ratio.

Patients with psoriasis and eczema are also considered to have enhanced absorption of topical salicylic acid,[17,18] but this is rarely a problem clinically. In one study, serum salicylate was undetectable throughout two weeks treatment of five patients with psoriasis and three patients with eczema with twice daily application of 3% salicylic acid ointment.[2] In another study, four psoriatic patients applied 6% salicylic acid to their entire body daily for five days. After application, the involved areas were covered with occlusive dressings. These patients absorbed 60% of the applied dose but peak serum salicylate remained below 5 mg/dL in all patients.[19]

Cases of toxicity from topical salicylate preparations are well documented but remain rare. In 1948, Gross and Greenberg published an extensive review of salicylate toxicity that included reports of 130 fatal cases. Of these, 11 cases were attributed to topical salicylates (salicylic acid in nine cases and methyl salicylate in two cases). These reports are unsatisfactory: salicylate levels were not documented and alternate causes of death were not explored in depth. All but one of these cases occurred in children.[20] In 1904, Summons reported the case of a 10-year-old child with psoriasis who was treated with topical salicylic acid and developed symptoms consistent with salicylism including deafness and hallucinations. Serum salicylate levels were not measured but the urine contained a large amount of salicylic acid.[21] The first well documented report of toxicity from topical salicylates in the English literature was published by Young in 1952, who reported a 10-year-old child with severe skin thickening who developed severe lethargy and hallucinations while being treated with topical salicylic acid. Her blood salicylate was 40 mg/dL.[22]

Table 2

Reports of Toxicity from Topical Salicylates

Age/Sex	Underlying Illness	Dose of Salicylic Acid	Days Until Diagnosis	Serum Salicylate mmol/L (mg/dL)	Reference	Clinical Presentation
10/F	icthyosis	3% 6x/d	5	3.08 (40)	22	abdominal pain, vomiting, lethargy, hallucinations
6/M	icthyosis	10% 3x/d (med error)	2	3.36 (46)	23	abdominal pain, vomiting, tachypnea, irritability, metabolic acidosis
39/F	psoriasis	6% 6x/d	11	4.67 (64)	17	nausea, dizziness, tinnitus, deafness, shortness of breath
47/F	psoriasis	3% 6x/d	7	3.36 (46)	17	headaches, dizziness, restlessness, tinnitus, shortness of breath, disorientation, paranoid delusions
55/M	psoriasis	6% 6x/d	4	3.43 (47)	17	vomiting, depression, tinnitus, deafness
12/M	icthyosis	10% 2x/d	3	3.36 (46)	30	not specified
42/M	psoriasis	40% 4x/d (med error)	1	5.33 (73)	25	sweating, flushing, deafness, metabolic acidosis
20/F	icthyosis	15% 1 application	few hours	5.18 (71)	25	abdominal discomfort, tinnitus
30/M	icthyosis	12% 2x/d	12	4.60 (63)	3	nausea, abdominal pain, deafness, tinnitus, hyperventilation, metabolic acidosis
72/M	icthyosis, renal failure	5% 8x/d (?)	7	1.02 (14)	26	not specified (metabolic acidosis attributed to salicylism but lactate = 29 mmol/L)
45/M	psoriasis	3% 3x/d	4	1.82 (25)	29	tinnitus
neonate/F	harlequin fetus	1% 8x/d	1	4.31 (59)	28	tachypnea, fever, metabolic acidosis
neonate/M	colloidion-like membrane covering skin	2% 6-8x/d	3	3.14 (43)	31	vomiting
72/M	psoriasis, renal failure	10% 3x/d	2	3.29 (45)	18	confusion, hypoglycemia, metabolic acidosis
79/M	psoriasis, renal failure	5% ? frequency	7	3.28 (45)	1	coma, hypoglycemia (patient also taking glyburide)
42/F	psoriasis	10% ? frequency	10	2.62 (36)	27	nausea, deafness, metabolic acidosis
80/F	erythroderma	10% 4x/d	7	3.36 (46)	Present case	confusion, hyperpnea, metabolic acidosis

This table includes all well documented cases of salicylism from topical salicylates found in a search of the English medical literature. Cases where salicylate levels were not reported are not included. Cases reported more than once are listed only once and credit is given to the original author. In this series all cases resulted from the use of salicylic acid in concentrations ranging from 1% to 40%. The two patients receiving 40% salicylic acid did so because of a medication error. Most patents in this series had metabolic acidosis.

Since Young's report there have been 20 additional reported cases of toxicity from topical salicylates,[1,3,5,17,18,21-31] including two deaths.[24] Of these, 17 cases documented the serum salicylate and are reported in Table 2. It is important to note that all of these cases occurred in patients with skin disease who received large body surface area applications of salicylic acid. Concentrations of salicylic acid ranged from 1% in a neonate to 40% in two adult cases. Time to diagnosis of salicylism varied from a few hours (after application of the 40% salicylic acid) to 12 d. The clinical presentation commonly included gastrointestinal symptoms, auditory symptoms, and alterations in mental status. Metabolic acidosis was documented in seven cases and two patients developed hypoglycemia. Table 2 summarizes these cases.

Three additional cases not included in Table 2 because of failure to document blood salicylate deserve comment. Two deaths occurred in brothers who had applied an antifungal solution containing 20.7% salicylic acid, 3.2% iodine, and 2.8% potassium iodide in alcohol to 50% of their body. They developed confusion, tachypnea and fever and both died the following day. Although these deaths were attributed to salicylate poisoning, no salicylate concentrations were documented.[24] There is a single recent case report of possible salicylate poisoning occurring in a patient with normal skin. This patient was a 62-year-old male who used 18% methyl salicylate and a heating pad for diffuse aches. While the patient developed a metabolic acidosis, it is unfortunate that no blood salicylate was measured.[5]

CONCLUSION

We report a case of salicylism resulting in mental confusion and acidosis in a patient with erythroderma who received topical salicylic acid. Salicylism from topical salicylate preparations, although rare, continues to occur. All well documented cases in the English literature have occurred in persons using large body surface applications of salicylic acid to treat severe skin disorders. Salicylism should be sought in all patients with an unexplained anion gap, acidosis and deterioration in mental status. Physicians prescribing topical salicylate preparations should be aware of the potential risk of dermal absorption and should closely follow the patient for signs of salicylism. Higher concentrations of salicylic acid, large body surface area applications, abnormal skin, young age, and renal insufficiency are all risk factors for toxicity from dermal absorption of salicylic acid. Routine monitoring of blood salicylate in high risk patients is advisable.

REFERENCES

1. Maurer TA, Winter ME, Koo J, Berger TG. Refractory hypoglycemia: a complication of topical salicylate therapy. *Arch Dermatol* 1994;130:1455-1457.
2. Gip L, Hamfelt A. Percutaneous absorption of betamethasone-17, 21 dipropionate and salicylic acid during the treatment of psoriasis and eczema. *J Int Med Res* 1976;4:106-110.
3. Davies MG, Briffa DV, Greaves MW. Systemic toxicity from topically applied salicylic acid. *BMJ* 1979;1:661.
4. Roberts MS, Favretto WA, Meyer A, Reckmann M, Wongseelashote T. Topical bioavailability of methyl salicylate. *Aust N Z J Med* 1982;12:303-305.
5. Heng MC. Local necrosis and interstitial nephritis due to topical methyl salicylate and menthol. *Cutis* 1987;39:442-444.
6. Rose FA, Wiemer DR. Platelet coagulopathy secondary to topical salicylate use. *Ann Plast Surg* 1983;11:340-343.
7. Oziomek RS, Perrin DH, Herold DA, Denegar CR. Effect of phonophoresis on serum salicylate levels. *Med Sci Sports Exerc* 1991;23:397-401.
8. Lotte C, Wester RC, Rougier A, Maibach HI. Racial differences in the *in vivo* percutaneous absorption of some organic compounds: a comparison between black, Caucasian and Asian subjects. *Arch Dermatol Res* 1993;284:456-459.
9. Guy RH, Hadgraft J. Structure-activity correlations in percutaneous absorption. In: *Percutaneous Absorption: Mechanisms-Methodology-Drug Delivery*, 2nd ed. Bronaugh RL, Maibach HI, eds. New York: Marcel Dekker, 1989:95-109.
10. Rougier A, Dupuis D, Lotte C, Maibach HI. Stripping method for measuring percutaneous absorption *in vivo*. In: *Percutaneous Absorption: Mechanisms-Methodology-Drug Delivery*, 2nd ed. Bronaugh RL, Malbach HI, eds. New York: Marcel Dekker, 1989:415-434.
11. Wester RC, Malbach HI. Dermal decontamination and percutaneous absorption. In: *Percutaneous Absorption: Mechanisms-Methodology-Drug Delivery*, 2nd ed. Bronaugh RL, Maibach HI, eds. New York:

Marcel Dekker, 1989:335-342.
12. Bailey RB, Jones SR. Chronic salicylate intoxication. A common cause of morbidity in the elderly. *J Am Geriatr Soc* 1989;37:556-561.
13. Anderson RJ, Potts DE, Gabow PA, Rumack BH, Schrier RW. Unrecognized adult salicylate intoxication. *Ann Intern Med* 1976;85:745-748.
14. Roskos KV, Maibach HI, Guy RH. The effect of aging on percutaneous absorption in man. *J Pharmacokinet Biopharm* 1989;17:617-630.
15. Danon A, Ben-Shimon S, Ben-Zvi Z. Effect of exercise and heat exposure on percutaneous absorption of methyl salicylate. *Eur J Clin Pharmacol* 1986;31:49-52.
16. Sanchez MR. Dermatologic principles. In: *Goldfrank's Toxicologic Emergencies*, 5th ed. Goldfrank LR, Flomenbaum NE, Lewin NA, *et al.*, eds., Norwalk Connecticut: Appleton and Lange, 1994:319-344.
17. Von Weiss JF, Lever WF. Percutaneous salicylic acid intoxication in psoriasis. *Arch Dermatol* 1964;190:614-619.
18. Raschke R, Arnold-Capell PA, Richeson R, Curry SC. Refractory hypoglycemia secondary to topical salicylate intoxication. *Arch Intern Med* 1991;151: 591-593.
19. Taylor JR, Halprin KM. Percutaneous absorption of salicylic acid. *Arch Dermatol* 1975;111:740-743.
20. Gross H, Greenberg LA. *Salicylates: Critical Bibliographic Review*. New Haven, Connecticut: Hillhouse Press, 1948.
21. Summons WH. Clinical notes: Case 1. Poisoning from skin absorption of salicylic acid. *Intercolon Med J* 1904:518-519.
22. Young CJ. Salicylate intoxication from cutaneous absorption of salicylic acid. *South Med J* 1952;145: 1075-1077.
23. Cawley EP, Peterson NT, Wheeler CE. Salicylic acid poisoning in dermatological therapy. *JAMA* 1953; 151:372-374.
24. Lindsey CP. Two cases of fatal salicylate poisoning after topical application of an antifungal solution. *Med J Aus* 1968;1:353-354.
25. Anderson JA, Ead RD. Percutaneous salicylate poisoning. *Clin Exp Dermatol* 1979;4:349-351.
26. Smith WO, Lyons D. Metabolic acidosis associated with percutaneous absorption of salicylic acid. *J Okla State Med Assoc* 1980;73:7-8.
27. Dwyer CM, McCloskey RH, Keri RE. Poisoning from topical salicylic acid. *Postgrad Med J* 1994;70: 146.
28. Ward PS, Jones RD. Successful treatment of a harlequin fetus. *Arch Dis Child* 1989;64:1309-1311.
29. Shupp DL, Schroeter AL. An unusual case of salicylate toxicity. *J Am Acad Dermatol* 1986;15: 300-301.
30. Aspinall JB, Goel KM. Salicylate poisoning in dermatological therapy. *BMJ* 1978;2:1373.
31. Galea P, Goel KM. Salicylate poisoning in dermatological treatment. *Arch Dis Child* 1990;65: 335.