A review of toxicity from topical salicylic acid preparations

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Topical salicylic acid is often used in dermatologic conditions because of its keratolytic, bacteriostatic, fungicidal, and photoprotective properties. The bioavailability of salicylic acid differs depending on the vehicle used and pH of transcellular fluids. Although rare, salicylic acid toxicity (salicylism) can occur from topical application. Physicians should be mindful of the potential for salicylism or even death from topically applied salicylic acid. (J Am Acad Dermatol 2014;70:788-92.)

Key words: ichthyosis; psoriasis; salicylic acid; salicylism; skin absorption; topical; toxicity.

Salicylic acid is the most widely consumed analgesic, antipyretic, and anti-inflammatory agent in the world.[1] It is a natural product found in the bark of a willow tree and has been used for centuries to relieve fever and pain.[2] Salicylic acid is a precursor to acetylsalicylic acid, better known as aspirin (Fig 1).[3]

Salicylic acid is used topically for its keratolytic, bacteriostatic, fungicidal, and photoprotective properties. Topical application has been shown to reduce the rate of keratinocyte proliferation. It also inhibits cholesterol sulfotransferase, an enzyme responsible for cholesterol sulfate formation within keratinocytes. Salicylic acid directly solubilizes the stratum corneum by dissolving the intercellular cement. Through these mechanisms, salicylic acid increases the elimination of squames from the stratum corneum.[4]

The principal use of topical salicylic acid in dermatology is as a keratolytic agent. Warts and localized hyperkeratosis can be treated with salicylic acid concentrations of 10% to 40%. At lower concentrations, it is used in the treatment of plaque psoriasis and comedonal acne.[4] Other indications include acanthosis nigricans, actinic keratosis, ichthyosis, superficial chemical peels, and tinea nigra.[5] In general, over-the-counter preparations for treatment of acne and xerosis contain concentrations of 5% or less, and solutions or adhesive plasters for treatment of warts and calluses contain concentrations of 10% to 40%. Prescription-strength creams and lotions contain concentrations of 6% or above.

The potency and toxicity of salicylic acid is changed by substitutions on the carboxyl or hydroxyl groups of its chemical structure. Its action is also influenced by the ortho position of the hydroxyl group. This structure allows for the effects of salicylic acid on pain, body temperature, respiration, acid-base balance, kidneys, heart, gastrointestinal tract, uric acid excretion, blood, and rheumatic, inflammatory, and immunologic processes as well as causing local irritation.[1] The benzene ring of salicylic acid functions to transform ultraviolet radiation into longer wave radiation that is emitted from the skin as heat, thereby providing a sunscreen effect.[6]

Salicylism, the syndrome of salicylic acid toxicity, can be acute or chronic and develops when blood concentrations of salicylate are greater than 35 mg/dL. Symptoms of salicylism include nausea, vomiting, confusion, dizziness, delirium, psychosis, stupor, coma, and death. The medullary respiratory center is activated at these levels, which leads to hyperventilation and respiratory alkalosis.[6] Metabolic abnormalities, including acidosis, hypoglycemia in children and hyperglycemia in adults, can occur as well.[1] Salicylate toxicity causes tinnitus because of increases in labyrinthine pressure and effects on cochlear hair cells.[6]

When ingested orally, salicylic acid is absorbed rapidly and can reach a peak value in about 1 hour.

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Absorption from topical application is variable but can be rapid.[1] Percutaneous absorption may be vehicle-dependent. One study compared different vehicles of topical salicylic acid administration. By analyzing urine 26 hours after application, it was found that salicylic acid 5% in magistral mineral oil/petrolatum formulation was absorbed 2.5 times more than salicylic acid 5% in a solution containing polyethylene glycol, glycerol, and petrolatum. The relative absorption of salicylic acid 5% in the magistral mineral oil/petrolatum formulation was slightly more than that of salicylic acid 10% in a similar solution. The total absorption was greatest with the 10% solution.[7]

CAPSULE SUMMARY

- Salicylic acid toxicity (salicylism) can occur with topical use of 6% salicylic acid over as little as 40% body surface area.
- A search of the literature from 1966 to the present found 25 cases of toxicity with 4 deaths attributed to the use of topical salicylic acid.
- There is a potential for salicylism or even death from topically applied salicylic acid.

The percutaneous absorption of salicylic acid is normally 60% with intact skin.[8] Systemic effects of topical salicylic acid are minimal when it is applied to intact skin in low to moderate doses. Conversely, with a break in the stratum corneum, measurable levels of salicylic acid can be found in the body even after application of low concentrations in hydrophilic ointment.[9] Using cutaneous microdialysis, it was shown that salicylic acid with petrolatum or ethanol applied to tape-stripped skin is absorbed 150 times more than when applied to intact skin.[10,11]

Once absorbed, salicylates are distributed to body tissues and transcellular fluids primarily by pH-dependent processes. The volume of distribution is 170 mL/kg in healthy individuals but can increase to 500 mL/kg at high therapeutic doses. In all, 80% to 90% of the salicylate in plasma is bound to protein and a much smaller percentage can actually be detected. It is biotransformed predominantly in the endoplasmic reticulum and mitochondria. Half-life is dose-dependent and elimination occurs in the urine.[1,12]

The following scenario is an estimate of the exposure to salicylic acid in a theoretical dermatologic case. If a patient applies lotion to 70% of the body surface area (approximately most of the arms, legs, and trunk), a single application is roughly 16 g.[13] If we assume the patient applies 16 g of a 6% salicylic acid lotion, this amounts to 1 g of salicylic acid. If 60% is absorbed, the maximal plasma level would be 0.6 g. The volume of distribution is equal to the total amount of drug in the body divided by the drug plasma concentration:

V_d = Total amount of drug in body/drug plasma concentration

170 mL/kg[11] = 0.6 g/Drug plasma concentration

Drug plasma concentration = 3.5 g/mL = 350 mg/mL = 35 mg/dL

The level at which salicylic toxicity begins is 35 mg/dL.[6] The half-life of salicylic acid can range from 2 to 12 hours depending on the dose. If 16 g of lotion is applied twice a day, salicylic acid could accumulate in the body and levels could even become high enough to cause death.

A PubMed search from 1966 to the present revealed toxicity directly linked to topically applied salicylic acid in 13 cases of psoriasis, 8 cases of ichthyosis, 2 cases of tinea imbricata, 1 case of erythroderma, and 1 case of seborrheic dermatitis (Table I). Toxicity often appeared within a few days of use. The most severe cases, leading to coma and death, occurred in patients with psoriasis. The age at

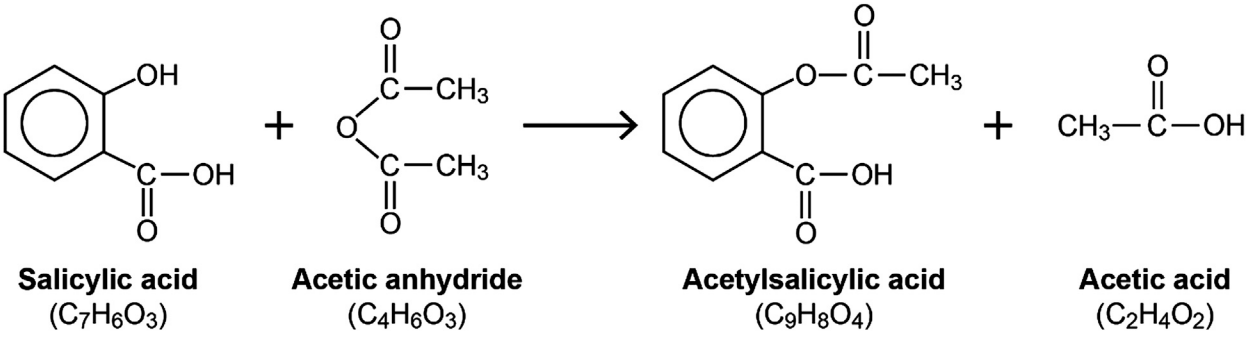

Fig 1. Biochemical pathway demonstrating the formation of acetylsalicylic acid (aspirin) from salicylic acid. Left to right: salicylic acid ($C_7H_6O_3$); acetic anhydride ($C_4H_6O_3$); acetylsalicylic acid ($C_9H_8O_4$); and acetic acid ($C_2H_4O_2$).

Table I. Cases of toxicity from topically applied salicylic acid; PubMed search 1966 to present

Year published	Age—gender	Concentration and vehicle	Plasma/serum concentration, mg/L (toxic = 350 mg/L)	Day	Underlying disease	Symptoms	Reference
2012	6 wk—NR	23% Salicylic acid in petroleum jelly, under occlusion on scalp	580	3	Seborrheic dermatitis	Tachypnea, impaired consciousness	22
2003	58 y—M	10% Ointment to >80% BSA	435	5	Psoriasis	Death	23
2003	35 y—M	10% Ointment to >80% BSA	510	4	Psoriasis	Death	23
2002	Newborn—M	20% with Oral retinoid BID over whole body	1190	7	Ichthyosis (collodion baby)	Tachypnea, renal and heart failure	24
2002	31 y—M	30% Applied to back and 4 limbs continuously	309	2	Psoriasis, HIV	Coma	25
1997	5 y—F	10% Plus urea, entire body BID	290.5	1.5	Ichthyosis	Fever, respiratory alkalosis, comatose state	26
1996	7 y—M	10% Ointment over large area, once a week	985	28	Ichthyosis	Wheezing, vomiting, tinnitus, vertigo, hyperventilation, deep somnolence	27
1996	80 y—F	2%-10%, 4 times day	465	6	Erythroderma	Confusion, hyperpnea, metabolic acidosis	28
1994	3 mo—F	4% with 6% Sulfur over large area	550	2	Ichthyosis	Diarrhea, vomiting, metabolic acidosis	29
1994	79 y—F	2%-5% with Coal tar over large area	450	7	Psoriasis	Unresponsive	30
1994	42 y—F	10% of ±50 g a day	360	10	Psoriasis	Nausea, deafness, tachycardia	31
1992	27 y—M	40%-41% BSA once	836	1	Psoriasis	Nausea, vomiting, tachycardia, hyperthermia	32
1991	72 y—M	10% TID over 80% BSA	443	21-28	Psoriasis	Confusion, hypoglycemia, metabolic acidosis, chronically ill	33
1990	Neonate—M	2% in Aqueous cream Q3-4 h	429	3	Collodion-like membrane	Vomiting, metabolic acidosis	34
1990	12 y—M	2%-10% BID to whole body	457	8	Ichthyosis	Salicylate toxicity	34
1989	Neonate—F	1% Q3 h to whole body	587	1	Harlequin fetus	Tachypnea, fever	35
1986	45 y—M	3% TID with coal tar to whole body	252	5	Psoriasis	Tinnitus	36
1980	48 y—M	20% Salicylic acid in petrolatum	810	6	Psoriasis	Coma	37
1979	30 y—M	4%-12% BID to trunk and limbs	455	20	Ichthyosis	Malaise, nausea, tinnitus, deafness	38
1975	62 y—F	10% BID to 75% BSA	2234	15 y	Psoriasis	Dry mouth, headache, tinnitus	39
1968	NR—M	50% BSA with 20.7% salicylic acid solution BID	NR	1	Tinea imbricata	Comatose, death	40

1968	NR—M	50% BSA with 20.7% salicylic acid solution BID	NR	1	Tinea imbricata	Comatose, death	40
1964	39 y—F	6% 6 times a day with Sulfur to skin and scalp to >60% BSA	640	2	Psoriasis	Dyspnea, nausea, vomiting, headache, dizziness, tinnitus	14
1964	47 y—F	3% Salicylic acid in topical emollient applied 6 times a day to >60% BSA	460	4	Psoriasis	Dyspnea, nausea, thirst, headache, dizziness, agitation, hallucinations, fever	14
1964	55 y—M	6% in Hydrophilic ointment applied 6 times daily to >60% BSA	470	3	Psoriasis	Anorexia, dizziness, vomiting, agitation	14

BID, Twice a day; *BSA*, body surface area; *F*, female; *M*, male; *NR*, not reported; *Q*, every; *TID*, 3 times a day.

which toxicity occurred was evenly distributed between adults and children. Toxicity with application of as little as 1% to 2% salicylic acid has been reported in neonates. In every case salicylic acid was applied to a large body surface area. In addition, before 1964 there was mention of 13 deaths caused by topical salicylic acid toxicity. Of those, 3 patients had psoriasis, 5 scabies, 3 dermatitis, 1 lupus vulgaris, and 1 congenital ichthyosiform erythroderma.[14]

Toxicity from other topical salicylate medications has been described. Although 10% topical methyl salicylate and 3% menthol had no side effects when used for back pain, toxicity developed when higher concentrations were applied for longer times.[15] The plasma concentration of a commercially available topical pain reliever containing methyl salicylate was 29.5 ± 10.5 ng/mL when applied for 8 hours.[16] Oil of wintergreen containing 98% methyl salicylate has been associated with toxicity when applied topically.[17] Examples of toxicities reported include reversible constriction of fetal ductus arteriosus after maternal use, salicylism in a patient with psoriasis, local necrosis and interstitial nephritis, and potentiation of warfarin anticoagulation.[18-21]

Formal dose-response and toxicity studies are warranted to establish the maximum safe topical dose of salicylic acid, particularly for patients with an impaired skin barrier. Special care should be exercised when prescribing topical salicylic acid for conditions that involve large body surface areas, such as psoriasis and ichthyosis, and for children.

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