

# Percutaneous Absorption of Salicylic Acid in Man after Topical Administration of Three Different Formulations

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## Key Words

Salicylic acid • Percutaneous absorption • Tape stripping • Topical bioavailability • Poisoning

## Abstract

**Objective:** To determine the amount of drug which is absorbed during 1 day following topical application of three different preparations containing salicylic acid.

**Methods:** Ten grams of the formulations, either (a) Kerasal<sup>TM</sup> 5% ointment, (b) salicylic acid 5% or (c) 10% in petrolatum, were administered consecutively to a 600-cm<sup>2</sup> area on alternating sides of the back of healthy volunteers (n = 9). Thirty minutes after application, a skin area of 2.54 cm<sup>2</sup> was stripped with D-Squame<sup>TM</sup> adhesive disks to determine the amount of salicylic acid in the stratum corneum. The entire application site was then covered by a thin gauze bandage and was not washed for the next 24 h. Urine was collected for 26 h following administration, hydrolyzed and assayed by HPLC analysis. **Results:** The absolute amounts absorbed and excreted were 52.6 ± 29.4 mg (mean ± SD), 127.1 ± 43.9 mg and 208.0 ± 81.7 mg, and the doses absorbed in relation to the doses applied (500 mg salicylic acid in case of formulations a and b and 1,000 mg for formulation c) were 9.3 ± 3.8, 25.1 ± 8.5 and 20.2 ± 7.7%, respectively. The amounts of salicylic acid in the skin 30 min after application were 36.3 ± 16.5, 18.2 ± 11.9 and 31.3 ± 15.4 µg/cm<sup>2</sup> as determined by the tape stripping procedure.

**Conclusions:** Significant differences in the doses absorbed were detected between the two formulations a and b (same concentration) with different vehicles (p value < 0.001) as well as between b and c (same vehicle) with different concentrations (p value = 0.018) using Student's paired t test. These results demonstrate that salicylic acid is well absorbed by healthy skin.

## Introduction

In dermatology, salicylic acid has been used for a long time for keratolytic treatment. In 1882, Unna [1] gave a first overview on the therapeutic properties of topical salicylic acid. Today salicylic acid is commonly used as a remedy for the keratolytic treatment of psoriasis, eczema and ichthyosis.

In the last century, there was a heated debate on the permeability of intact skin. The major interests were focused on water and vapor absorption. However, auxiliary substances such as salicylic acid were also incorporated into water to investigate skin permeability. Inadequate experimental settings and the researchers' personal anticipation of the existence or nonexistence of skin permeability led to an unscientific and controversial debate.

Bourget [2] was one of the first who recognized that an appropriate study design, sampling techniques and an accurate analytical assay are necessary to produce reliable

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results. In his publication in 1893 [2] he stated that salicylic acid was absorbed through skin rapidly and to a significant extent. He stated that the absorption rate and the quantity absorbed were influenced by the vehicle, age and state of the skin.

Since the beginning of this century, several attempts have been made to quantify the extent of percutaneous absorption of salicylic acid. In 1929, Moncorps [3] recovered 0.72% of the dose applied from urine after having applied 5% salicylic acid in petrolatum occlusively onto the legs of volunteers. The metabolism of salicylic acid was neglected.

Würbach [4] investigated in 1964 the urinary excretion of salicylic acid and metabolites (gained by acidic hydrolysis) after topical, occlusive administration. For salicylic acid 5% and 10% in petrolatum, he determined an absorption rate of 7.4 and 14.8% of the dose applied, respectively. In 1975, Taylor and Halprin [5] published the data of a pilot study in 4 psoriatic patients. Nine to twenty-three grams of an alcoholic preparation, containing salicylic acid 6%, were topically administered for 5 consecutive days on diseased skin areas under a 10-h occlusion. Urinary excretion within 7 days was approximately 70% of the dose applied. In a very recent investigation, Davis et al. [6] determined the relative bioavailability of salicylic acid (2%) in a hydroalcoholic and a cream formulation after repeated application (14 days) in three different skin conditions (normal, aged and acne-genic skin). Bioavailabilities among normal skin types were 58 and 44% for the hydroalcoholic and cream formulation, respectively. No relevant differences were observed for aged and acne-genic skin.

Apart from the previous paper on percutaneous absorption of 2% salicylic acid from two over-the-counter formulations no systematic in-depth information on the influence of vehicle and drug concentration on the amount absorbed is currently available. Against this background we investigated the percutaneous salicylic acid absorption of two magistral and one brand name formulation in 9 healthy volunteers using the standard tape stripping and urine recovery techniques [7], respectively.

Based on these data a risk assessment for topical salicylic acid as a keratolytic agent is made and compared with clinical information on salicylic acid toxicity following topical administration.

## Materials and Methods

### *Subjects and Ethical Considerations*

Nine healthy (7 male, 2 female) subjects entered the study. The study was performed in accordance with the 1989 version (Hongkong) of the Declaration of Helsinki and approved by the ethical committee

of the Department of Internal Medicine of the University Hospital, Basel, Switzerland. All subjects gave their written, informed consent before participation in the trial. The subjects were 25–67 years of age ( $34.7 \pm 13.5$  years) and weighed in the range from 54 to 84 kg ( $71.6 \pm 9.9$  kg). All subjects were judged to be healthy based on medical history, physical evaluation and clinical laboratory testing (hematology, blood chemistry). The application areas of all subjects were free from skin diseases, uneven skin tones, sunburn, tattoos and scars. There were neither dropouts nor protocol violators among the study population.

### *Study Design and Medication*

The study was designed as a monocentric, open, randomized, three-way crossover comparison. Three formulations containing salicylic acid were used in this trial: (a) Kerasal™ ointment which contained salicylic acid 5% and urea 10% in a base consisting of polyethylene glycol, glycerol and petrolatum; Kerasal ointment was supplied by Spirig Ltd., Egerkingen, Switzerland; (b) salicylic ointment 5% and (c) salicylic ointment 10% were obtained from the Institute of Hospital Pharmacy, University Hospital, Basel, Switzerland; both contained salicylic acid in a concentration of 5 and 10%, respectively, in a mixture of mineral oil and petrolatum.

Each study period was separated by a washout period of at least 2 weeks.

*Application.* The medications studied were administered in the morning between 8 and 9 a.m. The washing procedure of the skin before the treatment was performed individually by the volunteers according to their daily routine. In each cycle a 600-cm<sup>2</sup> area, alternating between both sides of the back (left/right/left and vice versa), was delimited with Sparablanc™ tape (IVF, Schaffhausen, Switzerland). Ten grams of ointment were spread manually over the application area by gentle rubbing. This corresponded to salicylic acid doses of 0.83 mg/cm<sup>2</sup> for Kerasal and salicylic ointment 5%, and 1.67 mg/cm<sup>2</sup> for salicylic ointment 10%. The whole site was left uncovered for 1 h from the time point of application. It was then covered by a thin gauze bandage.

*Stratum corneum Samples.* Thirty minutes after application, a small area on the border of the application site was gently wiped with four independent soft cloth tissues in order to remove the remaining ointment. A small piece of polypropylene foil with a hole (18 mm diameter) was then placed onto the cleansed skin and affixed by a piece of self-adhesive tape (Cover-Roll™ Stretch, Beiersdorf Inc., Norwalk, Conn., USA) from which a hole of 25 mm diameter had been cut out. This template ensured that all tape stripping procedures took place at the same site. The skin was stripped 21 times with adhesive disks (D-Squame™; Difa Cooper S.p.A., Caronno, Italy). The first disk was discarded. Five sequential tape strip disks were combined in 15-ml Falcon™ polypropylene conical screw-capped tubes (Becton Dickinson Labware, Franklin Lakes, N.J., USA) for extraction and submitted to HPLC analysis for quantification of drug content.

*Urine Samples.* Salicylic acid is metabolized rapidly when the amount present in the body is low [8], and it is reported that approximately 80% of an oral sodium salicylate dose ( $\leq 1$  g) can be recovered from urine within 24 h [9]. For that reason it is possible to recover considerable fractions of the absorbed amount of salicylic acid within 26 h following topical application.

Before each application, a urine sample was collected to prove absence of salicylates prior to administration of the study medication. Urine was quantitatively collected in plastic containers during the 26-hour period following topical administration. At the end of a

collection interval, the urine was mixed and aliquots of 10 ml were transferred to 3 Falcon screw-capped tubes (see above) and immediately frozen. The tubes were stored at  $-20$  to  $-30$  °C until analysis.

**Plasma Samples.** In 1 subject serial plasma samples were drawn after each topical treatment and additionally subsequent to a comparative intravenous administration of 20 ml of a parenteral sodium salicylate solution (equivalent to 300 mg of salicylic acid).

Blood was collected in chilled 5.5-ml test tubes (Monovette™ LH; Sarstedt, Nümbrecht, Germany) containing 15 IU lithium-heparin/ml.

#### Analytical Procedures

Methods for sample preparation and quantification were developed by modification of different methods published in the literature [10–13].

#### Materials

**Reagents.** The reagents used include: salicylic acid (Siegfried Ltd., Zofingen, Switzerland; pharmacopeial grade); sodium salicylate (Hänseler Ltd., Herisau, Switzerland; pharmacopeial grade); salicylic acid (Sigma-Chemical, St. Louis, Mo., USA; analytical grade); anhydrous potassium dihydrogen phosphate, hydrochloric acid 37%, perchloric acid 20% and orthophosphoric acid 85% (Fluka Ltd., Buchs, Switzerland; all analytical grade); acetonitrile, methanol and water for chromatography (E. Merck Ltd., Dietikon, Switzerland; LiChrosolv™ grade).

Distilled water was obtained from the Institute of Hospital Pharmacy. Phosphate buffer for chromatography was prepared by dissolving 2.72 g of potassium dihydrogen phosphate in distilled water. By addition of orthophosphoric acid 85% the pH was adjusted to 2.00. Distilled water was added to produce 1 liter and the solution was filtered (Nylon 66 membrane,  $0.45 \mu\text{m} \times 47 \text{ mm}$ ; Supelco Inc., Bellefonte, Pa., USA) and degassed before use by ultrasonication for 15 min.

**Solid-Phase Extraction.** Solid-phase extraction was performed using Chromabond™ C18, 3-ml columns packed with 500 mg of sorbent (Machery-Nagel Ltd., Oensingen, Switzerland). Pressure was applied by a 10-ml syringe which was fixed with an adapter at the top of the column.

**Apparatus.** Our chromatographic system for determination of stratum corneum concentration of salicylic acid consisted of a Merck-Hitachi L-6200A solvent pump, an AS 4000A autosampler, a T6300 column thermostat, a D 6000 interface, an L4250 UV-VIS detector and an L3000 photodiode array detector (all Hitachi Ltd., Tokyo, Japan). The system was equipped with a LiChrospher™ 100 RP-18 column ( $250 \times 4 \text{ mm i.d.}$ ,  $5 \mu\text{m}$  average particle size) and a LiChrospher™ 100 RP-18 guard column ( $4 \times 4 \text{ mm i.d.}$ ,  $5 \mu\text{m}$  average particle size; both from E. Merck Ltd.).

Plasma and urine samples were assayed by a Waters 2690 separation module Alliance™ equipped with a Waters 996 photodiode array detector which were controlled by Millennium™ 2010 software, version 2.21 (all Waters Corp., Milford Mass., USA). Separation and quantification of analytes was performed on a reversed-phase Symmetry™ C18 column ( $150 \times 2.1 \text{ mm i.d.}$ ,  $5 \mu\text{m}$  average particle size; Waters Corp.).

#### Sample Preparation

**Stratum corneum Samples.** The tapes were extracted twice with methanol. This was performed by adding 2 ml methanol to the tube and vortex-mixing for 1 min. The two extracts were transferred to a volumetric flask and methanol was added to a total of 5 ml. The samples

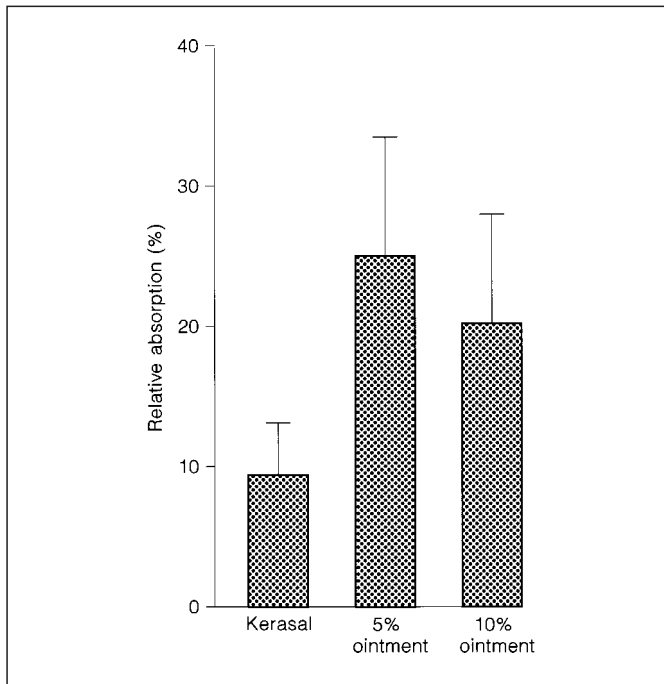
were stored in a deep freezer at  $-30$  °C. Aliquots of  $20 \mu\text{l}$  were injected onto the column for HPLC quantification. The mobile phase consisted of 75% phosphate buffer, pH 2.0, and 25% acetonitrile. The flow rate was 1.0 ml/min and the column was kept at  $34$  °C. The absorption was measured at 237 nm. Calibration was done by running standards in every sample set by linear regression of peak area versus concentration (standard concentrations: 0, 0.5, 1, 5, 10, 25  $\mu\text{g/ml}$  salicylic acid in methanol). The mean retention time for salicylic acid was 13 min and the coefficients of correlation were  $r \geq 0.998$ .

**Urine Samples.** Urine samples were hydrolyzed to transform the metabolites (salicylic acid and glucuronides of salicylic and salicylic acid) back to free salicylic acid. Gentisic acid, a metabolite which is formed to a very small extent (approx. 1%) was ignored [14, 15]. Six milliliters of thawed urine were transferred to a 20-ml glass vial and mixed with 6 ml of hydrochloric acid. The vials were heated for 1 h at  $120$  °C. After cooling, the vial was vortexed for 15 s. The hydrolyzed urine was then purified and concentrated by means of solid-phase extraction. For this, the extraction column was first conditioned with 2 ml of acetonitrile, then twice with 2 ml of distilled water. Hydrolyzed urine was put onto the column in five portions of  $2,000 \mu\text{l}$ , each fraction being pressed manually through the column. The column was then washed with 2 ml of phosphate buffer. The column was eluted with 2 ml of a mixture of 20% phosphate buffer and 80% acetonitrile, which was slowly pressed through the column. The eluent was collected in a volumetric flask and mobile phase was added to give a volume of 5 ml.

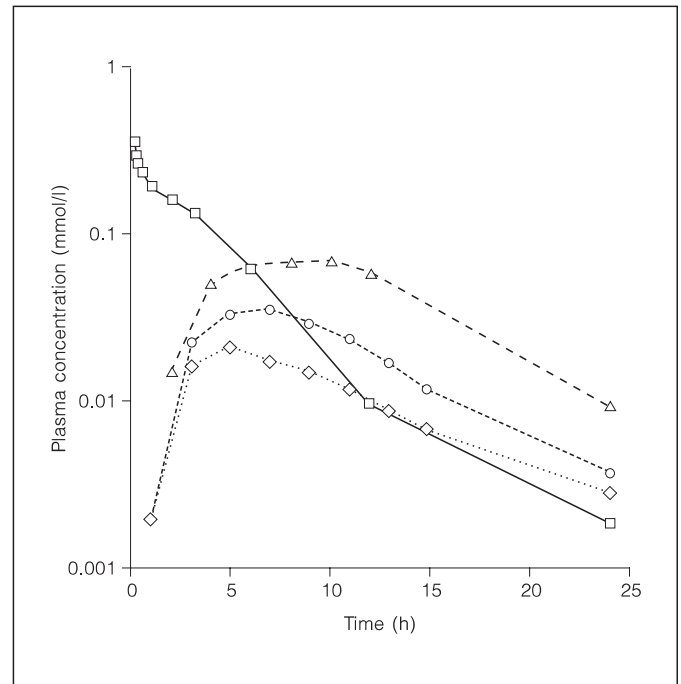
Hydrolysis of salicylic acid was judged to be complete by the quantitative recovery as salicylic acid ( $98.4 \pm 1.27\%$ ,  $n = 5$ ) from salicylic acid added to blank urine.

Aliquots of  $10 \mu\text{l}$  were injected onto the column for HPLC quantification. The mobile phase consisted of 75% phosphate buffer, pH 2.0, and 25% acetonitrile and the flow rate was 0.3 ml/min. The samples were kept at  $20$  °C and the column was heated to  $34$  °C. After each sample run of 10 min, the column was washed for 5 min with acetonitrile/water (25:75) at 0.35 ml/min and reconditioned for 7 min with the mobile phase at 0.35 ml/min. Identity and purity of the salicylate peak was determined with photodiode array detector data and quantification was performed at the absorption wavelength of 305 nm, which was chosen to avoid interference with endogenous compounds present in urine [16]. Calibration was done within every sample set by linear regression of peak area versus standard concentration (standards: salicylic acid in mobile phase at concentrations of 0, 0.5, 1, 5, 10, 20, 50, 100 and  $200 \mu\text{g/ml}$ ). The mean retention time was approximately 6.5 min and the correlation coefficients were  $r \geq 0.998$ . The limit of detection for salicylic acid was  $< 0.2 \mu\text{g/ml}$ . The recovery of salicylic acid added to blank urine ( $2$ – $200 \mu\text{g/ml}$ ) was  $100.0 \pm 2.6\%$  ( $n = 7$ ). The interassay standard deviation of the hydrolyzation, extraction and analytical procedure was 1.07% ( $n = 5$ ).

**Plasma Samples.** Plasma was separated by centrifugation at  $1,000 g$  for 10 min at  $4$  °C;  $2,000 \mu\text{l}$  of plasma were transferred to a conical tube (Falcon 15 ml; see above) and  $200 \mu\text{l}$  of perchloric acid 20% added. The mixture was then vortexed for 1 min and  $2,000 \mu\text{l}$  of methanol were added. The sample was vortexed for 2 min and centrifuged at  $1,500 g$  for 10 min. The clear supernatant solution was transferred to a  $350\text{-}\mu\text{l}$  vial and placed in the autosampler. Aliquots of  $10 \mu\text{l}$  were injected onto the column for HPLC quantification. Chromatographic conditions (mobile phase, flow, column and sample temperature) were as per the urine assay. The run time was 15 min, and detection and quantification were done at 237 nm. Calibration was carried out by running standards for salicylic acid within every sample set by linear regression of peak area versus concentration. Standards were produced



**Fig. 1.** Relative amounts of salicylic acid absorbed.



**Fig. 2.** Plasma concentration (mmol/l) of salicylic acid after intravenous administration (square) and topical administration of Kerasal (rhombus), salicylate ointments 5% (circle) and 10% (triangle), respectively.

from spiked blank plasma according to the procedure mentioned above for the plasma samples. Concentrations were 0.2, 0.5, 1, 5 and 25  $\mu\text{g/ml}$  referred to concentration before processing. The correlation coefficient was  $r > 0.999$ .

#### Statistical Analysis

The different formulations were compared by the percentage of dose absorbed in relation to the dose applied. Kerasal ointment (a) was compared to salicylate ointment 5% (b), and salicylate ointment 5% (b) was compared to salicylate ointment 10% (c), by paired Student t test.

The null hypotheses were formulated that a and b as well as b and c were equivalent in terms of percent dose absorbed. The formulations were considered to be significantly different and the null hypotheses had to be rejected if the p values of both tests were  $< 0.025$  (significance value of 5% corrected by Bonferroni procedure).

## Results

The quantity of salicylic acid applied was approximately 500 mg for Kerasal and the salicylate ointment 5% and 1,000 mg for the salicylate ointment 10%, respectively.

The absolute amounts of salicylic acid recovered (mean  $\pm$  SD) from 26-hour urine and the doses recovered in relation to the doses applied are given in table 1 and visualized

in figure 1. In 1 volunteer, the gauze bandage and the shirt were extracted after each treatment period. The relative amounts recovered from bandage and shirt were approximately 50% and are comparable with previous data [17].

#### Comparison of Formulations a and b

These two formulations contained salicylic acid 5% in pharmaceutically different vehicles. The doses absorbed and recovered from urine within 26 h were significantly different. Percutaneous absorption from the magistral mineral oil/petrolatum formulation was more than 2.5-fold higher than from Kerasal, which contained polyethylene glycol, glycerol and petrolatum ( $p < 0.001$ ).

#### Comparison of Formulations b and c

These two formulations contained salicylic acid in concentrations of 5% (b) and 10% (c) in the same magistral mineral oil/petrolatum formulation. The relative absorption was slightly higher for the preparation with the lower concentration ( $p = 0.018$ ).

**Table 1.** Doses absorbed

Preparation	Absolute absorption <sup>a</sup>	Relative to dose applied	Range
Kerasal™	52.6 ± 29.4 mg	9.3 ± 3.8%	4.6–16.5%
Salicylate ointment 5%	127.1 ± 43.9 mg	25.1 ± 8.5%	13.8–40.4%
Salicylate ointment 10%	208.0 ± 81.7 mg	20.2 ± 7.7%	11.8–37.0%

p &lt; 0.001

p = 0.018

<sup>a</sup> Absolute amount recovered from urine.**Table 2.** Dose absorbed and amount of salicylic acid in stratum corneum determined by tape stripping, 30 min after administration

	Kerasal	Salicylate ointment 5%	Salicylate ointment 10%
Dose absorbed per area, µg/cm <sup>2</sup>	87.6 ± 48.9	211.9 ± 73.2	346.6 ± 136.1
Amount extracted from 20 tape stripping, µg/cm <sup>2</sup>	36.3 ± 16.5	18.2 ± 11.9	31.3 ± 15.4

### Plasma Concentration

The log plasma salicylic acid concentration-time plot is illustrated in figure 2. The  $t_{max}$  values were about 5, 7 and 10 h, and the  $C_{max}$  values were 0.021, 0.033 and 0.069 mmol/l for Kerasal, salicylate ointments 5 and 10%, respectively. The calculated  $AUC_{0-24 h}$  were 0.233, 0.408 and 0.997 mmol · h · l<sup>-1</sup>. There was a linear relation ( $r > 0.999$ ) between the amount excreted in 26-hour urine and the area under the plasma concentration-time curve from 0 to 24 h.

### Tape Stripping

The amounts of salicylic acid extracted from 20 D-Squame adhesive disks successively removed from the skin are summarized in table 2. No correlation between the amount of salicylic acid in the stratum corneum as determined by the tape stripping technique and the doses absorbed (table 2) was detected.

## Discussion

In vivo percutaneous absorption of salicylic acid through human skin and its systemic availability was in the range of 20–25% for the two magistral mineral oil/petrolatum preparations and a little less than 10% for the brand name preparation. Compared to earlier data [4] the extent of absorption in the present investigation was about twice higher. This difference may be explained by the different application sites (leg vs. back) or by different pharmaceutical properties of the preparation. The plasma concentration-

time curve of salicylic acid after topical administration, obtained from 1 subject, was in accordance with previous data [6, 18].

Despite the considerable amount of information on percutaneous salicylic acid absorption, few data on the influence of vehicle and drug concentration on the amount absorbed are currently available. The magistral product containing 5% salicylic acid in a petrolatum/mineral oil preparation showed a percutaneous absorption which was 2.5 times higher ( $p < 0.001$ ) than that of the brand name product Kerasal (5% salicylic acid in an ointment containing emulgators, glycerol and urea). A plausible explanation is that the self-occluding effect of petrolatum, the vehicle of the magistral formulations, may have led to an enhanced permeation. These findings suggest that different salicylic acid preparations at the same concentration level are not bio-equivalent. Doubling the drug concentration in the magistral salicylic acid preparation (from 5 to 10%) resulted in an increase in absolute drug absorption by a factor of 1.6, and in a decrease in relative drug absorption by the factor of 0.8, respectively (table 2).

Comparing drug penetration into skin and drug permeation through skin it is obvious that Kerasal delivered more salicylic acid to the stratum corneum than the two magistral formulations. From a therapeutic point of view it can be argued that the brand name product better fulfils the assignment to deliver the drug to the target organ – the stratum corneum – for keratolytic activity and has a lower potential for excessive drug delivery to the body. Rougier et al. [7] found a linear relationship between the stratum corneum

**Table 3.** Clinical references of toxicity from topical salicylates: a selection of references published from 1964 to 1997 where plasma/serum concentration data were provided

Published	Ref. No.	Gender and age	Underlying diseases	Concentration of ointment and dosing regimens	Plasma/serum concentration mmol/l	Clinical features
1997	19	f/5 years	ichthyosis	10% plus urea, entire body, three times in 36 h	2.1	tachycardia, lethargy, fever, hyperpnea
1996	20	m/7 years	ichthyosis	1,000 g ointment (10%) per week for 4 weeks	7.12	deep somnolence, tinnitus, vertigo, tachypnea, vomiting
1996	21	f/80 years	erythroderma	2–10%, 4×/day for 6 days	3.36	confusion, hyperpnea, metabolic acidosis
1994	22	f/79 years	psoriasis, hypertension, renal failure, diabetes (glyburide 2.5 mg b.i.d.)	2%, from days 1 to 3 5%, from days 4 to 5, frequency?	3.24	unresponsiveness, hypoglycemia
1994	23	f/42 years	psoriasis	10%, 50 g (estimated) per day for 10 days	2.6	deafness, nausea, metabolic acidosis
1992	24	m/27 years	psoriasis, alcoholism	40%, single application to 41% of body surface	6.04	nausea, vomiting, ague, sweating, hyperthermia, confusion, tachycardia
1991	25	m/72 years	psoriasis, renal disease, diabetes	10%, 3×/day to 80% of body surface for 3–4 weeks	3.2	fever, confusion, hypoglycemia, metabolic acidosis
1990	26	m/neonate	skin covered by collodion like membrane	2%, every 3–4 h for 3 days	3.1	vomiting, metabolic acidosis
1990	26	m/12 years	ichthyosis	2%, 2×/day for 2 days; 5%, 2×/day for 2 days; 10%, 2×/day for 4 days to the whole body	3.3	not specified in reference
1989	27	f/neonate	harlequin fetus	1%, every 3 h for 24 h only	4.24	tachypnea, fever
1986	28	m/45 years	psoriasis, psoriatic arthritis (naproxen 375 mg b.i.d.)	3% plus coal tar, 3×/day to entire body for 5 days	1.82	tinnitus due to increase in unbound plasma salicylate fraction(?) by concomitant naproxen competing for albumin binding
1975	29	f/62 years	psoriasis	10%, 2×/day to almost 75% of body skin surface for 1.5 years	16.15	discrete symptoms: tinnitus, dry mouth, headache; high salicylic acid concentrations tolerated due to chronic exposure
1964	30	f/39 years	psoriasis	6% plus sulfur, 6×/day to involved skin/scalp areas for 11 days	4.63 (11th day)	from 6th day on: tachypnea, lethargy, nausea, hearing impairment; diagnosis of intoxication on 11th day of treatment

reservoir content and the in vivo percutaneous absorption (total amount of drug permeated in 4 days) using the standard urinary excretion method. They showed for a variety of simple pharmaceutical vehicles that the percutaneous absorption of benzoic acid is vehicle dependent and can be predicted from the amount of drug within the stratum corneum 30 min after application. In the present study using the standard tape stripping methodology the amounts recovered from 20 consecutive tape strippings were on average 36.3, 18.2 and 31.3  $\mu\text{g}/\text{cm}^2$  for Kerasal, salicylate ointments 5 and 10%, respectively. This rank order is different from

the rank order of percutaneous permeation. In addition, no intrasubject correlation between penetration into skin and permeation through skin was found. The vehicle and the drug's inherent properties may directly influence the cohesion of corneocytes as well as the adhesive properties of the tapes. Both may influence the amount of stratum corneum being removed by the adhesive tapes and may therefore complicate the interpretation of the data.

From 1 subject in the present study, serial plasma samples were analyzed for salicylic acid concentrations. Peak plasma concentrations were 0.02, 0.033 and 0.069 mmol/l

for Kerasal, salicylate ointments 5 and 10%. Times to plasma peak concentrations after application of salicylic acid ointments were in the range of 5–10 h as shown in the present and an earlier [18] investigation. For a hydroalcoholic and a cream formulation, Davis et al. [6] determined the times to peak plasma salicylic acid levels to be approximately 2 and 4 h, respectively (note that the determination was done after 2 weeks of daily pretreatment). From these findings we can conclude either that percutaneous absorption of salicylic acid from hydroalcoholic and cream formulations is faster than from ointment formulations or that repeated applications lead to a faster absorption after some time resulting from the keratolytic activity.

For optimal anti-inflammatory therapy of rheumatic diseases plasma salicylate concentrations of 1.1–2.2 mmol/l are required. Tinnitus (above 1.4 mmol/l) may be a reliable index for therapeutic plasma concentration in rheumatic patients with normal hearing. Hyperventilation generally occurs at concentrations above 2.5 mmol/l and other signs of intoxication at concentrations above 3.3 mmol/l [15]. Elimination of salicylic acid is dose dependent. Due to the limited ability of the liver to form salicyluric acid and the phenolic glucuronide, the half-life increases from 2.4 h up to about 12–15 h at anti-inflammatory doses. These pharmacokinetic properties and the fact that salicylic acid is very well absorbed and not entirely removed from the systemic circulation within 24 h represent the potential for develop-

ing systemic intoxication. Once moderate to high salicylic acid plasma concentrations are reached continual dosing or drug absorption from the skin reservoir may result in a disproportionate increase in plasma concentrations.

A survey of the literature yielded several clinical references on systemic intoxication resulting from topical treatment (table 3). Our data and the data from the literature suggest that specific patient and age groups – e.g. the skin surface area per body weight ratio is 2.4 times higher in neonates (620 cm<sup>2</sup>/kg) than in adults (260 cm<sup>2</sup>/kg) [31] –, the area treated (in our study 600 cm<sup>2</sup>), the vehicle and repeated application to diseased skin are risk factors for topical intoxication. The sudden, disproportionate increase in salicylate plasma concentrations into the toxic range from constantly high (borderline) levels, due to its inherent pharmacokinetic properties (see above), represents a major risk to develop a systemic intoxication.

Nevertheless, compared to other routes of administration (e.g. oral) adverse systemic drug effects of topical drug formulations are observed infrequently; a brief overview is given by Breathnach and Hintner [32].

The current investigation has provided new information on the percutaneous absorption of salicylic acid from two magistral formulations and one brand formulation used in keratolytic treatments. The pharmacokinetic information allows for an improved estimate of the contribution of systemic salicylic acid from topically applied products.

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