Pharmacokinetics

SERUM CONCENTRATIONS OF SALICYLIC ACID FOLLOWING TOPICALLY APPLIED SALICYLATE DERIVATIVES

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OBJECTIVE: To compare the rate and extent of systemic salicylate absorption following single and multiple applications of two topically applied analgesics, one containing methyl salicylate and the other containing trolamine salicylate.

DESIGN: Two-period, two-treatment, randomized, crossover, multiple-dose study in healthy men and women volunteers.

PARTICIPANTS: Six men and six women volunteers, 21–44 years of age.

INTERVENTIONS: Subjects applied 5 g of an ointment containing 12.5% methyl salicylate twice daily for 4 days (8 doses) or a cream containing trolamine 10% twice daily for two doses, to a 10-cm² area on the thigh. Treatment order and leg (right or left) were assigned randomly. Subjects were crossed over to the alternate treatment on the other leg after a minimum washout period of 7 days.

MAIN OUTCOME MEASURES: The total amount of salicylate recovered in the urine during two dosing intervals (24 hours) on each study day, relative to the applied dose, was used to calculate the bioavailability of each product. Mean standard pharmacokinetic parameters including area under the curve, maximum concentration (C_{max}), time to maximum concentration, and minimum concentrations at steady-state were determined from serum concentrations. Serum concentrations were fit to three pharmacokinetic models and the suitability of each model was evaluated. Estimates of absorption rate constant, clearance, volume, and fraction absorbed on day 1 were estimated by using the best-fitting model.

RESULTS: Salicylic acid could not be detected in serum after trolamine application. However, concentrations between 0.31 and 0.91 mg/L were detected within 1 hour of the first application of methyl salicylate and C_{max} between 2 and 6 mg/L were observed following the seventh application on day 4. Both the extent and rate of absorption changed after the first 24 hours. The absorption rate constant increased significantly from the first to the seventh dose (first dose absorption rate constant: 0.16 h^{-1}; seventh dose: 0.28 h^{-1}; $p < 0.035$). Urinary recovery of total salicylate (salicylic acid and principal metabolites of salicylic acid) during the first 24 hours of the methyl salicylate phase averaged 175.2 mg, exceeding the 6.9 mg ($p < 0.05$) recovered during the trolamine phase. The recovery of salicylate in the urine in the first 24 hours after application of methyl salicylate was significantly greater than the 1.4% recovered after application of trolamine ($p < 0.05$). Furthermore, the fraction of methyl salicylate recovered in the urine increased significantly from 15.5% on day 1 to approximately 22% on the second, third, and fourth days.

CONCLUSIONS: A considerable amount of salicylic acid may be absorbed through the skin after topical application of methyl salicylate products and this may increase with multiple applications. Caution is warranted in patients for whom systemic salicylate may be hazardous or problematic.

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COMMON INGREDIENTS of topically applied external analgesics are methyl salicylate and trolamine salicylate. In Canada and the US there are more than 20 and 40 nonprescription preparations, respectively, that contain either methyl salicylate or trolamine,[1-3] and similar products are available in many other countries. These products are generally regarded as safe, since they are considered to exert their effect from local action rather than from percutaneous absorption and systemic effects.[2,4] Consequently, when this study was initiated, many of the product labels in Canada provided rather indefinite directions for use, such as "as often as required" or "as necessary," without recommending a maximum number of applications per day, an interval between applications or the maximum amount that should be applied.

Several case reports suggest that these indefinite directions may place patients at risk and that significant amounts of salicylate may be absorbed through the skin when these products are applied in large amounts or for prolonged periods.[5-7] These case reports describe a marked prolongation of prothrombin time in several patients receiving mainte-

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nance warfarin therapy after use of topical salicylate derivative analgesics. In these three reports, most of the 14 patients were found to have measureable concentrations of salicylate in the blood.

We also have observed a case of systemic salicylate toxicity that was attributed to the excessive use of a methyl salicylate-containing ointment.[8] A 62-year-old man presented to the emergency department at our institution with a 3-day history of tinnitus, blurred vision, and shortness of breath. A salicylate concentration of 518 mg/L (therapeutic range 150–300 mg/L) was reported, along with a mixed metabolic acidosis/respiratory alkalosis. These were both consistent with salicylate use. No aspirin or other oral medications containing salicylate had been ingested. However, the patient admitted to using a methyl salicylate ointment on his thigh, twice daily, for several weeks.

Therefore, we conducted this study in healthy volunteers to compare the rate and extent of systemic salicylate absorption following application of two different topically applied analgesics, one containing methyl salicylate and the other containing trolamine. The second objective of the study was to evaluate changes in the rate and extent of absorption with multiple doses of one methyl salicylate-containing product.

Methods

STUDY DESIGN

Six men and six women aged 21–44 years participated in the study after giving written informed consent approved by the research ethics committee at our institution. All were judged healthy by laboratory screening and physical examination. Volunteers with a hypersensitivity to salicylate, women not protected from pregnancy, or those with any abnormal findings or conditions associated with the integumentary system were excluded.

The subjects refrained from consuming alcohol and food or beverages containing salicylate[9,10] for 48 hours before beginning the study and for the duration of the study periods. The subjects did not take any medications for 1 week before and throughout the study periods, including the washout period.

In a randomized, crossover fashion, subjects applied 5-g doses every 12 hours of either a cream (2 doses total) containing trolamine 10% (Myoflex, Adria Laboratories of Canada Ltd., Mississauga, ON; lot 004; equivalent to 241 mg of salicylate) or an ointment (8 doses total over 4 d) containing methyl salicylate 12.5% (Rub A-535, Carter Products, Mississauga, ON; lot OL59; equivalent to 567 mg of salicylate). The leg for application was determined randomly. The first application of the study product was applied between 0800 and 0900, and the second application occurred 12 hours later, between 2000 and 2100. Each subject received a 10-cm² template from which they traced the designated application site on the anterior aspect of the thigh. The subjects were instructed to apply all 5 g of the study product evenly onto the premarked square so that the entire area was covered. The site was then protected with a nonocclusive dressing consisting of ordinary gauze and Micropore tape. Subjects were allowed to bathe and shower as usual before applying a dose. After a 1-week washout period, the subjects were crossed over to the alternate treatment.

On day 1 prior to the first application of methyl salicylate or trolamine and on day 4 prior to the seventh application of methyl salicylate, a catheter was inserted into an arm vein for blood collection. The catheter was kept patent with intermittent 1-mL injections of NaCl 0.9%. Blood samples were drawn on each of days 1 and 4, just before the morning application and at 1, 2, 3, 4, 6, 8, 12, and 24 hours after that application. The 24-hour blood sample was obtained by venipuncture. All samples were allowed to clot, centrifuged for 10 minutes, and the serum separated and stored frozen at –20 °C until time of assay.

A 24-hour urine collection was started immediately before each days' morning application. Subjects voided prior to applying the dose. For each subject there were a total of four 24-hour collections for the methyl salicylate segment of the study and one 24-hour collection for the trolamine segment. The total volume of urine per 24-hour collection was measured and recorded and an aliquot was stored in a glass vial at –20 °C until time of assay. A second aliquot was used for quantification of creatinine to allow calculation of urinary creatinine recovery to confirm the completeness of urine collection. If the lowest creatinine recovery rate was more than 15% lower than the mean urinary creatinine recovery from the subjects' other three collections, the urine collection was judged incomplete.

ANALYTIC PROCEDURES

Serum. Serum salicylate concentrations were determined using a specific HPLC method described by Cham et al.,[11] with minor modifications (methanol was used as a precipitant in place of acetonitrile). This assay has a minimum sensitivity of approximately 0.3 mg/L. The intraassay coefficient of variation for salicylic acid (SA) was less than 5% for concentrations between 1 and 4 mg/L and less than 10% for concentrations between 0.3 and 1 mg/L. SA concentrations are reported to the nearest 0.1 mg/L.

Urine. Urine samples were first assayed for methyl salicylate, SA, and salicyluric acid (SUA). Without prior preparation, 15 µL of a urine sample was injected, in duplicate, into the chromatographic system. The amount of each glucuronide (salicyl acyl glucuronide [SAG] and salicylic phenolic glucuronide [SPG]) in each urine sample was calculated by subtraction after acid hydrolysis. Briefly, acid hydrolysis cleaves all trolamine, methyl salicylate, SUA, and glucuronides present in the urine to yield SA. Acid hydrolysis was completed by mixing 1 mL of a urine sample with 1 mL of concentrated hydrochloric acid and incubated at 90 °C in a propylene glycol bath for 24 hours.[11,12] Each sample was prepared in duplicate. The limit of quantification for all compounds (methyl salicylate, SA, SUA) in urine was 1 mg/L and the intraassay coefficient of variation for replicate samples never exceeded 8%. All concentrations were reported to the nearest 0.1 mg/L.

The concentrations of methyl salicylate, SA, and the major salicylate metabolites (SUA, SPG, SAG) were multiplied by the recorded urine volume to obtain the amount of each recovered in the urine during each 24-hour collection. These amounts were then converted to SA equivalents using the known molecular weights of these compounds. Total SA recovery was obtained by multiplying the SA concentration determined following acid hydrolysis, by the urine volume.

DATA REDUCTION AND STATISTICAL ANALYSIS

Sample Size. The number of subjects chosen to participate in this trial was determined using a power calculation[13] that set the two-tailed level of significance at 0.05, the power at 80%, and the minimum detectable difference in serum salicylate area under the curve (AUC) between treatments at 20%. This calculation assumed that the intrasubject coefficient of variation observed for AUC in previous oral SA bioavailability studies of 15%[14,15] would hold true for a topical salicylate bioavailability study. Errors in these assumptions will affect the ability to detect a difference.

Serum. Serum SA concentration–time profiles for each subject were constructed using serum concentration data. From these profiles, the highest concentration observed (C_{max}), the time that the highest concentration was observed (t_{max}), and the concentration observed at the end of the dosing interval (C_{min}) was determined and the AUC from 0 to 12 hours (using the trapezoidal rule) was calculated. In addition, best-fit pharmacokinetic parameters for three different pharmacokinetic models were estimated for the methyl salicylate data using NONMEM IV, version 2.1.[16] The number and choice of pharmacokinetic models tested grew out of the inability of a one-compartment model with first-order elimination and first-order oral absorption to accurately predict day 4 concentrations based on day 1 concentrations. Each subject's concentration–time profile for days 1–4 was fit as a single data set using the amount of salicylate recovered in the urine on days 2, 3, and 4 as the observed bioavailability. Tested models assumed a single compartment, and either first-order elimination or nonlinear elimination and a fixed absorption rate constant throughout the 4 study days, or one that changed between the first and fourth day. Estimates for clearance (Cl), absorption

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rate (k_a), volume (V) and fraction absorbed (F) on day 1 were determined for the first-order elimination models. A terminal phase half-life was calculated from fitted estimates of Cl and volume (Cl/V). For the nonlinear elimination model, estimates of Michaelis–Menten constants (Km, V_{max}), k_a, V, and F on day 1 were determined. The goodness of fit for each model in each subject was compared based on the credibility of the parameter estimates (estimates were physiologically reasonable, positive values), the standard error of these estimates, direct comparison of observed and expected concentrations, and Akaike's information criterion (AIC)[17] values determined for that subject's data set. The AIC value was calculated using the "minimum value of the objective function" (a NONMEM reported statistic[16]), with the knowledge of the number of parameters in the model.

Statistical Methods. Differences within women and men, and the study sample as a whole in the amount of salicylate recovered in urine, the bioavailability expressed as a percent of applied dose, C_{max}, t_{max}, AUC, C_{min}, and estimated k_a between trolamine and day 1 and 4 of methyl salicylate therapy were compared using two-way ANOVA or paired Student's *t*-test, as appropriate. Fisher's protected least significant difference test[18] was used as the multiple range test following ANOVA to find significant differences. Since variances for different serum concentration pharmacokinetic endpoints displayed marked differences between days, violating an assumption of parametric statistical tests, the Wilcoxon ranked sign test was also used to detect differences between days. The a priori level of significance was set at $p < 0.05$ for all tests.

Results

SERUM

When analyzed by liquid chromatography, no unchanged methyl salicylate or trolamine was detected in any of the serum samples. Serum concentrations of SA observed following treatment with methyl salicylate ranged from 0.3 to 0.9 mg/L within 1 hour of the first application and between 2 and 6 mg/L on day 4. A mean concentration–time profile for day 1 and day 4 is shown in Figure 1. During the trolamine phase, however, SA concentrations were below the limit of detection (0.3 mg/L) in all samples.

Mean serum pharmacokinetic parameters after each treatment appear in Table 1. The SA C_{min} observed on methyl salicylate treatment day 1 at 12 hours was significantly ($p < 0.019$) lower than the C_{min} observed on day 4 (0, 12, and 24 hours), but is consistent with the accumulation of SA following multiple applications.

Initial attempts to determine estimates of linear pharmacokinetic parameters from serum concentration–time profiles demonstrated that estimates which accurately fit the day 1 concentration–time profile did not describe the concentration–time profile observed on day 4 in most subjects. Comparison of best-fit parameters from days 1 and 4 indicated that significant differences existed between days 1 and 4 for the k_a and an estimate of the apparent volume of distribution (V/F) but not for the elimination rate constant (Cl/V). This could imply model misspecification, and as changes in volume terms could be due to changes in fraction absorbed, three potential pharmacokinetic models were tested. All three models used the observed fraction of SA recovered in the urine on days 2, 3, and 4 as the fraction absorbed on those days and estimated the bioavailability on day 1, since steady-state may not have been achieved within the first 24 hours. Two of the models assumed first-order elimination, one allowing k_a to change between the first and fourth dose; the third model assumed first-order absorption and nonlinear elimination. The AIC was calculated for each of the models in each subject. In 8 of 12 sub-

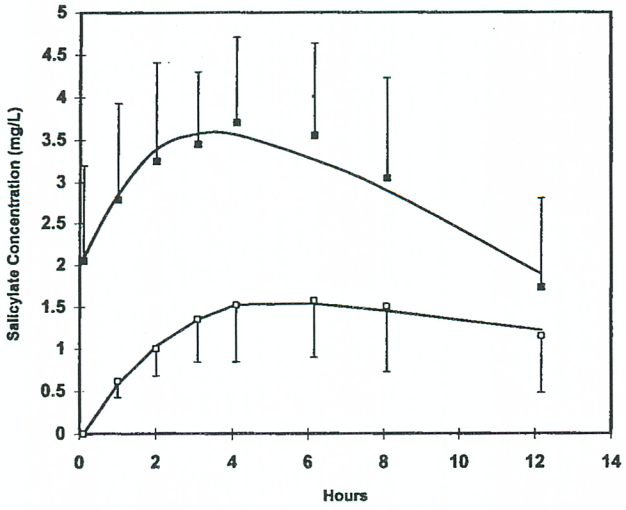

Figure 1. Mean salicylate concentration–time profile observed following application of the first dose of methyl salicylate ointment on day 1 (open squares) and the last dose given on day 4 (closed squares). Error bars represent standard deviations. The solid lines represent mean predicted concentrations based on best-fit pharmacokinetic parameters from a one-compartment model with first-order elimination and a first-order absorption rate constant that was allowed to change between days 1 and 4. The similarity of terminal phase slopes is not apparent in this rectilinear plot.

Table 1. Mean Pharmacokinetic Values[a]

VARIABLE	METHYL SALICYLATE DAY 1	METHYL SALICYLATE DAY 4	TROLAMINE DAY 1
C_{min} (mg/L)			
0 h	0.00	2.0 ± 1.1	BLOQ
12 h	1.2 ± 0.7	1.7 ± 1.1[b]	BLOQ
24 h	1.5 ± 0.8	1.9 ± 1.0	BLOQ
C_{max} (mg/L)	1.7 ± 0.7	3.9 ± 1.2[b]	BLOQ
t_{max} (h)	6.0 ± 2.0	4.4 ± 1.3	NA
AUC_{0-12} (mg•h/L)	15.3 ± 6.6	35.8 ± 11.8[b]	NA
Apparent oral clearance (L/h)			
men	3.82 ± 1.31		
women	3.92 ± 1.45		
combined	3.89 ± 1.32		
Apparent oral volume of distribution (L)			
men	19.53 ± 7.12		
women	21.03 ± 5.59		
combined	20.28 ± 6.15		
Elimination rate constant (h^{-1})			
men	0.1978 ± 0.0314		
women	0.1932 ± 0.0572		
combined	0.1955 ± 0.0441		
Absorption rate constant (h^{-1})			
men	0.1675 ± 0.0460	0.1962 ± 0.0459[c]	
women	0.1532 ± 0.0611	0.3645 ± 0.3424[d]	
combined	0.1608 ± 0.0441	0.2803 ± 0.2489[d]	

AUC = area under the curve; BLOQ = below limit of quantification; C_{max} = maximum concentration; C_{min} = minimum concentration; NA = not applicable; t_{max} = time to maximum concentration.
[a]Reported as mean ± SD of 12 determinations.
[b]Significantly different from the mean value for day 1.
[c]No significant difference between absorption rate constant on day 1 and day 4.
[d]Significantly different from day 1 values by Wilcoxon signed rank test, $p < 0.035$.

jects, a changing k_a and first-order elimination provided the best fit; in an additional 2 subjects, a model with first-order elimination and a single estimate of k_a was identified as the best descriptor of the concentration–time profile. In only 2 subjects did the model with nonlinear elimination describe the profile better than either of the models with first-order elimination. On the basis of these results we selected the model with first-order elimination and allowed k_a to change between the first and fourth dose. The mean results of best-fit pharmacokinetic parameters for this model are provided in Table 1. The estimates are separated by sex and indicate that the absorption rate increased significantly in the combined group of 12 subjects, with an increase in the absorption rate constant in 4 of 6 men and 6 of 6 women.

URINE

The calculation of creatinine recovery in the urine demonstrated that all collections in all subjects were within 15% of the mean urinary creatinine recovery. This was interpreted as an indication that urine collections were complete.

Table 2 shows the mean amount of SUA, unchanged SA, glucuronides, and total SA (in mg) recovered in the urine per day for each topical product. For the methyl salicylate phase, analysis of the urine samples revealed that no unchanged methyl salicylate was detected in the urine for any subject (all concentrations were below the limit of detection of 1 mg/L). However, SUA and unchanged SA were observed in all urine samples in concentrations up to 491.9 mg/L and 15.6 mg/L, respectively. SA and SUA concentrations observed in urine collected during the 24 hours of the trolamine phase were frequently below the level of detection (1 mg/L). As is evident from Table 2, the amount of total SA recovered during the trolamine phase was significantly ($p < 0.001$) less than that recovered during the methyl salicylate phase. Even after correction for dose, bioavailability of trolamine is one-tenth the bioavailability observed in the first 24 hours following methyl salicylate application.

Mean total SA recovered during the first 24 hours of methyl salicylate application averaged 175.2 mg. Recovery increased significantly ($p < 0.05$) from day 1 to days 2, 3, and 4, with no significant differences between the last 3 days. The pharmacokinetic model that best described the observed data estimated the mean fraction absorbed on day 1 at 15.7%. Since the mean elimination-rate constant (Table 1) reflects a half-life of 3.5 hours, steady-state should be achieved within 24 hours. Therefore, urinary recovery of salicylate on days 2, 3, and 4 would reflect the amount of drug absorbed.

ADVERSE EFFECTS

All 12 subjects experienced some degree of burning, stinging, and erythema of the area where methyl salicylate was applied. Eleven subjects also described pruritus and prolonged erythema for up to 7 days after the end of the treatment phase. No subject, however, withdrew from the study as a result of these local reactions. In contrast, the trolamine treatment was well tolerated, with only 1 subject reporting prolonged pruritus and erythema over the affected area. No other adverse effects occurred during the study.

Discussion

This study demonstrated an increase in both the rate and extent of absorption from a methyl salicylate ointment after multiple applications. Bioavailability increased from 15% after the first two doses to 22% of the applied dose after the third to eighth dose. An increase in extent of absorption was observed in four of six men and four of six women. An increase in rate of absorption was observed in four of six men and in six of six women. This increase in rate and extent could be due to an effect of the methyl salicylate ointment on the skin. After two to three applications, most subjects (men and women) reported pain and discomfort at the site of application, which may have indicated a change in the condition of the skin. "Intactness" of the skin is one of the most important factors preventing

Table 2. Urinary Recovery of Salicylic Acid and Its Metabolites[a,b]

	METHYL SALICYLATE 12.5% OINTMENT				TROLAMINE 10% CREAM
FORM OF SA	DAY 1	DAY 2	DAY 3	DAY 4	DAY 1
SUA (mg)	108.6 ± 32.6	146.6 ± 46.7	169.8 ± 56.0	167.7 ± 34.3	9.1 ± 6.8
Unchanged SA (mg)	4.0 ± 3.1	5.6 ± 3.6	3.8 ± 1.8	4.6 ± 3.8	1.8 ± 1.9
Glucuronides (mg)	62.6 ± 72.2	96.9 ± 65.9	80.1 ± 52.5	79.2 ± 59.2	nil[c]
Total SA (mg)					
men	198.3 ± 127.3	271.1 ± 96.7	254.4 ± 79.4	249.4 ± 50.1	5.1 ± 4.4
women	152.2 ± 46.0	227.0 ± 35.8	253.8 ± 30.6	253.4 ± 67.9	8.7 ± 7.6
combined	175.2 ± 94.4	249.0 ± 73.3	254.1 ± 57.4	251.4 ± 56.9	6.9 ± 6.2
% Recovered[b]	15.5 ± 8.3[d]	22.0 ± 6.5	22.4 ± 5.1	22.2 ± 5.0	1.4 ± 1.3

SA = salicylic acid; SUA = salicyluric acid.
[a]All values reported as mean ± SD of 12 determinations.
[b]Percent recovered (% SA recovered in the urine as a fraction of the dose) was calculated by dividing total SA recovered in urine on the study day by the amount of SA in 10 g (2 × 5 g applications) of the study product (this is equivalent to 1134 mg and 482 mg of SA for methyl salicylate 12.5% ointment and trolamine cream, respectively).
[c]Since glucuronides were calculated by difference, the variability in the small amount recovered in urine results in this number being negative (–4.1 mg).
[d]The estimated fraction absorbed (bioavailability), as determined by a one-compartment model with linear elimination and a first-order absorption rate constant, was 15.7% ± 5.5%.

drug penetration and changes in the integrity, hydration, or thickness of the skin could lead to a change in both the rate and extent of absorption from topical products.[19] The present data do not indicate if further changes in absorption would occur if ointment application was continued beyond 4 days. This study also demonstrated that the amount of salicylate recovered in the urine in the first 24 hours after two applications of a 10% trolamine cream was 1.4%, which is significantly lower than the bioavailability observed following application of a methyl salicylate ointment.

As part of the analysis we have demonstrated that a pharmacokinetic model with first-order elimination describes the concentration–time profile better than a model with nonlinear elimination. Although the pharmacokinetics of salicylate are well known to be concentration or dose dependent,[20] it is not surprising that linear pharmacokinetics best describe these data, since peak concentrations observed on day 4 are well below concentrations in the normal therapeutic and nonlinear range (>150 mg/L),[20] averaging 3.9 mg/L (range 2.1–5.8).

The observed salicylate recovery in the first 24 hours is in agreement with the results from an Australian study[21] that showed about 12–20% of a single dose of topically applied methyl salicylate was recovered in the urine within 10 hours after application. Similarly, Rabinowitz and Baker[22] showed that following the application of 10 g of trolamine 10% cream to the knee, the concentration of ^{14}C-salicylate in urine was approximately 0.02 mg/L after 1 hour and 0.18 mg/L at 2 hours. In the present study, concentrations of total SA (SA and metabolites) in urine following trolamine treatment (2 × 5 g applications 12 h apart) were higher, ranging from 0 to 25.6 mg/L. Rabinowitz and Baker[22] also reported concentrations of ^{14}C-salicylate in blood following topical application of trolamine ranging from 0.03 to 0.08 mg/L. The sensitivity of our method for detection of SA in serum was 0.3 mg/L; this could explain why no SA was detected in serum during the trolamine phase.

The effect of dose and surface area on the bioavailability of salicylate products cannot be evaluated with this study design. However, it is reasonable to expect that doses applied to a larger surface area would generally be larger and would be expected to produce higher concentrations of salicylate in serum. The study design used by Danon et al.[23] demonstrated some of these factors. In their study an unknown quantity of methyl salicylate was applied to a larger surface area under conditions of prolonged heat exposure and sustained exercise. The serum SA concentrations observed were two- to tenfold greater than concentrations observed in our study after a single dose.

Conclusion

We recommend that salicylate-derivative external analgesics be used with caution in people for whom salicylate may be hazardous, as these products can be absorbed through the skin. This would particularly include patients who are hypersensitive to salicylates or those who are taking medication known to interact with salicylates, even in low dosages (e.g., warfarin).[5-7]

Caution is also warranted in individuals who use these products without supervision, in large amounts, or for prolonged periods, since a wide intersubject variation in the amount of SA absorbed may result in large, possibly harmful amounts of SA reaching the systemic circulation. Furthermore, prolonged use (>3–4 applications) may enhance the absorption of salicylate and lead to a change in the condition of the skin. Based on these data, the Health Protection Branch of Canada has revised the labeling standards for nonprescription counter-irritants containing methyl salicylate to include specific directions with respect to the allowable duration and frequency of treatment before recommending a consultation with a physician. Proper labeling of these products may assist in preventing potential toxicity from overzealous use of these products. ≏

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EXTRACTO

OBJETIVO: Comparar la cantidad y la razón de absorción sistémica de salicilato después de aplicaciones sencillas y múltiples de dos analgésicos de uso tópico, uno que contiene metilsalicilato, y otro que contiene salicilato de trolamina.

DISEÑO: Estudio aleatorio cruzado de dos tratamientos en dosis múltiples ralizado en dos períodos de tiempo en voluntarios masculinos y femeninos.

PARTICIPANTES: Doce voluntarios saludables (seis hombres y seis mujeres) entre las edades de 21 a 44 años.

INTERVENCIONES: Los voluntarios se aplicaron 5 g de un ungüento que contenía 12.5% de metilsalicilato 2 veces al día por 4 días (ocho dosis) o una crema que contenía 10% de trolamina 2 veces al día por 1 día (dos dosis) en un área de 10 cm^2 en el muslo de la pierna. El orden de tratamiento y la pierna (derecha o izquierda) fueron asignados aleatoriamente. Luego de un período de 7 días se alternó el tratamiento en los voluntarios.

MEDICIÓN DE RESULTADOS: La biodisponibilidad de cada producto fue determinada utilizando la cantidad total de salicilato recobrado en la orina durante los intervalos de dosificación (24 horas) en cada día de estudio relativo a la dosis de salicilato aplicada. Parámetros farmacocinéticos, incluyendo el área bajo la curva, la concentración máxima (C_{max}), el tiempo necesario para alcanzar la concentración máxima (t_{max}), y las concentraciones mínimas en estado estacionario ($_{min}$), fueron calculados a base de las concentraciones séricas. Las concentraciones séricas fueron utilizadas en tres modelos farmacocinéticos y la adecuacidad de cada modelo fue evaluada. El mejor modelo fue utilizado para estimar la constante de absorción, la depuración, el volumen de distribución, y la fracción absorbida el primer día.

RESULTADOS: No se pudo detectar ácido salicílico en el suero después de la aplicación de trolamina. Sin embargo, se detectaron concentraciones entre 0.31 y 0.91 mg/L en la primera hora de la primera aplicación de metilsalicilato y un C_{max} entre 2 y 6 mg/L después de la séptima aplicación de metilsalicilato en el cuarto día. Tanto la cantidad como la razón de absorción cambiaron después de las primeras 24 horas. La constante de absorción aumentó significativamente de la primera a la séptima dosis (primera dosis = 0.16 hr^{-1}, $p = 0.035$). El promedio de la recuperación total de salicilato (ácido salicílico y sus metabolitos principales) en orina durante las primeras 24 horas después de la aplicación de la fase de metilsalicilato fue mayor que la recobrada durante la fase de trolamina (175.2 mg vs. 6.9 mg, respectivamente; $p < 0.05$). La recuperación de salicilato en la orina durante las primeras 24 horas de la aplicación de metilsalicilato fue significativamente mayor que el 1.4% recobrado después de la aplicación trietanolamina ($p < 0.05$). La fracción de metilsalicilato recobrada en la orina aumentó significativamente de 15.7% en el primer día a aproximadamente 22% en el segundo, tercer y cuarto día.

CONCLUSIONES: Una cantidad considerable de ácido salicílico puede absorberse a través de la piel después de la aplicación de productos que contienen metilsalicilato. Este efecto puede aumentar con aplicaciones múltiples. Se recomienda tener precaución en pacientes que puedan presentar problemas con el uso de salicilatos.

HOMERO A MONSANTO

RÉSUMÉ

OBJECTIF: Comparer la vitesse et l'étendue de l'absorption de salicylate suivant une application unique ou des applications répétées d'analgésiques topiques; l'un contenant du salicylate de méthyle et l'autre du salicylate de trolamine.

DEVIS EXPÉRIMENTAL: Étude prospective, randomisée en chassé-croisé comparant des applications répétées de chacun des agents.

PARTICIPANTS: Douze volontaires (six femmes et six hommes) âgés entre 21 et 44 ans.

INTERVENTIONS: Les sujets appliquaient 5 g de pommade ou de crème deux fois par jour sur une surface de 10 cm^2 localisée sur la portion antérieure de la cuisse. La pommade contenant 12.5% de salicylate de méthyle faisait l'objet de huit applications alors que la crème contenant 10% de salicylate de trolamine faisait l'objet de deux applications. L'ordre des traitements ainsi que la cuisse (droite ou gauche) étaient assignés au hasard. Le premier traitement était appliqué sur une cuisse puis, après une période de retrait d'au moins 7 jours, l'autre traitement était appliqué sur la cuisse contralérale.

MESURES DE L'EFFET: La biodisponibilité de chaque produit était calculée à partir de la quantité totale de salicylate récupérée dans l'urine au cours de deux intervalles posologiques (24 heures) pour chaque jour de l'étude. Les paramètres pharmacocinétiques moyens dont la surface sous la courbe, la concentration maximale (C_{max}), le temps pour la concentration maximale (t_{max}), et la concentration minimale à l'état d'équilibre (C_{min}) étaient déterminés à partir des concentrations sériques. Les concentrations sériques étaient modélisées selon trois modèles pharmacocinétiques et le plus approprié a été retenu. Les valeurs de la constante d'absorption, de la clairance, du volume, et de la fraction absorbée étaient estimées par le modèle pharmacocinétique le mieux adapté.

RÉSULTATS: L'acide salicylique n'a pas été détecté dans le sérum suite à l'application de salicylate de trolamine. Par contre, des concentrations de salicylate entre 0.31 et 0.91 mg/L ont été détectées au cours de l'heure suivant la première application de salicylate de méthyle et une C_{max} entre 2 et 6 mg/L a été observée après la septième application de salicylate de méthyle au jour 4. La vitesse d'absorption ainsi que la quantité totale absorbée étaient modifiées après les premières 24 heures. La consante d'absorption a augmenté significativement entre la première et la septième dose (constante premier dose: 0.16 h^{-1}; constante septieme dose: 0.28 h^{-1}; $p = 0.035$). La quantité totale moyenne de salicylate urinaire (acide salicylique et principaux métabolites) récupérée pendant les premiers 24 heures du traitement avec le salicylate de méthyle, était plus élevée que la quantité récupérée pendant le traitement avec le salycilate de trolamine soit 175.2 mg contre 6.9 mg ($p < 0.05$). De plus, la fraction de salicylate de méthyle récupérée dans l'urine a augmenté significativement de 15.7% au jour 1 à 22% aux jours 2, 3, et 4.

CONCLUSIONS: Une absorption cutanée significative d'acide salicylique est possible lors d'application de produits contenant du salicylate de méthyle et celle-ci peut augmenter lors d'applications répétées. Ceci incite à la prudence chez les patients pour qui les salicylates systémiques peuvent être contre-indiqués.

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