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This study was supported by National Institutes of Health Grant No. 5 R01 GM 24611.

Permeation of Skin and Eschar by Antiseptics II: Influence of Controlled Burns on the Permeation of Phenol

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Abstract □ The safe antiseptic use of phenol over the burn-traumatized surface depends on knowledge of how the systemic accumulation of phenol is affected by burn processes. To gain insight into the underlying permeation phenomenon, the diffusion of phenol and a reference cosolute, methanol, through both scalded and branded dorsal skin sections of the hairless mouse was studied as a function of burn temperature using *in vitro* diffusion cells. Temperatures up to 100 and 150° were used for scalding and branding, respectively, using a 60-sec exposure time. Permeability coefficients of the traumatized skins were assessed at 37° and compared with control values. Coefficients of both permeating species were not increased significantly by burn temperatures up to 70° applied either by scalding or branding, however, at higher temperatures exaggerated increases in permeation rates were noted. A limiting increase of ~7 times the control value was noted for phenol irrespective of the burn method. Permeability of methanol was altered even more dramatically and at 100° by scalding and 150° by branding was over 50 times the control rate. At 80 and 100° for methanol and at 80° for phenol, scalding produced larger increases in the permeability coefficients than branding. Since contact for 1 min at 60° is capable of producing a full-thickness burn injury, it is clear that eschar permeability to phenol immediately postburn is not related to the clinical degree of burning, but is a function of the thermal intensity (hotness) of the burn stimulus. Full-thickness wounds can be expected to have highly variable rates of systemic absorption as a direct consequence of the wide-ranging permeability possible for such burns, with the risks of topical application varying accordingly.

Keyphrases □ Permeability—of phenol and methanol, through burn-traumatized skin □ Phenol—permeability through burn-traumatized skin □ Methanol—permeability through burn-traumatized skin

Survival of patients with extensive deep partial-thickness (second-degree) and full-thickness (third-degree) burns depends, in part, on limiting microbial colonization of the wound surface. Topical antiseptics are used for this purpose since eschar is nonvascularized and all but inaccessible systematically. Virtually every known antiseptic chemical has been applied to burns, all too often with serious systemic consequences due to excessive transeschar adsorption. Phenol has proven to be one of these toxic agents (1, 2).

In previous studies using model permeating species originating from these laboratories, the permeation behavior of hairless mouse skin has been shown to be altered in unique ways by both scalding (3, 4) and branding (5, 6). Skin permeation rates for water and the *n*-alkanols were maximally increased two- to fourfold when the skins were burned at 60°, irrespective of burn duration. However, when skins were burned for 60 sec at various temperatures, large increases in the permeabilities were noted beginning at ~80°; the effect was greater the more polar the permeating species. In branding experiments, it was possible to use temperatures >100° and correspondingly larger permeability increases were observed for sensitive compounds. These studies provided basic insights into the conditions for and mechanisms of thermal alteration of skin permeation.

The permeability of phenol through hairless mouse skin in its normal state and in a stripped condition was also investigated in these laboratories (7). The overall behavior of this animal tissue to phenol was found to be similar quantitatively and qualitatively to the behavior reported for the human epidermis (8, 9), including exact agreement on the concentration level where self-acceleration of permeation rates due to chemical denaturation of the stratum corneum began. Since there are reports that the percutaneous absorption of phenol through thermally damaged tissue is greatly enhanced (1, 10), the present study was undertaken to quantitate this clinically serious limitation to the topical use of phenol. Specifically, this study was aimed at investigating the influences of incrementally increased burn temperature by scalding or branding on the permeation of phenol through skin.

EXPERIMENTAL

Chemicals—[^{3}H]methanol[1] and [^{14}C]phenol[1] were diluted with 0.9% sodium chloride irrigation[2] (saline) to prepare solutions for the permeation experiments. The final chemical concentrations of the permeating species in the external diffusion medium were $\leq 10^{-4}$ *M*.

Animals—Male hairless mice of SKh-hr^{-1} strain[3] were used. Their care was as described in the preceding paper (7).

Radioisotopic Assay—Concentrations of the radiolabeled permeating species were determined using a liquid scintillation counter[4] and a suitable liquid scintillator[1]. Permeation of both methanol and phenol was studied simultaneously using a technique involving dual labels (11).

Scalding Procedure—Immediately following sacrifice, the dorsal

[1] New England Nuclear, Boston, Mass. (Supplier-estimated purity >98% in each case.)
[2] Abbott Laboratories, North Chicago, Ill.
[3] Skin Cancer Hospital, Temple University, Philadelphia, Pa.
[4] Beckman Liquid Scintillation Counter, Model LS 9000, Beckman Instruments, Inc., Fullerton, Calif.

0022-3549/83/0400-0397$01.00/0

Table 1—Summary of the 60-Sec Scalding Data

Burn Temperature,°	Mouse Age, Days	$P \times 10^3$, cm/hr Mouse 1	2	3	4	5	Mean ± *SD*	Mean S-Values ± *SD*[a]
				Methanol				
37	—	—	—	—	—	—	—	1.0
60	110	1.7	2.6	2.3	3.4	—	2.5 ± 0.7	1.3 ± 0.3
70	110	8.8	5.9	4.6	4.7	6.8	6.2 ± 1.7	3.1 ± 0.9
80	111	52.8	52.3	48.2	70.9	49.6	54.8 ± 9.2	27.4 ± 4.6
90	111	99.6	76.9	75.7	76.4	—	82.2 ± 11.6	41.1 ± 5.8
100	115	94.9	120.6	92.5	124.6	—	108.2 ± 16.8	54.1 ± 8.4
				Phenol				
37	—	—	—	—	—	—	—	1.0
60	110	21.1	22.4	21.7	28.7	—	23.5 ± 3.5	1.0 ± 0.2
70	110	54.8	38.3	32.1	28.5	39.2	38.6 ± 10.1	1.7 ± 0.5
80	111	175.1	160.3	139.9	172.0	147.1	158.9 ± 15.3	6.9 ± 0.7
90	111	180.8	145.6	146.8	162.4	—	158.9 ± 16.5	7.0 ± 0.7
100	115	146.2	160.6	154.4	177.4	—	159.7 ± 13.2	7.0 ± 0.6

[a] Computed by using Eq. 2. The control *P*-values are: methanol, 1.9×10^{-3} cm/hr and phenol, 20.3×10^{-3} cm/hr. These values were abstracted from Refs. 7 and 8.

surface of each mouse was scalded by immersing it in water contained in a jacketed beaker (3). A desired burn temperature was achieved by perfusing water from a constant-temperature water bath through the beaker.

Branding Procedure—The dorsal sites of the mice were burned immediately following sacrifice by bringing them in contact with the upper, polished surface of a branding device (5). The desired burn temperature was achieved by perfusing the device with hot mineral oil from a constant-temperature oil bath.

Diffusion Cell and Permeation Procedure—A two-chamber glass diffusion cell (3–7, 11) was employed to determine the permeability of the skin. Mice were sacrificed by spinal cord dislocation, weighed, and visually examined for skin defects and hair distribution. The animals were selected from within a narrow age range (110–155 days) to minimize age-related effects (12). The dorsal surfaces were scalded (at temperatures ranging from 60 to 100°) or branded (at temperatures ranging from 60 to 150°) for a 60-sec duration. Each burned skin section was excised from the animal and mounted in a diffusion cell, and permeation experiments were conducted immediately, as previously described (7). Each experiment lasted for ~2 hr. This procedure ensured, insofar as possible, that the data would not be affected by the unavoidable hydrating conditions of the *diffusional system* (11). Three to five mice of about the same age were used for each compound per experimental condition. The details of the operation of the diffusion cell were as described previously (7).

Data Analysis—The data were plotted as the receiver compartment concentration (in cpm) as a function of time. The permeability coefficient was computed from the quasi steady-state slope from (3–7, 11, 12):

$$P = \frac{V}{A}\frac{(dC/dt)}{\Delta C} \qquad \text{(Eq. 1)}$$

where P is the permeability coefficient (cm/hr); A is the diffusional area (~0.6 cm^2), ΔC is the concentration difference across the membrane, which was taken to be equal to the donor concentration (cpm); V is the half-cell volume (1.4 ml); and dC/dt is the steady-state slope (cpm/cm^3/hr) from the receiver concentration *versus* time profile. The scalding coefficients (S-values) and the branding coefficients (B-values) were calculated from (3, 5):

$$\text{S-Value} = \frac{\text{dorsal (scalded) permeability coefficient}}{\text{dorsal (normal) permeability coefficient}} \qquad \text{(Eq. 2)}$$

and

$$\text{B-Value} = \frac{\text{dorsal (branded) permeability coefficient}}{\text{dorsal (normal) permeability coefficient}} \qquad \text{(Eq. 3)}$$

The normal dorsal permeability coefficients were averages for those found in previous studies (11, 12).

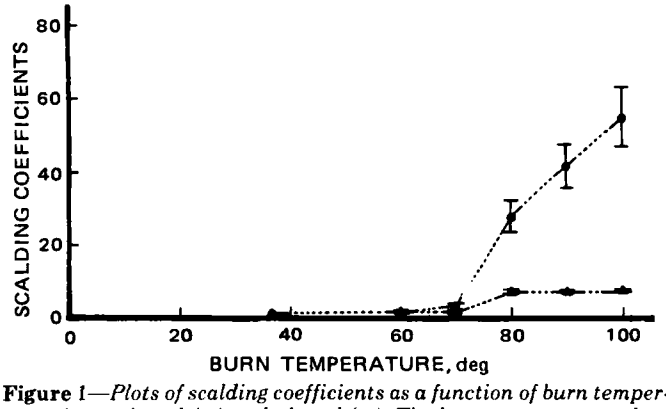

Figure 1—*Plots of scalding coefficients as a function of burn temperature for methanol (●) and phenol (▲). The bars represent standard deviations for each mean value.*

RESULTS AND DISCUSSION

Tables I and II contain summaries of data obtained in the scalding and the branding experiments, respectively. Data are tabulated separately for methanol and phenol, two solutes that diffused through the skin simultaneously. The permeability coefficients of the normal dorsal skins were abstracted from previous studies (11, 12). Figures 1 and 2 contain graphical illustrations of the burn coefficients as a function of the burn temperature for scalding and branding experiments, respectively.

Factors Influencing the Experimental Course of Action—In previous studies (3–6) two simple methods of giving graded, reproducible burns were practiced: burning at 60° for varied lengths of time and burning for 60 sec at systematically increased temperatures. Although burn wounds of third-degree depth were effected at 60° by scalding or branding for ≥1 min, the permeabilities of a spectrum of nonelectrolytes were only slightly elevated by such treatment. On the other hand, when scalding or branding was done at temperatures exceeding 70°, extraordinary augmentation of the permeabilities of some solutes was obtained. The lower the natural permeability of a species, the greater was the effect; therefore, polar solutes, held back by the effectively lipid nature of the stratum corneum, were the most affected.

The varied temperature–fixed burn duration experimental protocol yielded the optimum insight into the extent of burn enhancement of permeability, and it was therefore selectively used in these investigations. Another early observation bearing on the present study was that burns given to mice immediately postsacrifice behaved the same diffusionally as burns applied to living animals when each was studied immediately postburn. Humaneness, therefore, dictated the former procedure should be used. Since a 60-sec burn at 60° yielded a full-thickness injury, this duration was considered to be more than adequate at higher temperatures. However, retaining the duration used for the original protocol allowed direct comparison of the behavior of phenol to that of the *n*-alkanols.

Influences of Scalding on the Permeabilities of Methanol and Phenol—Scalding produced only marginal increases in the permeability coefficient for methanol up to 70° (Fig. 1). Beyond this temperature, systematic increases in the permeability coefficients are seen. At the higher temperature the scalding coefficients for methanol are quite large, reaching a value of 54 at 100°. Previously an S-value of ~31 was reported at 98° (4). The 1.7-fold difference in the quotients is more apparent than real. Previous quotients were computed with permeability coefficients of abdominal skins obtained concurrently with those of the scalded dorsum, a within-animal control method. In the present study, historical

Table II—Summary of the 60-Sec Branding Data

Burn Temperature,°	Mouse Age, Days	$P \times 10^3$, cm/hr Mouse 1	2	3	4	5	Mean ± *SD*	Mean B-Values ± *SD*
				Methanol				
37	—	—	—	—	—	—	—	1.0
60	148	2.3	1.8	2.7	2.2	1.8	2.2 ± 0.4	1.1 ± 0.2
80	148	41.4	30.0	31.3	27.4	28.7	31.8 ± 5.6	15.9 ± 2.8
100	155	79.3	81.1	77.6	92.7	52.2	76.6 ± 14.9	38.3 ± 7.4
150	155	146.0	106.5	106.6	100.6	77.6	107.5 ± 24.6	53.7 ± 12.3
				Phenol				
37	—	—	—	—	—	—	—	1.0
60	148	23.9	20.7	25.1	22.3	17.8	22.0 ± 2.9	1.1 ± 0.1
80	148	129.4	95.0	96.6	98.9	80.9	100.1 ± 17.8	5.0 ± 0.9
100	155	175.1	140.6	142.2	187.4	102.6	149.6 ± 33.3	7.4 ± 1.6
150	155	197.4	144.8	150.1	147.0	105.4	148.9 ± 32.7	7.3 ± 1.6

[a] Computed by using Eq. 3. The control P-values are: methanol, 1.9×10^{-3} cm/hr and phenol, 20.3×10^{-3} cm/hr. These values were abstracted from Refs. 7 and 8.

means for the normal dorsal skin permeability coefficients were used in lieu of running a complete set of control skins with each experiment. When the same technique of computation is used with the previous data, a 98° S-value of ~43 is obtained which is in better agreement with the present value of ~54. It is important to note that a small, absolute variation in the control permeability coefficient yields a large difference in quotients such as the S-values. To further stress this point, the absolute P-values of the burned skins can be compared. The dorsal permeability to methanol was $8.49 \pm 1.27 \times 10^{-2}$ cm/hr in the earlier experiments when the burn temperature was 98° and the mouse age was 106 days. In the present study a value of $10.8 \pm 1.68 \times 10^{-2}$ cm/hr was obtained when the burn temperature was 100° and the mouse age was 115 days. The absolute permeabilities can be considered approximately the same. Given the overall qualitative parallelism between the two studies, it can be concluded that the present results compare well with the previous results for methanol.

Like methanol, increases in the permeation rate of phenol are also marginal up to 70° (Fig. 2). Thereafter, the permeability coefficient increases to a plateau reached within the 70–80° temperature span. A limiting S-value of ~7.0 is observed (Table I). Qualitatively and quantitatively, this behavior is comparable to the data for hexanol (4) where a plateau value of 6.8 was reported for burn temperatures of 80, 90, and 98. This parallel is mechanistically interesting, especially because the two permeating species have almost identical permeability coefficients when the skin is used in its natural state of hydration (11). This is not to say that the permeation of the stratum corneum is the same for both. The permeability of hexanol through intact mouse skin doubles on long aqueous soaking (11), while the permeability of phenol is little affected (7), indicating some fundamental differences in their abilities to cross the barrier layer. Hexanol and phenol do, however, exhibit nearly the same permeation rates through highly burn-impaired skin, which is not surprising given their comparable molecular weights and the aqueous nature of the residual functioning elements of the overall skin barrier after scalding.

Permeability of Phenol and Methanol Through Branded Skins—Data for methanol indicate large branding coefficients at ≥80°. As in all previous studies, 60° branding was without pronounced effect.

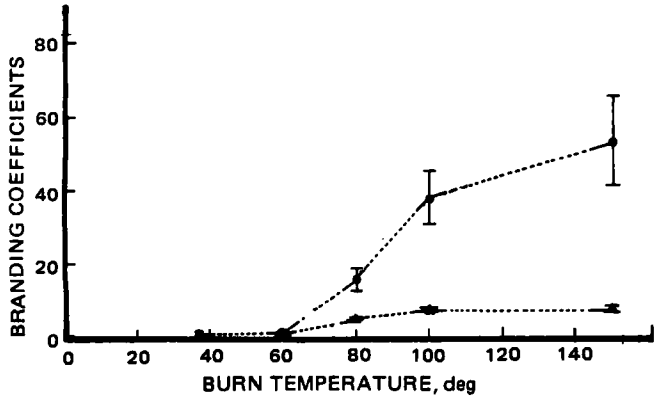

Figure 2—*Plots of branding coefficients as a function of burn temperature for methanol (●) and phenol (▲). The bars represent standard deviations for each mean value.*

While no 70° data were gathered, earlier work indicates that a transition from marginal to exaggerated burn effects took place at ~75°, which is not inconsistent with the present results. At a given temperature, branding coefficients appear consistently smaller than the scalding coefficients, suggesting that branding is an intrinsically less efficient means of damaging (presumably by denaturing the protein) the stratum corneum. At 80° for instance, the S-value is 27.4 ± 4.6, while the B-value using the same method of calculation is only 15.9 ± 2.8. At this temperature, values are significantly different ($p < 0.05$ by t test). There are several factors that might contribute to the scalding–branding disparity. In the course of scalding, the skin surface is in direct contact with the heated water; heat transfer should thus be more efficient than when there is a metal surface between the skin and the circulating thermal medium (branding). Additionally, moist heat may be more destructive than dry heat, a phenomenon that finds precedent in sterilization by autoclaving. Lastly, in the case of methanol, it appears that the closeness of the 100° S-value (54.1 and the 150° B-value (53.7) is not accidental but the consequence of the maximum possible disruption of the barrier function of the horny layer.

Branding data for phenol follow a pattern similar to that seen with scalding except that B-values again lag in magnitude behind the S-values at a given temperature. Within the limits imposed by the temperature spacing, the plateau for branding is not attained until 100° opposed to 80° for the scalding procedure. Again, the upper limit of the effects is nearly the same across burn methods: ~7 for scalding and ~7.4 for branding. The magnitude of the branding coefficients for phenol is only slightly smaller than the limiting value of ~9.5 for hexanol seen previously over the temperature range of 80–150° (6), providing another interesting parallel in the behaviors of these alkyl and aryl 6-carbon analogues.

Lastly, it has been suggested here that the barrier properties of the horny layer are destroyed at the extremes of the thermal treatments. This is true in the sense that the normal permeation selectivity is completely lost. However, permeability coefficients at their maximum for each compound are only 0.10–0.15 cm/hr, while earlier data showed stratum corneum-stripped permeability coefficients to be ~0.3 cm/hr and isolated dermis permeability coefficients to be slightly higher. It is therefore concluded that the denatured remains of the stratum corneum still offer a general diffusional resistance and are approximately as impermeable as the rest of the skin.

Clinical Relevance of the Phenol Studies—Presently, phenol is still used clinically as a local anesthetic and antipruretic, generally in whole percentage concentrations or in combination with other topical drugs (13). Its vehicles usually contain adsorptive solids and/or solvents, either of which reduces the thermodynamic activity of phenol below that of a strictly aqueous solution of the same concentration. Nevertheless, these topical preparations could be dangerous if used over burned tissue. A clinical fatality that occurred in 1949 (1) appears to be an instance where the worst possible combination of factors came together. A youth was burned by flash fire with superficial and partial-thickness burns covering 25–30% of his body. The method by which the burn was received and the clinical description of the fresh wound suggest that the burn was of short duration but very high thermal intensity: conditions which this research shows allows facile absorption through the skin. Although the phenol used for treatment was only 2% concentration in a 90% corn oil vehicle, the extensive area (fact) and highly permeable nature of the eschar (speculation) predisposed the patient to fatal systemic accumulation. Based on the work reported here, adsorption was possibly a logarithmic order

greater than it would be from the same application placed on normal skin. Given the variable but potentially high, permeability through eschar and the violent systemic toxicity (14), phenol should not be used for burn-wound antiseptics.

Another factor is that the chemical burn effected by the highest phenol concentration (6% w/v) in a preceding study (7) and the thermal burns effected here at temperatures >80° are of comparable permeability. This suggests that the chemical and thermal treatments cause the same type of destructive alteration of the stratum corneum, albeit by vastly different mechanisms, resulting in a functional impairment of the same order. We regard this as strong evidence that the stratum corneum proteins are involved and denatured by extreme treatments of either kind. It is hard to envision a means whereby these different treatments could produce like effects in purely lipid domains in the stratum corneum. By either procedure the stratum corneum loses some or all of the ability to differentiate permeating species on the basis of polarity, depending on the intensity of the burn.

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ACKNOWLEDGMENTS

This work was presented at the 128th Annual Meeting of the American Pharmaceutical Association held in St. Louis, Missouri, March 28–April 1, 1981.

Supported by National Institutes of Health Grant GM 24611.

Low-Melting Phenytoin Prodrugs as Alternative Oral Delivery Modes for Phenytoin: A Model for Other High-Melting Sparingly Water-Soluble Drugs

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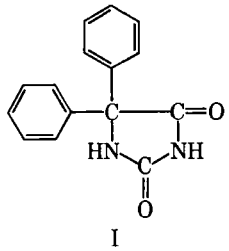
Abstract □ Phenytoin is a high-melting, weakly acidic, and sparingly water-soluble drug. Because of these physicochemical properties, phenytoin is subject to erratic bioavailability in a variety of dosage forms both in its acidic as well as sodium salt forms. A homologous series of 3-acyloxymethyl derivatives of phenytoin (acetyl through decanoyl) were synthesized and various physicochemical properties measured. The prodrugs were more readily soluble in various metabolizable glycerol esters such as tributyrin, trioctanoin, and triolein than phenytoin. The solubility of the prodrugs in the various organic vehicles studied was closely correlated to the melting point of the prodrug: the lower the melting point the greater the solubility. The cleavage rates of the prodrugs in plasma and tissue homogenates followed a parabolic relationship with chain length. The prodrug, 3-pentanoyloxymethyl-5,5-diphenylhydantoin when administered in tributyrin gave superior oral phenytoin bioavailability in rats when compared with sodium phenytoin administered as an aqueous solution.

Keyphrases □ Phenytoin—low-melting prodrugs, alternative oral delivery modes, model for high-melting sparingly water-soluble drugs □ Prodrugs—use in alternative oral delivery modes, model for high-melting sparingly water-soluble drugs, phenytoin

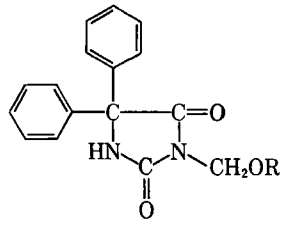
Phenytoin (I), a high-melting (293°) weakly acidic (1, 2) drug is sparingly soluble in water (2). Because of its physicochemical properties phenytoin is subject to erratic bioavailability in a variety of dosage forms both in the acidic as well as the sodium salt forms (3–6).

Since the problems associated with the release from the various dosage forms can be attributed to both the limited aqueous solubility and the weakly acidic nature of the phenytoin, it is likely that dissolution plays an important



I

R	
H-	II
CH_3CO-	III
C_2H_5CO-	IV
C_3H_7CO-	V
C_4H_9CO-	VI
tert-C_4H_9CO-	VII



II–XII

R	
$C_5H_{11}CO$	VIII
$C_6H_{13}CO$	IX
$C_7H_{15}CO$	X
$C_8H_{17}CO$	XI
$C_9H_{19}CO$	XII

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