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Enhancement of naloxone penetration through human skin in vitro using fatty acids, fatty alcohols, surfactants, sulfoxides and amides

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Summary

Human skin permeation of naloxone was examined in vitro using various vehicles and penetration enhancers. To screen various chemicals as penetration enhancers propylene glycol containing 10% adjuvant was used. Fatty acids and fatty alcohols were very effective promoters of naloxone flux. In both the acid and alcohol series, maximum flux was with C_{12} adjuvants, and for C_{18} acids and alcohols unsaturated adjuvants were more effective than saturated ones. Other effective skin penetration enhancers included some non-ionic and cationic surfactants, decylmethylsulfoxide, Azone, and N-alkylpyrrolidones. Lauric acid and lauryl alcohol in isopropanol, polyethylene glycol 400, and mineral oil vehicles were not as effective in promoting naloxone skin penetration as when dissolved in propylene glycol. Sodium lauryl sulfate in propylene glycol slightly increased flux, but a much greater effect was observed using a mineral oil vehicle. Concentration/enhancement profiles were determined for lauric acid and lauryl alcohol. Skin penetration enhancing effects are, to some extent, specific and dependent on the drug, vehicle, enhancer concentration and probably other factors. Possible mechanisms of altering skin permeability are discussed.

Introduction

The major advantages that transdermal drug delivery can offer are: (1) avoidance of first-pass metabolism often associated with oral dosing; and (2) sustained and more constant plasma concentrations of the drug. The 3-hydroxymorphinan and hydroxybenzomorphan opioid analgesics and antagonists as a class have poor oral bioavailability, due to a high first-pass metabolism effect. These drugs also generally have short elimination half-lives and 4–5 h durations of action. Because of these problems, they are logical candidates for transdermal delivery.

Naloxone-HCl (Narcan, DuPont Pharmaceuticals) is a potent opioid antagonist. It is presently available in 0.4 mg unit doses for injection, and is used for reversal of narcosis. The terminal half-life of naloxone after i.v. injection in normal volunteers was reported to be 64 min (Ngai et al., 1976) and 151 min (Aitkenhead et al., 1984) in two separate studies. Because of this short half-life, it has been suggested that infusion may be preferred in some cases of narcosis (Bradberry and Raebel,

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1981; Gourlay and Coulthard, 1983). In addition, recently naloxone has been shown to have other potential applications. Naloxone has shown beneficial effects in treatment of cardiovascular shock (McNicholas and Martin, 1984), chronic idiopathic constipation (Kreek et al., 1983), senile dementia of the Alzheimer's type (Reisberg et al., 1983a and b), and for appetite suppression (Atkinson, 1982). A regimen of frequent injections would not be acceptable for these uses, and transdermal delivery might be more appropriate. In addition, it has been reported that topical naloxone has antipruritic effects (Bernstein et al., 1982).

Human skin permeability of naloxone was examined. In order to maximize naloxone delivery through skin, penetration enhancers were evaluated. The agents studied include various types of chemicals, some of which are known to enhance skin penetration of other drugs. The primary objective of the work presented here was to identify agents which increase naloxone skin permeability. In addition, however, the data that were obtained provide some insight on the selectivity of certain penetration enhancers, and to some extent relationships between structure and penetration enhancing effect were developed. Although there are many papers reporting the effects of one or several penetration enhancers, relative comparisons of various classes of enhancers and within a homologous series, as we have done, are much less frequent. The more practical aspects of developing a transdermal delivery system, including the toxicology of these adjuvants, will be given separate consideration.

Materials and Methods

Skin penetration

Naloxone diffusion rates through human cadaver skin were measured using Franz diffusion cells (Crown Glass). The reservoir volume was 7–9 ml and was maintained at 37°C with a water jacket or dry block heater. The reservoir contained saline (0.9%) and was stirred with a bar magnet. Sink conditions were maintained by removing the entire reservoir volume and replacing with drug-free saline. The skin surface area available for diffusion was 1.8 cm^2. The volume of vehicle applied was generally 0.5 ml, except for semisolid drug donors, for which an unmeasured amount was spread onto the skin. The donor chamber was closed to the atmosphere with parafilm or a rubber stopper.

Human cadaver skin was obtained from a local hospital. The thickness of these specimens was 0.4 mm, which based on average skin layer thickness includes the stratum corneum, the epidermis, and part of the dermis. Skin was stored at −20°C indefinitely. The average age of the donors was 43 years with a standard deviation of 19 years and a range of 16 to 72 years. 18% of the donors were female and 15% were black. Vehicles and skin specimens were randomly matched, with the exception that any vehicle-specimen combination was used only once. Prior to use, each skin specimen was visually inspected for integrity.

Naloxone concentrations in the reservoir were determined by HPLC, using UV detection at 284 nm, and a 25 cm × 4.5 mm octylsilane column (Zorbax C_8, DuPont). The mobile phase was acetonitrile/tetrahydrofuran/0.05 M phosphate buffer (10 : 0.8 : 89.2). The amount of drug penetrating through skin during any time interval was calculated as the sample concentration multiplied by the reservoir volume. Individual plots of cumulative amount penetrating versus time were made, and from the slope of the linear portion of such plots naloxone steady-state flux was calculated. There were at least 3 experiments per group. All data are expressed as mean ± S.E.

Vehicles

In the initial experiments, the effects of various agents on naloxone skin penetration were examined. For these experiments, vehicles were prepared by dissolving the adjuvants in propylene glycol (Fisher Scientific). Propylene glycol was selected so that both hydrophilic and hydrophobic adjuvants could be dissolved. The arbitrary concentration of adjuvant was 10% (w/v or v/v), however, not every adjuvant was completely dissolved at this concentration. The adjuvants and their sources are presented in the Results section. Naloxone base was added to the adjuvant/pro

pylene glycol vehicle in amounts in excess of its solubility. This maximized the thermodynamic activity of naloxone in the vehicle, since the objective was to maximize naloxone flux through skin.

Lauric acid, lauryl alcohol, and sodium lauryl sulfate were also tested in isopropanol (Fisher), polyethylene glycol 400 (Fisher), and mineral oil (Nujol, Plough) vehicles. In addition, lauric acid/isopropyl myristate vehicles were examined. The concentration of adjuvant was 10% (w/v) and naloxone was added as a suspension. Propylene glycol vehicles containing various concentrations of lauric acid or lauryl alcohol were also prepared and naloxone added in excess of its solubility.

Solubility determinations

Naloxone base solubility was determined for some of the vehicles tested. Vehicles were prepared and naloxone was added and the suspensions stirred for at least 20 h at room temperature (22–24°). Suspensions were centrifuged and the supernatant removed and filtered through glass wool packed into a transfer pipette. These solutions were diluted with 0.1 N HCl and assayed by HPLC as previously described.

Partition coefficient

Naloxone partitioning between propylene glycol or 10% lauric acid in propylene glycol and isopropyl myristate was determined. Lauric acid was dissolved in propylene glycol and naloxone was added in excess of its solubility. The suspension was then mixed with an equal volume of isopropyl myristate (Eastman Kodak) and tumbled at room temperature for 24 h. After centrifugation both phases were filtered and aliquots diluted with 0.1 N HCl and assayed by HPLC.

Results

Effects of various adjuvants

Naloxone skin penetration rates were determined using propylene glycol vehicles containing various potential absorption promoters at a concentration of 10% (w/v or v/v). An example of the effects of enhanced skin penetration is illustrated in Fig. 1, which shows average data using

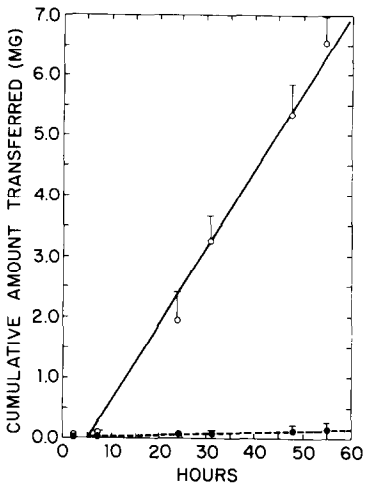

Fig. 1. Representative averaged profiles for naloxone diffusion through human skin using propylene glycol (●) or myristic acid/propylene glycol (○) vehicles.

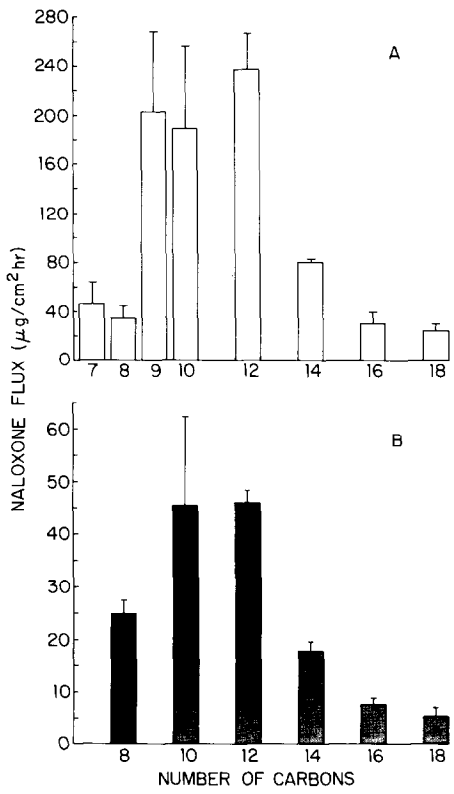

Fig. 2. Dependence of naloxone flux on chain length of fatty acid (A) or fatty alcohol (B) adjuvants (10% in propylene glycol).

TABLE 1

EFFECTS OF VARIOUS ADJUVANTS (10% IN PROPYLENE GLYCOL) ON NALOXONE FLUX THROUGH HUMAN CADAVER SKIN

Adjuvant [a]	Supplier	Naloxone flux [b] ($\mu g/cm^2 \cdot h$)	Number of experiments
None	–	1.6 ± 0.4	10
(A) Non-ionics			
Caprylic alcohol	Fisher	24.8 ± 2.6	3
Decyl alcohol	Sigma	45.3 ± 16.9	3
Lauryl alcohol	Pfaltz and Bauer	45.8 ± 2.4	3
2-Lauryl alcohol	Pfaltz and Bauer	43.9 ± 9.4	3
Myristyl alcohol	Sigma	17.7 ± 1.8	3
Cetyl alcohol [c]	Sigma	7.5 ± 1.2	3
Stearyl alcohol [c]	Sigma	5.2 ± 1.7	3
Oleyl alcohol	Sigma	25.0 ± 8.5	3
Linoleyl alcohol	Sigma	69.9 ± 28.0	4
Linolenyl alcohol	Sigma	116.3 ± 64.2	4
Propylene glycol laurate	Pfaltz and Bauer	43.8 ± 5.5	3
Sorbitan laurate [d]	Span 20, Sigma	27.9 ± 4.6	3
Polysorbate 20	Tween 20, Sigma	1.5 ± 0.4	3
Laureth 4	Brij 30, Sigma	34.5 ± 8.3	3
Laureth 23	Brij 35, Sigma	1.5 ± 0.6	3
PEG-4 laurate [d]	PEG 200 Monolaurate, Emery	11.8 ± 1.8	3
PEG-4 dilaurate [d]	PEG 200 Dilaurate, Emery	11.0 ± 1.2	3
Glyceryl laurate	Sigma	23.4 ± 3.6	3
Glyceryl dilaurate [d]	Stepan	18.7 ± 1.8	3
Dilauroyl lecithin	Avanti	8.2 ± 2.1	3
Sorbitan oleate [d]	Span 80, Sigma	9.9 ± 1.1	3
Sorbitan trioleate [d]	Span 85, Sigma	14.3 ± 4.6	3
Oleth-20	Brij 99, Sigma	1.6 ± 0.7	3
Glyceryl oleate [d]	Stepan	20.7 ± 2.0	3
Dilauroyl lecithin	Avanti	14.1 ± 4.5	3
Poloxamer 188 [c]	Pluronic F68, Ruger	4.2 ± 2.3	4
Poloxamer 401 [c]	Pluronic L121, BASF	5.8 ± 0.9	3
Cocomorpholine	Lonza	32.0 ± 3.9	3
(B) Anionics			
Heptanoic acid (7 : 0)	Celanese	46.2 ± 17.8	4
Caprylic acid (8 : 0)	Sigma	34.3 ± 10.0	3
Pelargonic acid (9 : 0)	Celanese	201.9 ± 65.4	3
Capric acid (10 : 0)	Sigma	187.9 ± 67.5	4
Undecylenic acid ($11 : 1^{\Delta 10}$)	Fluka	115.1 ± 4.5	3
Lauric acid (12 : 0)	Sigma	235.2 ± 29.9	3
Myristic acid (14 : 0)	Emery	78.1 ± 2.4	3
Palmitic acid (16 : 0) [c]	Sigma	27.8 ± 9.4	3
Stearic acid (18 : 0) [c]	Ruger	21.8 ± 5.6	3
Oleic acid ($18 : 1^{\Delta 9}$)	Emery	35.6 ± 9.8	3
Linolenic acid ($18 : 2^{\Delta 9,12}$)	Sigma	103.0 ± 14.1	3
Linolenic acid ($18 : 3^{\Delta 9,12,15}$)	Sigma	93.8 ± 14.7	3
Arachidonic acid ($20 : 4^{\Delta 5,8,11,14}$)	Sigma	47.8 ± 12.0	3
Sodium laurate	Sigma	7.3 ± 0.8	3
Sodium lauryl sulfate	Sigma	4.6 ± 0.9	3
Sodium oleate	Aldrich	3.8 ± 0.5	3
Dodecanedioic acid [d]	DuPont	2.0 ± 0.4	3
Trans-dodecenedioic acid [d]	Traumatic acid, Sigma	7.4 ± 2.4	3

TABLE 1 (continued)

Adjuvant [a]	Supplier	Naloxone flux [b] ($\mu g/cm^2 \cdot h$)	Number of experiments
Retanoic acid [d]	Sigma	7.4 ± 2.9	4
Lauroyl sarcosine	Hampshire	7.2 ± 3.0	3
(C) Cationics			
Dodecylamine	Fluka	25.1 ± 0.9	3
Stearylamine	Fluka	19.4 ± 7.0	4
(D) Amphoterics			
Lauroamphoglycinate	Mona	5.2 ± 0.2	3
Lauroamidopropylbetaine	Mona	5.8 ± 1.5	3
(E) Sulfoxides			
Dimethylsulfoxide	Sigma	1.7 ± 0.9	3
Decylmethylsulfoxide	Wateree	49.2 ± 19.8	5
(F) Amides			
Urea	Fisher	0.4 ± 0.1	3
Dimethylacetamide	Fisher	2.0 ± 0.3	3
Diethyltoluamide	Sigma	8.6 ± 2.9	3
1-Dodecylazocycloheptan-2-one	Azone, Nelson	25.2 ± 5.4	3
N-Methylpyrrolidone	GAF	1.8 ± 0.3	3
N-Hydroxyethylpyrrolidone	GAF	1.8 ± 0.1	3
N-Cyclohexylpyrrolidone	GAF	3.4 ± 1.4	3
N-Dimethylaminopropylpyrrolidone	GAF	3.9 ± 2.0	3
N-Cocoalkylpyrrolidone	GAF	55.2 ± 12.2	4
N-Tallowalkylpyrrolidone	GAF	38.4 ± 2.9	3

[a] CTFA adopted name if applicable.
[b] Mean ± S.E.
[c] Semisolid vehicle.
[d] Adjuvant not completely soluble/miscible at 10% concentration.

propylene glycol and propylene glycol/myristic acid vehicles. In this example, naloxone flux was increased 48-fold in the presence of myristic acid.

Fatty acids and fatty alcohols were among the most potent agents in increasing naloxone skin penetration. Within both the acid and alcohol series, the magnitude of enhancement was related to the chain length of the hydrophobic group (Fig. 2). The maximum naloxone flux was with the C_{12} acid and alcohol. The enhancing effects of unsaturated C_{18} acids and alcohols were also examined. Increasing the number of double bonds generally resulted in greater enhancement of naloxone skin penetration (Fig. 3). Based on these results, the other adjuvants selected for evaluation were predominantly those containing laurate or oleate hydrophobic groups.

Table 1 summarizes the effects of the various

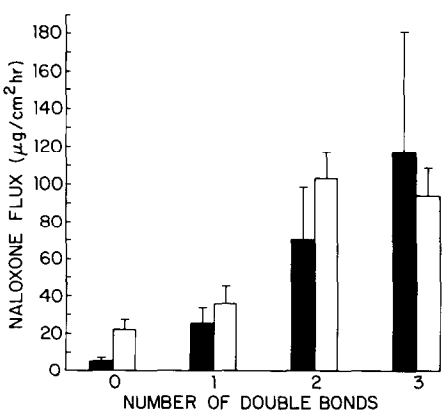

Fig. 3. Effects of saturated and *cis*-unsaturated C_{18} fatty alcohols (closed bars) and fatty acids (open bars) on naloxone skin penetration. The adjuvants were dissolved in propylene glycol at a concentration of 10%.

adjuvants tested. Although fatty acids were very effective penetration enhancers, the sodium salts, sodium laurate, sodium oleate, and sodium lauryl sulfate had minimal effects on naloxone skin penetration. The C_{12} diacids, dodecanedioic acid (saturated) and *trans*-dodecenedioic acid (unsaturated), also did not appreciably increase naloxone flux.

The ester and ether non-ionic surfactants were generally less effective than fatty acids in enhancing naloxone skin penetration. Naloxone flux was plotted versus the hydrophil–lipophil balance (HLB) value for the non-ionic and anionic surfactants with laurate hydrophobic groups (Fig. 4). A trend was clearly apparent for surfactants with low HLB values (e.g. more hydrophobic) to have greater effects on naloxone skin penetration. However, there was not a general relationship for all surfactants between HLB value and naloxone flux. For example, Poloxamer 188 (HLB = 29.0) and Poloxamer 401 (HLB = 0.5) had similar effects on naloxone flux.

The two amphoteric surfactants tested only slightly increased naloxone flux. The two cationic surfactants examined, both of which are known skin irritants, increased flux significantly.

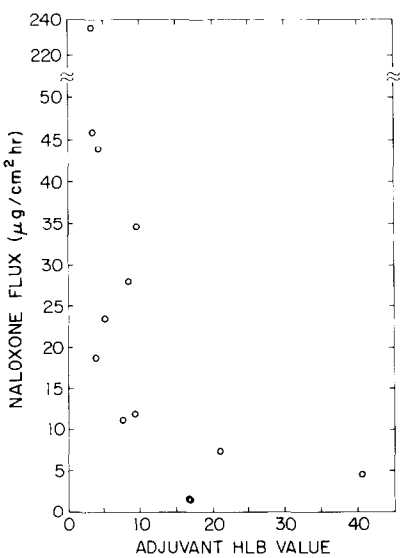

Fig. 4. Naloxone flux as a function of the hydrophil–lipophil balance (HLB) value of the adjuvant, for adjuvants with laurate hydrophobic groups. The adjuvant concentration in propylene glycol was 10%.

A number of sulfoxides and amides known to act as skin penetration enhancers were also evaluated. Decylmethylsulfoxide was a very effective skin penetration enhancer for naloxone, whereas dimethylsulfoxide was not. Urea and dimethylacetamide had no effects on naloxone flux. Diethyltoluamide increased flux slightly. Generally, solvents like DMSO and DMA must be at higher concentrations to influence skin permeability. Azone increased flux approximately 15-fold. The effects of the pyrrolidones were dependent on the substituent group on the nitrogen atom. Although N-methylpyrrolidone (NMP) has been frequently used as a skin penetration enhancer (e.g. Akhter and Barry, 1985), naloxone flux was unaffected by 10% NMP. Higher concentrations of NMP did, however, increase naloxone penetration (data not shown). The most effective pyrrolidone skin penetration enhancers tested had cocoalkyl [1] and tallowalkyl [2] hydrophobic groups. To the best of our knowledge, these agents have not been previously used to promote percutaneous absorption. The relationship between flux and the hydrophobic group of the enhancer is consistent with results for the other classes of compounds. That is that C_{12} and C_{18} unsaturated hydrophobic tails maximize penetration enhancement.

Influence of vehicle

The penetration enhancing effects of lauric acid, lauryl alcohol, and sodium lauryl sulfate were also examined using vehicles other than propylene glycol. Results are summarized in Table 2. In the absence of a penetration enhancer, naloxone flux was similar using propylene glycol, PEG400, or mineral oil as the vehicle. This would be expected when: (1) the thermodynamic activity of the drug is the same in each vehicle (saturated solution); and (2) the vehicles do not alter the barrier properties of skin (Higuchi, 1960). Naloxone flux values from saturated solutions of isopropanol and isopropyl myristate were significantly higher than with the other vehicles. It could thus be inferred

[1] Approximate composition: $C_8 = 5\%$, $C_{10} = 10\%$, $C_{12} = 59\%$, $C_{14} = 17\%$, $C_{16} = 9\%$ (GAF product literature).

[2] Approximate composition: $C_{18\,sat.+unsat.} = 62\%$, $C_{16sat.} = 34\%$, lower alkyl = 4% (GAF product literature).

TABLE 2

EFFECTS OF LAURIC ACID, LAURYL ALCOHOL, AND SODIUM LAURYL SULFATE ON NALOXONE SKIN PENETRATION USING VARIOUS VEHICLES CONTAINING 10% ADJUVANT AND NALOXONE IN EXCESS OF SATURATED SOLUBILITY

Vehicle	Naloxone flux ($\mu g/cm^2 \cdot h$)			
Adjuvant:	None	Lauric acid	Lauryl alcohol	Na lauryl sulfate
Propylene glycol	1.6 ± 0.4	235.2 ± 29.9	45.8 ± 2.4	4.6 ± 0.9
Isopropanol	16.6 ± 4.7	160.6 ± 60.0	28.4 ± 11.8	31.5 ± 19.8
PEG 400	1.8 ± 0.6	46.1 ± 25.3	12.2 ± 5.4	1.6 ± 0.5
Mineral oil	1.3 ± 0.3	18.8 ± 6.4	11.1 ± 2.7	42.4 ± 32.3
Isopropyl myristate	7.7 ± 0.1	20.0 ± 3.0		

that isopropanol and isopropyl myristate increased skin permeability. Isopropanol (Coldman et al., 1969) and isopropyl myristate (Bronaugh et al., 1981) were previously shown to increase skin permeability to other solutes.

The addition of 10% lauric acid or lauryl alcohol to each of the four vehicles increased naloxone flux, but the greatest increases were with propylene glycol. In propylene glycol and isopropanol, sodium lauryl sulfate approximately doubled naloxone flux, and had no effect when dissolved in PEG400. However, in a mineral oil vehicle, sodium lauryl sulfate had a more significant effect on naloxone flux. From these results, it is apparent that the effects of penetration enhancers are dependent on the vehicle.

Concentration / effect relationships

Naloxone skin penetration was evaluated as a function of lauric acid or lauryl alcohol concentration, using various penetration enhancer/propylene glycol concentrations. These results are illustrated in Fig. 5. 1% lauric acid only slightly increased naloxone flux, relative to the propylene glycol control, but with further increases to 2.5% and 5% concentrations, flux increased tremendously. Maximum flux was observed using 20% lauric acid. The most effective lauryl alcohol concentration was 5%. Higher adjuvant concentrations decreased flux, possibly due to a reduction of the skin/vehicle partition coefficient of naloxone.

Partition coefficients

The solubility of naloxone base in lauric acid/

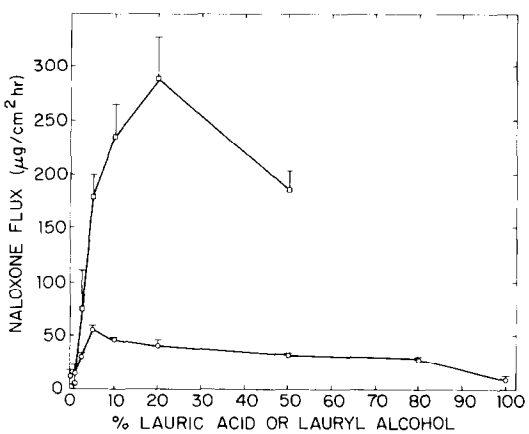

Fig. 5. Concentration dependence of the effects of lauric acid (□) and lauryl alcohol (○) on naloxone skin penetration, using propylene glycol as the solvent.

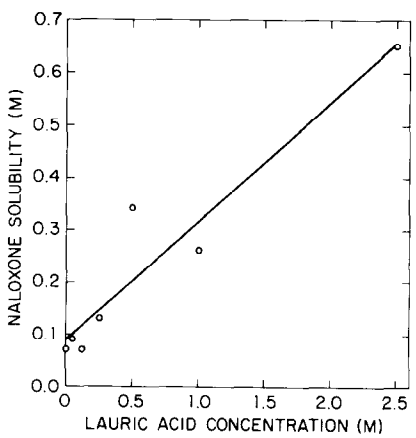

Fig. 6. Effect of lauric acid concentration in propylene glycol on naloxone base solubility.

propylene glycol vehicles was proportional to the concentration of lauric acid (Fig. 6). It seemed possible that naloxone base solubilization by lauric acid could be due to the formation of a charge transfer complex. This could contribute to the increased naloxone skin penetration if the complex had a higher skin/vehicle partition coefficient (K_p) than free naloxone. Increased naloxone solubility could have also been due to micelle formation. Fatty alcohols had only minor effects on naloxone solubility. To examine whether increased naloxone flux might have been due to formation of a complex with a higher K_p, the effect of lauric acid on naloxone K_p was determined. The K_p for isopropyl myristate/propylene glycol was 0.17, and that for isopropyl myristate/10% lauric acid in propylene glycol was 0.15.

Discussion

Naloxone skin penetration rates were determined using various vehicles, and in the presence of numerous adjuvants which were considered potential skin penetration enhancers. Some of these agents markedly increased naloxone flux, while others had little or no effects. This prompts questioning: (a) the mechanisms of enhancement; and (b) whether skin penetration promoting effects are selective for certain drugs.

Specificity can be addressed by examining the literature on these skin penetration enhancers, where different diffusing solutes were studied. Maximum naloxone flux was observed using fatty acid or fatty alcohol/propylene glycol vehicles. In the saturated fatty acid and alcohol series, the most effective penetration enhancers had 12 carbon atoms. Unsaturated C_{18} acids and alcohols were more effective enhancers than the corresponding saturated acid or alcohol. Oleic acid and oleyl alcohol (0.1 M in propylene glycol) have been used previously to increase the human skin penetration of salicylic acid (Cooper, 1984) and acyclovir (Cooper et al., 1985). Similarly, oleic acid (5% in propylene glycol) increased the penetration of both mannitol and hydrocortisone (Bennett and Barry, 1985). However, neither lauric acid or capric acid (0.1 M in propylene glycol) had much effect on salicylic acid skin penetration (Cooper, 1984). Metronidazole and estradiol penetration from vehicles containing equal parts of propylene glycol and a $C_{8\text{-}18}$ fatty alcohol was determined in another study (Mollgaard and Hoelgaard, 1983). Metronidazole penetration was not significantly affected by any of the fatty alcohols, but estradiol penetration was promoted by palmityl and stearyl alcohols. $C_{8\text{-}14}$ alcohols did not increase estradiol penetration. Collectively, these reports suggest some measure of selectivity for fatty acid and fatty alcohol skin penetration enhancers.

Several agents known to be skin penetration enhancers had minor or no effect on naloxone skin permeability when dissolved in propylene glycol. These include sodium lauryl sulfate, sodium laurate, N-methylpyrrolidone and dimethylacetamide. Cooper (1982) reported that sodium lauryl sulfate increased the skin penetration of urea and pentanol 8300-fold and 7-fold, respectively. The effects of other enhancers, including, for example, PEG10 laurate (Walters et al., 1984) and 2-pyrrolidone (Southwell and Barry, 1983) are also apparently greater for polar solutes than for nonpolar solutes. Additional confounding variables in comparing these studies, however, are differences in the vehicle and adjuvant concentrations, both of which can significantly influence the effectiveness of a skin penetration enhancer, as we have demonstrated.

A number of mechanisms for promotion of skin permeability can be proposed. These include: increasing drug solubility in skin; dissolving skin lipids; altering the conformation or denaturing skin proteins, e.g. keratin; disruption of water structure in skin; and increasing membrane fluidity.

These are not necessarily separate actions, since several of these effects may be operative in concert. For example, Scheuplein (1970) has proposed that organic solvents extract lipids, thus creating holes; but that this also results in a loss of water binding capacity. He further suggested that hydrogen-bonding solvents, like dimethylsulfoxide, displace structured water in the membrane, and that anionic surfactants disrupt protein structure, which

also results in a loss of water binding capacity. Akerman et al. (1979) also proposed that aliphatic and cyclic amides, including dimethylacetamide and N-methylpyrrolidone, displace bound stratum corneum water and thus increased the penetration of lidocaine. Cyclic amides with a hydrophobic tail (e.g. N-alkylpyrrolidones and Azone) probably have additional effects on other membrane components, acting as surfactants as well as solvents. It was recently reported that Azone treatment of human stratum corneum was associated with removal of lipids, as indicated by differential scanning calorimetry (Goodman and Barry, 1985).

Initially we suspected that fatty acids might promote naloxone skin penetration by increasing its solubility in skin (partitioning into skin). Fatty acids increased naloxone solubility in propylene glycol, possibly by complexation. However, the isopropyl myristate/propylene glycol partition coefficient of naloxone was not increased in the presence of lauric acid. Fatty acids and fatty alcohols apparently increase flux by altering the diffusion coefficient rather than K_p. The mechanisms of effect of fatty acids and fatty alcohols on skin permeability is not known.

One intriguing aspect of this study is that maximum skin penetration enhancement was observed with C_{12} saturated hydrophobic groups, and that agents with unsaturated groups were more effective than saturated ones. This relationship had not been previously described for fatty acids and alcohols affecting skin. However, similar phenomena have been described for other enhancers or membranes. In the alkyl methyl sulfoxide series, C_{10}MSO was a more effective enhancer of nicotinic acid skin penetration than DMSO, C_6MSO, C_{12}MSO, or C_{14}MSO (Sekura and Scala, 1972). For a series of polyethylene alkyl ethers, maximum effects were seen with dodecyl hydrophobic groups for hemolysis of red blood cells (Zaslavsky et al., 1978), absorption of paraquat through the gastric mucosal membrane (Walters et al., 1981), and methyl nicotinate flux through hairless mouse skin (Walters and Olejnik, 1983). Oleyl ethers were more effective than stearyl ethers. N-alkylpyrrolidones also appeared to exhibit this relationship in promoting naloxone skin permeation.

At least two hypotheses have been proposed to explain why C_{12} hydrophobic groups have maximum effects on membranes. Florence et al. (1984) suggested that increasing the carbon chain length within a homologous series increases the lipophilicity, but decreases the critical micelle concentration. C_{12} hydrophobic groups have the greatest membrane penetration because of an optimal balance of partition coefficient and monomer concentration. Another theory was proposed by Dominguez et al. (1977). They suggested that surfactants do not necessarily adopt a linear structure in skin, but rather form a coiled, "open-cyclohexane" structure. The molecular size of the surfactants forming these "open-cyclohexane" structures was postulated to be minimum when the hydrophobic chain is C_{12}. Minimizing molecular size favors increased membrane penetration.

It is also known that lipids of like structures pack tightly together, but mixtures of long and short chain lipids, or saturated and unsaturated lipids, form loosely organized structures (Small, 1984). The most abundant stratum corneum lipids are free fatty acids, triglycerides, cholesterol, and ceramides. The majority of these lipids, including the free fatty acids, have 16 or more carbon atom hydrophobic groups (Elias, 1983). One could hypothesize, therefore, that the introduction of shorter fatty acid chains disrupts the crystalline lipid packing and results in a more fluid and permeable membrane.

In conclusion, agents to increase naloxone penetration through human skin have been identified. Generally, penetration enhancing effects are via alteration of the normal skin structure and could be expected to be associated with an inflammatory response. The next step in applying this information to practice, for transdermal or topical naloxone administration, is to optimize the penetration enhancement while minimizing skin irritation.

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