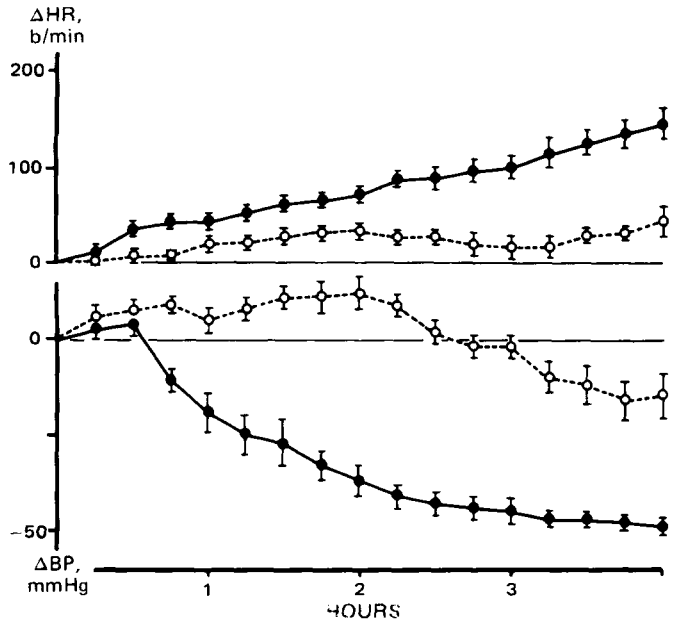

Figure 1—*Influence of a lyophilized ethanol extract of leaves of* Cecropia obtusifolia *on the blood pressure and heart rate of anesthetized rats. Also shown are the changes in these parameters observed in animals receiving the vehicle (15% propylene glycol). Circles correspond to means of six experiments; vertical lines denote standard errors. Key: (●—●) extract, 10 mg/kg; (○- - -○) vehicle.*

propylene glycol concentration of 15%. Groups of six rats received the extract at intravenous doses of 3.1, 10, or 31 mg/kg; an additional group received the vehicle.

The dose of 10 mg/kg produced a slowly developing fall in blood pressure, which began 45 min after injection and reached a maximum at ~3 hr (Fig. 1). This was accompanied by a progressive increase in heart rate. Rats receiving the vehicle showed a slight tachycardia and a decrease in blood pressure toward the end of the 4-hr observation period. The 31-mg/kg dose (not shown) produced a virtually identical hypotensive response and a smaller rise in heart rate; the 3.1-mg/kg dose (not shown) elicited changes similar to those seen in the vehicle-treated animals.

The blood pressure-lowering effect of relatively low doses of lyophilized ethanol extracts of *C. obtusifolia* leaves is interesting in view of its delayed onset and long duration. Such characteristics are theoretically desirable in an agent potentially useful in the treatment of arterial hypertension. Studies are continuing to confirm this effect in more suitable models of hypertension and to identify the active principle involved.

(1) A. Gilbert and P. Carnot, *Bull. Sci. Pharm.*, **11**, 200 (1905).
(2) F. Gstirner and H. Syring, *Arch. Pharm.*, **294**, 783 (1961).

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Received October 14, 1981.
Accepted for publication December 31, 1981.

Effect of Propylene Glycol on Subcutaneous Absorption of a Benzimidazole Hydrochloride

Keyphrases □ Propylene glycol—effect on subcutaneous absorption of a benzimidazole hydrochloride □ Absorption, subcutaneous—effect of propylene glycol on subcutaneous absorption of a benzimidazole hydrochloride □ Pharmacokinetics—effect of propylene glycol on subcutaneous absorption of a benzimidazole hydrochloride

To the Editor:

In the field of parenteral preparations, several water-miscible nonaqueous solvents are known to enhance either the stability or solubility of certain drugs. Reviews on the subject are available (1, 2). A third use of these nonaqueous solvents is to alter the absorption rate of the drug from the injection site. Absorption rates of several intramuscularly administered drugs were shown to decrease when the ethanol content of each preparation increased (3). This inhibitory effect was attributed to the combined effects of an increased viscosity of the vehicle and a decreased connective tissue permeability in the presence of ethanol (3). In systems involving propylene glycol, glycerin, or polyethylene glycol 400 as a cosolvent, the viscosity increased was found to be solely responsible for absorption rate reduction of intramuscularly administered isonicotinamide (4). A similar viscosity effect was revealed from a comparison of the duration of action of a prostaglandin administered subcutaneously to beagles in polyethylene glycol 400 and in water (5). However, these past studies investigated only nonionic drugs. Yet, many parenteral drugs are soluble salts of weak acids or weak bases. Very little is known about how the water-miscible nonaqueous solvents might affect the absorption rate of a drug delivered in a salt form. This communication reports the effect of propylene glycol on the subcutaneous absorption of a benzimidazole hydrochloride, 5(6)-isobutylsulfinyl-2-carbomethoxyaminobenzimidazole hydrochloride (I).

An aqueous solution and a propylene glycol–water (1:1) solution of 2-^{14}C-I (1.01 μCi/mg) were made with distilled water and propylene glycol, USP, at 100 mg/ml equivalent to the free base of I. The propylene glycol solutions of 2-^{14}C-I were made at 50 and 75 mg/ml. These solutions were administered subcutaneously to six heifers at 5 mg/kg free base equivalent. The two propylene glycol solutions, 50 and 75 mg/ml, were administered to groups 1 and 2, three heifers in each group, respectively. On the eighth day postinjection, the same groups 1 and 2 were administered the propylene glycol–water solution and the aqueous solution, respectively. In all cases, blood was drawn periodically into heparinized tubes following each administration. Plasma was obtained immediately after collection and frozen until analyzed. Total radioactivity in the plasma was determined by liquid scintillation counting[1]. The results are reported as free base equivalents (Fig. 1). Each point represents a mean plasma concentration of three animals. Vertical bars represent the standard error of each mean.

Figure 1 exhibits an apparent trend of relative absorption rate in the decreasing order for the four injections tested: 75 mg/ml propylene glycol solution >50 mg/ml

[1] LS 8100, Beckman Instruments, Inc.

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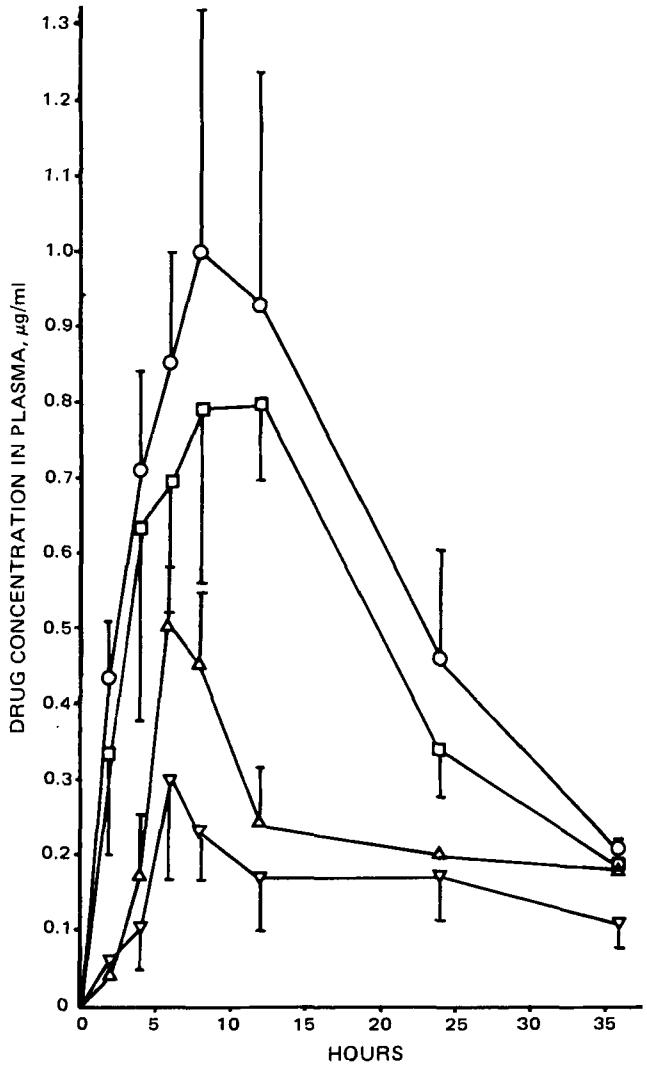

Figure 1—*Plasma concentration of I in heifers. Key: ○, 75 mg/ml propylene glycol solution; □, 50 mg/ml propylene glycol solution; △, 100 mg/ml propylene glycol–water (1:1) solution; and ▽, 100 mg/ml aqueous solution.*

propylene glycol solution >100 mg/ml propylene glycol–water (1:1) solution >100 mg/ml aqueous solution. The absorption rate difference between the two propylene glycol solutions revealed that concentration and/or injection volume had some effect on the subcutaneous absorption of I. Since the dose was kept constant, the injection volume varied inversely with the concentration. For a given increase in the injection volume, there exists a disproportionate ratio between increase in surface area and the increased volume. Therefore, from the passive diffusion standpoint, the smaller the injection volume, the faster the absorption. Atropine (6), sodium ion (7), sugars (8), testosterone (9), and aminoglycosides (10) were all found to be absorbed more rapidly when the compounds were administered in smaller injection volumes. This injection volume effect has been reviewed previously in review articles on intramuscular and subcutaneous injections (11, 12). The injection volume effect appears to be responsible for the rate difference between the absorption of I from the two propylene glycol solutions. However, the effect is ambiguous when the dose volume is relatively small. It was reported (4, 13, 14) that the intramuscular

Table I—Pharmacokinetic and Physicochemical Parameters of the Solutions Investigated

Solutions[a]	C_{max}, μg/ml	AUC, μg/ml hr	1/Viscosity,[b] cp^{-1}	Solubilities, mg/ml I	Solubilities, mg/ml Free Base
A	1.03 ± 0.30	21.29 ± 5.71	0.04	89.9	21.7
B	0.89 ± 0.19	17.10 ± 3.25	0.04	89.9	21.7
C	0.50 ± 0.14	8.60 ± 2.34	0.25	130.0	4.17
D	0.30 ± 0.08	5.61 ± 2.15	1.45	v. soluble	0.44

[a] A = 75 mg/ml propylene glycol solution of I; B = 50 mg/ml propylene glycol solution of I; C = 100 mg/ml propylene glycol-water (1:1) solution of I; D = 100 mg/ml aqueous solution of I. [b] From ref. 4.

absorption of isonicotinamide was independent of the injection volume which ranged from 5 to 20 μl. It was postulated that the effective absorption area might not vary in the case of small injection volume ranging from 5 to 20 μl. In yet another case, a reversed relationship between the injection volume and the absorption rate of I was observed in rabbits that were injected subcutaneously 0.5, 1.0, and 2.0 ml of a propylene glycol solution of I (15). The authors attributed this deviation from the result predicted by diffusion controlled absorption to the precipitation of I at the interface of the injected solution and surrounding tissue.

From the plasma concentration curves shown in Fig. 1, the following can be observed: the drug is absorbed faster from the propylene glycol solution than from the aqueous solution, the absorption rate of I from the propylene glycol–water solution is intermediate between those from the propylene glycol and the aqueous solution. These results at first may seem paradoxical to the previous finding (4) that propylene glycol, *via* its contribution to vehicle viscosity, inhibits intramuscular absorption. One could speculate that factors affecting intramuscular absorption might not be applicable to subcutaneous absorption. Nevertheless, the viscosity effect on subcutaneous absorption was shown to be operative for polyethylene glycol 400 solution of a prostaglandin (5). The paradox might be explained by the following analysis. Table I summarizes the maximum plasma concentration (C_{max}) and the area under the concentration–time curve (AUC) for the curves shown in Fig. 1. Also listed are solubilities of I and its free base in the respective vehicles. From Table I it appears that both C_{max} and AUC can be correlated to the free base solubility. Because the pKa and the aqueous solubility of I are low (3.4 and 0.44 mg/ml, respectively), it is likely that I is converted to its free base and precipitated to some degree at the injection site due to the infiltration of tissue fluid that has a pH of 6.0 (12). Consequently, the higher the free base solubility in the vehicle, the more available the drug for absorption. In the case of propylene glycol injection, the ionized drug concentration will decrease due to neutralization; however, the free base species would be maintained because of the relatively high solubility of the free base in propylene glycol. In the case of the aqueous injection, both the salt species and the free base species would decrease because of neutralization and precipitation. The change in drug solubility is apparently the predominant factor governing the absorption rate of I in the present study. Therefore, absorption of I by subcutaneous injection is enhanced, rather than inhibited, by propylene glycol.

(1) A. J. Spiegel and M. M. Noseworthy, *J. Pharm. Sci.*, **52,** 917 (1963).
(2) K. S. Lin, J. Anschel, and C. J. Swartz, *Bull. Parenter. Drug Assoc.*, **25,** 40 (1971).
(3) H. Kobayashi, Y. Miyoshi, K. Kitamura, Y. Yoshizaki, S. Muranishi, and H. Sezaki, *Chem. Pharm. Bull.*, **25,** 2862 (1977).
(4) K. Kakemi, H. Sezaki, K. Okumura, H. Kobayashi, and S. Furusawa, *ibid.*, **20,** 443 (1972).
(5) B. H. Vickery, G. I. McRae, J. S. Kent, and R. V. Tomlinson, *Prostaglandins Med.*, **5,** 93 (1980).
(6) H. Schiriftman and A. A. Kondritzer, *Am. J. Physiol.*, **191,** 591 (1957).
(7) G. F. Warner, E. L. Dobson, N. Pace, M. E. Johnston, and C. R. Finney, *Circulation*, **8,** 732 (1953).
(8) R. B. Sund and J. Schen, *Acta Pharmacol. Toxicol.*, **21,** 313 (1964).
(9) T. Tanaka, H. Kobayashi, K. Okumura, S. Muranishi, and H. Sezaki, *Chem. Pharm. Bull.*, **22,** 1275 (1974).
(10) M. Pfeffer and D. R. Van Harken, *J. Pharm. Sci.*, **70,** 449 (1981).
(11) B. E. Ballard, *ibid.*, **57,** 357 (1968).
(12) F. L. S. Tse and P. G. Welling, *J. Parenter. Drug Assoc.*, **34,** 409 (1980).
(13) K. Kakemi, H. Sezaki, K. Okumura, C. Takada, and S. Furusawa, *Chem. Pharm. Bull.*, **19,** 2058 (1971).
(14) K. Kakemi, H. Sezaki, K. Okumura, and S. Ashida, *ibid.*, **17,** 1332 (1969).
(15) J. S. Kent, R. V. Tomlinson, C. M. Ackley, and J. Hsu, *Drug Dev. Ind. Pharm.*, **7,** 261 (1981).

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Received December 3, 1981.
Accepted for Publication December 30, 1981.
The authors thank Vickie L. Cain for her technical assistance and Dr. B. Poulsen for his support and helpful comments.

BOOKS

REVIEWS

Antitumor Agents Based on Natural Product Models. Edited by JOHN M. CASSADY and JOHN D. DOUROS. Academic, 111 Fifth Ave., New York, NY 10003. 1980. 500 pp. 15 × 23 cm.

This text is volume 16 of *Medicinal Chemistry, A Series of Monographs*. The emphasis of the book is on lead or novel antineoplastic agents, structure–activity relationships, modes of action, and toxicology of natural products. The choice of agents which is discussed in the monograph is rational and appropriate for the scope of the text. The book serves the purpose of assimilating diverse topics on natural product antineoplastic agents of clinical importance. In general, the text is well-written, concise and well-referenced, and includes pertinent structures, synthetic schemes, and biological data. The text is written with emphasis on the current development or status of a given group of agents and states scientific areas where further development is required.

The book is divided in the following contributions by individual authors:

Chapter 1, "The Development of New Antitumor Anthracyclines" (F. Arcamone), details the basic chemical modifications at the C-9, C-13, and C-14 of the amino sugar residue and of the chromophore of anthraquinone comparing the antitumor activity against HeLa cell, L-1210, P-388, and gross leukemia growth.

Chapter 2, "Trichothecanes" (T. W. Doyle and W. T. Bradner), discusses the history, mechanism of action, toxicity, metabolism, bioassay, cytotoxicity, and structure–activity relationships for antitumor activity in the P-388, L-1210, and B-16 tumor models.

Chapter 3, "Nucleosides" (M. Ohno), summarizes the structure–activity relationships of C- and N-pyrimidine nucleosides required to block the growth of tumors, bacteria, and viruses as evaluated by several investigators.

Chapter 4, "Mitomycins" (W. A. Remers), relates the history, chemical properties, mode of action, and structure–activity relationships for antibacterial and antitumor activity in the L-1210 and P-388 tumors, and the newly synthetic analogues of mitomycin.

Chapter 5, "Recent Progress in Bleomycin Studies" (H. Umezawa), deals with the chemistry and biosynthesis of bleomycin and phleomycin, including a revised structure of bleomycin, copper and iron complexes of bleomycin, the mechanism of action against squamous cell carcinomas, and other therapeutic uses of the agents.

Chapter 6, "Streptozocin" (P. F. Wiley), reviews the fermentation and isolation processes of streptozocin from bacterial cultures, its pharmacology, toxicology, carcinogenicity, mutagenicity, antibacterial, and antineoplastic modes of action, chemical studies, and the structure–activity relationships of several analogues.

Chapter 7, "Terpenoid Antitumor Agents" (J. M. Cassady and M. Suffness), correlates the structures, possible modes of action, and structure–activity relationships in the KB cytotoxicity screen of NCI of mono- and sesquiterpenes, diterpenes, bufadienolides, cardenolides, with anolides, cucurbitacins, and quassinoids.

Chapter 8, "Dimeric Catharanthus Alkaloids" (K. Gerzon), surveys the history, clinical observations, assay methods, mode of action, toxicity, polarity, and structure–activity relationships of vinblastine and vincristine, including a discussion of chemical modification of vinblastine.

Chapter 9, "Podophyllotoxins" (I. Jardine), discusses the history, clinical aspects, structures and chemical synthesis, and modes of action of podophyllotoxins, VM26, VP16-213, and steganacin against the P-815 mastocytoma and L-1210 leukemia cell growth.

Chapter 10, "Maytansinoids" (Y. Komoda and T. Kishi), reviews the isolation of natural and chemical synthesis of novel derivatives of maytansinoids and antitumor activity, toxicity, and effects on cellular growth and biochemical parameters.

Chapter 11, "Harringtonine and Related Cephalotaxine Esters" (C. R. Smith, Jr., K. L. Mikolajczak, and R. G. Powell), relates the characteristics, configuration, and antineoplastic activity of cephalotaxine and its esters. Total synthesis of cephalotaxine, chemical conversion to its naturally occurring esters, biosynthesis of ester analogues and structure–activity relationship against P-388 and L-1210 tumor growth are reviewed.

Chapter 12, "Camptothecin" (M. E. Wall and M. C. Wani), covers the naturally occurring, total and semisynthesized camptothecin analogues, antitumor activity, effects on RNA and DNA components of the cell, and structure–activity relationships.

Chapter 13, "Microbial Transformation as an Approach to Analogue Development" (J. P. Rosazza), offers a general discussion of the use of microorganisms to transform metabolic compounds to new, highly active antitumor agents. Examples used for transformation include bacterial and plant natural products and miscellaneous agents.

Chapter 14, "Miscellaneous Natural Products With Antitumor Activity" (M. Suffness and J. Douros), surveys a series of antitumor agents

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