The plasma concentration (C) *versus* time (t) curve for a drug obeying linear kinetics can be described by:

$$C = \sum_{l=1}^{n} A_l e^{-\lambda_l t} \quad \text{(Eq. 1)}$$

following a single dose, or by:

$$C_N = \sum_{l=1}^{n} A_l \left(\frac{1 - e^{-N\lambda_l \tau}}{1 - e^{-\lambda_l \tau}}\right) e^{-\lambda_l t} \quad \text{(Eq. 2)}$$

following the administration of multiple doses at a fixed time interval of τ. In Eq. 2, C_N is the plasma concentration during a dosing interval at any time following the Nth dose. Once steady state is achieved, the concentration (C_{ss}) is given by:

$$C_{ss} = \sum_{l=1}^{n} A_l \left(\frac{1}{1 - e^{-\lambda_l \tau}}\right) e^{-\lambda_l t} \quad \text{(Eq. 3)}$$

The fraction of the steady-state concentration (f_{ss}) can be defined as the ratio of the average plasma concentration during the Nth dosing interval ($\overline{C}_N$) to the average plasma concentration at steady state ($\overline{C}$), that is:

$$f_{ss} = \overline{C}_N / \overline{C} \quad \text{(Eq. 4)}$$

where

$$\overline{C}_N = AUC_N / \tau \quad \text{(Eq. 5)}$$

and

$$\overline{C} = AUC / \tau \quad \text{(Eq. 6)}$$

AUC_N and AUC are the areas under the plasma concentration–time curves during the Nth dosing interval and at steady state, *i.e.* $\int_0^\tau C_N\,dt$ and $\int_0^\tau C_{ss}\,dt$, respectively. Integrating Eqs. 2 and 3 from time zero to τ, substituting these values for AUC_N and AUC in Eqs. 5 and 6, and solving for f_{ss} in Eq. 4 using the resulting values for $\overline{C}_N$ and $\overline{C}$ yields:

$$f_{ss} = \frac{\sum_{l=1}^{n} A_l (1 - e^{-N\lambda_l \tau})/\lambda_l}{\sum_{l=1}^{n} A_l/\lambda_l} \quad \text{(Eq. 7)}$$

This relationship for f_{ss} can be expanded to give

$$f_{ss} = \frac{\sum_{l=1}^{n} A_l/\lambda_l - \sum_{l=1}^{n} A_l e^{-N\lambda_l \tau}/\lambda_l}{\sum_{l=1}^{n} A_l/\lambda_l} \quad \text{(Eq. 8)}$$

The total area under a plasma concentration *versus* time curve following a single dose of a drug equals $\Sigma_{l=1}^{n} A_l/\lambda_l$ (*i.e.*, the integral of Eq. 1), therefore,

$$f_{ss} = \frac{AUC - \sum_{l=1}^{n} A_l e^{-N\lambda_l \tau}/\lambda_l}{AUC} \quad \text{(Eq. 9)}$$

Furthermore, the integral of Eq. 1 from time t to ∞ provides an expression for the area under a plasma concentration *versus* time curve following a single dose from time t to ∞, AUC_t^∞:

$$AUC_t^\infty \sum_{l=1}^{n} A_l e^{-\lambda_l t}/\lambda_l \quad \text{(Eq. 10)}$$

Because $N\tau$ in Eq. 9 equals the time since the beginning of dosing, *i.e.*, t, AUC_t^∞ can be substituted for $\Sigma_{l=1}^{n} A_l e^{-N\lambda_l \tau}/\lambda_l$ in Eq. 9 to yield:

$$f_{ss} = \frac{AUC - AUC_t^\infty}{AUC} = \frac{AUC_0^t}{AUC} \quad \text{(Eq. 11)}$$

Therefore, the fraction of steady state reached at time t after initiation of a multiple dosing regimen can be determined by knowing the areas, AUC and AUC_t^∞ or AUC_0^t obtained from a single dose of the drug. No model has to be assumed to permit the use of Eq. 11 for determining f_{ss}.

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Donald Perrier[x]
College of Pharmacy
University of Arizona
Tucson, AZ 85721

Milo Gibaldi
School of Pharmacy
University of Washington
Seattle, WA 98195

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Hypotensive Activity of *Cecropia obtusifolia*

Keyphrases □ *Cecropia obtusifolia*—ethanol extract, hypotensive activity □ Hypotensive activity—effect of *Cecropia obtusifolia*, ethanol extract

To the Editor:

Cecropia obtusifolia Bertol is a medium-sized tree of the Moraceae family which grows wild in the tropical areas of Mexico. In the traditional medicine of tropical America, different species of *Cecropia* have been credited with a variety of therapeutic properties, such as antitussive, anti-inflammatory, and antidiarrhetic. Since the beneficial effects of extracts of *Cecropia* leaves in the treatment of heart failure were documented in a clinical study (1), it seemed of interest to determine the cardiovascular effects of *C. obtusifolia* in view of its widespread distribution in Mexico.

The material investigated[1] was collected in the area of the botanical station of Los Tuxtlas operated by the Institute of Biology of the University of Mexico and located in the Gulf coast state of Veracruz. Two kilograms of the leaves were ground and extracted with hexane in a Soxhlet apparatus. The residue was then treated with ethanol and the resulting extract dried by lyophilization. One portion of the 104-g extract was used for pharmacological studies; the other for further extraction [shown previously (2)]. The results of this work, which led to the isolation and identification of two compounds, will be reported elsewhere.

The cardiovascular activity of the extract was determined in male Wistar rats anesthetized with a 1.8 g/kg ip dose of urethane. Blood pressure and heart rate were recorded continuously, the former with a transducer connected to a cannulated femoral artery and the latter with a tachograph triggered by the pressure pulse. The extract was dissolved in propylene glycol and diluted with isotonic saline to a final concentration of 10 mg/ml, resulting in a

[1] The plant material used in this investigation was identified as *Cecropia obtusifolia* Bertol (Moraceae) by J. I. Calzada, Institute of Biology, National University of Mexico. A specimen (Number MEXU-237314) representing material collected for this investigation is available for inspection at the Herbarium of the Institute of Biology, National University of Mexico.

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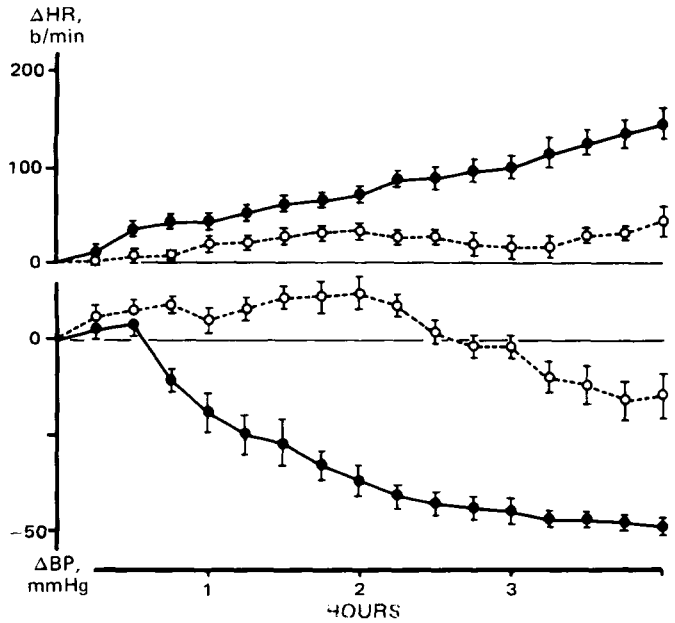

Figure 1—*Influence of a lyophilized ethanol extract of leaves of* Cecropia obtusifolia *on the blood pressure and heart rate of anesthetized rats. Also shown are the changes in these parameters observed in animals receiving the vehicle (15% propylene glycol). Circles correspond to means of six experiments; 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.

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H. Vidrio ˣ
F. García-Márquez
Department of Pharmacology
School of Medicine
J. Reyes
R. M. Soto
Department of Pharmaceutical Chemistry and Natural Products
School of Chemistry
National University of Mexico
Mexico, D. F. 04510

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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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