Biphasic Elimination of Noscapine

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Published data concerning the elimination of noscapine from various species were critically re-examined. It would appear that noscapine is distributed into a third compartment prior to exponential elimination. An analogy between the pharmacodynamics of noscapine and the barbiturate, thiopental, is considered.

NOSCAPINE, an isoquinoline alkaloid of opium, is an antitussive agent which depresses the medullary centers and suppresses the cough reflex. Pharmacological and clinical investigations have confirmed the value of noscapine as a potent nonaddictive cough suppressant (1).

Despite the antiquity of this opium derivative, little is known concerning its absorption, distribution, and elimination in the body. In 1961, Vedsö (2) studied the absorption and excretion of noscapine in man. More recently, Nayak *et al.* (3) investigated the rate of metabolism, urinary excretion, and organ distribution of noscapine in laboratory animals.

Vedsö concluded that the rapid disappearance of noscapine from the blood is attributable to rapid and cumulative tissue uptake. Conversely, Nayak and co-workers claimed that cumulation of the drug in the various tissues does not occur. These investigators indicated that the rapid disappearance of noscapine from the plasma and tissues is due to a rapid, first-order biotransformation. A further consideration of the data of both Vedsö (2) and Nayak *et al.* (3) strongly suggests that the elimination of noscapine involves a more complex mechanism than those postulated in either study.

DISCUSSION

Representative log tissue concentration *versus* time plots of noscapine, after intravenous administration of drug to rats, are shown in Fig. 1. These plots were constructed by utilizing literature data (3). As may be observed in Fig. 1, the blood, kidney, and skeletal muscle data demonstrate linearity after a lag of about 8 min. It is, therefore, apparent that after 8 min., the drug is eliminated from both the tissues and blood in a first-order fashion. In accord with Teorell's model for drug distribution and elimination (4), the rate of elimination of noscapine from the blood is in good agreement with the elimination rate found in the tissues. The half-lives for the elimination of noscapine from the blood, kidney, and muscle were calculated by the method of least squares and were found to be 12, 13, and 15 min., respectively.

Rapid first-order elimination of noscapine has been observed in a number of species. Nayak *et al.* (3) report that the first-order disappearance of noscapine from the blood of both mice and rabbits has a half-life of about 9 min. Vedsö (2), who contended that biotransformation was not involved in the elimination of noscapine, did not attempt to quantify the elimination rate in man. However, his data provide sufficient evidence to indicate that the plasma concentration-time curve contains a postabsorptive semilogarithmic phase. Representative semilog plots are presented in Fig. 2. Contrary to Vedsö's conclusions, the elimination of a significant portion of the noscapine from human plasma follows first-order kinetics with a half-life, according to our calculations, of about 40 min.

Further examination of the plots presented in Fig. 1 reveals an interesting phenomenon. Each of the plots is biphasic, consisting of a very rapid initial elimination component and a significantly slower elimination component; the latter phase is observable about 8 min. after administration. Biphasic elimination of noscapine also appears to occur in the rat brain and liver (3). To interpret the significance of these phenomena it is relevant to consider the pharmacokinetics of distribution after intravenous administration.

Theoretical Considerations of Drug Distribution.—Numerous studies have shown that a semilog plot of plasma concentration *versus* time, after rapid intravenous injections of various substances, demonstrates linearity only after a certain time has elapsed (5). The initial rapid fall in blood concentration is generally attributable to the diffusion of drug from the blood to other body fluids and tissues. The start of the linear portion of the plot is considered to coincide with the steady state of distribution where the apparent volume of distribution has reached a maximum and, thereafter, remains constant. The duration of this initial phase of elimination from the plasma is a function of the drug properties. A highly water-soluble substance, restricted to the extracellular fluid, will rapidly attain steady-state conditions. Drugs which can penetrate to deeper tissues will generally show a more prolonged initial phase prior to exponential elimination.

After intravenous administration, in a two-compartment model system, tissue concentration increases continually to a maximum and, thereafter, declines in a first-order fashion at a rate equivalent to the rate of decline of drug in the plasma. According to the steady-state approximation, the time required for maximum tissue concentration coincides with the time lag before the initiation of exponential elimination of drug from the plasma (5, 6). Furthermore, in the idealized two-compartment system, the fraction of drug in each compartment is independent of amount of drug in the body. Thus, plasma concentration is directly proportional to the amount of drug in the body. For compounds which adhere to

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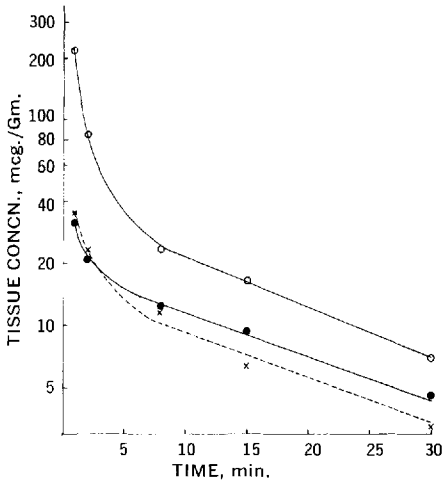

Fig. 1.—Semilog plots for the disappearance of noscapine from various tissues after intravenous administration of 25 mg./Kg. in rats. Plots were constructed with data taken from *Reference 3*. Key: O, kidney; ●, muscle; ×, blood.

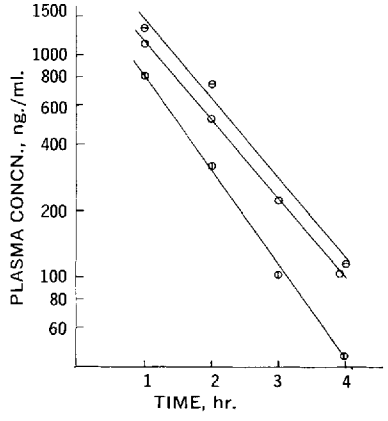

Fig. 2.—Semilog plots for the disappearance of noscapine from the plasma of three humans after oral administration of 250–300 mg. of noscapine chloride. Plots were constructed with data taken from *Reference 2*.

Teorell's model for distribution and elimination, a plot of plasma level, at time t, after intravenous administration *versus* dose, will be rectilinear (5).

Pharmacokinetic Interpretation of Noscapine Data.—Nayak *et al.* (3) state that there is a rapid disappearance of noscapine from the blood concomitant with a rapid uptake by organs perfused by a rich vascular supply. This is evidenced by the fact that drug concentration is maximal, within 1 min. after administration, in the brain, kidneys, lungs, liver, and skeletal muscle. However, as shown in Fig. 1, plasma concentration continues to decline rapidly until about 8 min. after administration. If uptake, by the tissues studied, was responsible for the very rapid initial elimination of noscapine from the plasma, drug concentration in each organ should be maximal at about 8 min. This is obviously not the case.

Although the various tissues studied constitute a compartment separate from the plasma, the rate of distribution between compartments is apparently so rapid that the defined system is kinetically indistinguishable from a one-compartment system.

Despite the fact that noscapine is very quickly distributed into a relatively large volume, it is evident from the data in Fig. 1 that, at the time of maximal tissue level, noscapine has not yet achieved its ultimate apparent volume of distribution. If the initial rapid loss of noscapine from the plasma is simply due to rapid uptake by the tissues studied, the steady-state approximation could be applied at the first minute, and each of the drug concentration-time plots in Fig. 1 could be described by a simple exponential expression. Quite to the contrary, each set of data in Fig. 1 was found to be fitted by an equation which is the sum of two exponentials. Using the method of least squares, the following equations were calculated:

$$C_B = 42e^{-0.80t} + 17e^{-0.057t} \quad \text{(Eq. 1)}$$

$$C_M = 50e^{-1.22t} + 18e^{-0.045t} \quad \text{(Eq. 2)}$$

$$C_K = 700e^{-1.33t} + 37e^{-0.055t} \quad \text{(Eq. 3)}$$

where C_B, C_M, and C_K refer to the concentrations of noscapine, at time t, in the blood, skeletal muscle, and kidneys, respectively.

At this point, it is reasonable to consider why such data are unusual. It is quite possible that many drugs really occupy a three-compartment model and distribution from the plasma into each compartment occurs at a somewhat different rate. Furthermore, sampling may be so spaced that the initial phase or phases of elimination from the plasma is not observed. For example, if Nayak *et al.* (3) had sampled at 10-min. intervals, only a single exponential elimination would be manifest. This interpretation of the noscapine data is in accord with Teorell's model but still leaves two unanswered questions.

First, since the pharmacokinetic evaluation has suggested the existence of a third compartment (real or hypothetical) what is the nature of this compartment? Second, as noted above, since a three-compartment model is not at variance with Teorell's model, one would expect a rectilinear relationship between plasma level and dose. However, as reported by Vedsö (2), noscapine plasma concentration, 2 hr. after oral administration of the drug, increased in a hyperbolic fashion as a function of dose (Fig. 3).

An explicit explanation for the pharmacokinetic behavior of noscapine is not possible without more extensive distribution and metabolism studies. However, the pharmacodynamic properties manifested by the barbiturate thiopental (7) are sufficiently analogous to consider in explaining the noscapine data.

Thiopental, like noscapine, is rapidly eliminated from the plasma and reaches maximal tissue levels in a number of organs, including the brain, liver, and muscle, almost immediately after administration. Nevertheless, plasma concentration continues to decline rapidly for a prolonged period of time after maximal tissue levels are achieved. Although drug concentration is maximal in a number of organs a few minutes after administration of thiopental, steady-state kinetics are not observed for a significant time thereafter (7). After a single 400-mg. dose of the

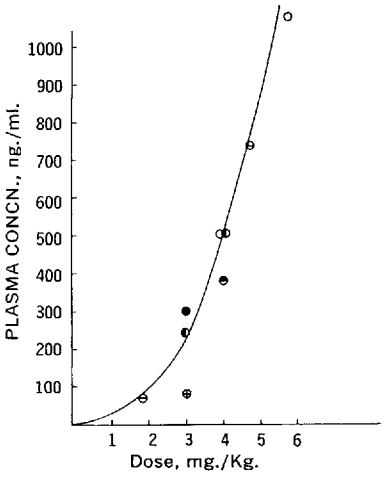

Fig. 3.—Relationship between dose of noscapine chloride and plasma concentration in various individuals 2 hr. after administration. (Taken from *Reference 2.*)

barbiturate to man, plasma levels fall abruptly and subjects awaken in about 10 min. Subsequently, the plasma level declines slowly, 10–15%/hr. (8). This rate reflects the true rate of metabolism of thiopental.

Studies designed to determine the movement of thiopental between plasma and tissue served to clarify this pharmacodynamic phenomenon. After intravenous administration, most tissue, including brain, rapidly take up considerable amounts of thiopental; the tissue levels then decline in parallel with the plasma level. In contrast, the level in fat, initially quite low, rises slowly, and approaches a peak in about 3 hr., when it is then 10 times higher than the plasma level.

The application of the thiopental distribution model to the noscapine data provides a near-perfect explanation of the results, but must remain speculative in the absence of experimental data of noscapine concentrations in adipose tissue. The organs selected by Nayak *et al.* did not include the adrenals or carcass, organs which would provide insight to drug deposition into a fat compartment.

Nevertheless, other analogies existing between noscapine and thiopental provide further support for the proposed hypothesis. The importance of lipid solubility in defining the pharmacological action of thiobarbiturates is emphasized by a comparison of thiopental and pentobarbital, its oxygen analog. Both drugs are distributed to almost the same extent in most tissues, but the concentration of pentobarbital is much less than that of thiopental in adipose tissue because of the decreased lipid solubility of the oxygen analog (8).

Noscapine, like thiopental, is a highly lipid soluble drug (9). An excellent indication of the comparable lipid characteristics of these drugs is provided by a consideration of transport across the blood-brain boundary, a process which is quite dependent on the lipid solubility of the permeating molecule. On the basis of distribution studies, both thiopental and noscapine show rate constants for entry into the central nervous system of about 0.8–1.0 min.$^{-1}$, significantly higher than rate constants observed for such drugs as pentobarbital (about 0.2 min.$^{-1}$), barbital (about 0.05 min.$^{-1}$), and salicylic acid (0.006 min.$^{-1}$) (3, 10). In view of the similar properties of noscapine and thiopental, it is not surprising that both drugs act in the central nervous system, and both show extremely prompt, but very fleeting, therapeutic activity.

Unfortunately, one piece of data does not fit well into the over-all scheme. Vedsö (2) has claimed the existence of a hyperbolic relationship between plasma level of noscapine and dose. Indirect evidence based on repetitive dosing leads one to believe that the hyperbolic relationship does not exist in the case of thiopental. For example, a dog can be anesthetized with a given dose of thiopental, then be allowed to recover, and this procedure can be repeated a number of times without having to reduce the dose to obtain the same depth of anesthesia. Each time, the recovery of the animal is due almost entirely to localization in fat, which acts as a seemingly infinite reservoir (7).

The third compartment proposed for noscapine, be it a fat compartment or not, does not share the ability of the fat compartment for thiopental, to function as a sink. Whether this difference is qualitative or simply a quantitative distinction remains to be determined.

The proposed model, based on fat distribution, is by no means the only possible way to explain the pharmacodynamics of noscapine. There are a number of other models which may be proposed to account for the data (11), including other compartments and complex biotransformation processes. Although these other models are mathematically correct, they do not appear to be as reasonable from physiologic and pharmacologic viewpoints.

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