Review Article

Sedative–Hypnotics

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THE DESIGNATION "sedative–hypnotic" may be one of the most confusing misnomers in modern therapeutics. It does not denote a specific drug action, but rather implies a spectrum of activity which may vary from sedation through hypnosis to general anesthesia and, finally, coma (death). Three of these actions are useful therapeutic goals, and each can be achieved with *any* sedative–hypnotic drug when a suitable dose is chosen. In practice, however, the suitability of a given agent for a specific therapeutic application is determined primarily by pharmacokinetic factors, *i.e.*, the properties of a particular drug with respect to absorption, distribution, metabolism and excretion. Certainly, differences among the specific effects of the various sedative–hypnotic drugs on the central nervous system and other target sites in the body do exist, but our limited understanding of these differences makes evaluation of their clinical importance exceedingly difficult. This review will consider therapeutic objectives and will discuss the effects of pharmacokinetic factors on these objectives. The clinical importance of toxicity (acute and chronic), drug interactions, tolerance, and dependence (psychic and physical) will also be considered.

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I. Therapeutic Goals and Classification of the Sedative–Hypnotic Drugs

A. Therapeutic Uses of Sedative–Hypnotics

From the clinical standpoint, consideration of this class of drugs is facilitated by a definition of therapeutic goals.

1) A sedative drug is expected to calm the patient or allay anxiety, but this fails to define the degree of depression accompanying the sedative state. It lacks quantification since, by way of extremes, it could apply equally well to the patient under halothane anesthesia and to the patient intoxicated by alcohol. Lacking a specific yardstick of CNS depression, it becomes necessary to describe sedative action by observing the operant behavior of the person taking the drug. Conventionally, "sedation" is quantified in the sense that the patient is arousable. Our definition of sedative action in man includes: allaying of anxiety with maintenance of coordinative and motor ability with minimal or no alteration in mentation. Acceptance of the validity of this definition places major limitations on the selection of a proper sedative drug, and perhaps more important, the appropriate dosage, and makes

it imperative for the clinician to apply these criteria carefully when selecting a drug.

2) Hypnosis is the state of sleep. Thus, a hypnotic drug must be capable of producing sleep that approximates the normal physiologic sleep-state. A desirable feature of hypnotic drug action is the limitation of this action to the period of sleep, so that "hangover," which is considered evidence of continued drug effect, is avoided.

3) Certain of the sedative–hypnotic drugs, for example, thiopental and methohexital, in sufficient doses may produce anesthesia. The suitability of an agent as an adjunct to anesthesia relates in large part to its pharmacokinetic properties, which determine rapidity of onset and duration of action.

4) All sedative–hypnotics have anticonvulsant properties, but there is selectivity among agents. The drugs most valuable in the treatment of seizure disorders (particularly grand mal and jacksonian epilepsy) are: phenobarbital; compounds converted to phenobarbital in the body, *e.g.*, mephobarbital (Mebaral); and diazepam. These drugs are characterized by their prolonged anticonvulsant actions at dose levels that are minimally depressant to other CNS functions (cerebration, motor function, etc.).

5) Sedative–hypnotics also differ in their effects on polysynaptic reflexes and internuncial transmission, suggesting the possibility of differences in muscle-relaxing properties. Such differences have not been demonstrated to have clinical importance at present and do not offer a basis for rational selection of one agent over another for the specific purpose of producing muscle relaxation.

B. Chemical Diversity of Sedative–Hypnotics

The chemically heterogeneous nature of the compounds classed as sedative–hypnotic drugs makes it difficult to consider the various agents as prototypes. Table 1 gives some indication of the chemical diversity of the sedative–hypnotics; yet, all of these compounds have CNS-depressant actions that are qualitatively similar. Although not included in the table, marijuana and certain antihistamines are also capable of producing sedative–hypnotic effects; they are excluded as clinically useful sedative–hypnotics by virtue of other properties which make their use difficult or impossible.

Table 1. Chemical Diversity of Commonly Used Sedative–Hypnotics

Chemical Class	Representative Examples
Barbiturates	Hexobarbital (Evipal) Pentobarbital (Nembutal) Phenobarbital (Luminal)
Thiobarbiturates	Thiopental (Pentothal) Methohexital (Brevital)
Piperidinediones	Glutethimide (Doriden) Methyprylon (Noludar)
Carbamates	Ethinamate (Valmid) Meprobamate (Miltown)
Benzodiazepines	Chlordiazepoxide (Librium) Diazepam (Valium)
Quinazolones	Methaqualone (Quaalude)
Alcohols	Chloral hydrate (Ethanol) Chlorobutanol (Chloretone)
Cyclic ethers	Paraldehyde

C. Sedative–Hypnotics vs. Tranquilizers

Other compounds, including the tranquilizers (phenothiazine derivatives and reserpine), are capable of producing CNS depression which may resemble sedative and hypnotic actions. A comparison of the pharmacologic activities of these agents with those of various sedative–hypnotic drugs reveals a number of differences (table 2). From the table it is apparent that our proposed definition of sedative–hypnotic activity does not apply to the tranquilizers. If the desired therapeutic goal is sedation and hypnosis, then the tranquilizers represent a poor choice because of easy arousal at any dose and the high incidence of autonomic and extrapyramidal side-effects at low doses.

Having introduced the term "tranquilizer" into this discussion, we are compelled to object to its use as a modifier or descriptive term for the sedative–hypnotic drugs. As some of the new nonbarbiturate sedative–hypnotic drugs have appeared, *e.g.*, meprobamate and chlordiazepoxide, claims have been made for their efficacy in producing a "tranquilizing"

effect. However, there is little information to support the notion that these compounds are anything but sedative–hypnotic in their actions.

II. Pharmacokinetic Aspects of Sedative–Hypnotic Drugs

Pharmacokinetics is the measurement of concentrations of a primary drug and its metabolites in body fluids and tissues with respect to *time*. The overall pattern of disposition of a drug, *i.e.*, the manner in which it is handled by the body in terms of absorption, distribution, metabolism and excretion, is influenced by its physiocochemical properties. To act within the central nervous system, a drug requires a suitable combination of properties, including a relatively high lipid:water partition coefficient and a low degree of ionization at body *p*H. There appears to be no exception to the rule that membranes are more permeable to the non-ionized form of a compound than to the ionized form. Most sedative–hypnotic drugs are either weak acids (*e.g.*, barbiturates) or weak bases (*e.g.*, benzodiazepines), although carbamates (*e.g.*, meprobamate) and paraldehyde are neutral compounds. A weak acid such as pentobarbital (pK_a 8.1) will be 83 per cent non-ionized, and a weak base, such as diazepam (pK_a 3.5), will be almost 100 per cent non-ionized at a *p*H of 7.4, favoring their passage across the blood–brain barrier. Lipid solubility plays a major role in determining the rate at which a drug penetrates (and leaves) the brain; this property is described operationally as a partition coefficient between a nonpolar organic solvent such as benzene or n-heptane and water. For example, pentobarbital, though less ionized than thiopental at *p*H 7.4, has a much lower partition coefficient (n-heptane:water) and, consequently, penetrates the blood–brain barrier more slowly. Similarly, 55 per cent of barbital (Veronal) exists in the non-ionized form at *p*H values that are physiologic, but the partition coefficient is so low that its rate of entry into the central nervous system is predictably slow, which partially explains the limited therapeutic value of this agent.

The wide variations in the chemical structures of the drugs that have sedative–hypnotic properties endow distinctive physicochemical properties to each agent; these are the basis for differences in the rate and extent of disposition events. Correlation of such differences in drug disposition and, hence, intensity and duration of action, with physicochemical properties of sedative–hypnotics may be of predictive value in the clinical use of these agents.

A. Absorption

Usually, sedative–hypnotic drugs are given orally. The major barrier to transport into plasma is the epithelial lining of the gut, which behaves as a "lipid sieve." In the stomach (*p*H near 1), weakly acidic drugs such as the barbiturates and the piperidinediones (see table 1) are almost completely non-ionized and, hence, are absorbed at rates dependent on lipid solubility. For example, barbital has approximately the same pK_a as amobarbital (Amytal) but is about 40 times less lipid-soluble. Therefore, in equal doses barbital will be absorbed more slowly from the gut and will produce lower plasma levels than amobarbital, offering a further explanation of the limited efficacy of barbital administered orally. A certain degree of water solubility is also desirable for adequate absorption from the gastrointestinal tract. The sodium salts of most barbiturates, including those used as anesthetic adjuncts, such as thiopental, are more water-soluble than the acid forms and, therefore, more readily absorbed from the stomach. Similarly, the extremely low water solubility of glutethimide probably contributes to the slow onset of action characteristic of oral ingestion of the drug. Weakly basic drugs such as chlordiazepoxide and diazepam are most effectively absorbed at or near neutral *p*H in the small intestine or colon.

In some clinical situations it is desirable to administer the sedative–hypnotic drugs parenterally. Obviously the intravenous route is the most rapid and affords the greatest control of rate of administration, features desirable in all anesthetic procedures. In many cases, however, the intramuscular or subcutaneous route is used, and it is often assumed that absorption of drugs from these sites is faster than that from the intestinal tract. This is not necessarily the case for weak acids of high lipid solubility, many of which are absorbed faster from the stomach than from

intramuscular sites. This phenomenon has received little attention in relation to the sedative–hypnotic drugs and, consequently, considerations of choice between oral administration and parenteral routes other than intravenous cannot rationally be made on the basis of any *assumed* differences in rate or extent of absorption.

B. Distribution

During the transport of a drug in the blood a dynamic situation develops in which drug molecules enter and leave tissue phases at rates primarily dependent upon blood flow, concentration gradients and permeabilities. The occurrence of a true equilibrium state must be considered a rarity in view of the continuous interaction of events such as absorption, metabolism and excretion. The kinetics of sedative–hypnotic distribution in man have received little attention, with the result that much information has been extrapolated from data obtained from animals.

In the blood many sedative–hypnotic drugs are bound to plasma proteins, notably albumin and the alpha and beta lipoproteins. It is assumed that extensive protein binding, by reducing the concentration of *free* drug in plasma, limits the ability of a drug to reach tissue sites both for pharmacologic effect and for metabolism, and also restricts glomerular filtration. Much emphasis has been placed on experimental observations of the percentages of drugs bound to plasma proteins. For example, thiopental is 78 per cent bound and thiohexital, 88 per cent. Such data could imply that at any given time following the administration of equal doses of the two drugs, the concentration of free thiopental would be approximately twice that of free thiohexital. Unfortunately, percentage binding figures are meaningless unless qualified by identification of the free drug concentration measured during steady-state conditions, since the degree of fractional binding is inversely proportional to free drug concentration. Apparent steady-state conditions may occur much later than the peak pharmacologic effect; consequently, it is difficult to make valid predictions as to the significance of protein binding in the *pharmacodynamic* actions of this group of agents.

Table 2. Pharmacologic Properties of Sedative–Hypnotics and Tranquilizers

	Sedative–Hypnotics	Tranquilizers
Sedation (low dose)	Yes	Yes
Easy arousal (higher dose)	No	Yes
Antipsychotic	No	Yes
Anticonvulsant	Yes	No
Extrapyramidal effects (parkinsonism-like symptoms)	No	Yes
Anesthesia	Yes	No
Autonomic effects		
Anticholinergic	No	Yes
α-adrenergic blockade	No	Yes
Respiratory depression	Yes	No
Physical dependence	Yes	No

The rates of blood flow to the brain and other tissues contribute markedly to the pharmacodynamic actions of certain barbiturates, notably the thiobarbiturates. For such drugs it is reasonable to assume that the pattern of distribution and redistribution (from one tissue phase to another) is the most important factor governing the observed pharmacologic effects. Following intravenous administration of thiopental or methohexital, the time of onset of central action is primarily related to the physicochemical properties (partition coefficient, pK_a) of the drug. The intensity of hypnotic action is a function of dose, which can also influence duration of action, although the latter is more closely related to the pattern of drug redistribution. Thus, the proportionally high cerebral blood flow, together with favorable physicochemical properties of the drug, is a major determinant of the onset of action of the intravenously administered barbiturates. Rapid redistribution of drugs to lean body tissues is primarily responsible for the short duration of hypnotic action.[1,2] Redistribution to other tissue sites (*e.g.*, fat)[2] and the roles of metabolic inactivation and excretion are of marginal significance with respect to termination of hypnosis and appear more closely related to the duration of posthypnotic sedation. A number of claims have been made that metabolism may play a greater role in awakening from the thiobarbiturates,[4,5] despite the failure of clinicians to find significantly prolonged responses to such agents in patients with hepatic disease.[6] Severe hepatic impairment in

experimental animals, which metabolize the barbiturates at much faster rates than man, can prolong the duration of hypnotic action. However, the metabolic inactivation rates of these agents in man are too low to contribute significantly to cessation of hypnotic action. For example, the metabolism of thiohexital in man is faster than that of any other barbiturate (25 per cent/hour)[7] and cannot reasonably be considered to account for termination of the hypnotic effects, which may last only a few minutes, though it could contribute to the shorter duration of sedation or "hangover." The rates of metabolism of other barbiturates in man, with their usual hypnotic durations when used at conventional clinical doses, are shown in table 3. None is metabolized at a rate commensurate with its duration of hypnotic action. It is suggested that redistribution may be responsible for the termination of hypnotic action of all the clinically useful barbiturates whether they are classed as intravenous, short-acting, or long-acting agents. Nonbarbiturate sedative–hypnotics have been examined much less thoroughly with regard to pharmacokinetic properties. In general, low metabolic rates and minimal urinary excretion of intact drugs are characteristic of such agents, including methyprylon, glutethimide, chlordiazepoxide, diazepam, ethinamate, and meprobamate. Hence, it is quite possible that distribution and redistribution processes are more important than metabolism or excretion in terminating the effects of these agents.

Studies of the transplacental passage of sedative–hypnotic drugs in man are technically difficult, and their significance relative to neonatal function remains uncertain. The principles underlying transfer of a drug across the placental barrier are analogous to those of drug transport from plasma to brain. Lipid-soluble compounds will cross the placental barrier, but the rate of achievement of apparent steady-state conditions between maternal and fetal blood is lower than that for the brain because of the lesser blood flow to the placenta. For example, nine minutes after intravenous administration thiopental has attained only half-equilibration with fetal blood. That alert infants with high Apgar scores may be born to mothers deeply anesthetized with barbiturates may be explained by incomplete equilibration of the barbiturates between fetal and maternal blood. However, the possibility of age-dependent differences in CNS sensitivity to these agents cannot be discounted. Other factors that must be considered are the uptake (and/or metabolism) of the barbiturates by the liver and other tissues and serial dilution of umbilical vein blood before it reaches the fetal brain. In other cases, the neonate may be deeply depressed at birth, which could reflect achievement of barbiturate equilibrium in maternal and fetal blood. Differences in the ratios of lean to other body tissues and the limited metabolic and renal function of the neonate may also contribute to prolonged depression. These observations argue strongly for some degree of conservatism when sedative–hypnotic drugs are administered before and during delivery. Short-acting volatile anesthetics may be preferable for lengthy anesthetic procedures where continuous use of sedative–hypnotics favors the build-up of fetal drug concentrations.

C. Metabolism

In the previous section we suggested that metabolic inactivation of the sedative–hypnotic drugs plays a relatively minor role in the awakening of patients from hypnosis. It cannot be denied, however, that metabolic transformation to less active products is ultimately significant in the total cessation of their effects. The specific aspects of the metabolism of sedative–hypnotics have been reviewed recently[6]; the present discussion is confined to general principles.

The liver is the most important site of metabolism of these drugs. The same physicochemical properties responsible for CNS action render such agents susceptible to hepatic microsomal enzymatic degradation. In general, the agents most rapidly metabolized, such as methitural (Neraval) and methohexital, are more lipid-soluble than those metabolized slowly (phenobarbital). Metabolic inactivation by hepatic enzymes is not confined to barbiturates, but also occurs with paraldehyde, glutethimide, methyprylon, ethinamate, chlordiazepoxide, diazepam, and meprobamate. Usually, metabolism involves the introduction of a polar group into the drug molecule or removal of a nonpolar group, often with subse-

TABLE 3. Barbiturate Metabolism in Man

Drug	Usual Oral Hypnotic Dose (mg)	Rate of Metabolism (Per Cent/Hour)	Reference	Per Cent Excreted Unchanged	Approximate Duration of Hypnosis (min)
Thiohexital	—	25	7	—	—
Methitural (Neraval)	—	20	30	—	—
Methohexital (Brevital)	350–500	15–19	31	—	15–45
Thiopental (Pentothal)	500–700	15	32	—	15–45
Hexobarbital (Evipal)	500–700	13	33	—	15–45
Secobarbital (Seconal)	100–200	2.5	34	—	180–300
Pentobarbital (Nembutal)	100–200	0.5–6	34,35	1	180–300
Phenobarbital (Luminal)	100–200	0.7–1	34,36	27	180–300
Barbital (Veronal)	300–500	—	—	95	—

quent conjugation. In most cases these derivatives are not only pharmacologically less active but more water-soluble, thus facilitating renal excretion. With the exception of phenobarbital and barbital, only minute quantities of sedative–hypnotic drugs are excreted in intact form. It is pertinent, therefore, to consider those factors that influence the metabolism of these agents and their clinical implications.

In experimental animals the metabolism of sedative–hypnotic drugs can be influenced by nutritional status, temperature change, endogenous hormone level (particularly adrenocortical steroids), age, hepatic function, and the concomitant administration of other drugs. Conclusions from animal data are not easily extrapolated to the clinical situation and, unfortunately, there have been no controlled studies in man to determine whether nutrition, temperature, and hormonal influences are major determinants of sedative–hypnotic metabolism. With respect to age, it is well established that fetal, neonatal, and even infant, hepatic enzyme systems may be underdeveloped or absent.[9] Glucuronide synthesis is deficient in the newborn, and it can be anticipated that drugs normally metabolized to a large extent by such conjugation will have prolonged effects when administered to the neonate in the same dose/weight ratio as that used for the adult. The predominant inactivation mechanisms for sedative–hypnotics occur via the microsomal mixed-function oxidase system, this activity also being influenced by age, at least in experimental animals. Extrapolations from animal data and observations from clinical use of barbiturates suggest that these mechanisms may also be underdeveloped at birth, rising to a peak activity in early childhood and declining with age. Logically, therefore, age is an important factor in any consideration of sedative–hypnotic dosage.

Numerous animal studies and a few studies of man [10, 11] have suggested that the durations of action of certain barbiturates may be prolonged when hepatic function is severely impaired. Whether such findings in man are related to decreased drug metabolism, other aspects of drug disposition, or changes in patient sensitivity in certain disease states is unclear. Certainly, many investigations [6] have failed to show a positive relationship between hepatic disease and a reduction in detoxification mechanisms manifest at the clinical level. Only for agents normally metabolized by the liver at very fast rates, such as paraldehyde, has this been well documented.[12] It is possible that a careful study of patients in the post-hypnotic state might reveal prolongation of sedative effects associated with severe hepatic disease. The rate of metabolic inactivation may become more important regarding duration and depth of hypnotic action as a result of cumulative doses of an agent. Continuous administration of drugs which have exceedingly low rates of biotransformation, such as phenobarbital and diazepam, to a patient with major hepatic impairment could result in prolonged hypnosis. Hepatic function may be an important determinant of the rates of onset of a few sedative–hypnotic drugs which are metabolized to active compounds. The alkyl-substituted barbiturates, mephobarbital and metharbital (Gemonil), are metabolized by the liver to phenobarbital and barbital, respec-

tively, with the latter compounds primarily responsible for pharmacologic action. Similarly, although the onset of hypnosis resulting from chloral hydrate may well be due to the drug itself, maintenance of the hypnotic state is the result of biotransformation to trichloroethanol.[13]

It has become increasingly apparent that the influence of one drug on the disposition of another can lead to unexpected pharmacologic responses which may manifest themselves at the clinical level as "drug interactions." A drug may enhance the metabolism of another by enzyme induction, resulting in marked changes in response to the second agent. Laboratory experiments have demonstrated that the barbiturates are particularly active enzyme inducers,[14] and this effect in animals has been extensively described.[15] In man, phenobarbital has been shown to increase the metabolic degradation of various drugs, including bishydroxycoumarin (Dicumarol), diphenylhydantoin (Dilantin) and griseofulvin (Fulvicin), and also to increase the rate of conjugation of bilirubin. Chronic administration of barbiturates may also enhance their own rate of metabolism, and self-induction has also been reported for glutethimide. The implications of these phenomena in the clinical use of sedative–hypnotics are obvious, especially where drugs are used on a chronic basis. Although it would appear unlikely that the sedative–hypnotics could have significant effects on either their own metabolism or the inactivation of other drugs when given for preanesthetic medication, the possibility should not be ignored; it is most likely to become a reality in the patient who has a history of excessive use of sedative–hypnotics. In animals the metabolic inactivation of barbiturates can be decreased in the presence of drugs such as iproniazid (Marsilid), nialamide (Niamid), isoproterenol (Isuprel), disulfiram (Antabuse), phenoxybenzamine (Dibenzyline), and diethyl ether. Such mechanisms may explain, in part, the potentiation of sedative–hypnotic actions which have been observed clinically with concomitant administration of other drugs.

Although the liver is the primary site of metabolism of most sedative–hypnotic drugs, some agents are metabolized at much lower rates in other tissues, including the kidney and brain. The metabolism of the eugenol derivative, propanidid (Epontol), is not primarily hepatic, but mostly by inactivation by plasma cholinesterases. Since 90 per cent of this agent is excreted in urine in the form of metabolites within two hours, a rate much more rapid than those of most other sedative–hypnotics, the search for a truly rapidly-inactivated sedative–hypnotic should be directed toward the eugenols rather than the barbiturates, where thiohexital metabolism (25 per cent/hour) currently represents the "ceiling."

It has been suggested that tolerance to sedative–hypnotics may be explained on the basis of altered enzymic activity, especially since the barbiturates are known to possess enzyme-inducing activity. The available evidence, summarized recently,[8] refutes this, however, and it is apparent that the phenomenon of tolerance may have another basis, such a change in CNS response to these drugs.

D. Excretion

The kidney is the major route of excretion of almost all sedative–hypnotic drugs. Again, physicochemical properties are significant in determining the rate and extent of renal clearance. Because of high lipid solubility and low ionization at physiologic *p*H, most sedative–hypnotics are not excreted in *unchanged* form to any great degree. Although certain compounds, including chloral hydrate and paraldehyde, are quite water-soluble, suggesting the possibility of renal excretion of the unchanged molecule, their extremely rapid rates of metabolic transformation do not permit this to occur to a significant extent. Barbiturates resistant to metabolic inactivation (phenobarbital and barbital) are excreted unchanged in the urine to a greater extent. However, drugs that have low rates of metabolic degradation are not necessarily always excreted by the kidney unchanged. Only trace amounts of the benzodiazepines (chlordiazepoxide, diazepam) appear in the urine of man. On theoretical grounds, impairment of renal function is unlikely to alter appreciably the duration of response to sedative–hypnotic drugs, other than those few excreted in unchanged form, at therapeutic dose levels. Indeed, there is little clinical evidence to suggest otherwise. The pK_a values of sedative–hypnotics suggest that

TABLE 4. Distribution of Natural Sleep

	NREM	REM
EEG	Slow waves and spindles (divided in four stages)	Low voltage, slow frequencies, 4–10/sec bursts of sawtooth waves with REM
Duration of each type/night	65–85 per cent	12–35 per cent
Chronic deprivation leads to	Impaired performance[13]	Personality disorders[13]
Respiration, heart rate, blood pressure	Relatively unchanged	Sharp and frequent fluctuations
Brain temperature	Decreased below waking	Increased above waking levels
Barbiturates and other hypnotics	—	Decreased signs of REM sleep

only phenobarbital (pK_a 7.2) is likely to be appreciably changed with respect to degree of ionization resulting from changes in urinary *p*H. Alkalinization of the urine to *p*H 8 will increase the clearance of phenobarbital four-fold, partly by increasing ionization and partly by diuresis. Unfortunately, most sedative–hypnotics have pK_a values well above (weak acids) or well below (weak bases) that of plasma *p*H or are neutral compounds, so that the rate of renal excretion is not influenced greatly by *p*H manipulation.

Many sedative–hypnotic drugs are able to pass from plasma into bile, but fecal excretion is not a significant route of elimination, since these compounds are all readily reabsorbed from the lower gastrointestinal tract. Other routes of excretion (sweat, saliva, etc.) are of marginal importance for these agents, with the exception of paraldehyde, which appears in small quantities along with its metabolic products in expired air.

III. Rational Therapy with the Sedative–Hypnotic Drugs

The information on pharmacokinetics presented in the previous sections can be combined with other observations to achieve satisfactory therapeutic results. This section presents: 1) aspects of the state of natural sleep compared with sleep induced chemically; 2) a number of clinical situations in which the sedative–hypnotic drugs are commonly utilized; 3) the toxicity and therapeutic misadventures encountered in such usage.

A. Natural Sleep vs. Drug-induced Sleep

Oswald[16] has defined sleep as "a recurrent healthy state of inertia and unresponsiveness and one which, in contrast to coma and anesthesia, is readily terminable by external stimuli." The two kinds of natural sleep that have been described are commonly termed NREM (non-rapid eye movement), orthodox, forebrain, or slow-wave sleep, and REM (rapid eye movement), paradoxical, hindbrain, activated, or desynchronized sleep (table 4).

On the basis of the electroencephalogram[17] during natural and drug-induced sleep, it is apparent that with increasing drug doses the sleep produced resembles natural sleep less and less. Noteworthy is the suppression of REM sleep by the hypnotics. Since evidence that deprivation of REM sleep may be related to emotional disorders and personality changes is accumulating[18] it may be that sedative–hypnotic drugs which do not alter the balance between NREM and REM should be sought.

Observations (table 4) of altered physiologic and psychological function during sleep can be used as yardsticks for measuring the changes produced by hypnotic compounds. A number of reviews[16, 20] on the sleep state and a comprehensive review[21] of currently available techniques for sedative–hypnotic drug evaluation have been included in the bibliography for the convenience of the reader.

Lasagna[22] has indicated that onset of action, duration of action, and "hangover" effect are three areas of concern in considering drug-induced sleep. Although sedative–hypnotics do differ in onset, duration, and hangover effect, these differences are often difficult to distinguish clinically, owing in part to the limitations of evaluation methods. For example, Lasagna[22] found remarkably little difference between durations of action of long-acting (phenobarbital) and intermediate-acting (seco-

barbital) barbiturates. Other reasonably well-controlled studies of barbiturate action in man support this comparison, prompting the suggestion that the classification of such drugs based on duration of action is unscientific.[23] Decisions about which drugs to choose for rapid action are academic, except in regard to their specific use as intravenous agents in anesthesia. However, oral administration of sodium salts of thiopental or hexobarbital may be desirable for patients who require a rapid and deep, but evanescent, hypnotic action.[24] Although the duration of hypnotic action is dependent on the inherent properties of the drug, it is also markedly influenced by dose. For example, chloral hydrate, 15 mg/kg, is quite effective in inducing sleep, but hypnotic action is prolonged when this dose is doubled. This does not mean that an agent conventionally classified as "short-acting" can be used arbitrarily to produce effects of longer duration merely by increasing dosage, as this could result in excessive CNS depression. Though more germane to the use of sedative–hypnotics on a continuing basis, the choice of a drug with respect to duration of action may be influenced by consideration of the nature of the "sleep problem." Many patients have difficulty getting to sleep, but experience little difficulty in remaining in that state once achieved. In such cases, satisfactory therapy may well be achieved using a relatively short-acting agent, such as sodium thiopental administered orally. Less frequently, the problem may involve difficulty in maintaining the sleep state, and logical therapy would indicate a drug with a more prolonged effect. In addition, decreased "hangover" effects have been associated with more rapid rates of metabolic inactivation.[7] Once again, the influence of dose should not be underestimated, since longer durations of both desirable (clinical) and less desirable actions can be expected when larger amounts of an agent are administered. The importance of drug dose can be illustrated by the lack of hypnotic equivalence between a dose of 500 mg of chloral hydrate and 100 mg of secobarbital.[23] This may explain why chloral hydrate is advocated as an excellent geriatric hypnotic and why secobarbital (as well as most other barbiturates) is considered a poor therapeutic choice for the older patient. In this case, selection of a proper dose (*i.e.*, 40–50 mg) of secobarbital may make it just as efficacious as chloral hydrate, 500 mg. The therapeutic index is the ratio of the toxic to the therapeutic dose. Thus, the larger the therapeutic index, the greater the margin between therapeutic and toxic doses. Marked differences between indexes for most sedative–hypnotic drugs have not been demonstrated, but clinical experience with at least one drug (diazepam) strongly suggests a high therapeutic index, which means that the dose can be altered dramatically without producing a large change in response to this drug.

B. Nighttime Sedation

At least three considerations should concern the anesthetist when prescribing bedtime medication:

1) What is the clinical setting in which the drug will be administered, and to whom? The personality of the patient, his or her anxiety over the medical or surgical problem, and the environment in which the drug will be taken are all important considerations. There is no way of quantifying all these variables for a single patient, and these variables are good reasons for not selecting a "standard" dose of any drug for any patient.

2) Does the physical condition of the patient present significant contraindications to the use of such hypnotic medication? For example, a history of acute intermittent porphyria is an absolute contraindication to the use of barbiturates. Severe respiratory disease, severe uremia, advanced age, etc., may be contraindications in a relative sense but probably are not in an absolute sense, since each clinical situation is unique and by *dosage manipulation* safe hypnotic effects can be achieved.

3) What has been the past experience of the patient with other drugs, as well as compounds of the sedative–hypnotic type? Remember that ethyl alcohol and the nonbarbiturate sedative–hypnotics (diazepam, meprobramate, etc.) are sedative–hypnotic drugs. The patient who has a history of continuous prior use of these compounds is liable to be tolerant to any drug of the same type. Whether this is a true pharmacodynamic tolerance or, in fact, a matter of psychological conditioning

on the part of the patient depends on dose and length of exposure to the drug.

The selection of the hypnotic drug should be made with all of the preceding clinical information, as well as the pertinent pharmacokinetics, in mind. Since the newer nonbarbiturate hypnotics differ little from the barbiturates, it would seem prudent to use the older, tried compounds in most situations. Pentobarbital, secobarbital and chloral hydrate are available in enough different dose levels that selective therapy for any patient should be possible. In the event that one of the newer compounds is utilized it must be realized that the potentials for abuse (suicide or addiction), hangover, the very rare problem of paradoxical excitement, tolerance, physical dependence, and allergy all can be encountered, just as with the barbiturates.

A note on the use of compounds possessing primarily antihistaminic properties, such as hydroxyzine (Vistaril) and doxylamine (Decapryn), for sedative–hypnotic action must be made here. Their hypnotic activity is frequently unpredictable or too weak, making their use of questionable value. Doxylamine is an example of a drug which has potent hypnotic activity but overdosage (in animals at least) induces convulsions, which is quite the opposite of the effect seen with the classic hypnotics. Methapyrilene, another antihistamine, is the CNS depressant commonly included in many over-the-counter (non-prescription) preparations, and there is significant doubt that it possesses any depressant action beyond its placebo effect when taken in the usual dosage.

C. Preoperative Medication

Consideration of whether to select a sedative–hypnotic drug for immediate preoperative medication must take into account three important questions: 1) What is the attitude of the patient towards the operation which he or she is about to experience? 2) Is it desirable to produce chemical sleep with premedication? 3) What will be the impact of the drug on anesthetic management? The first question is answered at the time of the preoperative evaluation and subsequently will determine the answer to the second. Familiar to every anesthetist are the frightened child, the patient for radical cancer surgery, and the anxious teenager, for whom hypnotic drugs in sufficient doses to produce sleep are desirable. So long as this can be achieved without reaching the point of dysinhibition (loss by the patient of sufficient control over his response to external stimuli) and without marked interference with the actual conduct of anesthesia, it seems desirable.

In the selection of a particular sedative–hypnotic drug and consideration of its dosage, the same factors mentioned in the section on bedtime medication are important. One way to achieve this objective in the preoperative situation may be the use of oral dosage forms of the so-called "ultrashort-acting" barbiturates (*e.g.*, hexobarbital, thiopental), which will allow rapid induction of sleep but, because of their short durations of action, little interaction between the hypnotic drug and the anesthetic drugs would be predicted. Another alternative might be to use a drug with a dose–response curve which appears to be relatively flat (diazepam), thus allowing the clinician a greater margin for error in dose selection.

D. Intraoperative Use

The last area of immediate concern to the anesthetist is that of intraoperative sedation used to supplement general or regional anesthesia. It would seem best to confine the choice of drugs used intraoperatively to those which act rapidly and have evanescent effects or to those which act somewhat more slowly but have similar effects over fairly wide dosage ranges (flat dose–response curves). The first type of drug, best represented by thiopental, has the advantages of rapid onset and short duration of action. Short duration of action is an advantage if one wants only a few minutes of sedation or if one misjudges the dose, but it is certainly a disadvantage if the inconvenience of repeated dosing and the possibility of cumulative effect are considered. The latter type of compound may be best represented by diazepam, which acts rapidly and is quite stable, and cumulative effects are rarely seen unless a gross overdose is given. The use of certain sedative–hypnotics for induction of anesthesia has been reviewed recently.[25] The relative merits and disadvantages of various barbiturates, propanidid, and diazepam with

respect to respiratory and cardiovascular depression, excitatory phenomena, and "hangover" effect have received extensive consideration.

IV. Toxicity and Therapeutic Misadventures

The pharmacology of any drug group requires attention to not only beneficial effects but also possible toxicity and/or disease related to the use of the drugs.

A. Direct Actions of the Drug

Depression of the CNS is primarily dose-related; there is great variability among patients merely as a function of biologic variation. This in no way implies different pharmacologic activities for the drug, but rather that a small dose in one individual may produce effects obtainable in another individual only at a much higher dose. Failure to appreciate this factor can mean overdosing the sensitive patient and therapeutic failure in the less sensitive patient. These variations are seen in any patient population. This normal variation becomes still more important when advanced age, cardiovascular abnormalities or respiratory disease complicate the situation.

Intentional overdosages of these compounds are unfortunately common. The treatment of such medical emergencies is not pertinent to this paper, but the rationales for 1) symptomatic and supportive care, 2) use of analeptics, and 3) stimulation of drug excretion have been considered by Mark and Papper.[26]

B. Alteration in Drug Response

The use of sedative–hypnotic drugs may result in both qualitative and quantitative changes in pharmacologic response. They include alterations in response due to tolerance and physical dependence, allergic reactions, and the possibility of changes resulting from enzyme induction and inhibition. The impact of enzyme induction on medications used by the anesthetist probably is not very significant unless the patient has a history of continuous sedative–hypnotic use. One area of enzyme induction important to remember is that in which hepatic synthetase is induced by the barbiturates, with a resultant increase in body porphyrins. Fortunately, porphyria is rare, although purportedly it can be exacerbated by a single dose of barbiturate.

As mentioned earlier, the question of tolerance remains unanswered, and its answer probably will depend on the elucidation of pharmacodynamic factors rather than factors of altered metabolism. One very pertinent point is the matter of cross-tolerance between agents in the sedative–hypnotic class. The clinician's best clue to patient tolerance of the sedative–hypnotic drugs is a reliable drug history.

Physical dependence on these drugs is well documented, although for many years the teaching was that only habituation (psychological dependence) occurred. The phenomenon appears to be dose-related, and the type of drug (short- *vs.* long-acting) determines to some extent the time of onset of symptoms when the drug is withdrawn from a dependent patient. The signs and symptoms are fairly classical: restlessness, autonomic activity, frank convulsions. Treatment is with long-acting sedative–hypnotic drugs and gradual withdrawal. It is interesting to note that the tolerance mentioned above is a kind of "driving force" that puts the individual abuser at a dose level of drug which makes him susceptible to the withdrawal problem.

As with any molecule foreign to the body and introduced into it, there is a chance that the body will reject the molecule. The body's allergic response to the sedative–hypnotic drugs fortunately seems confined in most cases to dermatologic evidence of allergy.[27] This is not to say that all of the various allergic responses up to and including anaphylactoid reaction cannot occur, but fortunately they are rare.

C. Drug Interactions

The last consideration is that of the interaction of sedative–hypnotic drugs and other concurrent therapy. Drugs that can be classified as CNS depressants act in an additive fashion, which makes this interaction easy to recognize. The interactions between the major tranquilizers (the phenothiazines and reserpine), certain antihypertensive agents (alpha-methyldopa, reserpine), and the antihistaminics are more subtle. The possibility of additive responses due to the inhibition of drug-me-

tabolizing enzymes by monoamine oxidase inhibitors and adrenergic blocking agents has already received comment. Although the potentiation of sedative–hypnotic action by agents such as tolazoline (Priscoline) and phentolamine (Regitine) may be due to direct inhibition of microsomal enzymes, animal studies [28] suggest that decreased drug metabolism could result from hypothermic responses during adrenergic blockade. The significance of possible drug interactions during the intravenous use of sedative–hypnotics, which have been suggested to underlie increased frequency and severity of excitatory, respiratory and cardiovascular complications,[25] is still questionable. Antagonism (negative interaction) is another possible interaction which must be considered in this age of increasing use of CNS-stimulating drugs (amphetamines, etc.) as anorectics and antidepressants. Little clinical evidence about the responses to the sedative–hypnotics of patients taking therapeutic doses of these CNS stimulants is available. It is possible that the doses of the sedative–hypnotics may need to be increased in such cases. The sedative–hypnotics frequently are used by the amphetamine abuser to "turn off" the stimulant action of the drug at the end of a long "run," and they also have some therapeutic value in cases of CNS-stimulant toxicity. An interesting effect was found in individuals taking large intravenous doses of methamphetamine: the sedative–hypnotics (particularly the barbiturates) intensified the aggressive and violent behavior caused by amphetamine.[29] This suggests that interactions between these two drug groups are more complex than simple neutralization of CNS-stimulant or CNS-depressant actions.

We hope that these examples, although they are by no means exhaustive, will encourage the clinician to be attentive to the possibility of both unusual and predictable interactons, in the interest of more effective patient care.

Summary

Our objective is to promote the utilization of available information about the sedative–hypnotic drugs to achieve the most satisfactory clinical result. It must be admitted that differences between drug A and drug B frequently may be undetectable either because there is no real difference or because the differences are not appreciated. It is our conviction that the understanding and application of fundamental pharmacologic principles such as the pharmacokinetic aspects emphasized in this review will aid the physician in identifying those characteristics that truly make one sedative–hypnotic drug different from another.

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Pediatrics

LARYNGEAL EDEMA In the postanesthetic period, laryngeal edema and tracheitis with obstructive croup-like symptoms occur in some children who undergo intubation for surgery. In some children the obstruction progresses despite the usual therapy with cool humidification and corticosteroid therapy and requires more active means to establish a normal airway. Positive-pressure assistance to ventilation and nebulization of racemic epinephrine have been effective in relieving the obstruction in all children with this complication without recourse to reintubation or tracheotomy. (*Jordan, W. S., and others: New Therapy for Postintubation Laryngeal Edema and Tracheitis in Children, J.A.M.A. 212: 585 (April) 1970.*)

MAGNESIUM SULFATE During a 14-year period, 7,000 infants were born of mothers who had received magnesium sulfate parenterally for treatment of preeclampsia or eclampsia. Magnesium sulfate was administered intramuscularly in doses of 30 to 40 g/24 hours and was maintained for as long as necessary provided reflexes remained active, urinary output exceeded 100 ml/4 hours, and respiration was not depressed. Magnesium levels in umbilical cord blood of 118 infants and in 42 mothers were determined. The level of magnesium in the serum of the fetus rapidly approached that of the mother, but was not associated with any deleterious effects upon either fetus or newborn. (*Stone, S. R., and Pritchard, J. A.: Effect of Maternally Administered Magnesium Sulfate on the Neonate, Obstet. Gynec. 35: 574 (April) 1970.*)