THE CLINICAL USE OF (SODIUM 5 ETHYL-5 (1-METHYL-1 BUTENYL) BARBITURATE) VINBARBITAL SODIUM * AS A PREANESTHETIC AGENT

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IN the specialty of anesthesiology the barbiturates are used frequently as preanesthetic sedatives. It has been found that when adequate sedatives have been given before the patient goes to surgery, he possesses a greater degree of equanimity, and a much smoother induction may be obtained by the anesthesiologist. Furthermore, there is a reduction in the amount of anesthetic agent necessary to maintain an even anesthesia.

The anesthesiologist has numerous barbiturates at his disposal for this purpose. The agents most frequently used are nembutal, or pentobarbital sodium, sodium amytal, ortal sodium and cyclopal. All these agents have been used with satisfactory results by various clinicians; however, each has been found to have various and sundry side reactions which are occasionally objectionable. Therefore, the search for a newer barbiturate is warranted at all times so that the clinician may obtain the most suitable drug with the least possible side reactions.

If a newer barbiturate, which would be acceptable to use as a preanesthetic sedative, is developed, it should produce few toxic effects, should be rapid in its induction of sedation and have a satisfactory duration of action. Sedation should be accomplished by the administration of small doses of the drug, and a wide margin of safety should exist between the minimal therapeutic and lethal doses.

The ideal barbiturate, therefore, would be one which acts essentially as a depressant of the central nervous system to produce calmness, to induce sleep and to depress the motor cortex. The sleep produced should be dreamless and refreshing and there should be no, or only slight, "hangover" effects upon awakening. It should possess only a slight depressant effect, if any, upon the blood pressure, pulse or cardiovascular system and the respiration, and no toxic effects either clinically or pathologically upon the excretory organs, particularly the kidneys and liver.

With this purpose in mind, a study of the clinical effects of vinbarbital sodium, or, as it is more commonly known, delvinal sodium, is

* Vinbarbital Sodium is supplied by Sharpe and Dohme under the trade name of Delvinal Sodium.

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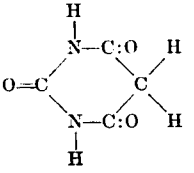
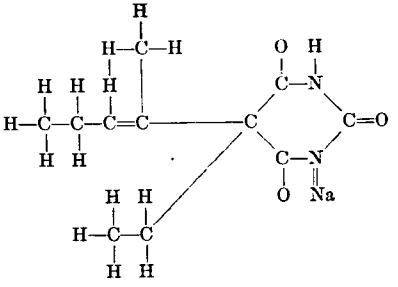
justified. Chemically the different barbiturates are formed by substitution of various radicals into the barbituric acid nucleus.



Cope and Hancock (1) substituted a vinyl group containing five carbon atoms into the barbituric acid nucleus and found a barbiturate which upon preliminary test showed a comparatively wide margin of safety in animals. The most promising compound being formed was called 5 ethyl 5-(1-methyl 1-butenyl) barbituric acid. The sodium salt has the empirical formula $C_{11}H_{15}O_2N_2Na$ and is represented structurally as follows:



Pharmacologic studies by Hendrix (2) with vinbarbital sodium showed the drug to be less depressant to the blood pressure than amytal. This was observed clinically by Davidoff (3) and Davidoff and Goodstone (4) in psychiatric patients when small doses were used, but the opposite effect resulted when large doses were employed.

The greatest danger that one encounters when barbiturates are used is respiratory failure. Hendrix found less depression of the respiratory center with vinbarbital sodium than with amytal. This factor is of great importance for if respiratory depression does occur during anesthesia, it is essential that stimulation may be carried out effectively by the inhalation of carbon dioxide. Clinically, this factor may be of distinct advantage to the obstetrical patient, particularly when fetal respiratory depression occurs from excessive doses of a barbiturate. It has been found clinically by Bernstine and Prince (5) that vinbarbital

sodium does not affect the fetal respiratory mechanism, as fetal respiration occurred spontaneously in the majority of cases.

Pathologic studies were made upon the various organs of the body by Corman (6). He was not able to demonstrate abnormal changes in the various organs which might have resulted from the use of vinbarbital sodium. Tolerance studies to vinbarbital sodium were undertaken by Carmichael and Thompson (7) to determine its accumulative effect. Repeated administration of large doses of the drug indicated that guinea pigs show a tolerance to vinbarbital sodium. The average length of hypnosis dropped from 191.9 minutes to 104.1 minutes, and the average weight of the guinea pigs increased 50 per cent.

Vinbarbital sodium was first used clinically by Frederic Hanes (8) who found that 0.1 Gm. (1½ gr.) seemed to be about the average dose necessary to produce sleep. No toxic effects were observed upon these patients; furthermore, the patients had a quiet sleep for approximately four to seven hours. Marvin (9) studied its use as a preanesthetic sedative and indicated its great possibilities; he was unable to observe any deleterious effects from its use.

As preliminary studies on vinbarbital sodium showed that it had good possibilities to supplant the other barbiturates, it was decided to make a clinical investigation of its usefulness as a preanesthetic sedative and determine whether or not it affected the respiration, pulse and blood pressure and central nervous system. Preliminary studies further justified the fact that vinbarbital sodium meets all the requirements of being a satisfactory preanesthetic drug since it acts primarily upon the higher centers, and its effects upon the respiration, pulse and blood pressure were only negligible. Furthermore, the desired preoperative effects, namely, relaxation and drowsiness were accomplished without preliminary excitation. Also, when the patients awakened, they were usually refreshed and free from headaches, mental haziness, and the so-called barbiturate "hang-over."

In this study on the use of vinbarbital sodium as a preanesthetic sedative, particular attention has been paid to the degree of respiratory depression, its circulatory effects, the mental attitude of the patient upon arrival in the operating room during the course of anesthesia, and the immediate postoperative effects.

Vinbarbital sodium was used by the anesthesia department of the University of Kansas Hospitals in approximately 1,369 cases ranging in age from 18 months to 89 years.* Table 1 shows the age distribution of these patients with the dosage range in each grouping.

From table 1, it is observed that the dosage varied from ½ grain to 4½ grains. In children under 10 years of age the dosage of vinbarbital sodium varied from ½ grain to 1½ grains, and it was found best to administer it rectally, a procedure which has been used at the Univer-

* Since these data have been collected we have now used vinbarbital sodium (delvinal sodium) in over 1,600 cases with satisfactory results.

TABLE 1

DISTRIBUTION OF PATIENTS, WITH DOSAGE

Age Groups	Dosage in Grains							Total
	4½	3	2	1½	1	¾	½	
0- 9				22	46		59	127
10-19	1	54	9	99	27		1	191
20-29	4	107	7	33				151
30-39	3	113	16	24	1			157
40-49	1	128	13	50				192
50-59	1	75	6	125				207
60-69	1	21	2	150	17	2	2	195
70-79		5		78	35	8		126
80-89		2		7	10	4		23
Totals	11	505	53	588	136	14	62	1369

sity with all other barbiturates. The rectal route is preferable because of the reluctance of some children to take medication by mouth. Absorption occurs readily from the rectum, although it is stated that the barbiturates retain only two-thirds of their activity when administered by this method. In adults, vinbarbital sodium was usually given orally unless contraindicated, such as when a gastric resection was to be done or in the presence of a malignancy of the esophagus, when it would be given rectally.

The dosage found to be most effective in children is 1½ grains for those above 6 years of age. With this dosage it has been found that the children were asleep when they were brought to the operating room, and they were relieved of all apprehension and the fear that they normally possess toward the anesthetic and their strange surroundings. Induction is always much smoother than when no premedication is given, and the most noticeable effect is the freedom from excitation. Furthermore, induction time has been decreased and the amount of anesthetic agent necessary for maintenance of anesthesia reduced. The pediatric nursing staff has also informed me that the children usually awakened more refreshed and not as excited as formerly, eliminating the constant supervision necessary heretofore.

In the middle-aged adult, dependent upon the metabolism of the patient, as the barbiturates tend to reduce the metabolic rate, the dosage of vinbarbital sodium found to be most satisfactory is 3 grains. This dosage varied, however, from 1½ grains to 4½ grains. In one extremely thyrotoxic patient who had a preoperative basal metabolic rate of + 40, 3 grains was not enough to produce sufficient quiescence to administer the anesthetic, as the patient developed a ventricular tachycardia during induction of anesthesia. In the hyperthyroid patient the usefulness of the barbiturates is dependent upon the sedative action rather than any specific effect upon the metabolic rate. The operation

was postponed another day and 6 grains of vinbarbital sodium was used in combination with morphine sulfate, ¼ grain and scopolamine, 1/200 grain. This time the patient was asleep when she was brought to the operating room. The induction was smooth and the operation completed without complications.

For the aged patient and those suspected of having severe hepatic damage, it has been found that all the barbiturates should be used with caution. Vinbarbital sodium was used alone and in combination with morphine-scopolamine in approximately 344 patients over 60 years of age. The dosage of barbiturate varied from ½ grain to 4½ grains. With a dosage of 1½ grains or more, circulatory depression has been pronounced, and when spinal anesthesia is employed, the depression may become alarming. It was found that when vinbarbital sodium was used in conjunction with morphine sulfate, ⅛ grain, and scopolamine, 1/400 grain, the most satisfactory dosage is ½ grain. When vinbarbital is used alone, 1½ grains may be used with impunity.

The degree of circulatory depression that occurred was determined by taking the blood pressure within twelve hours before the patient is brought to surgery, without medication and after he has been acclimated to his surroundings. This pressure was then compared with that obtained upon arrival in the operating room. A pressure drop of 20 mm. of mercury was considered significant.

TABLE 2

CIRCULATORY DEPRESSION OCCURRING WITH VINBARBITAL SODIUM IN CONJUNCTION WITH MORPHINE AND SCOPOLAMINE IN PATIENTS OVER 60 YEARS OF AGE WITH SPINAL ANESTHESIA

Vinbarbital Dosage	Preoperative B.P.	Average Drop in B.P.	Number of Patients
Gr. 1	90–110	0	3
	115–145	31	6
	150–195	44	12
Gr. 1ss	90–110	0	4
	115–145	28	15
	150–195	41	24
	200–over	51	6
Gr. 111	90–110	0	1
	115–145	0	3
	150–195	45	5
	200–over	20	1
			80

Table 2 shows the average drop in blood pressure which occurred in approximately 80 patients over 60 years of age who received vinbarbital sodium as indicated, with morphine sulfate, 1/6 grain and scopolamine, 1/300 grain.

It is apparent from the table that when the preoperative systolic pressure is over 150 mm. of mercury, a greater drop in the blood pres-

sure will occur. In the elderly, hypertensive patient who has received an excessive dosage of medication, the blood pressure reading will frequently fall as a result of the sedative action produced by the medication. Large doses of barbiturates tend to depress the central vasomotor center, and peripheral dilatation and hypotension will occur. Exception may be found to this statement when 3 grains produced a drop of only 20 mm. in the systolic pressure in one case. A greater number of cases would more than likely show a greater depression of the systolic blood pressure. When a spinal anesthetic is given to this type of patient, a marked degree of hypotension may result, as observed from the anesthetic record. It need only be emphasized that when operation and anesthesia are contemplated in the aged, extreme caution should be used in the prescribing of preanesthetic barbiturates. Furthermore, if a barbiturate need be used, then only the minimal dose necessary for sedation need be administered.

The pulse rate showed a definite increase when vinbarbital sodium was used as a preanesthetic agent. This disagrees with the results obtained by Hendrix and Marvin who found no appreciable change in the pulse rate.

TABLE 3

THE EFFECTS OF VINBARBITAL SODIUM UPON THE PREOPERATIVE PULSE RATE

Dosage	% Increase	% Decrease
Gr. ¾	30	0
Gr. 1	40	4.0
Gr. 1½	40	8.3
Gr. 111	51	11.8

From table 3 it is observed that an increase in the pulse rate occurs. This increase occurred in 740 cases out of 1,369. A pulse change was recorded if there occurred a difference of plus or minus 10 over the rate observed twelve hours before anesthesia. A patient who has been confined to a hospital bed for some time will show a decrease in the pulse rate compared to that taken just before operation. During the course of anesthesia, when the patient is in surgical anesthesia and all reflex stimuli removed, the pulse rate always shows a definite decrease. This indicates a slight degree of apprehension on the part of the patient who is given an anesthetic. The question of anxiety must be considered a factor in these patients. It is also probable that a decrease in the oxygen consumption is a factor to be considered. This increase of pulse rate need not be attributable to the use of vinbarbital sodium, as it has also been known to occur when other barbiturates have been the agent of choice. Irregularities of pulse were not observed by palpation.

The respiratory rate was not affected by the use of vinbarbital sodium. The barbiturates in sedative doses are only slightly depressant to respiration. Large doses of barbiturates are directly depressant to the medullary respiratory center so that the rate and depth of breathing

TABLE 4

RESPIRATORY RATE

Dosage	% Increase	% Decrease
Gr. ¾	0	0
Gr. 1	0	0
Gr. 1½	0.38	0.13
Gr. III	5.5	2.17

are decreased. Table 4 shows the percentage of change occurring in the respiratory rate.

A respiratory change was recorded if there occurred a difference of plus or minus 6 over the preoperative rate taken twelve hours before operation.

During the operation, particular attention was paid to the degree of respiratory depression that might occur. A marked degree of depression was observed in 76 cases out of 1,369. It was found that cyclopropane alone, or in combination with other agents, was the causative factor in approximately 64 of 442 cases. This is attributed to the respiratory depressant effects of cyclopropane, and not to vinbarbital sodium. With other agents, respiratory depression occurred in 12 cases out of 927.

TABLE 5

CASES SHOWING RESPIRATORY DEPRESSION DURING ANESTHESIA AFTER ADMINISTRATION OF VINBARBITAL SODIUM AND MORPHINE-SCOPOLAMINE

Total No. of Cases	No. of Cases with Respiratory Depression	Percentage
1369	76	5.5
442 (Cyclopropane alone and with other agents)	64	14.48
927 (Other agents)	12	1.2

A further study was made to determine the time interval when the most desired sedative effects were obtained. It is considered the desired sedative effect when the patient enters the operating room asleep, but, when spoken to, will respond immediately. Furthermore, the mental attitude of the patient is such that he is oblivious to surroundings and what is being done to him preparatory to administration of the anesthetic. This is shown in table 6. This observation was made in 1,528 cases.

TABLE 6

TIME REQUIRED TO ATTAIN THE MAXIMUM SEDATIVE EFFECT AFTER ADMINISTRATION OF VINBARBITAL SODIUM

Time After Administration (minutes)	Total No. Cases	Cases Unsatisfactory	Percentage
30 to 90	445	103	23
105 to 120	381	46	12
120 to 150	560	72	12.8
165 to 240	142	30	21

It will be observed from this table that, when the patient had received vinbarbital sodium approximately two hours before operation, he usually entered the operating room in the desired stage of sedation. Hypnosis or sleep may occur before this, but its maximal effects, as desired by the anesthesiologist, are attained approximately one and one-half to two hours before operation. At this time the patient falls asleep when left alone, but, when spoken to, responds. The apprehension and fear of suffocation which occasionally occur when the mask is placed over the patient's face are eliminated. Induction of anesthesia, therefore, is much smoother than when adequate sedation is not obtained.

From this study it is recommended that when vinbarbital sodium is the agent of choice, the proper dosage should be administered approximately two hours before operation. Supplemental medication, when necessary, may then be given one hour before the start of anesthesia.

Vinbarbital sodium has been used as a preanesthetic sedative for all types of anesthetic agents. Table 7 lists the anesthetic agents used with the number of cases in each group.

TABLE 7

ANESTHETIC AGENTS USED IN CONJUNCTION WITH VINBARBITAL SODIUM

Agent	No.
1. Vinethene with Ether (open drop)	333
2. C_3H_6 (closed)	296
3. Spinal	212
4. Intravenous (pentothal and evipal)	200
5. C_3H_6 with Ether (closed)	76
6. Nitrous Oxide with Oxygen (semi-open)	75
7. C_3H_6 (closed with spinal)	70
8. Local	36
9. Vinethene (open drop)	35
10. Nitrous Oxide-Oxygen with Ether (closed)	30
11. Ether (open)	3
12. Pentothal with Nitrous Oxide-Oxygen	2
13. Caudal	1
	1369

It is observed from table 7 that the inhalation anesthetics comprise the greatest number of cases, with spinal, intravenous and local anesthesia following. Satisfactory results were obtained with all agents and the use of vinbarbital sodium is not contraindicated with any anesthetic agent. It may be said, however, that, when cyclopropane is the agent of choice, more careful consideration should be given to the patient's metabolism and general condition before a barbiturate is used. It is recommended that if vinbarbital sodium is the agent of choice when cyclopropane is to be used, the dosage of vinbarbital sodium should be approximately half of that which might normally be used. With nitrous oxide-oxygen anesthesia, adequate oxygen may be administered when the maximal doses of vinbarbital sodium have been used. This is

a result of the reduction of the basal metabolic rate as well as a decrease in the oxygen consumption.

In postoperative cases, careful attention was paid to determine what part vinbarbital sodium may have played in the production of irrationality. This was determined by observing the degree of postoperative restlessness and excitement. From this observation it was estimated that vinbarbital sodium may have been the factor in approximately 20 cases, or 0.5 per cent of the total number of cases. Three of these patients in particular required restraints to keep them in bed. It is difficult to estimate the exact degree of irrationality in surgical cases as various other factors must also be considered, particularly the amount of pain the patient is experiencing, the mental attitude of the patient before operation, the age and the all important factor of cerebral anoxia which may occasionally occur if circulatory depression has been present for any length of time.

From the results obtained, vinbarbital sodium may be considered to be a useful preanesthetic barbiturate for sedative purposes. Its toxic effects as determined experimentally have been found to compare favorably with other more commonly used barbiturates. Furthermore, as observed from its clinical effects, no deleterious action is noted upon the respiration unless the drug is given in too large a dose when cyclopropane is the agent of choice. It is recommended that not more than 1½ grains be used with cyclopropane. This dosage may be considerably increased in the hyperthyroid patient to produce the desired sedation. The pulse rate shows a definite increase when vinbarbital is used. The causative factor responsible for this increase is difficult to evaluate. Preoperative excitement may play an important part, although the patient appears to be perfectly calm. It must be realized that any patient undergoing operation will present a marked increase in pulse rate as compared with the pulse rate twelve hours before. It is doubtful whether or not vinbarbital sodium should be considered an important factor in the increase in pulse rate. The blood pressure is definitely depressed in the aged person when the barbiturate is used in conjunction with a standard dose of morphine and scopolamine, but this does not occur when vinbarbital sodium is used alone. Again, circulatory depression may occur with any of the barbiturates that are used. It is thought that when vinbarbital sodium is to be employed in the elderly patient, it should be used alone; however, when used with an opiate, the dosage should not exceed 1 grain at the most. In regard to postoperative restlessness, vinbarbital sodium definitely decreases the incidence of excitement. Patients awaken much more refreshed than heretofore and children particularly are not as difficult to handle. Disregarding all other factors, this decrease in the degree of restlessness alone would make vinbarbital sodium the barbiturate of choice and should make its use more prevalent.

In conclusion, vinbarbital sodium (delvinal sodium) is a valuable adjunct in the field of barbiturate therapy since it meets nearly all the requirements for an ideal agent. From a study of approximately 1,369 cases it was found that vinbarbital sodium possesses the following attributes:

1. Cerebral excitation is markedly decreased.
2. Respiratory depression is not apparent; but, when the drug is given in excessive dosage with cyclopropane, respiratory depression may occur.
3. It is not depressant to the blood pressure except when used in excessive dosage in the elderly patient.
4. The desired time necessary to attain the maximum sedation before operation is approximately one and one-half to two hours.
5. When spinal anesthesia is the agent of choice, the patients are cooperative throughout the entire procedure and the majority sleep if they are not disturbed.
6. The use of vinbarbital sodium in children is especially recommended because of its sedative action to the patients, relieving them of all apprehension and allowing the anesthesiologist to obtain a smooth induction phase and to maintain anesthesia with a minimal amount of anesthetic agent.
7. Adequate concentrations of oxygen may be maintained with mixtures of nitrous-oxide-oxygen when maximal doses of vinbarbital sodium have been used.

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