THE ANALGESIC AND HYPNOTIC ACTIONS OF BARBITURATES *

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It has been a frequent observation in our laboratory that animals under the influence of barbiturates are reactive to many stimuli even though the dosage of the drug has been so high that death later results. On the other hand, many clinicians and some pharmacologists believe that these drugs decrease sensitivity to pain. Thus a difference of opinion exists as to the effects of barbiturates on pain perception.

Several statements in the literature are pertinent to a consideration of this controversy. Wolff, Hardy and Goodell, in 1941 (1) working with human subjects found that evipal sodium in a dosage of 0.5 gm. (7½ grains) orally produced a rise of about 21 per cent in pain threshold. This is within the limits of psychogenic effects as shown in a later report by the same authors (2). In the same year Andrews and Workman stated (3), "A dose of nembutal sufficient to produce definite hypnosis showed no threshold-raising effect." Their work was done on dogs and their method has not been used sufficiently to evaluate its reliability. Again in 1941, Gruber (4) stated that neither evipal nor pentothal produces "anesthesia" in rats. He used the term "anesthesia" to signify absence of response to painful stimuli in addition to unconsciousness. In 1943, Smith, D'Amour and D'Amour (5) studied eight different barbiturates in rats. Only cyclopal and pentobarbital produced any rise in pain threshold by their technic and the observed rises seem of questionable significance. Unfortunately, these authors used only one dosage of each drug. Woolfe and Macdonald, in 1944 (6), studied several dosages of phenobarbital in mice and concluded that there was no analgesic action doses lower than the "anesthetic" dose. Objection may be made to this work on the basis of the failure of their method to detect analgesia after administration of acetylsalicylic acid.

In contrast to these statements stands the clinical use of barbiturates, either alone or in combinations with other drugs, for the relief of pain in labor and in other circumstances, and also the widespread use of thiopental sodium (pentothal sodium) for surgical anesthesia.

Apparently no attempt has been made to study various barbiturates

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in different dosages under controlled conditions using a method which can be shown to detect mild analgesic action. Since we have such a method available, it seemed appropriate to attempt a study of this problem.

METHODS

Freshly prepared solutions of the sodium salts of four barbiturates were administered by the intraperitoneal route. Dosages were chosen to approach from below that which would produce the typical depression in most of the rats. The presence or absence of hypnosis and of analgesia was determined fifteen minutes after injection of the drug and every thirty minutes thereafter for a suitable period.

Hypnosis was considered to be present when the rat would not resume his normal posture if placed on his back or side. We use this term in its usual pharmacologic sense to describe the state of depression produced by the barbiturates. It should be emphasized that this usage conveys no information as to the responsiveness of the rat to external stimuli.

The method we have used to detect analgesia is a modification of that used by D'Amour and Smith (7), which is in turn a modification of that developed by Hardy, Wolff and Goodell (8). Basically, the method involves measurement of the duration of a constant-intensity stimulus required to produce a characteristic response in a rat. The stimulus used is intense heat produced by a 50 candle-power incandescent light, concentrated by a reflector and a lens to a small area. Constant intensity is accomplished by using a storage battery as the source of current. The stimulus is applied to the terminal centimeter of a rat's tail, and the duration is measured with the aid of an electric stop-clock. Our modification consists in arranging the apparatus so that the animal's tail is exposed to a moderate degree of warmth for a reasonable period before the high intensity (pain) stimulus is applied. This is accomplished by passing the current through a suitable resistance in a series with the light and then short-circuiting this resistance. We believe it desirable to permit the rat to become adapted to a sensation of warmth before the painfully hot stimulus is applied. A stop-clock is started at the time the resistance is short-circuited and is stopped when the response is observed. The response is a characteristic twitch of the tail which after short experience can readily be differentiated from a fortuitous movement.

Analgesia is considered to be present when the response time of the rat is two seconds or more greater than normal for that particular animal. (Normal is taken as the average of three observations made at about half hour intervals just prior to administration of the drug.) This criterion was adopted after an analysis of the variability of observations on untreated rats. The degree of analgesia is not considered; the effect is handled as if it were all-or-none.

Results

The results of the experiments are summarized in table 1. The four barbiturates used do not seem to differ in their analgesic actions, and the only action which seems to vary regularly with dosage is hypnosis. Therefore, it appears justifiable to use the totals as a summary. Of the 130 rats used, 36 showed analgesia at some time after administration of a barbiturate. Only 11 of these, however, showed analgesia without concurrent hypnosis. This is an over-all incidence of about 8 per cent. The maximum incidence of analgesia without hypnosis in any single experiment was 3 in 16, or about 19 per cent. This occurred with thiopental sodium in the lowest dose used (30 mg. per kilogram). Administration of phenobarbital sodium in a dosage of 75 mg. per kilogram showed a similar incidence of analgesia without hypnosis.

TABLE 1

Analgesia, Hypnosis and Mortality in Rats Following Administration of Barbiturates

Drug	Dose (mg./kg.) i.p.	Number Used	Incidence of Analgesia			Incidence of Hypnosis		Mortality
			Total	Hypnosis present	Hypnosis absent	Total	Analgesia absent	
Phenobarbital sodium	75	22	4	0	4	0	0	0
	100	16	6	4	2	13	7	0
Pentobarbital sodium (nembutal)	25	10	2	0	2	1	1	0
	40	11	7	7	0	11	4	1
Seconal sodium	25	12	1	1	0	9	8	1
	40	12	1	1	0	8	7	1
Thiopental sodium (pentothal sodium)	30	16	5	2	3	2	0	2
	35	15	1	1	0	6	5	1
	40	16	9	9	0	16	7	4
Total	—	130	36	25	11	66	39	10

More interesting is the incidence of hypnosis without analgesia. The over-all incidence of this phenomenon was 39 in 130, or about 30 per cent. It occurred in 8 of 12 rats (75 per cent) with 25 mg. per kilogram of seconal sodium, in 7 of 12 (58 per cent) with 40 mg. per kilogram of the same compound and in 7 of 16 (44 per cent) with 40 mg. per kilogram of thiopental sodium. In only two of the nine experiments was this phenomenon completely absent.

Discussion

The ability to detect analgesic action in compounds of low potency by this method is indicated in table 2. In general it may be said that with this method we have not yet failed to detect analgesia following administration of a drug which has been found clinically useful as an

analgesic. Not all clinically useful compounds have been studied, but we believe the list is adequate.

TABLE 2

COMPARATIVE POTENCY OF VARIOUS ANALGESICS AS DETERMINED BY OUR METHOD

	A D 50* mg./kg.	Relative Potency
Morphine sulfate	4.5	100
Codeine sulfate	12.0	38
Dihydromorphinone hydrochloride	0.6	750
Demerol	13.0	35
Acetylsalicylic acid	450	1
Sodium salicylate	125	3.5
Antipyrine	220	2.0
Aminopyrine	750	0.6
Acetanilid	175	2.5
Acetophenetidin	560	0.8

* Dose required to produce significant analgesia (see text) in 50 per cent of a group of animals.

The results presented indicate that previous workers have arrived at valid conclusions despite the incomplete nature of their studies. If anesthesia be defined as a state of simultaneous hypnosis and analgesia, it may be said that barbiturates do not safely produce anesthesia. In our experiments doses adequate to produce this state also caused death in some animals. Phenobarbital, in a dose of 100 mg. per kilogram, is the only exception to this statement. Since we have used the same ranges of dosage as are commonly used for "anesthesia" in laboratory animals, we feel justified in stating that barbiturates should not be considered true anesthetic agents for animals.

Considerable caution is appropriate in applying conclusions drawn from animal experiments to human beings. We believe, however, that certain collateral evidence makes it reasonable to apply our conclusions to man. It is known that various depressants of the central nervous system have different effects on the electrical activity of the cerebral cortex as measured by electro-encephalographic technics. Furthermore, the differences between drugs are similar in animals and in man. The barbiturates characteristically do not depress the cortical activity while ether and other true anesthetic agents usually suppress this activity almost completely. This seems indirectly confirmatory of our findings, and appears to indicate that the barbiturates act similarly in animals and in man.

The successful use of thiopental sodium as a clinical anesthetic agent can be explained, we believe, primarily on the basis of the amnesia produced. The patient has no memory of discomfort regardless of his experiences at the time. In addition, the degree of depression is frequently so great that selective alteration of responsiveness to pain plays only a minor part in the total effect.

The usefulness of barbiturates in the control of pain in clinical circumstances is perhaps explainable in the light of the findings of Wolff, Hardy and Goodell (9). These workers believe that the pain experience must be a combination of two separable factors—percep-

tion of pain *per se*, and the reaction pattern to pain—and that these two factors may be affected differently by drugs. The reaction to pain may be influenced by barbiturates independently of alteration in perception. Such a conclusion would seem to be supported by Beecher (10) who described a patient who had a very severe battle injury which resulted in a temporary mania. Administration of "a small dose of a sedative" to this patient produced a very light sleep from which he was easily aroused, but completely controlled his maniacal behavior. This would indicate modification of the patient's reaction to pain presumably independently of pain perception.

Summary

The ability of various doses of four representative barbiturates to produce analgesia and hypnosis has been studied in rats.

It has been shown that these drugs produce their depressant effects (hypnosis) without altering pain threshold at least as often as they produce a significant rise in pain threshold (analgesia).

The incidence of analgesia following administration of barbiturates does not seem to be related to dosage nor does there appear to be any real difference between the various members of the group in this respect.

We, therefore, conclude that the barbiturates are not anesthetic agents in the best sense of that word, that is, they cannot be relied upon to reduce sensitivity to pain.

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