TECHNICAL PAPERS

The Effect of Body Temperature on the Duration of Barbiturate Anesthesia in Mice

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Both toxicity and duration of action of many central nervous system depressants are influenced by temperature. Most investigators have dealt chiefly with the influence of environmental temperature on the toxicity of these drugs (*4*). The few available investigations which have considered the influence of temperature on the duration of action have failed to specify the changes in body temperature resulting from exposure of the animals to varied environmental temperatures. The body temperatures of small animals at extremes of environmental temperature are well known to be unstable even without anesthesia. It is apparent that for the anesthetized animal the determination of environmental temperature alone is inadequate.

Cameron (*2*) and Gaylord and Hodge (*5*), using pentobarbital in rats, and Raventos (*7*), using evipal in mice, found the duration of sleep with a given dose of the barbiturate to increase with decrease in environmental temperature. Although body temperatures were not reported, it seems certain that marked changes must have occurred at the environmental temperatures employed.

In order to determine the influence of body temperature on the duration of action of some barbituric acid derivatives, the experiments summarized in Table 1 were carried out. Albino mice of both sexes were used, and the experiments with a given drug were performed simultaneously at two temperatures. To obviate differences in rate of absorption due to temperature, the animals were all injected at room temperature, which was maintained until anesthetization. Half of the group were then transferred to a chamber maintained at 35–37° C., and the other half were rapidly cooled to a body temperature of 25–27° C. by contact with a metal plate at approximately 0° C. The two groups were then maintained at *body* temperatures of about 37° C. and 27° C., respectively, by varying the rate of heat loss through warming or cooling. Body temperatures were determined in each mouse in rotation, using two potentiometers and iron-constantan thermocouples inserted rectally to a depth of 15 mm. Sleeping time was taken as the interval between loss and recovery of the righting reflex.

Table 1 shows that the duration of action of pentobarbital and Sandoptal[1] is greatly prolonged by a reduction in body temperature of 10° C., while that of barbital is scarcely affected by such a reduction in temperature. The chief difference between barbital and the other two derivatives studied lies in their fate in the body. Barbital (diethylbarbituric acid) is relatively stable and is readily excreted in the urine; its action is prolonged by bilateral nephrectomy but not by hepatic damage or by subtotal hepatectomy. Pentobarbital (ethyl-1-methylbutyl-barbituric acid) and Sandoptal (allyl isobutyl barbituric acid), on the other hand, are excreted in the urine only in traces; their anesthetic action is prolonged by liver damage or by hepatectomy but not by bilateral nephrectomy. Therefore, barbital is detoxified chiefly by urinary excretion, while pentobarbital and Sandoptal are detoxified by inactivation in the tissues, of which the liver probably is the most important. Sandoptal was included here because it is intermediate in duration of action but is readily inactivated by the tissues. Although the mechanism of tissue inactivation of pentobarbital, Sandoptal, and other short-acting barbiturates is not understood, it seems probable that it is enzymic in nature and that, in common with other enzymic processes, it is slowed by a reduction in temperature. Masson and Beland (*6*) have classified the barbiturates on the basis of the mechanism of detoxification (tissue inactivation or elimination by the kidney, or both). In general it is to be expected that the duration of action of those barbiturates which are inactivated in the tissues will be prolonged by a reduction in body temperature, while that of derivatives excreted by the kidney will be little affected by changes in body temperature, except for a possible

TABLE 1

DURATION OF BARBITURATE ANESTHESIA IN MICE AT TWO LEVELS OF BODY TEMPERATURE*

	Barbital	Pento-barbital	San-doptal
Dose (Na salt) (mg./kg.)	290	37.5	55
Body temperature, 37°C.:			
No. of animals	12	11	9
Mean body weight (grams)	22.4	20.1	20.5
Mean sleeping time (min.)	314.5	17.6	76.9
Standard Error	20.02	3.33	12.21
Body temperature, 27°C.:			
No. of animals	11	11	7
Mean body weight (grams)	22.4	21.5	23.3
Mean sleeping time (min.)	331.5	61.8	202.7
Standard Error	22.14	4.51	20.08
P†	0.1	<0.001	<0.001
Ratio, $\frac{\text{Sleeping time, 27°C.}}{\text{Sleeping time, 37°C.}}$	1.05	3.5	2.6

* All barbiturates were administered intraperitoneally as the sodium salt in solutions of such strength that the dose was contained in 0.1–0.3 ml.

† P expresses the probability that the difference between the sleeping times at the two body temperatures would occur through errors in random sampling; see Fisher (*3*) for method of calculation.

[1] The Sandoptal was kindly supplied by Mr. Harry Althouse, Sandoz Chemical Works, West Coast Branch, San Francisco.

effect of this temperature on the rate of their excretion in the urine.

Many years ago Brunton (*1*) found that warming reduced the incidence of death in animals poisoned with chloral hydrate, a depressant which is largely detoxified by conjugation in the liver, and recommended that victims of acute chloral poisoning be kept warm. The data presented here also provide a rational basis for the application of warmth in cases of acute barbiturate poisoning involving short-acting barbiturates which are inactivated by the tissues.

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Hyperheparinemia: Cause of the Hemorrhagic Syndrome Associated With Total Body Exposure to Ionizing Radiation[1]

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Hemorrhage is one of the most striking features of the syndrome which follows acute whole-body exposure to ionizing radiations in the midlethal range. This irradiation-induced bleeding phenomenon occurs in man as well as in many experimental animals. In our experience the dog proved more suitable for study than the rabbit, guinea pig, rat, mouse, or goat, and the picture displayed by the dog later proved to be very similar to that seen in man following the bombing of Hiroshima and Nagasaki (*3*).

The hemorrhagic disease of irradiation is accompanied by a thrombocytopenia. Both bleeding and clotting times are prolonged, and clot retraction is impaired. At death, both animal and man show extensive hemorrhages which may occur in all organs of the body but which are first seen in the organs of motions, such as the intestines, heart, lungs, skeletal musculature, and urinary bladder.

This disease has been thought to result from the associated thrombocytopenia (*2*). However, in a study carried out on dogs during the past three years we have concluded that the thrombocytopenia plays only a secondary role in producing hemorrhage (*1*). Of greatest significance in this disease is the presence in the blood of an increased amount of free heparin. These conclusions are based on the following observations:

(1) The clotting time in both man and dog may be greatly prolonged or the blood rendered entirely incoagulable after acute exposure to ionizing radiations such as X-rays delivered over the entire body. If the clotting time is sufficiently prolonged, the blood of an irradiated dog will delay the clotting time of normal blood, thus demonstrating the presence of an active anticoagulant not normally present in blood.

(2) Evidence that this anticoagulant is heparin is based on the fact that specific antiheparin substances, such as toluidine blue and other members of the thionine series, and protamine

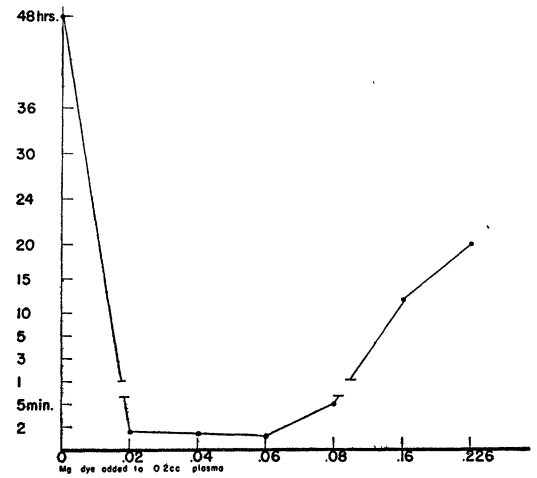

Fig. 1. The antiheparin and the anticoagulant effect of toluidine blue on the clotting time of plasma in an irradiated dog (Dog 108).

will return the clotting time to normal both *in vivo* and *in vitro*. These substances will prevent or stop hemorrhage even though the platelet count may be less than 50,000. The effect of toluidine blue on the *in vitro* clotting time of an irradiated dog is shown in Fig. 1. It will be noted that the dye is both coagulant and anticoagulant, and that its effective antiheparin range gives way to its anticoagulant property as the concentration of the dye increases. The clotting time of the blood of

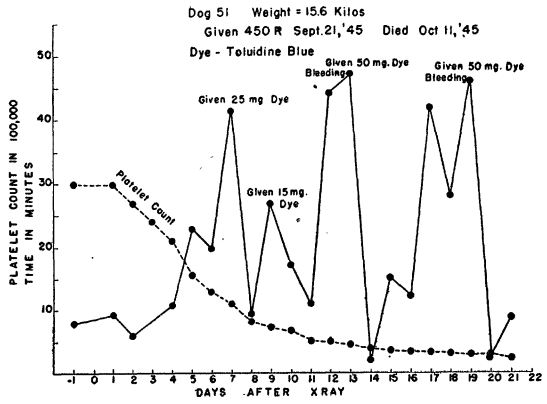

Fig. 2. The effect of repeated injections of toluidine blue on the whole-blood clotting time of an irradiated dog.

this animal was greater than 48 hours, but after the intravenous injection of 24 mg. of toluidine blue the clotting time returned to normal within 20 minutes after dye administration.

(3) An anticoagulant which was indistinguishable from heparin, was isolated from the blood of irradiated dogs, and on the basis of the number of units of potency per milligram of

[1] This paper is based on work performed under Contract No. W-7401-eng-37 with the Manhattan Project for the University of Chicago. It will appear in Volume 22B of the *Manhattan Project Technical Series* as a part of the contribution from the University of Chicago Project.