THE EFFECT OF INTRAVENOUS PENTOTHAL SODIUM
WITH OR WITHOUT INHALATION OF OXYGEN
ON LIVER FUNCTION* †‡

C. H. WALTON, M.D.,§ J. SALDAMANDO, M.D., AND W. M. EGNER, B.S.

Chicago, Illinois

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The anesthetic management of the surgical patient with hepatic damage presents a challenge to the anesthesiologist, particularly in regard to an accurate evaluation of the patient's available vital reserve. The response of the normal and damaged liver to various anesthetic agents, as measured by laboratory tests, is an important aspect of this over-all problem. Conclusive evidence has been presented showing that various anesthetic agents, particularly halogenated hydrocarbons, produce definite parenchymatous liver damage, which is modified by high alveolar oxygen concentration (1, 2, 3). There has also been shown a variable degree of subclinical liver involvement following surgical procedures, without definite relation to the anesthetic agent, as evidenced by abnormal liver function tests postoperatively (4, 5, 6). Among the various factors contributing to this transient hepatic damage, hypoxia and the current nutritional state are considered to be exceedingly important (6). In regard to the effect of oxygen want, it has been shown that, in animals, the fundamental pathologic physiology involved in halogen liver poisoning may be a centrolobular hypoxia secondary to an initial toxic swelling of the parenchyma (7). Thus a mildly toxic agent, even in the presence of adequate peripheral oxygenation, may result in a transient hepatic damage from a central hypoxia, which may be subsequently aggravated by low oxygen tensions. The nutritional factor is also inextricably woven into this complex pattern, as dietary deficiency may predispose to, or even produce, similar parenchymal swelling, with a resulting circulatory embarrassment of the liver lobule (8).

In view of the popularity of pentothal sodium as a primary or supplementary anesthetic agent, its tendency toward respiratory depression (9, 10) and the controversial nature of the present knowledge concerning its detoxification, it was thought to be of importance to

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‡ From the Department of Surgery (Anesthesiology), University of Chicago.
§ Anesthesiologist, Carle Hospital Clinic, Urbana, Illinois.
determine its effect on the function of the normal and damaged liver of the dog, with particular emphasis on the influence of inhalation oxygen.

Pentothal sodium has been reported to have produced deleterious effects in patients, both with and without liver damage (11, 12). Evidence implicating the drug as the sole factor is lacking, however, and increasingly large series of pentothal sodium anesthesias are being reported with low mortality and morbidity (13, 14). Nevertheless, in a recent clinical report, Shideman et al. (15) definitely related a prolonged recovery time, following a standard dose of pentothal sodium, to the amount of liver damage, as shown by liver function tests. Mark et al. (16) found that in man pentothal sodium breaks down slowly (15 per cent per hour), contrary to previous assumption. They believed that early recovery is a function of plasma-tissue shift rather than a rapid breakdown.

In the laboratory animal various attempts have been made to establish the site of detoxification of pentothal sodium, based on partial hepatectomy, Eck fistula technic, hepatotoxin administration and both in vitro and in vivo tissue distribution studies (17–23). Considerable disagreement has been noted, perhaps because of the many variables involved. Histologic evidence of liver damage has been found following administration of thiobarbiturates, including pentothal sodium, though again with some apparent contradiction (24, 25, 26). On the basis of comparative plasma decay curves in normal dogs and those with Eck fistulas, heart-lung, heart-lung-liver and heart-lung-kidney preparations, Kelly and Shideman (27) believe that the liver is the major organ of detoxification of pentothal sodium in the dog.

Previous work in this laboratory (28) revealed retardation of return to normal function of the chloroform damaged liver of the dog when one dose of pentothal sodium (20 mg. per kilogram of body weight) was administered intravenously at the height of dysfunction, but when 100 per cent oxygen was given with the pentothal sodium, the return rate was normal. This suggests that, in moderate dosage, pentothal sodium is deleterious to the liver only by virtue of its respiratory depression and hemodilution, with consequent hypoxemia. Correction of the oxygen deficiency apparently eliminated the adverse effect.

In the present study an attempt was made to determine whether pentothal sodium per se had any toxic effect on the liver of normal dogs. Plasma prothrombin and serum bilirubin levels were used to detect minimal changes in function. It is realized that liver function tests are numerous and that a battery of tests is required to completely evaluate hepatic function (29). However, in view of the fact that both plasma prothrombin and serum bilirubin levels were among those tests showing some correlation between postmortem structural alteration and antemortem function (30), they were deemed adequate for de-
termining mild dysfunction. An added advantage was the small daily blood sample required (5 cc.), thus minimizing the important factor of chronic blood loss. By eliminating so far as possible the factors of oxygen want and inadequate nutrition, it was thought that any demonstrable effect from pentothal sodium under these conditions might be due to the drug per se.

**Experimental Methods**

Stock dogs of 8 to 12 kg. in weight were used. Pentothal sodium was prepared in a 1 per cent solution on the day of usage. A standard intravenous dose of 20 mg. per kilogram of body weight of pentothal sodium was given twice daily for a period of fourteen days. Maintenance of adequate food intake was considered essential. Of two groups of dogs, one received 100 per cent oxygen inhalations by mask (semiclosed) until recovery, and the other was allowed to breathe room air. Recovery was defined arbitrarily as the time when muscle tonus was adequate to maintain the head erect. "Sleep time" thus represents the period from the start of the intravenous injection until return of muscle tonus of the neck. Daily determinations of prothrombin time were made by the one stage method of Quick (31), using Maltine thromboplastin. Serum bilirubin was determined daily by the Malloy and Evelyn technic (32). Blood arterial oxygen saturation was estimated by the methods of Van Slyke and Neill (33) on four dogs before and after pentothal administration, with and without oxygen inhalation, in order to confirm the elimination of hypoxemia.

**Results and Discussion**

A preliminary group of 3 dogs, when given 20 mg. of pentothal sodium per kilogram of body weight intravenously twice the first day, slept through the first night and consumed no food. This marked sensitivity, together with starvation, made it difficult to evaluate an initial fall in prothrombin time to 62 per cent of normal. On the third day, however, they were started on one dose of 20 mg. per kilogram of body weight of pentothal sodium daily, combined with 100 per cent oxygen inhalations. This regimen was continued daily for three weeks. On this dosage schedule, the prothrombin time returned to and remained within normal ranges before discontinuance of the pentothal sodium.

Twelve additional dogs selected from the stock supply were divided into two groups, one group being given pentothal sodium alone, while the other group received pentothal sodium with oxygen. Each group was given the same dosage of pentothal sodium (20 mg. per kilogram of body weight) twice daily for fourteen days, and adequate food intake was insured daily. One animal in each group died in the first week from pneumonia, the diagnosis being confirmed by autopsy. The mean prothrombin time of the remaining 10 animals is shown in figure
1. A mild depression of prothrombin time was noted about the second day, with a maximum mean low of 76 per cent of normal, occurring approximately on the fifth to seventh days. Upon discontinuance of the pentothal sodium after the fourteenth day, however, the values returned to normal ranges within four days. In figure 2, the mean serum bilirubin in milligrams per 100 cc. is presented. There was a slight increase during the first few days, reaching a maximum on the fifth day, but a gradual return to normal levels was seen before the end of the fourteenth day. Figure 3 represents the mean "sleep time" of the two groups. There was a wide individual variation in "sleep time," both from dog to dog and from day to day in the same dog. A tendency to vary inversely with the prothrombin time depression was noted, with the greatest increase in "sleep time" during the first five days and some indication of tolerance thereafter.

The variation between the two groups, however, was never sufficient to be of statistical significance in regard to either prothrombin time, serum bilirubin levels or "sleep time." Thus it appears that in this dosage schedule pentothal sodium has a mildly toxic effect on the liver regardless of the protective measures of oxygen inhalation and...
adequate food intake. While this may not be accepted as further evidence for partial hepatic detoxification of the drug, it does agree with other evidence previously presented in this regard. In view of the fact that one dose of pentothal sodium daily, with adequate oxygen and food intake, did not maintain depressed prothrombin levels, whereas twice that amount resulted in only mild depression, it would appear that the amount of drug required to produce this effect in the normal dog is considerably in excess of any conceivable clinical usage. With the usual reservations about the clinical interpretation of laboratory evi-

![Image of graph showing sleep time vs days with and without pentothal]

**Fig. 3.** "Sleep time" showing wide variation with some tendency to development of tolerance to pentothal. No significant difference with oxygen protection.

dence, however, it might be suggested that in the patient with considerable preoperative liver dysfunction, pentothal sodium might well be a sufficient added burden to exceed the limits of tolerance. In any event, its use in such patients must be attended with extreme caution, even in the presence of the usual safeguards.

**Summary**

Intravenous pentothal sodium, in doses of 20 mg. per kilogram of body weight, was given twice daily to normal dogs for periods of two to three weeks. Hepatic function, as determined by prothrombin time and serum bilirubin levels, was mildly depressed, with complete return to normal four days after the last injection of pentothal sodium. Inhalation of 100 per cent oxygen had no modifying effect on the depression of liver function produced by the employed dosage of pentothal sodium.

**REFERENCES**


26. Richards, R. K.: Personal communication to the authors.


