THE EFFECTS OF CERTAIN PREMEDICANTS ON TRAUMATIC SHOCK PRODUCED IN ANIMALS UNDER ETHER ANESTHESIA * †

CHARLES D. ANDERSON, M.D., AND HIRAM E. ESSEX, PH.D.

Rochester, Minnesota

MANY investigations such as that of Stange (1) have been reported on the effects of various premedicants used with certain anesthetic agents. In various animals, the barbiturates (2) and avertin with amylene hydrate (3) have been shown to diminish the time of induction, to prolong the duration of action and to allow the use of a smaller concentration of nitrous oxide for anesthesia. Similar effects with ethylene anesthesia have been noted with amytal, dial, avertin with amylene hydrate and chloral hydrate (4). Calderone (5) has stated that the margin of safety in ether anesthesia is neither increased nor decreased by preliminary medication with sedative doses of morphine or sodium amytal. Other workers (6, 7) have reported that dial, neonal and pentobarbital sodium decrease the amount of ether needed to produce a given depth of anesthesia.

It has been noted that under a standard method of producing traumatic shock in animals sodium amytal (8) or pentobarbital sodium anesthesia (9, 10) results in a definite delay of the onset of shock and death as compared with ether anesthesia. Pentothal sodium anesthesia produced an effect similar to that of ether anesthesia as regards onset of shock and death (10).

Seeley, one of us (Essex) and Mann (8) in their investigation of traumatic shock under certain anesthetic agents made the observation that administration of sodium amytal preliminary to ether anesthesia resulted in a definite delay of the onset of shock and death (8a). An investigation of the effects of other premedicants on traumatic shock seemed to be indicated and this investigation was instituted to determine the effects of premedication with morphine sulfate, atropine sulfate and pentobarbital sodium when given singly and in various combinations to animals in which traumatic shock was produced under ether anesthesia.

METHOD

The premedication was given subcutaneously and the animal was observed for thirty minutes thereafter before being anesthetized with

* Abridgment of thesis submitted by Dr. Anderson to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M.S. in Anesthesia.

† From the Department of Anesthesia and the Division of Experimental Medicine, Mayo Foundation, Rochester, Minn.

ether. For maintaining ether anesthesia an intratracheal tube was connected with an auto-inhalation (11, 12) apparatus provided with a set of valves described by Mousel and Seldon (13). A cannula was inserted in the left carotid artery and connected to a mercury manometer for kymographic recording of the arterial blood pressure. Heparin (1 per cent) was used as the anticoagulant. The abdomen was opened with a midline incision. Rubber sheeting with a slit in the middle, corresponding to the size of the incision, was placed over the abdomen. The edges of the slit were sewed to the sides of the incision. The apron was fastened by its corners to standards, thus producing a hammock on which the intestines could be exposed and which also provided a means of collecting the intestinal transudate.

The method of producing traumatic shock in this investigation was intestinal manipulation and exposure as described by Seeley, one of us (Essex) and Mann (8). The moment when the small intestines were delivered through the incision was considered zero time in all experiments.

Samples of blood, for estimations of hemoglobin by the method of Sanford and Sheard (14), were obtained, before the premedication was given, at the end of the preanesthetic period, at the beginning of intestinal manipulation and every hour thereafter until death. The mean blood pressure, pulse rate, rectal temperature and room temperature were noted at the beginning of intestinal manipulation, at the end of intestinal manipulation and every thirty minutes thereafter. The depth of anesthesia was maintained at a level just sufficient to abolish the corneal reflex but not the wink reflex.

Nine series of seven experiments each were performed. The first series, in which no premedication was used, served as a control. In the other series premedication was given as shown in table 1.

TABLE 1

THE PREMEDICATION USED IN THE NINE SERIES OF EXPERIMENTS UNDER ETHER-AIR ANESTHESIA. SEVEN ANIMALS WERE USED IN EACH SERIES

Series	Premedication	Dose, mg. per kg. of Body Weight
1	No premedication Control series	
2	Morphine sulfate	Various doses from 1.1 to 2.0
3	Morphine sulfate	0.25
4	Atropine sulfate	0.0065
5	Morphine sulfate	0.25
	Atropine sulfate	0.0065
6	Pentobarbital sodium	1.3
7	Pentobarbital sodium	1.3
	Atropine sulfate	0.0065
8	Pentobarbital sodium	1.3
	Morphine sulfate	0.25
9	Pentobarbital sodium	1.3
	Morphine sulfate	0.25
	Atropine sulfate	0.0065

It will be noted that in all series of experiments, from series 3 to series 9 inclusive, the dose of the premedicant is similar to that which might be used preoperatively on human patients.

Appreciation of the technical assistance given by Mr. W. A. Meeker is expressed.

RESULTS

The main criteria used to determine the onset of shock were: (1) a sustained decreased mean blood pressure (15, 16) of 70 mm. of mercury or less, (2) a hemoconcentration of 130 per cent (15) or more, the preanesthetic or control value being arbitrarily considered 100 per cent. The average decline of mean blood pressure during intestinal manipulation and the amount of intestinal transudate are given in table 2.

TABLE 2

AVERAGE DECLINE OF MEAN BLOOD PRESSURE DURING INTESTINAL MANIPULATION AND AMOUNT OF INTESTINAL TRANSUDATE

Premedication	Average Mean Blood Pressure, mm. of mercury		Decrease of Mean Blood Pressure During Intestinal Manipulation, mm. of mercury	Intestinal Transudate, range in cc.
	At Beginning of Intestinal Manipulation	At End of Intestinal Manipulation		
Control	140	115	25	0–260
Morphine sulfate, varying doses	131	102	29	8–265
Morphine sulfate, 0.25 mg. per kg.	143	103	40	0–175
Atropine sulfate	131	112	19	40–265
Morphine sulfate and atropine sulfate	155	134	21	0–100
Pentobarbital sodium	149	125	24	25–185
Pentobarbital sodium and atropine sulfate	150	125	25	0–240
Pentobarbital sodium and morphine sulfate	142	133	9	0–155
Pentobarbital sodium, atropine sulfate and morphine sulfate	157	137	20	0–130

The Control Series of Experiments.—The average survival time of the seven animals was eight hours and fourteen minutes, with a range of survival time from five hours and twenty minutes to ten hours and fifteen minutes. A hemoconcentration of 130 per cent of the control value was reached on the average in four hours and thirty-seven min-

utes, with variation in time between three hours and six and a half hours. The average value for hemoglobin, for the seven experiments, at the beginning of intestinal manipulation was 105 per cent of the control value. At death, the lowest value for hemoconcentration was 130 per cent and the highest was 143 per cent of the control value. The mean blood pressure became depressed to the critical level of 70 mm. of mercury or less in an average of seven hours and eleven minutes. In six of the seven experiments, the animal died within an hour after the critical level for blood pressure had been reached. The average decrease of temperature was 7.0 C. with a range of temperature loss between 2.0 and 10.0 C.

Premedication with Morphine Sulfate in Varying Doses.—The subcutaneous injection of morphine sulfate caused every animal either to vomit or to defecate during the period of observation before anesthesia. In fact 5 of the 7 animals both vomited and defecated. When the abdomen was opened the small intestine and especially the ileum and cecum were in a state of hypermotility and hypertonicity which became more marked after intestinal manipulation had been started. The average survival time was eleven hours and ten minutes, with variation in survival time from seven hours and thirty-eight minutes to sixteen hours and fifty-three minutes. A hemoconcentration of 130 per cent of the control value appeared on the average in three hours and forty-one minutes, with a variation in time of appearance from one hour and five minutes to seven hours and thirty-five minutes. The average value for hemoglobin at the end of the preanesthetic observation period was 99 per cent of the control value and at the beginning of intestinal manipulation the average hemoglobin values had risen to 110 per cent. At death the lowest and highest values for hemoglobin in the experiments in this series were respectively 130 and 163 per cent of the control value. The mean blood pressure became depressed to the critical level of 70 mm. of mercury in an average time of seven hours and eleven minutes. The average decrease of temperature was 7.1 C. with a range of temperature loss between 3.5 and 10.5 C.

Premedication with Morphine Sulfate, 0.25 mg. per kg.—Morphine affected the animals in this series in a way similar to that observed in the preceding series, although the effects were invariably milder. The average survival time was eight hours and six minutes. A hemoconcentration of 130 per cent was reached on the average in four hours and three minutes. At the end of the preanesthetic observation period, the average hemoglobin level was 100 per cent; at the beginning of intestinal manipulation the average value had risen to 113 per cent. At death the lowest hemoglobin level was 130 per cent and the highest level was 167 per cent. The mean blood pressure became depressed to the critical level, on the average, in six hours and fifty minutes. The average temperature loss was 5.1 C.

Premedication with Atropine Sulfate.—Atropine, in the dosage

used, did not produce symptoms or signs in the animals during the preanesthetic observation period. The average survival time was ten hours and fifty-four minutes. The hemoglobin value reached a concentration of 130 per cent in an average time of three hours and nine minutes. The average hemoglobin value at the end of the observation period was 97 per cent; at the beginning of intestinal manipulation it was 114 per cent. At death the lowest and highest hemoglobin values were 143 and 164 respectively. The mean blood pressure on the average entered the critical level in seven hours and forty-seven minutes. The average temperature loss was 7.1 C.

Premedication with Morphine Sulfate and Atropine Sulfate.—The presence of the atropine did not influence the effects of the morphine sulfate, which were similar to those described in series 3. The average survival time was ten hours and eleven minutes. A hemoconcentration of 130 per cent occurred on the average in five hours and fifty-one minutes. At the end of the preanesthetic observation period the average hemoglobin level was 94 per cent; at the beginning of intestinal manipulation it was 105 per cent. At death the lowest and highest hemoglobin values for these experiments were respectively 130 and 146 per cent. The mean blood pressure was depressed to 70 mm. of mercury in eight hours and forty-six minutes. The average temperature loss was 4.9 C.

Premedication with Pentobarbital Sodium.—During the preanesthetic period of observation of the animals sedative effects of the drug were not evident. The average survival time was nine hours and forty-four minutes. The hemoglobin value reached a concentration of 130 per cent in four hours and fifty-one minutes. At the end of the preanesthetic observation period the average hemoglobin value was 91 per cent; at the beginning of intestinal manipulation it was 107 per cent. At death, the lowest hemoglobin value was 131 per cent and the highest value was 157 per cent. The mean blood pressure was depressed to the critical level in eight hours and thirty-four minutes on the average. The average temperature loss was 5.1 C.

Premedication with Pentobarbital Sodium and Atropine Sulfate.—During the preanesthetic period of observation there was no difference in the behavior of the animals before and after receiving pentobarbital sodium and atropine sulfate. The average survival time was ten hours and forty-five minutes. The hemoglobin reached the critical value of concentration, on the average, in four hours. At the end of the preanesthetic observation period the average hemoglobin value was 92 per cent; at the beginning of intestinal manipulation it was 112 per cent. At death, the lowest and highest hemoglobin values were 131 and 163, respectively. The mean blood pressure was depressed to the critical level, on the average, in ten hours and four minutes. The average temperature loss was 6.3 C.

Premedication with Pentobarbital Sodium and Morphine Sulfate.—Signs and symptoms of a moderate degree, characteristic of the pres-

ence of morphine in the premedication, were evident. The average survival time was nine hours and thirty-six minutes. A hemoconcentration of 130 per cent was reached in five hours and twenty-one minutes on the average. At the beginning of intestinal manipulation the average hemoglobin value was 94 per cent. At the end of intestinal manipulation the average value was 97 per cent. At death the lowest hemoglobin value was 127 per cent. This animal displayed all the criteria of shock except hemoconcentration to 130 per cent. As the last determination was made forty-five minutes before death, the hemoglobin value may have reached the critical level before death. All other animals in this series had values of 130 per cent or more at death, the highest value being 158 per cent. The mean blood pressure reached its critical level in eight hours and thirty-nine minutes, on the average. The average temperature loss was 4.2 C.

Premedication with Pentobarbital Sodium, Morphine Sulfate and Atropine Sulfate.—The characteristic reaction to the injection of morphine was observed. The average survival time was ten hours and forty minutes. The blood concentrated to 130 per cent of the control value in an average time of three hours and thirty-four minutes. At the end of the preanesthetic observation period the average hemoglobin value was 95 per cent; at the beginning of intestinal manipulation the value was 111 per cent. At death the lowest and highest hemoglobin values were 138 per cent and 157 per cent of the control value. The mean blood pressure reached 70 mm. of mercury in nine hours and thirty-nine minutes on the average. The average loss of temperature was 5.6 C.

COMMENT

In this investigation only one variable, the type of premedicant used, was introduced; an effort was made to maintain all other factors constant. It may be seen from figure 1 that the survival time of the animals in the various series falls into roughly three groups. The results of the control series and those of the morphine sulfate series in which 0.25 mg. per kilogram of body weight was used may be put in one group since they show the shortest survival time. The second group contains the four series of experiments which had the longest survival time, namely, the morphine sulfate series with varying doses; the atropine sulfate; the pentobarbital sodium and atropine sulfate; the pentobarbital sodium, atropine sulfate and morphine sulfate series of experiments. The third group consists of those remaining series of animals having a survival time intermediate between the other two groups.

The survival time of the control series of animals is essentially the same as that which Pender and one of us (Essex) (10) obtained using similar methods.

It is interesting to note the effect on survival time when different

doses of morphine sulfate were used. When relatively massive doses of morphine sulfate were used, the survival time was the longest. On the other hand, when morphine sulfate in a dose of 0.25 mg. per kilogram of body weight was used, the survival time was essentially the same as that in the control series (fig. 1). This difference has not been explained. The relatively massive dose of morphine sulfate was at least four to eight times as great as is used ordinarily as a premedicant with human patients.

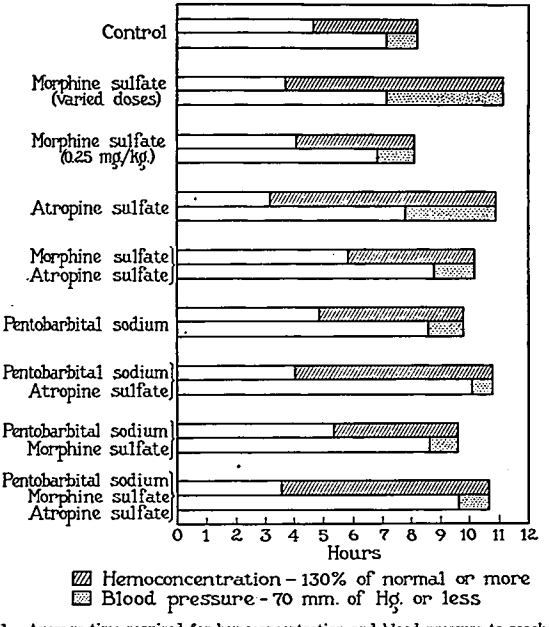

FIG. 1. Average time required for hemoconcentration and blood pressure to reach critical levels in each series of experiments. Average time of death is shown by the end of the bar in each instance.

If the series of animals receiving morphine sulfate in relatively large doses is not considered, the series of animals receiving atropine sulfate alone as a premedicant had the longest survival time (fig: 1), amounting to a 32 per cent increase of survival time over the control series of animals. Whenever atropine sulfate was given, the survival time of the animals in that series was longer than that of those animals which had not received it.

The average survival time in each series in which pentobarbital sodium was used in the premedication was greater than the average survival time of the control series (fig. 1). However in the dose used (1.3 mg. per kilogram of body weight) pentobarbital sodium was not as efficacious as atropine sulfate.

A rather striking result was obtained in the series of animals receiving pentobarbital sodium, atropine sulfate and morphine sulfate premedication. There was less than two hours' difference in the survival times of animals in this series. Such a constancy of survival time was not observed in any of the other series. The animals in this series had an average survival time 30 per cent greater than that of the control series.

It has been reported (17) that hemoconcentration to a critical level is an early sign of shock whereas a depression of the mean blood pressure to its critical level may be a late sign. This was found to be essentially true in this investigation, although in a small number of experiments the reverse was observed. The averages for each series of experiments show that hemoconcentration to a critical level appeared in two to six hours before the blood pressure was depressed to a critical level. The presence of pentobarbital sodium in the premedication increased this difference markedly. Atropine sulfate when present in the premedication had a similar effect but to a lesser extent. The greatest difference in the time between the appearance of hemoconcentration to 130 per cent of the control value and the appearance of depressed blood pressure to 70 mm. of mercury was in that series of experiments in which pentobarbital sodium, atropine sulfate and morphine sulfate were used. The difference in these experiments amounted on an average to six hours and five minutes (fig. 1).

Bourne, Bruger and Dreyer (18) and also Adolph and Gerbasi (19), noted a decrease of blood solids with sodium amytal anesthesia. Seeley, one of us (Essex) and Mann (8) and others (10), while studying traumatic shock in animals under anesthesia with various barbiturates, described a preliminary temporary decrease of blood concentration which changed to hemoconcentration as a state of shock developed. This observation was also made in this investigation, even though the amount of barbiturates used was small, since it was merely a premedicant dose and not an anesthetic dose. At the end of the preanesthetic period of observation the concentration of the blood always decreased below the value for the animal before premedication was given. When the animal was anesthetized with ether, a restitution of the concentration of the blood occurred to about its normal level. As shock developed during the course of the experiment, hemoconcentration progressively occurred.

A depressed mean blood pressure to 70 mm. of mercury or less was usually a late sign of shock in these experiments, a fact which has been noted previously by others (15). Particularly was this so when bar-

biturates formed a part of the premedication. Under these conditions the animals would die in about an hour after the blood pressure had fallen to 70 mm. of mercury or less (fig. 1). Morphine sulfate in a dose of 0.25 mg. per kilogram of body weight had a similar but less pronounced effect. In the series of animals in which atropine sulfate was used alone, a depressed blood pressure to 70 mm. of mercury or less occurred about three hours before the death of the animal.

During barbiturate anesthesia, Pender and one of us (Essex) (10) observed that the mean blood pressure had an initial decrease lasting for several hours. Then the mean blood pressure would rise again for an hour or two. Following this, the mean blood pressure progressively decreased until death. This phenomenon was observed in this investigation in most cases, even though pentobarbital sodium was used only as a premedicant rather than as the anesthetic agent. When pentobarbital sodium was used alone, a secondary rise of mean blood pressure was observed in six of the seven experiments, occurring in three to five hours after the beginning of intestinal manipulation. When morphine sulfate was combined with pentobarbital sodium as the premedicant, a secondary increase of mean blood pressure was noted in only three of the seven experiments. When atropine sulfate was combined with pentobarbital sodium as the premedicant, a secondary increase of mean blood pressure was observed in four of the seven experiments. In the series of experiments in which pentobarbital sodium, atropine sulfate and morphine sulfate were used as premedicants, a secondary increase of mean blood pressure occurred in five of seven experiments. No explanation is available for this phenomenon.

Mann (20) and also Seeley, one of us (Essex) and Mann (8) observed during experiments on traumatic shock produced by intestinal manipulation that considerable fluid accumulates in the peritoneal cavity. Pender and one of us (Essex) (10) did not observe a relation between the amount of fluid obtainable and the increase of hemoconcentration. This investigation confirms that observation.

Ether in anesthetic amounts causes many alterations of the normal physiologic processes of animals. Barbour and Bourne (21) reported that the blood solids were increased during ether anesthesia. Searles and one of us (Essex) (22) and Bollman and his co-workers (23) reported that ether anesthesia produced an increase of the total circulating erythrocytes, apparently by extrusion of these cells from the spleen and also by a diminution of the volume of the circulating plasma.

Many investigations of the effects of morphine and atropine on the small intestine of man and of animals have been reported. Plant and Miller (24) worked both on dogs and on man. They observed that in the small intestine of dogs after administration of morphine there was an increase of tone, of frequency and amplitude, of peristaltic waves and of segmentation. In man they noted an early increase of tone and a later increase of the frequency of contractions after administration

of morphine. They observed that morphine increases the activity of the intestine during the relaxation produced by atropine and also that atropine failed to relax the small intestine during action of morphine.

The findings of Gruber and his co-workers (25) were not in agreement with the work just cited, since they found that the increased tone caused by morphine could be antagonized completely by an injection of atropine. Kanan (26) repeated all of this work and found that 2 mg. of atropine sulfate per kilogram, administered subcutaneously, did not antagonize the action of morphine but that larger doses would. Others (27–30) have substantiated these findings.

Elsom and Drossner (31) in studies on man noted that atropine sulfate in therapeutic doses produced a definite and prolonged effect on the small intestine, consisting of a marked decrease of tone and of peristaltic activity.

In this investigation the presence of morphine in the premedication could always be detected during the period of intestinal manipulation by the increased tone of the small intestine. When morphine sulfate was used alone in the premedication the increased tone was usually maximal. When morphine sulfate was combined with atropine sulfate or pentobarbital sodium or both there was always increased tone although not of so marked a degree as when it was used alone.

Barlow and Duncan (32) using nitrous oxide and oxygen as the anesthetic agent on white rats stated that the premedication value of morphine rose rapidly with doses of more than 7.86 mg. per kilogram; that with pentobarbital sodium as the premedicant the duration of anesthesia increased in proportion to the dose; that morphine and pentobarbital sodium used together were synergistic and would potentiate each other. Koppanyi (33) observed that atropine premedication decreased the amount of barbiturate necessary to produce anesthesia.

Bourne (34) stated that morphine as premedication protects the animal against concentration of blood. The results of this investigation do not substantiate his findings. The development of shock in our experiments was a common factor and in those series of experiments in which morphine sulfate was used as a premedicant the blood reached a concentration of 130 per cent of normal sooner than in the control series.

SUMMARY

The effects on hemoconcentration, blood pressure and so forth of morphine sulfate, atropine sulfate and pentobarbital sodium, used singly or in various combinations, as premedicants to ether anesthesia in animals in which traumatic shock was produced by intestinal manipulation, were studied.

Morphine sulfate as a premedicant in doses comparable to those given to human patients did not delay the onset of shock or death in animals under ether anesthesia, when compared with the time required

for onset of shock and death with ether anesthesia alone. When morphine sulfate was combined with atropine sulfate or pentobarbital sodium or both, the morphine appeared to decrease the effectiveness of the other premedicants in delaying the onset of shock and death in animals under ether anesthesia.

Atropine sulfate proved to be the most effective premedicant in delaying the onset of shock and death in animals under ether anesthesia. Particularly was this so when atropine sulfate was the only premedicant used. The effectiveness of atropine sulfate appeared to be reduced when it was combined with morphine sulfate or pentobarbital sodium or both of these drugs.

Pentobarbital sodium in the doses used was somewhat less effective than atropine sulfate in delaying the onset of shock and death, in animals under ether anesthesia.

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A series of radio broadcasts on Anesthesia has been arranged by the Committee on Publicity of the New York County Medical Society with the cooperation of the American Society of Anesthetists to be given over station WNYC at 11:45 a.m., Eastern War Time, as follows:

Sept. 16, 1943: "Anesthesia and Analgesia in Obstetrics" by Donald L. Burdick, M.D.

Sept. 23, 1943: "Anesthesia for Children" by George L. Burford, M.D.

Sept. 30, 1943: "Anesthesia in Modern Warfare" by Virginia Apgar, M.D.