COMPARISON OF THE CARDIOVASCULAR PROPERTIES
OF A NEW NONBARBITURATE INTRAVENOUS ANESTHETIC
AGENT WITH THOSE OF THIOPENTAL

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The general pharmacological properties of a new nonbarbiturate anesthetic agent, 5-ethyl-6-phenyl-m-thiazane-2,4-dione (Dolitrone), have been reported by Thompson, Smith, and Werner (1). The purpose of the authors in conducting the present investigation was to determine the actions of Dolitrone on the cardiovascular system of intact animals and to compare these effects with those produced by thiopental.

METHODS

The effects of the intravenous administration of Dolitrone and of thiopental on the cardiovascular system were compared in 16 experiments with 8 dogs. The dogs were prepared surgically for the direct measurement of the force of ventricular contraction by suturing a strain-gauge arch to the right ventricle three to six days prior to the experiments. The use of the strain-gauge arch for direct measurement of the force of ventricular contraction has been described in detail elsewhere by Cotten (2) and by Boniface, Brodie, and Walton (3). A permanent indwelling polyethylene catheter was placed in a femoral artery to permit measurement of the blood pressure with a Statham transducer in the unanesthetized animal. Injections of drugs were made through a similar catheter placed in a femoral vein. The dogs remained in apparent good health throughout the periods of the experiments.

The influence of Dolitrone and of thiopental on the incidence of arrhythmias produced by large doses of 1-epinephrine was studied in 10 additional dogs. Continuous recordings of the electrocardiogram were made before, during, and for several minutes after the injection of 1-epinephrine and of the 2 anesthetic drugs. Ten μg./kg. of 1-epinephrine were injected intravenously during a control period, followed approximately ten minutes later by 30 mg./kg. of Dolitrone or by 20 mg./kg. of thiopental. The administration of the anesthetic agents was followed five to eight minutes later by a second injection of 10 μg./kg. of 1-epinephrine. Each anesthetic agent was studied in each dog, Dolitrone being used first in half of the animals followed two days later by a similar experiment with thiopental. In the remaining animals, this

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order was reversed. The duration of anesthesia produced by the administration of 30 mg./kg. of Dolitrone and by 20 mg./kg. of thiopental was determined in these same dogs. The time at which the animals could stand unassisted was considered the end point of anesthesia.

The increase in heart rate produced by Dolitrone and by thiopental was studied in six dogs following premedication with 2.5 mg./kg. of morphine sulfate. Dolitrone was studied first in 3 animals, followed two days later by a similar study with thiopental. In the other 3 experiments, this order was reversed. Because of the additive depressant effect of morphine and thiopental on respiration, the dose of thiopental was reduced to 15 mg./kg. in these dogs. The influence of Dolitrone and of thiopental on the heart rate was also studied in 6 nonpremedicated rabbits and in 6 rabbits premedicated with 2.5 mg./kg. of morphine sulfate. Thirty mg./kg. of Dolitrone and 20 mg./kg. of thiopental were used in the nonpremedicated rabbits, while, in the rabbits premedicated with morphine, these doses were reduced to 15 mg./kg. of Dolitrone and 10 mg./kg. of thiopental. In all of these experiments with both dogs and rabbits, the changes in heart rate were determined from the electrocardiogram.

Thirty mg./kg. of Dolitrone and 20 mg./kg. of thiopental were administered to 12 rabbits following premedication with 5 mg./kg. of morphine sulfate in order to determine the effect of these drug combinations on the rate of the external respiratory movements. Additional observations were made with 12 similarly premedicated rabbits using smaller doses of the 2 anesthetic agents; namely, 25 mg./kg. of Dolitrone and 15 mg./kg. of thiopental. The respiratory rates were counted over 30-second intervals.

Dolitrone was prepared by dissolving the powder in a combination of 5 to 10 ml. of distilled water and 0.4 to 1.5 ml. of N NaOH added dropwise. The pH of such solutions ranged from 11.3 to 11.5. The solutions were prepared immediately prior to their injection. Thiopental sodium (Pentothal®) was injected as a 0.6 per cent aqueous solution prepared from the buffered powder. 1-Epinephrine was administered as the bitartrate (Suprarenin®), the dose being expressed in terms of the free base. Morphine sulfate was given intravenously in a 1 per cent solution, the doses being expressed in terms of the salt.

**Results**

The intravenous administration of Dolitrone produced a rapid and complete general anesthesia which was closely similar in character to that produced by thiopental. Thirty mg./kg. of Dolitrone were approximately equivalent in anesthetic potency to 20 mg./kg. of thiopental. In most cases, these doses were sufficient to result in a depth of anesthesia corresponding to planes 1 or 2 of stage III.

*Effects on Blood Pressure, Ventricular Contractile Force, and Heart Rate.* The characteristic effects of 30 mg./kg. of Dolitrone and
20 mg./kg. of thiopental on the systolic and the diastolic blood pressures, the force of ventricular contraction, and the heart rate are illustrated in figures 1 and 2. Dolitrotrone always produced an initial, transient decrease in both the diastolic and the systolic pressures which was followed by a rapid return to approximately control values. A similar initial decrease in blood pressure was not observed with thiopental. Except for the initial transient decrease in the blood pressure seen with Dolitrotrone, the 2 anesthetic drugs had variable effects on the general level of blood pressure which was slightly decreased, slightly increased, or unchanged following their intravenous administration.

The force of ventricular contraction was either unchanged or slightly to moderately decreased by both Dolitrotrone and thiopental.

![Graph](http://example.com/graph.png)

**Fig. 1.** Graphic representation of the effects of 30 mg./kg. of Dolitrotrone on blood pressure, ventricular contractile force, and heart rate. Dolitrotrone was administered by rapid intravenous injection through an indwelling catheter in the femoral vein while the dog was resting quietly. There was immediate development of complete general anesthesia to approximately plane 2. The blood pressure was measured from the femoral artery with a Statham transducer. Ventricular contractile force was measured with a strain-gauge arch sutured to the right ventricle at an operation performed four days prior to the experiment. Heart rates were determined from the electrocardiogram.

The average decrease in ventricular contractile force following Dolitrotrone was 24 per cent as compared with 15 per cent following thiopental. There was no statistically significant difference between these two averages ($t_1, * = 0.394; P = 0.7$).

The heart rate was increased markedly following the injection of either Dolitrotrone or thiopental. Dolitrotrone produced an average increase in heart rate of 101 beats per minute. For thiopental, the average increase was 84 beats per minute. However, there was no significant difference between these two averages ($t_2, = 1.562; 0.2 > P > 0.1$). The rapidity with which either of these anesthetic drugs was injected did not influence the increase in heart rate. Similar effects were

*Students "t" test.
obtained both with very rapid injections and with slower injections given over a period of two or three minutes. The marked increase in heart rate also did not appear to be due to the high alkalinity of the solutions containing Dolutrine (pH 11.3-11.5). Injections of equivalent amounts of vehicle of the same pH had no demonstrable effects on the cardiovascular system of either unanesthetized or anesthetized dogs.

Premedication of 6 dogs with 2.5 mg./kg. of morphine sulfate slowed the heart rate from an average of 112 beats per minute to an average of 70 beats per minute, but did not prevent a substantial increase in heart rate following the injection of either Dolutrine or thiopental. The average increase in heart rate in the dogs premedicated with morphine was 135 per minute following Dolutrine and 76 per minute following thiopental ($t_{0.01} = 3.1117; P = 0.01$). There was a statistically

![Image]

Fig. 2. Graphic representation of the effects of 20 mg./kg. of thiopental on blood pressure, ventricular contractile force, and heart rate. Same conditions as shown in fig. 1.

significant difference between these two averages but it should be noted that a smaller dose of thiopental was employed in these dogs premedicated with morphine than was used in the nonpremedicated dogs. Although it was not possible to prevent the development of the marked increase in heart rate by premedication with morphine, it was possible to decrease the severity of the tachycardia by the injection of a vasocostricor substance. The administration of 1 μg./kg. of 1-nor-epinephrine at the peak of the tachycardia produced by either Dolutrine or thiopental frequently reduced the heart rate temporarily to the preanesthetic control level.

To determine whether or not the increase in heart rate following the administration of Dolutrine was a feature specific for the dog, rabbits were anesthetized with Dolutrine and, for comparison, with thiopental. Both anesthetic agents had only slight effects on the heart
rate in the nonpremedicated rabbits, Dolitrone producing an average increase of 9 beats per minute and thiopental an average increase of 24 beats per minute. There was no significant difference between the 2 averages ($t_0 = 0.6749$; $0.6 > P > 0.5$). This absence of a substantial increase in heart rate probably was related to the very rapid heart rates in the control periods, which averaged 272 per minute. Premedication of the rabbits with 2.5 mg./kg. of morphine sulfate slowed the heart rate to an average of 166 per minute. The heart rate was increased substantially in each case when Dolitrone or thiopental was given to these premedicated rabbits. Dolitrone increased the rate by 97 per minute while the rate increase with thiopental was 85 per minute. There was no significant difference between the effects of the two drugs on the heart rate under these latter conditions ($t_0 = 0.4628$; $0.7 > P > 0.6$). Although the administration of the vehicle alone had no demonstrable influence on the cardiovascular system of the dog, the injection of the vehicle alone (pH 11.3) in 6 rabbits premedicated with morphine produced a moderate increase in heart rate. This increase represented approximately 45 per cent of the increase produced by Dolitrone or by thiopental.

**Effects of a Large Dose of 1-Epinephrine on the Electrocardiogram Before and After Dolitrone and Thiopental.** The intravenous administration of Dolitrone or of thiopental had no effect on the electrocardiogram beyond those effects usually associated with the development of tachycardia. Thus, depression of the S-T segment, inversion of the T-waves, and shortening of the Q-T interval frequently occurred following injections of the anesthetic agents.

The injection of 10 μg./kg. of 1-epinephrine before and after the administration of 30 mg./kg. of Dolitrone and before and after the administration of 20 mg./kg. of thiopental demonstrated that these anesthetic agents did not markedly sensitize the myocardium to epinephrine-induced arrhythmias. These results are summarized in table 1. There was a fifty per cent increase in the incidence of ventricular tachycardia following Dolitrone but only small changes in the frequency of other arrhythmias (table 1). The administration of 1-epinephrine following thiopental resulted in a 100 per cent increase in the incidence of ventricular tachycardia and a substantial increase in the incidence of coupling. Although there was an increase in the occurrence of epinephrine-induced ventricular tachycardia following both Dolitrone and thiopental, these arrhythmias were of relatively short duration and all of the dogs survived without any observable untoward effects.

**Duration of Anesthetic Action.** The average duration of the anesthesia produced by 30 mg./kg. of Dolitrone was 43 minutes, while that produced by 20 mg./kg. of thiopental was 55 minutes. Although the average duration of anesthesia was shorter for Dolitrone than it was
for thiopental, no statistically significant difference exists between the two values ($t_{is} = 1.4158; 0.2 > P > 0.1$).

**Recovery Phase of Anesthesia.** Recovery from the anesthetic effects of Dolitrone was quite smooth in most cases. However, in 5 of the 25 dogs anesthetized with Dolitrone, an interval of intense excitement occurred during the recovery phase of anesthesia. The excitement was characterized by generalized, coordinated muscular activity, howling, and loud barking, which lasted for fifteen to thirty minutes. This excitement did not appear to be related to the emergence delirium occasionally observed in dogs, but rather appeared to be due to either a specific effect of Dolitrone or to pain arising from the site of injection. Premedication with 2.5 mg./kg. of morphine sulfate did not pre-

| TABLE 1 |
| EFFECTS OF 10 MG./KG. OF 1-EPINEPHRINE ON THE CARDIAC RHYTHM OF TEN DOGS BEFORE AND AFTER DOLITRONE AND THIOPENTAL |

<table>
<thead>
<tr>
<th></th>
<th>Dolitrone 30 mg./kg.</th>
<th>Thiopental 20 mg./kg.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-Epinephrine Before</td>
<td>1-Epinephrine After</td>
</tr>
<tr>
<td></td>
<td>Dolitrone</td>
<td>Dolitrone</td>
</tr>
<tr>
<td>SA tachycardia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SA bradycardia</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>A-V block</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Nodal beats</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Nodal rhythm</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Nodal bradycardia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Coupling</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Premature beats</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Slow ventricular rhythm</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Alternating ventricular rhythm</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Multifocal ventricular tachycardia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>0</td>
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</tbody>
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vent the development of the excitement and no attempts were made to abolish it after its development. A similar picture of excitement was not noted in these same dogs during recovery from anesthesia with thiopental and no signs of excitement were noted in rabbits following either anesthetic drug.

**Effects on Respiration.** Dolitrone and thiopental did not change the rate of the external respiratory movements appreciable in nonpremedicated dogs in which the respiratory rates were between 16 to 24 per minute before the administration of the anesthetic drugs. In dogs in which the rate of respiration was above 24 per minute before the anesthetic drugs were injected, the rate of respiration was moderately decreased but never to rates below 16 per minute. In no instance was serious respiratory depression produced in the nonpremedicated
dogs by the administration of 10 to 40 mg./kg. of Dolitrone or by 10 to 20 mg./kg. of thiopental.

Six dogs premedicated with 2.5 mg./kg. of morphine sulfate tolerated the administration of 30 mg./kg. of Dolitrone without signs of respiratory difficulty. Similarly, no respiratory difficulty occurred when 15 mg./kg. of thiopental was given to 6 dogs premedicated with 2.5 mg./kg. of morphine. However, one dog given 5.0 mg./kg. of morphine expired from respiratory arrest following the injection of 20 mg./kg. of thiopental.

The administration of 30 mg./kg. of Dolitrone or of 20 mg./kg. of thiopental to 6 nonpremedicated rabbits reduced the rate of the external respiratory movements from an average of 123 per minute to an average of 45 per minute, but no signs of respiratory distress were noted in those animals.

The incidence of fatality in 24 rabbits given 25 and 30 mg./kg. of Dolitrone and 15 and 20 mg./kg. of thiopental following premedication with 5.0 mg./kg. of morphine are presented in table 2. All of 12 pre-

| TABLE 2 |
| SURVIVAL RATES OF RABBITS PREMEDICATED WITH 5.0 MG./KG. OF MORPHINE SULFATE |

<table>
<thead>
<tr>
<th>Dolitrone</th>
<th>Thiopental</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 mg./kg.</td>
<td>15 mg./kg.</td>
</tr>
<tr>
<td>Lived</td>
<td>Died</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
</tr>
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</table>

medicated rabbits tolerated anesthesia with 25 and 30 mg./kg. of Dolitrone but 10 of 12 premedicated rabbits anesthetized with 15 or 20 mg./kg. of thiopental expired from respiratory arrest.

DISCUSSION

The results demonstrate that the effects of Dolitrone and of thiopental on the blood pressure, the ventricular contractile force, the heart rate, and the electrocardiogram were essentially similar. Neither drug markedly predisposed the myocardium to epinephrine-induced arrhythmias.

The duration of anesthesia produced by single, equivalent anesthetic doses of Dolitrone and of thiopental was approximately the same. In this latter connection, it is of interest to note that Thompson, Smith, and Werner (1) have reported that repeated administrations of Dolitrone to rabbits did not result in anesthesia of increasing duration as contrasted with the well-known characteristic of thiopental to produce cumulative effects with repeated injections.

The marked increase in heart rate which follows the injection of
thiopental into dogs has been described previously by Gruber (4).
Recent experiments by Davis, Nash, and Woodbury (5) demonstrated
that, in the dog, thiopental produces a tachycardia and a decrease in
the cardiac index but little change in arterial pressure. These latter
observations suggest that the increase in heart rate produced by thiop-
ental is a reflex compensatory action. This interpretation is sup-
ported by the fact that, in the present experiments, the production of
peripheral vasoconstriction by nor-epinephrine at the peak of the tachy-
cardia reduced the heart rate to the pre-anesthetic control level. Of
interest here was the fact that the strong vagal stimulation produced
by morphine did not substantially influence the full development of
tachycardia with either thiopental or Dolitrone.

Several important differences existed between the actions of Doli-
trone and thiopental. The administration of full anesthetic doses of
thiopental to rabbits premedicated with morphine resulted in death
from respiratory arrest, while the administration of full anesthetic
doses of Dolitrone under these same conditions did not result in death
or in a substantial depression of the rate of the external respiratory
movements. This difference may be related to the fact that the dose
of Dolitrone required to produce complete general anesthesia rep-
sents a smaller fraction of the fatal dose than is the case with thiop-
ental. Thompson, Smith, and Werner (1) have reported that the
acute LD₉₀ for Dolitrone is approximately 3 times that for thiopental.
Thus, it appears that, in the rabbit and the dog, the therapeutic index
is greater for Dolitrone than it is for thiopental, although the equiva-
 lent anesthetic dose of Dolitrone is approximately 50 per cent greater
than that for thiopental on a weight basis. The development of an
interval of intense excitement during recovery from anesthesia in 5
of 25 dogs anesthetized with Dolitrone constituted a second difference
between the action patterns of the two anesthetic agents. The mecha-
nism responsible for its production was not determined, but it was not
prevented by premedication with morphine and was not noted in these
same dogs during recovery from anesthesia with thiopental.

Summary

The cardiovascular properties of a new, nonbarbiturate intravenous
anesthetic agent (Dolitrone) have been compared with those of thiop-
ental. Dolitrone and thiopental had only limited effects on the blood
pressure, the force of ventricular contraction, and the electrocardio-
gram, but produced a marked increase in the heart rate when equiva-
 lent anesthetic doses were administered to dogs. Although there was
a moderate increase in the incidence of epinephrine-induced arrhyth-
mias following the administration of both Dolitrone and thiopental,
fewer arrhythmias were produced by epinephrine following Dolitrone
than following thiopental. With equivalent anesthetic doses, the du-
ration of anesthesia was approximately the same for both drugs. Full
anesthetic doses of both agents did not reduce the rate of the external
respiratory movements to a serious level in nonpremedicated animals,
but, in animals premedicated with morphine, thiopental frequency pro-
duced fatal respiratory arrest while Dolitrone was well tolerated. In
5 of 25 dogs anesthetized with Dolitrone, an interval of intense excite-
ment was observed during emergence from anesthesia; a similar fea-
ture was not observed in these same animals given thiopental.

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