# THIAMBUTENE AND BARBITURATE ANÆSTHESIA IN THE DOG

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The analgesic and other properties of the dithienyl alkenylamines have been described by Green[1,2] and Green and his colleagues[3], who have shown that many of the members in this series of compounds have actions resembling those of morphine and also of pethidine. One of these compounds, 3-diethylamino-1 : 1-dithienylbut-1-ene hydrochloride (thiambutene) has also been found by the author to have marked sedative and hypnotic properties which are of considerable therapeutic value in veterinary practice. It has been found that premedication with this drug enhances and prolongs the action of barbiturates, and that the action of thiambutene is rapidly terminated by nalorphine. The purpose of this paper is to describe the advantages of the combined use of these drugs for surgical anæsthesia in the dog.

## Methods

All the observations were carried out on dogs which had been admitted to the Liverpool University Veterinary Hospital for surgical treatment of localised lesions. The animals were injected with thiambutene and then anæsthetised either with pentobarbitone sodium or thiopentone sodium, and after completion of the operation a number of dogs in each series were injected with nalorphine to terminate the anæsthesia.

The pulse and respiration rates of each animal were recorded by conventional clinical examination for 1-minute periods at frequent intervals. Temperatures were recorded at intervals by means of a sub-clinical mercury thermometer inserted into the rectum. The environmental temperature of the dogs was not rigidly controlled, but was usually 15° C. Immediately after operation the animals were covered with blankets until they recovered from the anæsthetic.

The action of thiambutene varied from slight inco-ordination of gait to sluggish response to all stimuli and complete abdominal relaxation. These effects were conveniently scored as light, medium and deep narcosis which will be described more fully elsewhere. Deep anæsthesia was characterised by the abolition of pedal, anal, conjunctival and pupillary reflexes, and light anæsthesia by re-appearance of the pedal reflex. The time for complete recovery from the anæsthetic varied considerably, but for the purposes of assessing the action of nalorphine, recovery was denoted by ability of the dog to stand and walk.

## Materials

Thiambutene solutions were prepared by dissolving tablets (50 mg.) of Themalon in sterile water to produce a concentration of 25 mg. to 100 mg./ml. according to the dose required; the volume of solution

injected was 0·5 to 5·0 ml. For pentobarbitone anæsthesia a solution containing 64 mg./ml. and for thiopentone anæsthesia fresh solutions containing 64 mg./ml. were used. Nalorphine was used at a concentration of 20 mg./ml.

## RESULTS

### 1. *Thiambutene–Pentobarbitone Anæsthesia*

18 dogs were injected subcutaneously with thiambutene (4·5 mg./kg.). 1 hour later, pentobarbitone sodium was injected intravenously in a dose sufficient to produce deep anæsthesia. 8 of these dogs subsequent to operation were injected intravenously with nalorphine (0·45 mg./kg.).

TABLE I

DURATION OF ACTION AND RECOVERY FROM ANÆSTHESIA WITH THIAMBUTENE AND PENTOBARBITONE IN 10 DOGS

| Case | Operation | Age | Thiambutene narcosis | Weight in kg. | Dose of pentobarbitone (mg.) | Duration of anæsthesia (hours) | Ability to walk (hours) |
|---|---|---|---|---|---|---|---|
| 1 | Castration | 3 mths. | deep | 7·5 | 48 | 2¾ | 10¼ |
| 2 | Fracture ulna | 3 mths. | deep | 6·8 | 114 | 3¾ | 11½ |
| 3 | Dental | 5 mths. | light | 6·4 | 160 | 2¼ | 7¾ |
| 4 | Fracture, radius | 5 mths. | deep | 8·9 | 146 | 1¾ | 4¼ |
| 5 | Mammary tumour | 1½ yrs. | light | 7·7 | 108 | 4 | 6½ |
| 6 | Castration | 2 yrs. | light | 20·0 | 290 | 4¾ | >12 <24 |
| 7 | Mammary tumour | 3 yrs. | light | 11·0 | 290 | 3½ | > 9 <19 |
| 8 | Bilateral aural resection | 6 yrs. | medium | 8·9 | 160 | 4¼ | 8 |
| 9 | Neoplasia eyelids. Abscess in foot | 8 yrs. | light | 9·3 | 160 | 2 | 10 |
| 10 | Anal adenoma | 8 yrs. | light | 9·3 | 160 | 2 | 10 |

A summary of the results on 10 dogs is shown in Table I. Data for the remaining 8 dogs are later described in Table II. From these it will be seen that the age and weight of the dogs varied over a wide range and that the effect of thiambutene varied from light to deep narcosis.

TABLE II

DURATION OF ACTION AND RECOVERY FROM ANÆSTHESIA WITH THIAMBUTENE AND PENTOBARBITONE AFTER NALORPHINE IN 8 DOGS

| Case | Operation | Age | Thiambutene narcosis | Weight in kg. | Dose of pentobarbitone (mg.) | Period of anæsthesia prior to nalorphine (hours) | Abolition of anæsthesia | Ability to walk after nalorphine (hours) |
|---|---|---|---|---|---|---|---|---|
| 1 | Spey | 4 mths. | deep | 6·4 | 145 | 1 | Almost immediate | 2½ |
| 2 | Bilateral entropion | 9 mths. | deep | 14·5 | 245 | 2 | Almost immediate | Unknown |
| 3 | Spey | 5 yrs. | medium | 8·0 | 108 | 1½ | Almost immediate | 4 |
| 4 | Sub-maxillary cyst | 5 yrs. | medium | 8·4 | 227 | 3¼ | 1 hour | >24 <30 |
| 5 | Abscess | 5 yrs. | light | 13·7 | 227 | 1 | Almost immediate | 3½ |
| 6 | Sebaceous cyst | 5 yrs. | medium | 19·0 | 320 | 1 | Almost immediate | 4¼ |
| 7 | Skin tumour | 8½ yrs. | medium | 8·0 | 108 | 1 | Almost immediate | 4 |
| 8 | Tumour of lip | 10 yrs. | medium | 21·0 | 275 | 35 mins. | 25 mins. | 2½ |

In all cases, however, no excitement was observed and the subsequent injection of pentobarbitone was readily carried out. In all cases the dose of pentobarbitone required was less than the estimated dose which would have been necessary if the animals had had no premedication, and ranged from 6·4 to 26·4 mg./kg., the mean dose used in 18 dogs was 17·8 mg./kg. (S.D. ±5·44), whereas the calculated mean expected dose is 30 mg./kg.

In the 10 dogs which were allowed to recover spontaneously the duration of anæsthesia varied from $1\frac{3}{4}$ to $4\frac{3}{4}$ hours with a mean of $3\frac{1}{4}$ hours recovery from the anæsthetic was quiet and uneventful and 7 dogs were able to walk within 12 hours. The shortest period of recovery was $4\frac{1}{2}$ hours; the longest, 36 hours. There was a marked fall in body temperature ranging from 3·1 to 12·3° F.; this began after the injection of thiambutene and continued during anæsthesia. The maximum fall usually occurred within 2 hours; towards the end of the anæsthesia the temperature began to rise and returned to within normal limits within 5 hours of the recovery. A typical response is plotted in Figure 1, which also shows concurrent changes in respiratory and pulse rates. The change in pulse rate gave rise to no particular anxiety, but on one occasion the respirations fell to 4 per minute which required resuscitation. Complete muscular relaxation was observed in all cases and there was no obvious increase in hæmorrhage during surgical procedures.

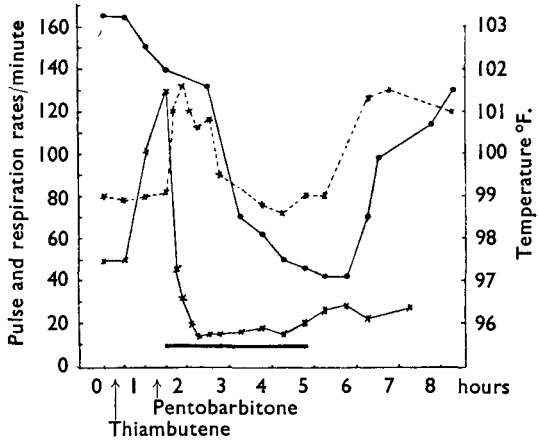


FIG. 1. Typical changes in pulse, respiration and temperature of a dog during anæsthesia with thiambutene and pentobarbitone.
3 year old bitch. Weight 11 kg. The bold line shows the duration of anæsthesia.
×– – –× Pulse. ●——● Temperature.
×——× Respiration.

It is clear that prior administration of thiambutene reduces the amount of pentobarbitone required, and that the total period of anæsthesia is considerably greater than that obtained when pentobarbitone alone is used.

2. *Termination of Thiambutene–Pentobarbitone Anæsthesia with Nalorphine*

The object of the following observations was to study the reversal of thiambutene–pentobarbitone anæsthesia by nalorphine.

8 dogs during deep anæsthesia with thiambutene–pentobarbitone were

each injected intravenously with nalorphine, as previously described. Anæsthesia terminated abruptly in 6 dogs, was reduced in depth in 1 dog, but 1 dog did not regain consciousness until 60 minutes after the injection. The recovery period was reduced, the ability to walk being restored within 2½ to 5 hours after nalorphine (Table II). The dog which had a delayed response to nalorphine did not fully recover until after 24 hours.

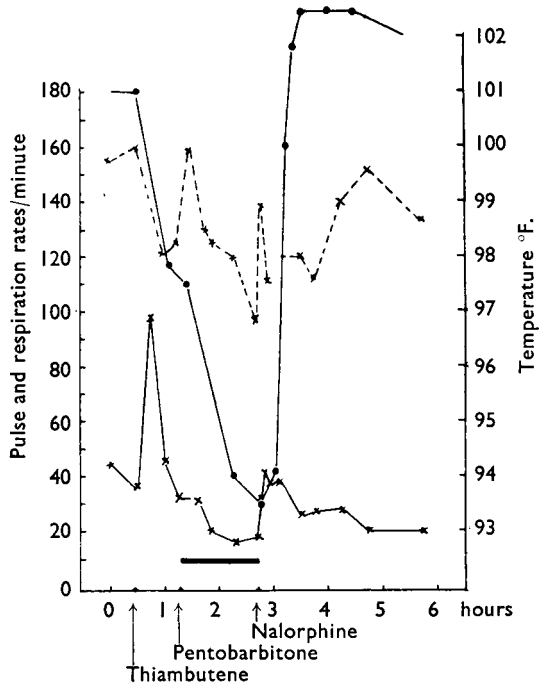


FIG. 2. Typical changes in pulse, respiration and temperature of a dog during anæsthesia with thiambutene and pentobarbitone and after the administration of nalorphine.
5 year old bitch. Weight 8 kg. The bold line shows the duration of anæsthesia.
×- - -× Pulse. ●——● Temperature.
×——× Respiration.

Violent shivering and a rapid return to normal or near-normal of body temperature were usually observed during recovery (Fig. 2). In some cases there was limb galloping and whining, as is often encountered during recovery from pentobarbitone alone.

4 dogs given pentobarbitone alone (30 mg./kg.) were similarly injected with nalorphine, but no changes were observed on the depth of anæsthesia, the recovery period, or the pulse and respiration rates.

### 3. *Thiambutene–Thiopentone Anæsthesia*

16 dogs were injected intravenously with thiambutene (0·9 mg./kg.); 10 to 15 minutes later thiopentone sodium was injected slowly during approximately 3 minutes. 6 of these dogs, subsequent to operation, were injected intravenously with nalorphine (0·45 mg./kg.).

A summary of the results on 10 dogs is shown in Table III. Data for the remaining 6 dogs are later described in Table IV. The age of dogs varied from 9 weeks to 9 years and the weight from 3·6 to 18·2 kg. Medium or deep narcosis occurred in all except 2 dogs.

The dose of thiopentone required ranged from 5·2 to 20·0 mg./kg., the mean dose was 13 mg./kg. (S.D. ±4·77), which is considerably less than the mean dose calculated to be necessary if the animals were anæsthetised with thiopentone alone (30 mg./kg.).

TABLE III

DURATION OF ACTION AND RECOVERY FROM ANÆSTHESIA WITH THIAMBUTENE AND THIOPENTONE IN 10 DOGS

| Case | Operation | Age | Thiambutene narcosis | Weight (kg.) | Dose of thiopentone (mg.) | Duration of anæsthesia (mins.) | Ability to walk (hours) |
|---|---|---|---|---|---|---|---|
| 1 | Remove dew claws | 9 wks. | deep | 5·0 | 48 | 19 | 1⅓ |
| 2 | Spey | 3 mths. | deep | 3·6 | 32 | 20 | 1 |
| 3 | Reduce and set fracture, tibia | 1 yr. | deep | 16·0 | 320 | 32 | 2½ |
| 4 | Castration | 1½ yrs. | medium | 10·7 | 160 | 23 | 1 |
| 5 | Reduce dislocation, hock | 2 yrs. | medium | 12·4 | 208 | 31 | 2 |
| 6 | Reduce dislocation, hip | 2 yrs. | medium | 6·8 | 130 | 24 | Unknown, left to rest |
| 7 | Open abscess. Scale teeth | 3½ yrs. | deep | 13·7 | 240 | 42 | 1¾ |
| 8 | Remove plaster cast | 5 yrs. | light | 12·2 | 227 | 42 | 2½ |
| 9 | Dental | 7 yrs. | deep | 17·0 (fat) | 195 | 23 | 1 |
| 10 | Dental | 7 yrs. | medium | 15·0 | 146 | 27 | 1¼ |

In the 10 dogs which were allowed to recover spontaneously the duration of anæsthesia varied from 19 to 42 minutes, with a mean of 28 minutes. Recovery was uneventful, no case of post-anæsthetic excitement occurred and ability to walk returned in 1 to 2½ hours after the induction with thiopentone.

The fall in body temperature was not so marked as that described in the previous method; the maximum fall was 4° F., beginning after the injection of thiambutene and continuing during anæsthesia. Pulse rates rose immediately after the thiopentone injection but fell again within a few minutes, a further slight fall occurring during anæsthesia. Respiratory rates were satisfactory throughout (Fig. 3). Muscular relaxation was complete in all cases and no obvious increase in hæmorrhage occurred during surgical procedures.

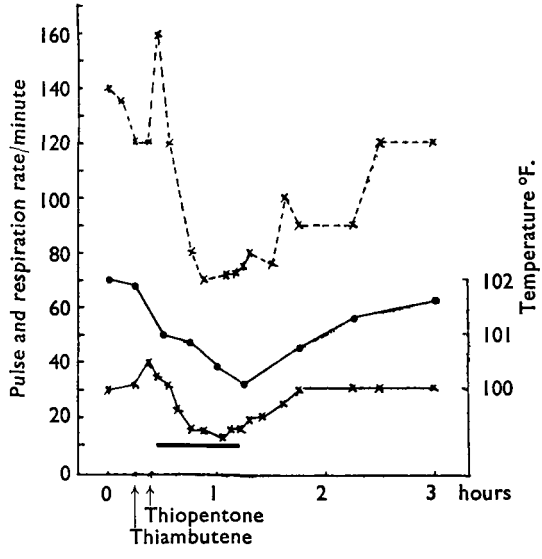


FIG. 3. Typical changes in pulse, respiration and temperature of a dog during anæsthesia with thiambutene and thiopentone. The bold line shows the duration of anæthesia.
5 year old dog. Weight 12·2 kg.
×---× Pulse. ●——● Temperature.
×——× Respiration.

Induction was smooth and uneventful except in 1 fat dog, deeply narcotised, which became apnœic and required artificial respiration for 15 minutes. A second dog also became apnœic for 3 minutes, but was readily resuscitated and recovered without further incident.

Thiambutene reduced the amount of thiopentone required and prolonged the total period of anæsthesia to approximately twice that obtained when thiopentone alone is used.

4. *Termination of Thiambutene–Thiopentone Anæsthesia with Nalorphine*

The object of the following observations was to study the reversal of thiambutene–thiopentone anæsthesia by nalorphine.

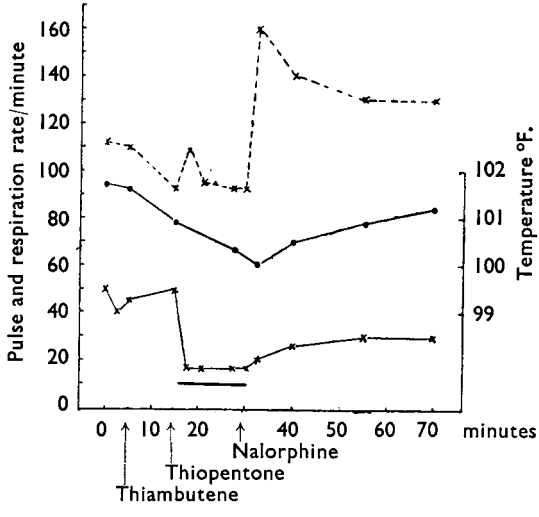


FIG. 4. Typical changes in pulse, respiration and temperature of a dog during anæsthesia with thiambutene and thiopentone and after the administration of nalorphine. The bold line shows the duration of anæsthesia.
1½ year old dog. Weight 18·1 kg.
×– – –× Pulse. ●——● Temperature.
×——× Respiration.

During the subsequent deep anæsthesia of the 6 dogs previously mentioned, the effects of an intravenous injection of nalorphine on the depth of anæsthesia and the period of recovery was noted (Fig. 4, Table IV). After nalorphine, anæsthesia terminated abruptly within 1 minute in all 6 dogs. Ability to walk returned in from 5 to 12 minutes and the recovery was uneventful and without excitement.

Four dogs given thiopentone alone (30 mg./kg.) were similarly injected with nalorphine but no changes were observed on the depth of anæsthesia, the recovery period or the pulse rates.

The duration produced by the two methods and its termination bynalorphine are conveniently summarised in Table V.

TABLE IV

DURATION OF ACTION AND RECOVERY FROM ANÆSTHESIA WITH THIAMBUTENE AND THIOPENTONE IN 6 DOGS

| Case | Operation | Age | Thiambutene narcosis | Weight (kg.) | Dose of thiopentone (mg.) | Period of anæsthesia prior to nalorphine (mins.) | Ability to walk after nalorphine (mins.) |
|---|---|---|---|---|---|---|---|
| 1 | Umbilical hernia | 3 mths. | deep | 5·0 | 48 | 14 | 10 |
| 2 | Amputation, abnormal tail | 4 mths. | light | 8·6 | 146 | 17 | 5 |
| 3 | Examination of œsophagus | 1½ yrs. | medium | 18·1 | 97 | 14 | 10 |
| 4 | Skin tumour | 6 yrs. | deep | 13·6 | 162 | 35 | 12 |
| 5 | Removal of mammary tumour | 8 yrs. | medium | 15·5 | 80 | 18 | 7 |
| 6 | Removal of mammary tumour | 8 yrs. | medium | 13·6 | 195 | 15 | 7 |

TABLE V

EFFECT OF NALORPHINE IN REDUCING THE TIME OF RECOVERY FROM ANÆSTHESIA WITH THIAMBUTENE–PENTOBARBITONE AND WITH THIAMBUTENE–THIOPENTONE

| | Hours | | Minutes | |
|---|---|---|---|---|
| | Thiambutene–pentobarbitone | | Thiambutene–thiopentone | |
| Dog No. | alone | + nalorphine | alone | + nalorphine |
| 1 | 18 | 4¾ | 108 | 12 |
| 2 | 14 | 4 | 108 | 10 |
| 3 | 8¼ | 4 | 89 | 10 |
| 4 | 7¼ | 3½ | 60 | 7 |
| 5 | 5½ | 2½ | 40 | 7 |
| 6 | 2½ | 2½ | 37 | 5 |

## DISCUSSION

Although various hypnotics and analgesics have been combined with barbiturates to produce anæsthesia in dogs there is no evidence from the literature that these drugs have produced the potentiating effect similar to that now reported with thiambutene.

Wright[4] stated that the duration of anæsthesia after pentobarbitone sodium varied from 15 minutes to an hour or more depending on the depth initially produced; with thiopentone injected slowly the expected duration varied from 10 to 20 minutes[5]. When morphine was administered prior to pentobarbitone, Wright[4] found that the amount of the latter drug required to produce anæsthesia was reduced but that the duration was shortened though the total period of narcosis was prolonged due to the morphine. Burns[6] in his review of veterinary anæsthesia stated that pethidine prolonged the duration of thiopentone anæsthesia.

The mechanism of the potentiating effect of thiambutene on the action of thiopentone and of pentobarbitone is not known. In view of the observations of Brodie, Bernstein and Mark[7] that the short duration of action of thiopentone is due to its rapid localisation in fat, it is relevant to emphasise the prolonged effects observed in fat dogs with combined thiambutene anæsthesia. It is not clear in what way thiambutene influences the clearance of barbiturate, though there is some evidence that thiambutene is localised in the body fat (Green—personal communication).

The indications and advantages of thiambutene–pentobarbitone combination in veterinary canine practice are similar to those of morphine–pentobarbitone anæsthesia described by Wright[4]. The premedication drug is particularly valuable in restraining vicious dogs and the long period of anæsthesia is useful in prolonged surgical techniques and prolonged recovery period with absence of galloping movements is also a valuable feature. No particular hazards have been encountered during these observations in respect to the fall in temperature and the change in respiration and pulse rate. The rapid reversal of anæsthesia and of depression of respiration by nalorphine is an additional advantage and safeguard.

The period of anæsthesia after thiambutene and thiopentone is usually sufficient for the majority of canine operations. The recovery period is reasonably short, but if more rapid recovery is required this is quickly obtained by nalorphine. Termination of anæsthesia by this drug has the additional advantage that after operation, dogs can be returned to the owner in a very short time. The termination also reduces the risks of post-operative anæsthetic mishaps associated with the peculiar pharynx and larynx of the brachycephalic breeds.

To eliminate the danger of apnœa when injecting thiopentone after premedication with thiambutene it is recommended that the injection be made very slowly, over a 3 to 4-minute period.

## Summary

A method of producing anæsthesia in dogs by thiambutene and barbiturates is described. Thiambutene was injected subcutaneously into 18 dogs and 1 hour later the dogs were injected intravenously with pentobarbitone sodium. The amount of pentobarbitone sodium was considerably less than that which would have been required if this drug had been injected alone, and the duration of anæsthesia was considerably greater than that obtained with pentobarbitone alone. When 16 dogs were injected intravenously with thiambutene and 13 minutes later with thiopentone similar effects were observed. In each series of observations nalorphine by intravenous injection abruptly terminated the anæsthesia and reduced the recovery period. A marked fall in body temperature occurred during anæsthesia with pentobarbitone sodium. A reduction in respiration and pulse rates was also observed, but these effects did not adversely influence the recovery of the dogs.

## Acknowledgments

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