

Review of Literature on Use of T-61 as an Euthanasic Agent

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Introduction

Euthanasia means, according to its Greek root, an "easy death" (17) and is, by definition the act of inducing death without pain (19). To a Doctor of Veterinary Medicine, trained in the healing art, the idea of euthanizing is not pleasant. However, millions of unwanted dogs and cats are brought to the public and private animal shelters annually, and the most humane disposition of these animals is to give them a "good death."

This entails an enormous ethical responsibility and the moral injunction that the method of killing be humane (causing the least possible distress, physically and psychologically). Therefore, there is an obligation, as a final ethical responsibility and demonstration of respect for the life that is to be terminated, to utilize the best available method of euthanasia: to induce a gentle and painless death without causing fear, stress, anxiety or suffering (21).

The tools of evaluating the degree of distress in animals being killed include electroencephalography (EEG), electrocardiography (ECG), and measurement of blood pressure and respiration. Sound clinical and behavioral observations should also not be abandoned in the evaluation process (21).

There are many methods which may be employed to reach the same end results, but the ideal method should satisfy several criteria (20):

1. It should be painless;
2. It should cause unconsciousness

instantaneously and death within minutes;

3. It should not cause undue anxiety, alarm, fear, panic, behavior, struggling, vocalization, muscle spasms or clinical signs of automatic activation (e.g., convulsions) before unconsciousness;

4. It should always cause death when properly used;

5. It should be safe for the properly trained person to use;

6. It should be easy for the properly trained person to use;

7. It should not be a drug subject to abuse in human beings;

8. It should be aesthetically unobjectionable. (This criterion depends on who the observers are);

9. It should be practical to use for the particular type of animal to be killed;

10. It should not create a problem of sanitation or environmental contamination;

11. It should not cause tissue changes which will alter postmortem examination or chemical tests; and

12. It should be economical.

The objective of this paper is to review the literature on the use of T-61* as an euthanasic agent and to determine to what extent it meets the above criteria.

Early Use of T-61

The use of T-61 solution for killing small animals was first reported in West

*Hoechst-Roussel Pharmaceuticals, Inc. Somerville, NJ. USA.

Germany by Fikmeier in 1962 (5) and for killing large animals by Kuepper in 1964 (10). Fikmeier concluded after killing 350 dogs and 300 cats that the material was very suitable for euthanasia. Its use in private practice has spread in some countries. In Italy, under the trade name "Tanax," this material is being widely used to kill unwanted animals in municipal animal pounds (21). In the United States, its clinical use in small animals was first reported by Quin in 1963 (16).

The Agent

T-61 is an injectable nonbarbiturate solution that consists of a mixture of three agents (3). Each milliliter contains:

1. 200 mg of N-[2-(m-methoxyphenyl) 2-ethyl-butyl-(1)]-gamma-hydroxybutyramide, having a strong narcotic effect on the central nervous system, where it also paralyzes the brain center controlling respiration;
2. 50 mg of 4.4-methylene-bis (cyclohexyl-trimethyl-ammonium iodide), which exerts a paralytic action on striated muscle and rapidly induces circulatory collapse (curariform-like action)*;
3. 5 mg of tetracaine hydrochloride, which is a local anesthetic added to reduce painful tissue reactions at the site of injection; with 0.6 ml of dimethylformamide in distilled water.

The manufacturers (3) recommend that, in dogs the injection should preferably be given intravenously. Intrapulmonary or intracardiac injections may be given where the intravenous injection is impractical, as in very small dogs and cats, or in a comatose animal with depressed vascular function. With the intrapulmonary route, care should be taken not to displace the lung tissue and inject into the pleural cavity. In cats the intrapulmonary route is considered by

the manufacturers to be the most practicable method (3). Intramuscular or subcutaneous injections are contraindicated.

T-61 is exclusively intended for the humane euthanasia of dogs, cats, mink, horses, laboratory animals (such as rats, mice, guinea pigs and rabbits), and birds such as pigeons and parakeets (3).

Two-thirds (2/3) of the total dose should be administered without interruption at the moderate rate of 1 ml each 5 seconds. The remaining one-third (1/3) may be administered rapidly. The correct injection technique is essential to effect euthanasia without excitation or pain because, when given too rapidly, transient anxiety and struggling may occur before unconsciousness (3).

The manufacturers (3) recommend that one should never overdose an animal with T-61, as this may lead to overexcitement and/or convulsions.

Effect on the Body

Euthanasia results from central nervous system depression, hypoxia and circulatory collapse. The AVMA Panel on Euthanasia (19) describes the drug as acting via a direct depression of the cerebral cortex, subcortical structures, vital centers and heart muscle. The ultimate cause of death is hypoxia and respiration ceases due to depression of vital centers and muscle paralysis.

A comparative study of T-61 and pentobarbital* indicated that either agent induced euthanasia smoothly and without undesirable reactions when properly administered (12, 13). The dogs given pentobarbital received a total dose of 57.1 mg/kg of body weight continuously at a rate of 1.2 ml/second. The dogs given T-61 received two-thirds of the total dose (0.3 ml/kg of body weight) at a rate of 0.2 ml/second with the last one-third given at 1.2 ml/second.

With both pentobarbital and T-61, the electroencephalogram changed from

*The curare-like drug is included to control seizures which may be triggered by the narcotic compound. According to one company's veterinary representative, it insures that "if the animal were to regain consciousness, it would die anyway from respiratory arrest," i.e. suffocation (21).

*Sodium Pentobarbital. USP 129.6 mg/ml.

a normal awake pattern to one of low frequency and increased amplitude for approximately 5 seconds followed quickly by electrical silence. The pentobarbital-treated dogs required 12 seconds longer for the occurrence of electrical silence. With both agents, alterations in electrocardiogram developed immediately and arterial pressure dropped to zero. However, three pentobarbital-treated dogs resumed an effective cardiac output and respiration. Analysis of the respiratory response from the start of injection until initial arrest indicated no significant difference between the two agents. Results of this study indicated that painless death is produced by pentobarbital or T-61 (12, 13, 19).

Dehner, cited by Quin (16), has stated: "For dogs, intravenous application of T-61 is the method of choice. The lethal effect frequently occurs even during the injection, otherwise, directly after this procedure. The animal collapses, muscular tonus dies away, and breathing stops. In the predominant number of cases, the animals die with no reaction of any kind, without resistant movements, outcrying, or shortness of breath. In rare instances where resistant movements occur, they persist only a few seconds. Ordinarily cardiac activity continues for a few seconds after breathing has stopped but rarely for as much as a minute."

Comparison of T-61 With Pentobarbital According to Criteria for the Ideal Method

As stated earlier, the ideal method for euthanizing animals should satisfy the following criteria:

1. It should be painless.

The manufacturers have added tetracaine hydrochloride, a local anesthetic, to T-61 solution to reduce painful tissue reactions at the site of injection. Wills (23) has found that injecting T-61 intravenously in the rear-leg of small cats

is very effective and painless ("about 100%"). However, McMurry (15) objects to the use of T-61 as an agent for euthanizing animals because of apparent severe pain upon injection. He states that tetracaine does not eliminate pain. When given intravenously as per instructions, there was obvious pain in 25 to 35% of the dogs euthanized (approximately 500) using T-61. He found that many of the dogs whine and/or howl. He also declares that if any of the material is injected perivascular, which can occur when encountering a highly excited animal, especially when injected by inexperienced personnel, the evidence of pain is very obvious.

Fox (7, 8), has likewise declared that even with the addition of the local anesthetic ingredient, pain reactions can be marked in some animals and may cause considerable excitation and distress.

2. It should cause unconsciousness instantaneously and death within minutes.

An appropriate technique for evaluating unconsciousness is electroencephalography (EEG). Up to 1974, there appeared to be no reported work giving EEG data from test cases of T-61 euthanasia. However, Rowsell investigated the use of T-61 for euthanasia in a rat and determined that the EEG became isoelectric (flat) within 4 seconds (21).

In 1978, Lumb (12) conducted EEG measurements in 21 dogs which indicated that T-61 rapidly (within 5 seconds) induced an isoelectric state indicating unconsciousness. These two studies, on one rat and 21 dogs, do not constitute sufficient proof that T-61 is effective in producing instantaneous unconsciousness in dogs, cats, horses, mink, laboratory animals and birds (as the manufacturers claim).

There is much conflicting anecdotal evidence on the efficacy of T-61. Wills (23) reported that intravenous injections of T-61 into the rear-leg of small cats is... "very effective because complete

unconsciousness occurs in 2 to 4 seconds and brain death in 10 to 20 seconds, whereas heart and motor functions cease in 20 to 30 seconds." However, no specialized apparatus to measure time of unconsciousness, brain death and heart and motor functions was used.

The Executive Director of the Animal Shelter in Alexandria, Virginia (4), objects to the use of T-61 for euthanasia under any circumstances because of the pain factor which, as reported by McMurry (15), affected one-quarter of the dogs that he euthanized with T-61 (according to the procedure recommended by the manufacturers).

3. It should not cause undue anxiety, alarm, fear, panic, behavior, struggling, vocalization, muscle spasms or clinical signs of activation (e.g. convulsions) before unconsciousness.

Stonehouse (22) says that studies have shown that T-61 given intravenously, does not produce any initial curariform or muscle relaxant action before central nervous system depression occurs. Nevertheless, there are doubts.

Baker (1) reports that T-61 was withdrawn in England because animals euthanized with this product exhibited distress, pain and convulsions prior to death. Baker noted that the "induction stage, anesthetic stage and respiratory paralysis do not occur in that order and animals tend to get respiratory paralysis prior to complete anesthesia."

McMurry (15) also objects to the use of T-61 as an euthanizing agent because respiration does not always cease immediately and the heart continues to beat for several minutes following the recommended lethal dose.

There are also doubts about whether the paralyzing effects of the curare-like compound in T-61 occur before unconsciousness sets in. Like many curariform drugs, it may cause transient muscular tremors (depolarization) prior to unconsciousness (21), but it is not known

how distressing this may be to animals (8, 15).

In contrast, the use of intravenous sodium pentobarbital has been shown to cause unconsciousness within the first seconds of injection, without any signs of distress or pain, or convulsions and howling (19).

There are also doubts about using T-61 by intracardiac or intrapulmonary routes, as recommended by the manufacturers (3), because of possible adverse reactions. For example, in the intrapulmonary route fluids in the lungs may cause significant distress and coughing prior to unconsciousness, and the intracardiac route is painful since the pericardium can be very sensitive to the needle (7).

With respect to the intraperitoneal route, the manufacturers recommend its use in mink but this is contraindicated. Uptake by this route is extremely slow and seizures may occur. In one study (16), three cats were given T-61 by intraperitoneal injection. They suffered spasms, excitement, a reflex bowel movement and dyspnea for 3 to 13 minutes before complete collapse.

Fogle (6) has noted in a letter that some veterinarians have stopped the use of T-61 because they felt it was not as humane as barbiturate intravenously. He declared that its main attraction was that it eliminated the "last gasp" that occurs with some dogs when they are euthanized with a barbiturate. This is hardly a suitable justification for an euthanasic agent.

In the study by Lumb (12), comparing T-61 and sodium pentobarbital for euthanasia, he notes that: "In most respects the effects of the two agents were similar; however, 3 of 12 dogs given pentobarbital resumed respiration and cardiac function. None of the 9 dogs given T-61 evidenced signs of recovery." He then argues that (13): "On a comparative basis T-61 is superior to double-strength pentobarbital, in that the latter

may not produce lasting cardiac and respiratory arrest."

However, Reilly (18) states that Lumb used a dose of pentobarbital sodium which was close to the *minimum lethal dosage*, which is no reason, to imply as Lumb did, that T-61 is superior to sodium pentobarbital. Furthermore, the pentobarbital solution was far weaker (130 mg/ml). Reilly argues that this is the reason why some of the dogs resumed cardiac function and respiration.

4. *It should always cause death when properly used.*

There are numerous agents that can cause death, but in the case of T-61, "it is a lethal drug that causes death but not necessarily euthanasia" (15).

5. *It should be safe for the properly trained person to use.*

The drug is marketed as a vial which reduces any possibility of human ingestion. However, if T-61 is inadvertently taken orally by humans it will be absorbed very slowly and the onset effect will be delayed. Therefore, there should be enough time after inadvertent swallowing to remove the drug from the stomach, thereby preventing serious poisoning (9).

If small amounts of T-61 inadvertently get into a wound or under the skin of a person injecting it to a struggling animal, there is no danger of toxicity (9). However, Fogle (6) reported that in England, in the early 70's, there was a flurry of correspondence to the *Veterinary Record* concerning possible dangers to the operator in the use of the drug because of its curare-like effect. However, the indications are that it is as safe, or safer, than many other euthanasic agents.

6. *It should be easy for the properly trained person to use.*

Wills (23) declared in a letter that injecting T-61 intravenously in the rear-leg of small cats "is easy to learn, requiring only small degree of medical knowl-

edge." But intravenous injections are not easy, even for properly trained persons. In addition, cats are hard to handle, which will make it more difficult to find a vein in the rear-leg. An advantage of sodium pentobarbital over T-61 for cats is that it can be given intraperitoneally; T-61 cannot. Also, cerebral excitation may occur if this drug is not injected according to the manufacturer's instructions (3) ("give the first two-thirds at a smooth rate of 1 ml per 5 seconds and then the rest rapidly"). Therefore, this compound will not be easy to administer and even experienced personnel can be expected to make mistakes, especially with nervous, struggling animals.

As stated before, no euthanizing drug should ever be given intrathoracically because of its inhumaneness, but in such cases where it is required to give T-61 via the intracardiac route, it is necessary that the administrator must be experienced and 100% confident of entering the heart every time (21).

Injection of sodium pentobarbital is easier than T-61 because it can be administered by several routes and the injection rate is not a critical factor.

7. *It should not be a drug subject to abuse in human beings.*

T-61 is not classified as a restricted drug by the Bureau of Veterinary Medicine of the Food and Drug Administration of the U.S. (11). However, its use is only permitted under veterinary supervision. By contrast, sodium pentobarbital is a schedule II drug and its use is closely regulated (11).

8. *It should be aesthetically unobjectionable. (This criterion depends on who the observers are.)*

When circumstances require the pet's owner to be present during the procedure, one must assure a smooth, rapid and obviously painless, euthanasia. According to reports, T-61 administration can be accompanied by agitation, anxiety and spasmodic body movements. So-

dium pentobarbital can also produce distressing body spasms (the so-called "last gasp").

9. *It should be practical to use for the particular type of animal to be killed.*

A certain proportion of the animals that are turned into shelters are in very poor condition. They may be injured, moribund or diseased. Under these circumstances T-61 cannot be used because the absorption and uptake of the compound may be delayed. Death is protracted with distressing convulsions and premature respiratory paralysis before narcotic unconsciousness can occur (7, 21). Therefore, T-61 is not an appropriate agent for euthanasia of these cases.

10. *It should not create a problem of sanitation or environmental contamination.*

T-61 and sodium pentobarbital do not have these kinds of problems; however, these two agents should not be injected into food animals designated for human or animal consumption.

11. *It should not cause tissue changes*

which will alter postmortem examination or chemical tests.

When T-61 is given at larger than recommended doses, pulmonary edema and other tissue lesions may be produced (19).

12. *It should be economical.*

In comparison with sodium pentobarbital, T-61 is a relatively expensive agent according to the information in Table I.

Conclusion

The available evidence indicates that there are many questions about T-61 as a satisfactory euthanasic agent. The only controlled study of animal EEG's after T-61 administration indicated that this compound could produce rapid unconsciousness. However, the drug was administered via an indwelling catheter, hardly the type of condition to be found in a shelter euthanizing 10 to 20 thousand animals a year. Furthermore, the investigator compared the T-61 results with the results of a weak and marginally lethal dose of sodium pentobarbital.

TABLE 1 Comparative Costs of T-61 and Sodium Pentobarbital

Product	Class*	Unit Price (1 bottle)	Unit Price**	Approx. Price (per 250 ml)
T-61	Not schedule	50 ml	\$13.60	\$68.00
		250 ml	\$55.00	\$55.00
Fatal-Plus ^a	C-II	250 ml	\$14.00	\$14.00
Euthanasia-6 ^b	C-II	100 ml	\$ 7.40	\$18.50
		250 ml	\$14.40	\$14.40
Beuthanasia-D ^c	C-III	100 ml	\$22.50	\$56.25

a. Vortech Pharmaceuticals Limited, Dearborn, MI. Each milliliter contains: 390 mg of sodium pentobarbital (powder reconstituted with ordinary water).

b. Veterinary Laboratories, Inc., Lenexa, KS. Each milliliter contains: 390 mg of sodium pentobarbital in an aqueous alcohol-propylene glycol base.

c. Burns-Biotec Laboratories, Inc., Omaha, NE. Each milliliter contains: 390 mg of sodium pentobarbital, 50 mg of phenytoin sodium, 10% of ethyl alcohol, 18% of propylene glycol, 0.003688 mg of rhodamine B (coloring) and 2% of benzil alcohol (preservative).

*Classification of a restricted drug by the Bureau of Veterinary Medicine of the Food and Drug Administration of the U.S. (11).

**These prices were obtained from the manufacturers.

The study was, thus, hardly a fair test.

Anecdotal evidence indicates that, in practice, T-61 euthanasia can be associated with many problems. In addition, it has to be injected intravenously in a carefully controlled manner to achieve optimal results. It is totally unrealistic to expect that routine euthanasia in a busy shelter will be able to keep to such a precise protocol which has only a small margin for error.

At present, T-61 cannot be recommended for routine practice when the more reliable, and apparently cheaper, alternative of sodium pentobarbital can be used. At best, T-61 should be used only as an emergency backup when the supplies of barbiturates have run out, and its use restricted to healthy animals that can easily be injected intravenously by an experienced person (7).

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