THE PRESENT STATUS OF TRICHLORETHANOL * †

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THE hypnotic property of trichlorethanol or trichlorethyl alcohol was first demonstrated by Külz (1) in 1884. Because of the similarity of action to tribromethanol in amylene hydrate and because the latter has been difficult to obtain due to war conditions, interest has recently been revived in some regions in the possibilities of its use as a basal anesthetic.

The physical properties of trichlorethanol offer certain advantages over tribromethanol. At ordinary temperature, tribromethanol is a white crystalline solid, while trichlorethanol is a sirupy liquid. The former is relatively unstable in watery solution while the latter is relatively resistant to decomposition (2). Measuring the dose of tribromethanol is facilitated by dissolving the crystalline substance in amylene hydrate. Such a solution is marketed under the name of avertin and will be referred to by that name. Trichlorethanol, being a liquid, can be measured satisfactorily, thus rendering unnecessary its admixture with another substance to act as a vehicle. Furthermore, the relative stability of the trichlorethanol solution renders testing unnecessary.

REVIEW OF THE LITERATURE

Pharmacological: The therapeutic index, which indicates the dosage range of a drug, is obtained by dividing the effective dose by the toxic dose. In this type of drug, the dose which produced sleep in one-half the animals was divided by the dose which caused death in one-half the animals. This index was found by Burtner and Lehmann to be 3.5 for avertin and 5.0 for trichlorethanol (3). Molitor and Robinson (2) obtained values of 1.8 for avertin and 3.0 for trichlorethanol. Case (4) found each to be approimxately 4.0. In no case then was trichlorethanol found to be more toxic than avertin. The effective dose of avertin is about four-fifths that of trichlorethanol in animals. Trichlorethanol has a higher specific gravity so that it seems safer to calculate doses in milligrams per kilogram rather than in cubic centimeters. The lethal dose, as well as the effective dose, of avertin is lower than that of trichlorethanol.

The effect of trichlorethanol on respiration was definitely less depressing than that of avertin when equal amounts per kilogram were used. For equivalent doses there was no consistent difference between the respiratory effects of the two drugs (4). When fatal doses of either drug were administered, the respiration failed before the heart.

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Circulation was affected to the same extent by the two drugs, according to Lehmann and Knoefel (5) and Molitor and Robinson (2). Extrasystoles were noted, however, when trichlorethanol was given intravenously. These comparisons were made using equal amounts per kilogram of body weight. The order of susceptibility to depression appeared to be as follows: medullary vasomotor center, spinal vasomotor center and the heart (5).

Hepatic function, as measured by the bromsulfalein test in rabbits and dogs, was found to be impaired to the same extent with each drug. This damage was not lasting (4). Repeated administration produced mild hepatic damage and occasionally slight renal damage of the same degree in rabbits and dogs for each drug, as shown by sections examined by the pathologist (4).

The period of sleep and the time before sleep took place were approximately the same for each drug in *equivalent doses.* Slightly more restlessness was encountered in dogs during induction and emergence when trichlorethanol was used (4).

Clinical: Two clinical reports have been published (6, 7) comparing the drug favorably with tribromethanol until a death was encountered in each case. Heiner and Belfrage (6), in England, administered the drug to 18 patients, with favorable results. The nineteenth patient was very ill and had a toxic goiter for which operation was advised. She died a few minutes after losing consciousness. This fatality was described as a cardiac death. Wood's case (7), the twenty-fifth in a successful series, was a young man who entered for encephalography. He was given 150 mg. per kilogram of trichlorethanol and was asleep in ten minutes. His color was good, pulse 84 with a few extrasystoles, and respiration 24. After ten minutes, during which 70 cc. of spinal fluid had been replaced by 70 cc. of ethylene, the patient became hyperpneic for fifteen seconds, and the pulse was faint. Other than a few "catch" respirations and a weak pulse for two or three minutes, there was no further sign of life. Although this dose was large, the type of death did not conform to that of overdose in animals. Necropsy disclosed a large flabby heart.

P. Wood (8) has an unpublished series of 500 cases in which he found the action of the drug in the main similar to avertin. Chief differences were less profound narcosis and a shorter period of hypnosis. There were no fatalities in his series.

Experimental: These deaths gave rise to the question of the effects of trichlorethanol in the presence of a damaged myocardium.

Six trained dogs were chosen and control electrocardiographic tracings were taken on each. The dogs were then given sublethal doses of diphtheria toxin intravenously (1/8000 cc. per kilogram in 1 : 250 dilution) in an attempt to damage the heart. They were ill for one week, with fever, prostration, and loss of appetite. When they had recovered, tracings were again taken but electrocardiographic changes were not noted. Trichlorethanol was then administered in hypnotic doses to each dog and tracings then taken at intervals of a half hour. One animal had moderate

tachycardia; no other abnormality appeared in the tracings. The animals were killed immediately after the last tracing was made. Some loss of striation of cardiac muscle fibers was found on pathologic section, indicating the presence of myocardial damage.

It has been frequently stated that amylene hydrate probably is the cause of part of the depression of the central nervous system produced by avertin. Von Mering (9), in 1887, reported on the administration of large doses of amylene hydrate to rabbits and dogs. It produced prolonged sleep, with diminished reflexes, accompanied by moderate slowing of respiration.

Amylene hydrate has the formula $C_5H_{12}O$—two methyl butanol, two dimethyl ethyl carbinol or tertiary amyl alcohol. It is a colorless liquid with a sweetish odor, having a specific gravity of 0.806 at 25 C. and a boiling point of 101.6 to 102.0 C. at 762 mm. of mercury (10).

In order to determine to what extent amylene hydrate is responsible for the depressant action of avertin, its effect was studied on rabbits. It was given by stomach tube in 6 to 12 per cent solution because of the volumes required. Four rabbits were used for each dose level. Doses up to 600 mg. per kilogram produced no noticeable effect; 1000 mg. per kilogram caused the animals to sleep about one hour. Larger doses caused correspondingly longer periods of sleep and took less time to produce sleep (table 1).

TABLE 1

EFFECT OF VARIOUS DOSES OF AMYLENE HYDRATE

No. rabbits	Amylene hydrate, mg. per kg.	Ataxia	Sleep
4	100	0	0
4	300	0	0
4	600	Sl.	0
4	800		
4	1000		30 min.–1 hr.
4	1250		4– 7 hrs.
4	1500		8–12 hrs.
4	1750		14–20 hrs.
4	2000		18–22 hrs.
4	2200		24 hrs. plus

Four of the ten animals survived doses of 2200 mg. per kilogram.

The cardiac rate was not depressed. The respiratory rate was slower than when the animal was awake, but little difference appeared between the very small and very large doses (tables 2 and 3).

Reflexes were present but less active as the dosage was increased.

The amount of amylene hydrate in avertin amounts to 0.5 Gm. per cubic centimeter; thus, in a lethal dose of avertin for rabbits (600 mg. per kilogram) there is not sufficient amylene hydrate to produce sleep.

When amylene hydrate was added to trichlorethanol and administered to dogs, there was no difference in time to produce sleep, in length of sleep, pulse or respiratory rate than when trichlorethanol was used alone.

TABLE 2

COMPARISON OF TEMPERATURE, PULSE AND RESPIRATORY RATE OF CONTROL ANIMALS AND THOSE RECEIVING AMYLENE HYDRATE

Amylene hydrate, mg. per kg.	Control animals			Experimental animals		
	Temperature	Pulse	Respiratory rate	Temperature	Pulse	Respiratory rate
1000	102.0	200	120	102.2	200	48
1250	101.6	190	100	102.0	200	44
1500	102.0	136	140	100.2	180	52
1750	103.8	132	154	100.4	148	44
2000	102.4	136	140	99.4	154	36

TABLE 3

TYPICAL PROTOCOL
ADMINISTRATION OF AMYLENE HYDRATE

Weight of Rabbit—2853 Gm.

	Temperature	Pulse	Respiratory rate
	102.0	136	140
11:56 a.m.	1500 mg. per kg. injected; posture lost		
12:00 m.			
1:00 p.m.	100.2	180	52
2:00 p.m.	100.0	160	40
3:00 p.m.	102.6	170	44
4:00 p.m.	102.0	160	44
6:00 p.m.	102.4	160	50
8:00 p.m.	102.2	180	48
9:00 p.m.		waking	

Reflexes present throughout

Clinical: Following the experimental work, trichlorethanol was administered to 30 patients. A 2.5 or 3 per cent solution in distilled water was used and the solutions tested with Congo red. Pure trichlorethanol is stable under ordinary conditions, but in the event that deterioration had taken place, this test would detect increased acidity.

As with animals, it was immediately noticed that the effective dose of trichlorethanol was greater than that of avertin—100 mg. per kilogram giving the effect of 80 mg. per kilogram of avertin. Individual variations in the response to the action of both agents were noted with about equal frequency. Respiration was little changed in rate, occasionally moderately slowed, and the color remained good. The heart rate remained the same in most cases. There was one instance of tachycardia, one of bradycardia, and in one patient extrasystoles occurred. Tachycardia and bradycardia occurred following injection of air for ventriculograms and encephalograms, respectively. The decrease in blood pressure was some-

what less than with avertin. There was occasionally a slight diminution in the pulse pressure (2 cases).

Restlessness was increased slightly during induction. The interval before sleep (three to ten minutes) was about the same as with avertin when equivalent doses were employed. The period of hypnosis was found to be about one and one-half hours shorter than with avertin. No difference was noted in postoperative restlessness, nausea and vomiting.

SUMMARY

1. The literature on trichlorethanol has been reviewed. Trichlorethanol is more easily measured, more stable and has a slightly higher effective and toxic dose than does avertin. The hypnotic and toxic effects in animals are equal with equivalent doses, except that trichlorethanol produces more change in cardiac rate and rhythm and tribromethanol more depression of blood pressure.

2. Electrocardiographic tracings showed no abnormalities following the use of trichlorethanol in dogs with damaged hearts.

3. Amylene hydrate was administered to rabbits and found to produce prolonged sleep with large doses—1000 to 2000 mg. per kilogram. The temperature and pulse were not altered. The respiratory rate was decreased when the animals slept, but the decrease was no greater with large than with small doses.

4. When trichlorethanol was given to patients, individual variation in response was considerable, as with avertin, but a larger dose was required. The hypnotic action was as prompt but not as lasting. Decrease of the blood pressure was definitely less. Otherwise the action of the two drugs was essentially the same.

CONCLUSIONS

From these observations it appears that trichlorethanol may be used interchangeably with avertin as a basal anesthetic.

Complete evaluation can be made only when thousands of cases have been studied.

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