EVALUATION OF "DOLITRONE"*

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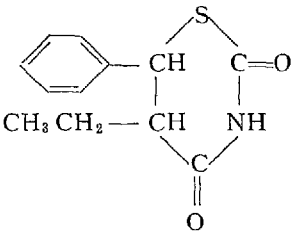
EARLY in 1954, Thompson, Smith, and Werner (1) first reported on some pharmacological properties of a new intravenous anaesthetic agent MRB-125, later to be named "Dolitrone."[1] This report was followed by three papers by Lundy in the same year (2, 3, 4). A further four publications by the same author in the following year (5, 6, 7, 8) reported on the clinical properties of the new agent with special emphasis on its general analgesic properties. Judging from these publications, Dolitrone seemed to be an agent worthy of thorough study. The work here reported relates to Dolitrone (*a*) as compared with the standard agent sodium thiopental (Pentothal®) under controlled conditions in volunteers, (*b*) as a general anaesthetic agent in clinical practice, and (*c*) as a general analgesic.

CHEMISTRY AND PHARMACOLOGY

Dolitrone is 5-ethyl-6-phenyl-m-thiazane-2,4-dione and has the following structural formula.



Thus Dolitrone is not a barbiturate It is a white crystalline powder with a melting point of 159°C It is insoluble in water but soluble in many organic solvents. The sodium salt is soluble in water, the pH of a 5 per cent solution is between 11 5 and 12 and that of a 2 5 per cent solution is 11.4. It is hygroscopic and unstable even in the anhydrous form. It must be dissolved in sterile water or normal saline since Dolitrone base will precipitate if the sodium salt is dissolved in glucose solution which is slightly acid The 2 5 per cent solution so prepared is isotonic with human blood

Pilot studies conducted in the laboratories of the Wm. S Merrill Company and reported by Thompson, Smith, and Werner (1), indicated that in laboratory animals respiration was not seriously depressed by Dolitrone and laryngeal reflexes were markedly diminished They also found that abdominal relaxation

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[1]Supplies of Dolitrone were made available through the courtesy of the Wm S Merrill Co of Cincinnati, Ohio, U S A , who also generously supported this study by a grant-in-aid.

was good with doses which did not appreciably alter respiration and that the margin of safety of Dolitrone was greater than that of the barbiturates. With intravenous injection in rabbits, the $L D_{50}$·M.H D. (minimal hypnotic dose) ratio was 16 for Dolitrone as compared to 5 for sodium thiopental. In laboratory animals there was little or no cumulative effect with repeated doses and recovery was rapid following prolonged anaesthesia, in contradistinction to the barbiturates

Duration of hypnosis in single 60 per cent $L D_{50}$ doses was 53 minutes for Dolitrone and 20 minutes for sodium thiopental. With intravenous injection in rabbits the acute $L D_{50}$ for Dolitrone was approximately 3 times that of sodium thiopental Minimal hypnotic doses for both agents were similar Blood pressure in dogs receiving repeated rapid intravenous injections of Dolitrone was not appreciably altered until the stage of respiratory arrest was reached. The heart rate in dogs was not affected by the prolonged administration of Dolitrone and no changes of blood picture, weight, gross and microscopic examination of vital organs were observed after dogs had been maintained in deep surgical anaesthesia with Dolitrone for two 90-minute periods Seldon (9) states that the capillaries in the rabbit's ear, as seen with the aid of a Clarke window, are smaller when Dolitrone is used than they are with ether, cyclopropane, ethylene, or sodium thiopental, and resemble somewhat the state of the capillaries under nitrous oxide-oxygen anaesthesia Cotten and Bay (10) found that in dogs both Dolitrone and sodium thiopental had only limited effects on blood pressure, force of ventricular contraction, and the electrocardiogram, but both produced marked tachycardia in equivalent doses They also stated that, following Dolitrone, fewer epinephrine-induced arrhythmias were found than after sodium thiopental. In contradistinction to Thompson, Smith, and Werner they found that with equivalent anaesthetic doses the duration of anaesthesia was approximately identical for both drugs The respiratory rate was not seriously reduced in non-premedicated animals, but following pre-treatment with morphine, Dolitrone was well tolerated whereas sodium thiopental frequently produced fatal respiratory arrest In 20 per cent of dogs, Cotten and Bay observed intense excitement during emergence, which was not seen after thiopental.

Comparative Study in Volunteers

Healthy volunteers, 9 males and 1 female, were selected and on each two studies were carried out at an interval of one week. During the first sitting sodium thiopental was studied and on the second sitting Dolitrone. The volunteers reported to the Department of Anaesthesia at 8.00 A.M having had no breakfast. They were admitted to the recovery room where their height and weight were recorded They were then made to rest for approximately one hour. No pre-anaesthetic medication whatsoever was given, except to volunteer 8 who was unable to hold the mouthpiece without gagging. He received meperidine (Demerol®) 50 mg. intravenously on each occasion.

Blood pressure, pulse, and respiration were recorded. An arterial puncture was done using a No 20 gauge Riley needle which was left *in situ* throughout the experiment. By means of a mouthpiece, nose clip, and three-way respiratory

valve, expired air was collected in a Tissot spirometer. Serial one-minute collections of expired air were made, usually four or five, until a steady state had been obtained as judged by the constancy of the minute ventilation volume. These collection periods also allowed for an adequate washout of the apparatus dead space As soon as a steady state had been reached the kymograph on the Tissot spirometer was started to measure respiratory frequency and a three-minute collection of expired air was obtained During the middle of this collection a sample of arterial blood was drawn anaerobically into oiled and heparinized syringes. A venous puncture was then carried out with a large bore needle and a Gordh needle mount was attached and securely fastened to the arm.

Samples were analysed as follows. The tidal volume was calculated from the three-minute expired volume divided by the total number of respirations. All volumes are corrected to B T P.S. (body temperature, pressure and saturated). A representative sample of the expired air was stored in a mercury reservoir and subsequently analysed using the micro-Scholander apparatus for carbon dioxide and oxygen contents In two experiments the expired air was analysed using a pulmo-analyser for carbon dioxide and a Beckman analyser for oxygen These two analysers had previously been calibrated against the micro-Scholander. Gas respiratory quotients and oxygen consumption were then calculated using the standard formulae (11).

The arterial blood was analysed for its oxygen and carbon dioxide content using the technique of Van Slyke and Neill (12) and the oxygen capacity was determined after equilibrium of the blood with room air in a tonometer for 15 minutes. The percentage of oxygen saturation was corrected for dissolved oxygen

At the first sitting anaesthesia was induced with sodium thiopental 2.5 per cent using a double sleep dose Immediately thereafter succinylcholine 20 or 30 mg was given. The larynx was exposed, and both cords and trachea were sprayed with 2 ml. of 1 per cent tetracaine (Pontocaine®) followed by insertion of a cuffed No 10 Magill endotracheal tube lubricated with cyclomethycaine (Surfacaine®) jelly 0 75 per cent. The same endotracheal tube was used in all experiments in order to keep resistance to respiration and dead space changes constant. If, following intubation, there was apnoea or inadequate respiratory excursion, mouth-to-tube breathing was carried out Oxygen was not used in order not to interfere with blood oxygenation studies. A period of 10-15 minutes was permitted to elapse until it was certain that all residual effects of the relaxant had worn off During this time and thereafter, fractional doses of sodium thiopental 1 per cent were administered by syringe to maintain the patient at a steady depth of anaesthesia as judged by the electroencephalogram. The level of anaesthesia chosen for each patient was the lightest which would permit retention of the endotracheal tube without bucking and straining, usually mid-second electroencephalographic level was required. If necessary, somewhat deeper levels were maintained At the end of the waiting period respiratory studies were repeated, expiratory air and arterial blood samples were taken again for gas analyses Thereafter anaesthesia was maintained for exactly 30 minutes at a steady level by means of fractional supplements of sodium thiopental 1 per cent The endotracheal tube remained connected to the non-

rebreathing valve throughout the experiment in order not to alter the dead space. All readings and blood samples were repeated at the end of the 30 minutes. While this study was in progress the patient's reaction to pain was determined by inserting a towel clip through the skin to one side of the umbilicus and the response was noted Blood pressure and pulse were recorded from time to time and the electrocardiogram was continuously observed and recorded.

At the conclusion of the experiment the subjects were extubated and observed in the recovery room where their response to verbal stimuli was noted. The point at which they opened their eyes on command was considered the end point of the experiment.

The same technique was used the following week for the Dolitrone experiment with the exception that after initial pilot runs it was found that maintenance of anaesthesia with 1 per cent fractional doses of Dolitrone was frequently impossible Therefore, after induction with Dolitrone 2 5 per cent, anaesthesia was maintained with Dolitrone 2 per cent. Maintenance of anaesthesia at the same level as that of sodium thiopental the previous week was attempted In many instances this was too light and the endotracheal tube was not tolerated, anaesthesia was then deepened to the lightest satisfactory level.

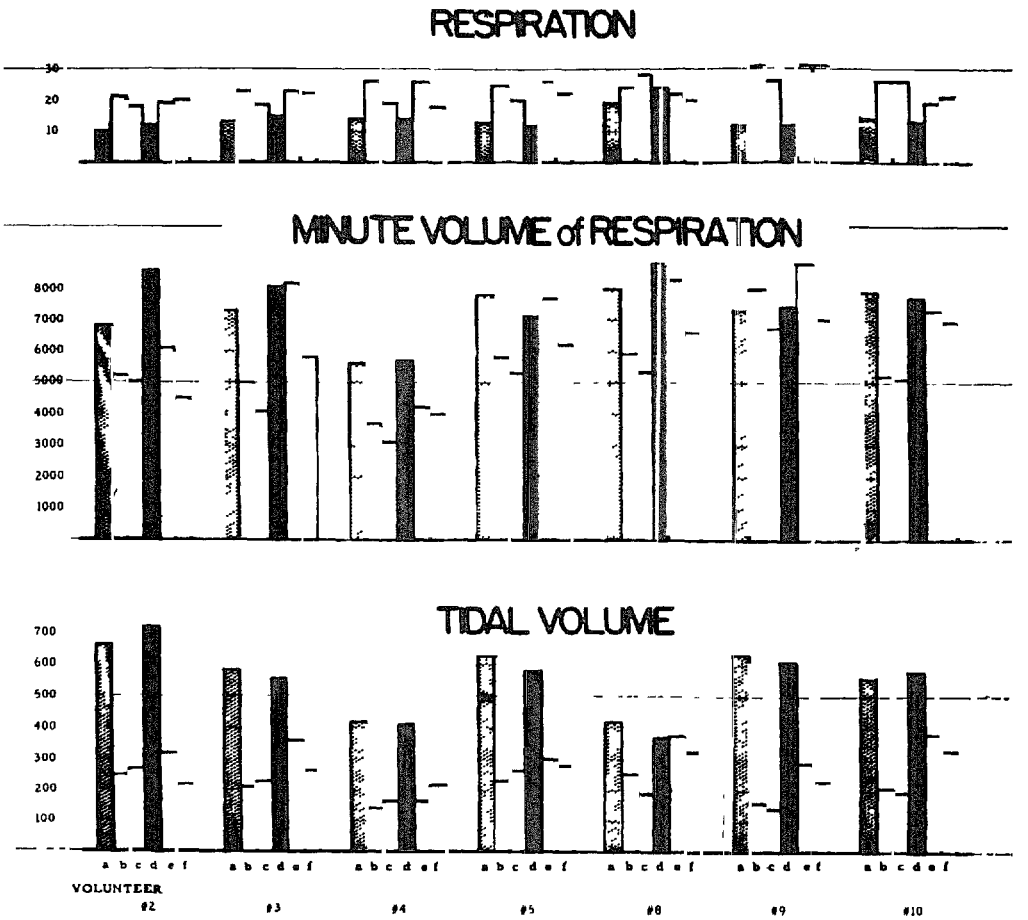

FIGURE 1. Pentothal: (*a*) control, (*b*) after induction, (*c*) after 30 minutes Dolitrone: (*d*) control, (*e*) after induction, (*f*) after 30 minutes.

After the necessary trial runs to test the experimental set-up, 9 volunteers were subjected to the experiment. With one of them smooth maintenance with Dolitrone proved impossible even with the most rapid possible rate of injection of the 2 per cent solution. One volunteer did not return for the second experiment, leaving 7 valid pairs of results for comparison.

Results

Tidal volume, respiratory rate and minute volume. Figure 1 shows the findings for each volunteer It is evident from the chart that neither tidal nor minute volume could in all cases be reproduced exactly in the control study of the second sitting. Where discrepancies between the two controls arise in the tidal volume these are exaggerated for the minute volume as one might expect. It is evident, however, that by and large respiratory changes during Dolitrone anaesthesia are not as marked as with sodium thiopental.

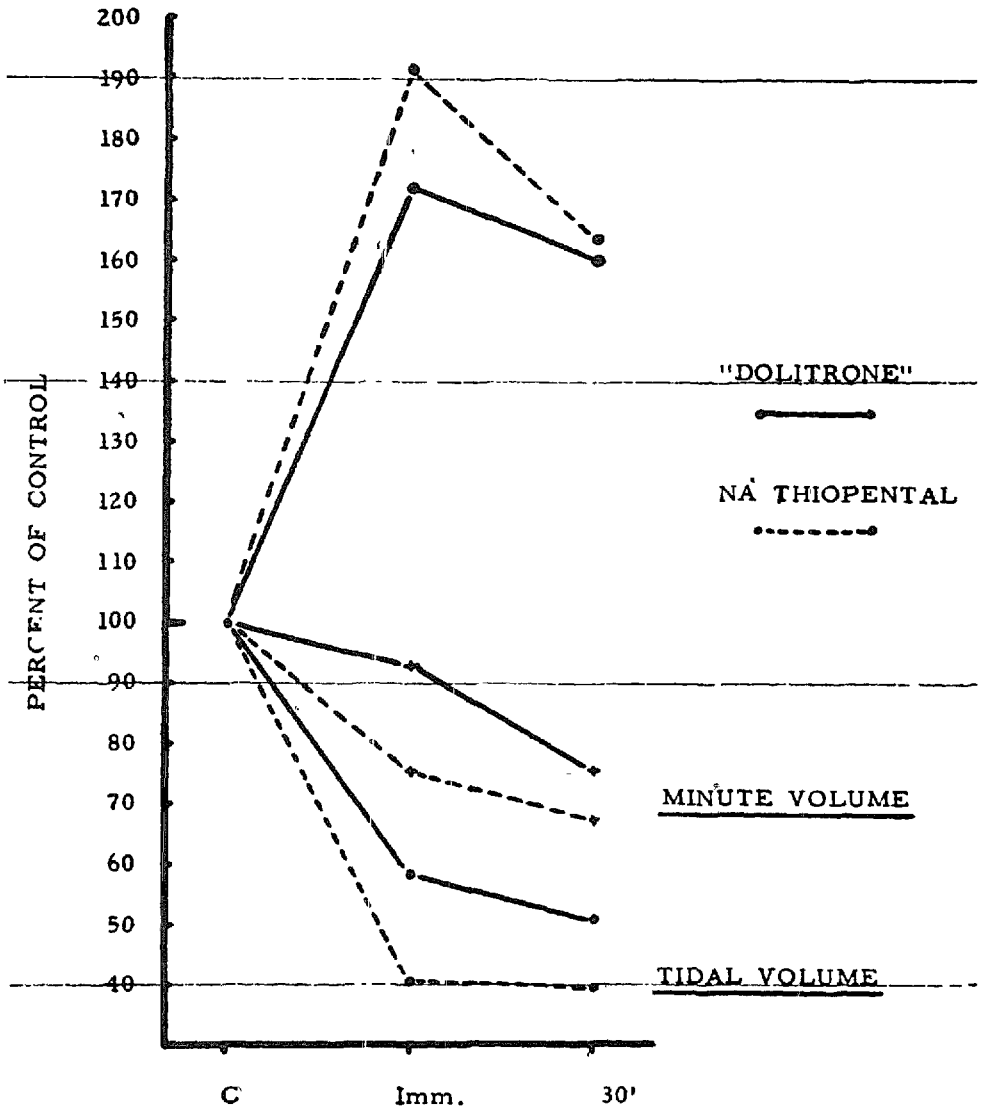

Figure 2 Respiratory rate

In order to demonstrate this better, averages for all seven studies were determined and were related to pre-anaesthetic control values arbitrarily set at 100 per cent. This chart (Fig. 2) shows that the *tidal volume* with sodium thiopental falls after induction to 40 per cent of normal and tends to remain at this level at the end of 30 minutes, whereas with Dolitrone the initial fall is to only 58 per cent of normal, at the end of 30 minutes, however, a further decrease in tidal volume with Dolitrone takes place. In the post-induction measurements the *respiratory rate* with sodium thiopental rises sharply to over 190 per cent of normal whereas with Dolitrone it only rises to 170 per cent. However, at the end of the 30-minute period, both agents show a decline, more pronounced with sodium thiopental than with Dolitrone. The resultant *minute volume* shows a tendency similar to the tidal volume, in that the initial depression of minute volume with sodium thiopental is markedly more pronounced than that with Dolitrone, but Dolitrone tends to approximate the sodium thiopental values at the 30-minute reading

Respiratory quotient In order to determine whether a steady state existed at the time samples were drawn, the respiratory quotient was determined for each reading and averages were plotted. Figure 3 shows that at the control experiment and the 30-minute reading the respiratory quotient for both agents is very close. There is a somewhat larger spread at the reading after induction of anaesthesia, but it is not a significant difference as far as a steady state of the patient is concerned.

Alveolar ventilation. The alveolar ventilation was calculated for each reading

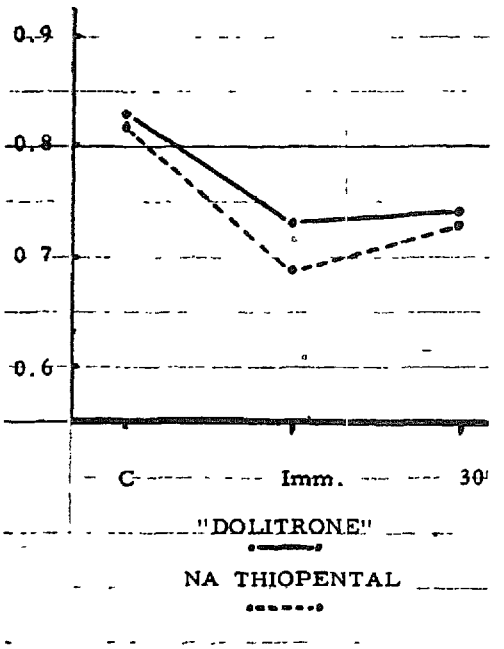

FIGURE 3. Respiratory quotient.

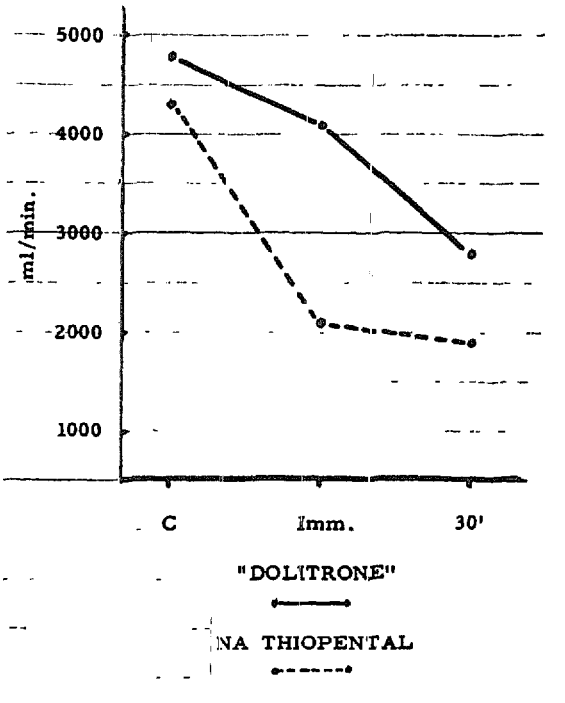

FIGURE 4 Alveolar ventilation.

in every volunteer and average values were plotted (Fig. 4). Calculations of alveolar ventilation were made on the basis of the formula

$$V_A = (V_T - V_{DS})\ frequency$$

where "V_T" represents tidal volume and "V_{DS}" dead space; 75 ml was determined for the non-rebreathing valve, 10 ml. for the endotracheal tube, and 10 ml. for the mouthpiece. An average value of 120 ml. anatomical dead space was postulated Thirty ml. was set for the anatomical dead space below the distal end of the endotracheal tube No adjustment was made for the presumed diminished dead space in the one female volunteer (No. 4) since allowance would also have had to be made for the presumably larger dead space in one or two of the volunteers with a larger body surface area. In the absence of direct determinations of dead space this would have been guess work It was therefore assumed that the dead space figures used constituted a fair average The average alveolar ventilation as plotted on the table approximates closely the minute volume tracings (Fig. 2).

Oxygen consumption Estimates of the average oxygen consumption per body surface area (Fig 5) show that a similar relationship obtains as in the previous tracings Oxygen consumption in millilitres per minute remains fairly steady for Dolitrone when the post-induction is compared with the control reading, but falls sharply towards the end of the 30-minute period, whereas with sodium thiopental the initial fall is very marked and the decline of oxygen consumption in the second period is less marked. Thus the oxygen consumption values for Dolitrone and sodium thiopental at the end of the 30-minute period again tend

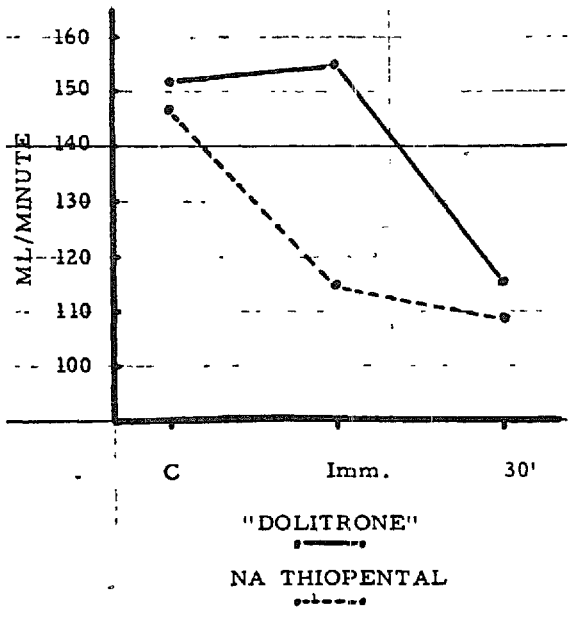

FIGURE 5 Oxygen consumption/body surface

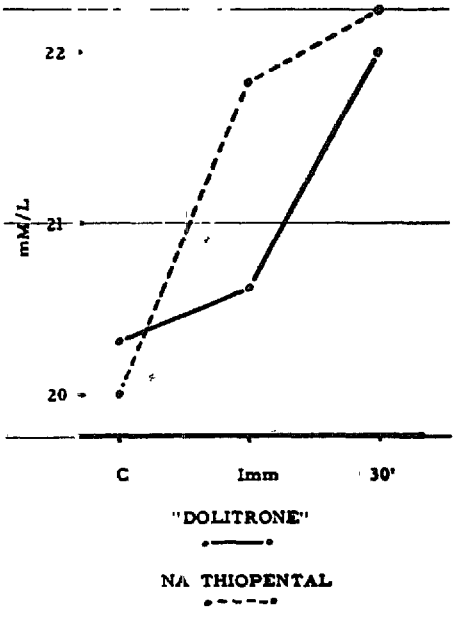

FIGURE 6 Arterial carbon dioxide content

to approximate each other. The difference between them at the end of the 30-minute period is almost identical to their difference in the control determinations.

Arterial carbon dioxide content. Carbon dioxide content in arterial blood (Fig. 6) shows the tendency one might expect from previous tracings, namely that the increase in arterial carbon dioxide for Dolitrone is less marked in the first than in the second period, whereas with sodium thiopental it rises sharply in the first period and more gradually in the second period. Again the values at the end of the 30-minute period seem to come closer.

Figure 7 is derived from the two preceding tracings by plotting alveolar ventilation against arterial carbon dioxide content. In comparing Figures 5 and 6,

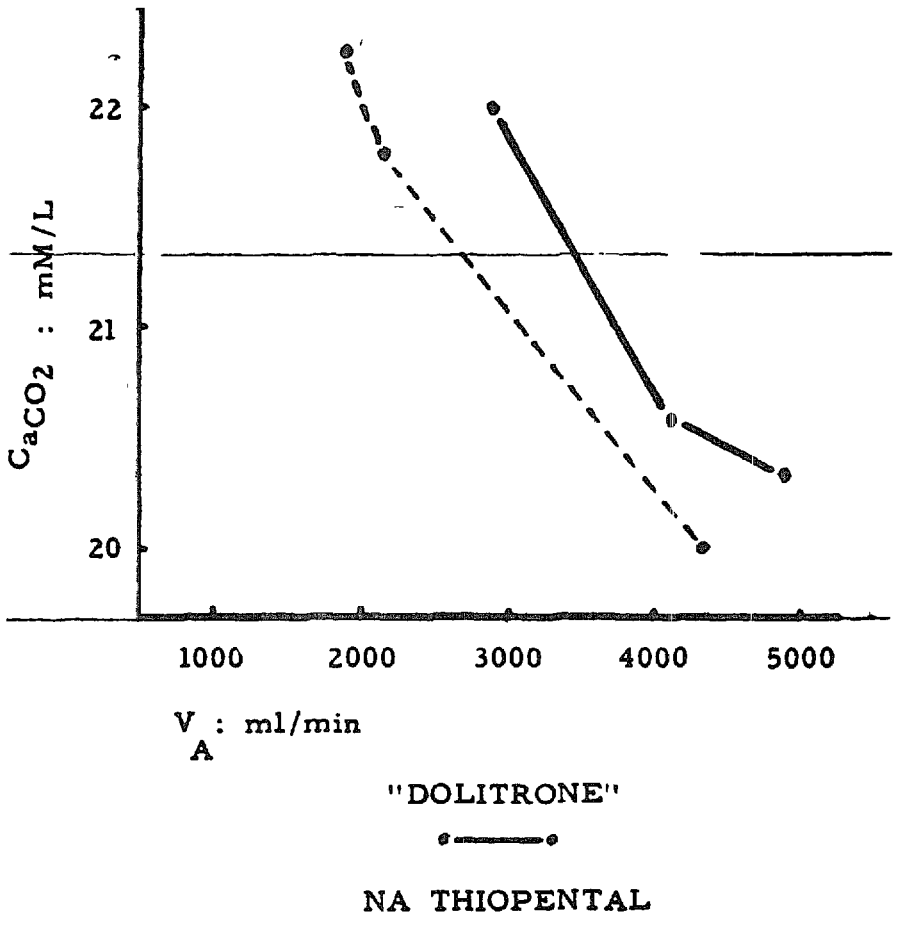

FIGURE 7. Alveolar ventilation Arterial carbon dioxide content

which represent almost picture images, one would expect a straight-line relationship of alveolar ventilation to arterial carbon dioxide content. This is indeed so The tracings are almost straight and parallel. The slight deviations which are seen are within the limits of experimental error.

Total amounts of anaesthetic. Since anaesthesia was of equal duration for each volunteer at both sittings, the amounts of sodium thiopental and of Doli-

trone both for induction and for maintenance of anaesthesia are compared by means of a graph (Fig. 8). All preoperative factors were equal for each volunteer, as was also the dose of relaxant required for endotracheal intubation. The graph shows that frequently, but not invariably, more Dolitrone than sodium thiopental is required for induction. Without exception more Dolitrone is required for maintenance of anaesthesia than sodium thiopental and only in one case

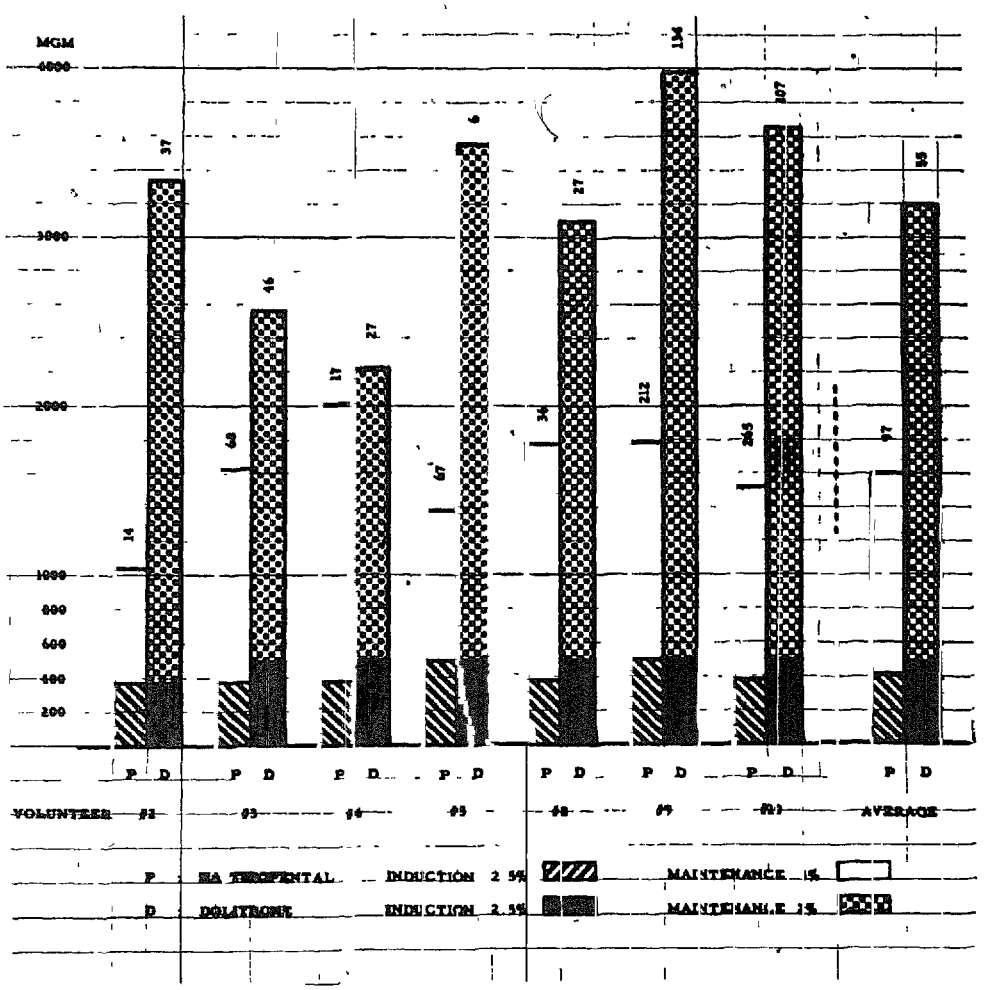

FIGURE 8 Amount of anaesthetic and postanaesthetic reaction time Bars represent amount of anaesthetic for induction and maintenance, numbers above bars denote reaction time in minutes

(No. 4) is the difference insignificant. The graph of averages reveals that for induction a slightly increased amount of Dolitrone is needed as compared with sodium thiopental For maintenance the dose of Dolitrone in milligrams is more than double that of sodium thiopental.

Awakening time. This has been entered on Fig. 8 above each bar as number of minutes. Only twice (volunteers 2 and 4) did the individual react to the spoken word earlier after sodium thiopental than after Dolitrone. However, in volunteer 2 the total dose of Dolitrone was more than three times that of sodium

thiopental. On the average, volunteers after sodium thiopental reacted to the spoken word after 97 minutes from the end of anaesthesia whereas after double the amount of Dolitrone they reacted within 55 minutes.

Clinical Study

Armed with the information gained from our studies on volunteers, we took Dolitrone into the operating room and used it in actual clinical anaesthesia on minor surgical and gynaecological cases The investigation was divided into four groups. With group I (9 cases) Dolitrone, 2.5 per cent solution, was used as an induction agent only. Group II comprises 10 cases where Dolitrone was given for induction and in fractional doses as a supplement to nitrous oxide and oxygen maintenance because with nitrous oxide alone satisfactory anaesthesia could not be maintained. With group III Dolitrone 2.5 per cent was used throughout for induction and maintenance of anaesthesia (15 cases). Group IV comprises cases in which again Dolitrone was used for induction and full maintenance of anaesthesia but as a 2 per cent solution (14 cases).

Group I: Dolitrone 2.5 per cent—Induction only (9 cases)

Table I lists the nine cases in this group. Preoperative medication with meperidine 50 mg. was standard in this group and the interval elapsing between premedication and start of anaesthesia was held as constant as is possible under clinical conditions. As in all other cases the induction dose was double the sleep dose. In other words, the amount of Dolitrone necessary for the patient to close the eyes was determined and a similar amount was then injected moderately fast.

In only two patients short apnoea followed induction. The presence or absence of apnoea did not seem to be related to the patient's weight and height or to the closeness of premedication to induction of anaesthesia. Only in one case was endotracheal intubation carried out and in this case the cords were found to be reacting actively to the stimulus of the laryngoscope and endotracheal tube. Eight inductions were considered satisfactory. One patient developed hiccoughs immediately upon induction and before the maintenance agent was started. The same patient also had some retching, but it is difficult to say whether this was due to Dolitrone or to the maintenance agent In all but two cases anaesthesia was maintained with nitrous oxide–oxygen 8:2. One patient was maintained with nitrous oxide–oxygen 7.2 and trichlorethylene (Trilene®), and one patient was maintained with cyclopropane In one case there was slight movement during the surgical procedure, not sufficient to warrant supplemental doses of Dolitrone.

Mild phlebitis, defined as a tender, hard vein at the site of injection without spontaneous pains or reddening was encountered once on the first postoperative day.

Group II. Dolitrone 2.5 per cent—Induction and supplementation of nitrous oxide (10 cases)

In all these cases nitrous oxide anaesthesia was supplemented by Dolitrone because nitrous oxide by itself proved insufficient to control the patient ade-

TABLE 1

INDUCTION ONLY
(Dolitrone 2.5 per cent)

Case #	Procedure	Weight (lbs)	Height (inch)	Premedication Meperidine (mgm)	Time before induction (min)	Dose (mgm)	Maintenance agent	Total duration of anaesthesia (min)	Apnoea	Intubated	Phlebitis	
1	E U A , D & C, Biopsy cervix	125	60	50	70	500	N_2O (8 2)	14	15″	No	No	Satisfactory
2	Oesophagoscopy	157	68	50	84	425	N_2O (7 2)TCE	9	No	Reactive	No	Satisfactory
3	E U.A., D & C	133	64	50	66	450	N_2O (7 2)	24	No	No	No	Satisfactory
4	E U A.	144	64	50	75	400	N_2O (8·2)	13	No	No	No	Satisfactory
5	E U A., D & C	126	70	50	99	500	N_2O (8 2)	14	30″	No	No	Hiccough, retching
6	Uterine Curettage	134	66	50	93	500	N_2O (8 2)	15	No	No	No	Moving
7	Cystoscopy	168	69	50	116	500	N_2O (8 2)	12	No	No	No	Satisfactory
8	E U A . Uterine curettage	115	62	50		500	N_2O (8 2)	14	No	No	+	Satisfactory
9	Biopsy vagina & cervix, Dilatation, E U.A.	126	63	50	125	500	Cyclo	28	No	No	No	Satisfactory

TABLE II

Induction and Supplement to General Anaesthesia
(Dolitrone 2.5 per cent)

Case #	Procedure	Weight (lbs)	Height (inch)	Premedication Meperidine i m (mgm)	Time before induction (min)	Dolitrone induction dose (mgm)	Maintenance agent	Dolitrone supplemental dose (mgm)	Supplemental started after induction (min)	Duration of Supplemental (min)	Total duration of anaesthesia (min)	Relaxation	Apnoea	Analgesia	Eyes open after Anaesthesia (min)	Phlebitis	
1	Hymenectomy, E.U A , D & C Biopsy cervix	191	66	25	50	400	N_2O (6 2)	225	5	5	27	S'Chol	No	?	?	No	Leg movements controlled with Dol Hypotension 30 mm Hg with supplements.
2	E U A , D & C	128	64	25	92	400	N_2O (8.2)	100	14	2	19	S'Chol	5"	?	4	No	Swallowing controlled by Dol. Carpo-pedal spasm.
3	E.U A , D & C	100	62	25	75	450	N_2O (8 2)	175	4	6	15	+	No	?	11	+	Movements controlled by Dol.
4	E U A , D & C	166	64½	50	65	450	N_2O (8 2)	50	12	S D.	17	S'Chol	No	?	13	No	Crowing controlled by Dol
5	E.U.A., D & C	136	60	50	85	450	N_2O (8 2)	25	8	S D.	15	+	No	+	5	No	Coughing controlled by Dol.
6	D & C	133	65	50	67	450	N_2O (8 2)	50	16	S D.	24	++	No	+	3	No	Movement controlled by Dol
7	E U A , D & C	126	61	50	113	400	N_2O (8.2)	50	11	S D.	24	+++	No	No	1½	+	Slight movement hands. Controlled by Dol.
8	Biopsy cervix E U A , D & C,	116	62½	25	110	375	N_2O (8 2)	100	1	S D	15	+	No	?	1	+	Movement limbs. Controlled by Dol.
9	E.U.A , D & C,	115	63	25	85	400	N_2O (8.2)	100	12	2	19	++	No	1'	3	No	Swallowing and laryngo-spasm. Controlled by Dol.
10	E U A , D & C Biopsy cervix	135	67	50	85	450	N_2O (8 2)	225	6	12	23	S'Chol	No	?4'	3	No	Repeated movement. Controlled by fract. Dol.

quately This was because of either movements which proved disturbing to the surgeon, or coughing, crowing, laryngeal stridor, or swallowing (Table II). In one case hypotension of 30 mm. Hg occurred with the supplement and one other patient developed carpo-pedal spasm This patient was shown to have a borderline blood calcium level and so carpo-peda spasm cannot be attributed to Dolitrone Apnoea of five seconds followed induction in only one case. Relaxation for the procedure, which was usually a pelvic examination under anaesthesia with or without dilatation and curettage, was excellent in one instance, good in two cases, fair in three cases There was no relaxation in four instances and succinylcholine was needed. The total time from the end of anaesthesia until the patient responded to verbal stimuli was unpredictable, varying between one and thirteen minutes and being unrelated apparently to the total dose of Dolitrone, body surface area, or premedication. However, there seemed to be a relationship between the amount of preoperative medication and the necessity for Dolitrone supplementation since five patients in this series only received meperidine 25 mg. Residual analgesia was tested in five of these patients. It was absent in one, definitely present in three, and possibly present in one patient However, since these patients had received nitrous oxide and were not always entirely co-operative when tested immediately at the end of operation, it is difficult to be certain whether analgesia did exist and the actual duration of it. None of the patients in this group were intubated Two developed mild phlebitis

Group III Dolitrone 2·5 per cent—Induction and full maintenance (15 cases)

After induction with double the sleep dose of Dolitrone, anaesthesia was maintained by intermittent fractional supplements of Dolitrone 2·5 per cent, given as required (Table III). All patients received oxygen by mask. Nine patients in this series required no further anaesthesia and in seven the anaesthetic obtained was entirely satisfactory. One had some slight movements which required no further anaesthetic. Hypertension with bradycardia developed in one patient. Relaxation was excellent in two of these patients, good in six, and fair in one, none required a relaxant Apnoea after induction was not seen and terminal analgesia was either absent or doubtful. There was a marked difference in the recovery time This varied between 6 and 34 minutes, and again was entirely unrelated to total dose, body surface area, or preoperative medication The disturbing feature in this group was the high incidence of severe phlebitis (3 cases) and marked phlebitis (1 case) defined as hardening and reddening of the vein along the arm with spontaneous pain and induration of the arm, requiring special treatment

In the same group are six cases in which induction and maintenance with Dolitrone proved unsatisfactory or even impossible and a change had to be made to other agents. In one case sodium thiopental was substituted and all other cases were managed either with nitrous oxide–oxygen or nitrous oxide–oxygen–trichlorethylene Muscle relaxation in these patients was much less satisfactory than in those maintained solely on Dolitrone. Apnoea during induction was again not seen nor was there evidence of postoperative analgesia The rate of severe phlebitis was very high (5 patients out of 6). One of the patients actually

TABLE III

A. Induction and Full Maintenance
(Dolitrone 2.5 per cent)

Case #	Procedure	Weight (lbs)	Height (inch)	Premedication Meperidine (mgm)	Time before induction (min)	Induction dose (mgm)	Maintenance dose (mgm)	Maintenance started after induction (min)	Duration of maintenance (min)	Oxygen L/min	Start anaesthesia to end operation (min)	Relaxation	Apnoea	Analgesia	Eyes open after last Dolitrone (min)	Phlebitis	
1	E U A, D & C	155	64	50	79	400	300	1½	8	4	10	++	No	No	11	++	Satisfactory
2	E U A, D & C Biopsy cervix	168	66	50	75	450	350	1	6	4	13	+	No	?2'	6	No	Satisfactory
3	E.U A, D & C, Manip retrovert uterus	140½	67	50	76	400	475	1	7	4	12	++	No	No	16	No	Satisfactory
4	E U A, D & C	135	64	25	70	400	325	1	9	4	10	++	No	?3''	5	+++	Satisfactory
5	E U A, D & C	175½	65	25	75	400	600	½	9½	4	16	+++	No	No	16	No	Movements not entirely controlled
6	E U A, D & C, Manip retrovert uterus	120	64	25	77	400	375	1	7	4	13	++	No	?	34	No	Satisfactory
7	Cystoscopy, E U A; D & C, Biopsy cervix	152	67	50	105	400	350	1	12	4	18	++	No	No	18	+++	Satisfactory
8	E U A, D & C	135	60	25	155	400	375	2	13	8	17	++	No	No	12	+++	Hypertension and bradycardia
9	E U A, D & C	112	65	50	108	500	500	1	9½	4	13½	+++	No	+	27	No	Movements during dilat. controlled by Dol.

TABLE III (*cont'd*)

B INDUCTION AND MAINTENANCE REQUIRING CHANGE TO OTHER AGENTS

Case #	Procedure	Weight (lbs)	Height (inch)	Premedication Meperidine (mgm)	Time before induction (min)	Induction dose (mgm)	Maintenance dose (mgm)	Maintenance started after induction (min)	Duration of maintenance (min)	Other agent	Duration of anaesthesia (min)	Relaxation	Apnoea	Analgesia	Eyes open after anaesthesia (min)	Phlebitis	Reason for other Agent
1	Laryngoscopy, biopsy vocal cords	179	71½	50	73	450	425	2	21	Pent 0 5 Gm	21	DMC	No	?	?	+++	Cords too reactive
2	E U A , D & C	129	61	25	82	400	600	1	5	N_2O-TCE-O_2	17	No	No			No	Movements not controllable by Dol 1 Gm.
3	E U A , Aspir Cul-de-sac, D & C	162	64	25	35(iv)	400	475	1	4	N_2O-O_2 (+Dol)	24	++	No	No	14	+++	Movements not controlled by Dol Another 75 mgm Dol with N_2O to control crowing
4	E U A , D & C, Biopsy cervix	138	62	25	151	400	600	1	19	N_2O-O_2	28	+	No	No	8	+++	Slight movements throughout N_2O after Dol 1 Gm
5	E U A , D & C	111	65	25	180	500	400	2	4	N_2O-TCE-O_2	19	No	No	No		+++	Severe movements not controlled with Dol
6	E U A., D & C, Manip Retrov uterus	145	65	50	130	500	500	2	5	N_2O-TCE-O_2	20	++	No		2	+++	Severe movements not controlled with Dol.

required prolonged physiotherapy treatment in order to correct the severe inflammatory process in her arm The vocal cords of the patient for laryngoscopy and biopsy of cords were too reactive. In others severe movements of the patient could not be controlled with Dolitrone. These movements were both spontaneous and on stimulation, manifesting themselves by flexion and rigidity of arms and legs to an extreme degree. One interesting feature was that in all perineal operations the perineum did not seem to withdraw from stimulation but remained immobile despite movement of the extremities Again, a marked variation was seen in the reaction time at the end of anaesthesia, similar to that in the previous group

Group IV. Dolitrone 2 per cent—Induction and maintenance (14 cases)

The change to 2 per cent solution was made in order to prevent if possible the high incidence of phlebitis which had been encountered in the group induced and maintained with Dolitrone 2 5 per cent In eleven of these fourteen patients Dolitrone alone was used satisfactorily (Table IV). No marked or severe phlebitis occurred and only four cases of mild phlebitis were noted. The 2 per cent solution of Dolitrone seemed to have the disadvantage of even less potency, with a larger number of patients showing either mild movements, phonation, moaning, sighing, or swallowing These did not significantly disturb the surgeon and therefore no further supplementation was required. One patient had very violent movements although a total of 1 5 Gm Dolitrone was given in order to determine whether increased amounts of the drug might not control these movements. This was not found to be so It is interesting in this connection to compare cases 8 and 9. Both patients were of approximately the same height and weight, and received the same premedication approximately the same time before induction of anaesthesia. The double sleep dose in both patients was equal, yet one of them required only 200 mg supplemental Dolitrone for a six-minute procedure whereas the other required 1100 mg for an eleven-minute procedure. In the patient who received a total of 600 mg. Dolitrone, anaesthesia was entirely satisfactory, whereas the patient with 1500 mg. moved violently and could not be controlled by this large dose. Yet despite the large discrepancy in the dosage both patients reacted to the spoken word within 23 minutes of the end of anaesthesia Again there was no apnoea in this group. Analgesia was conspicuous by its absence. Mild phlebitis occurred once.

In three further patients violent uncontrollable movements necessitated a change to nitrous oxide–oxygen–trichlorethylene after 1 Gm. of Dolitrone had been administered and in no way controlled the movements. They were so severe that the surgeon was unable to proceed with the operation. Despite the identical total amount of Dolitrone of 1 Gm. each and identical nitrous oxide–oxygen–trichlorethylene supplementation, the reaction time varied between 17 and 41 minutes.

Discussion

Tidal volume, minute volume, alveolar ventilation, and arterial carbon dioxide content all seem to indicate that under our standard experimental conditions Dolitrone depresses respiratory functions to a less degree than does sodium

TABLE IV

A. Induction and Full Maintenance
(Dolitrone 2 per cent)

Case #	Procedure	Weight (lbs)	Height (inch)	Premedication Meperidine (mgm)	Time before induction (min)	Induction dose (mgm)	Maintenance dose (mgm)	Maintenance started after induction (min)	Duration of maintenance (min)	Oxygen L/min	Start anaesthesia to end operation (min)	Relaxation	Apnoea	Analgesia	Eyes open after last dose Dol (min)	Phlebitis	
1	E.U A ; D & C, Biopsy cervix	109	63	50	79	400	240	1	9	4	17	++	No	No	25	No	Progressive fall systolic blood pressure
2	E U.A , D & C	120	64	50	86	480	520	1	10	4	13	++	No	No	34	No	Movements not entirely controlled
3	E.U.A , D & C, Biopsy cervix	172	63	50	86	400	300	2	6	5	12	++	No	No	5	No	Phonation, slight movement, moaning
4	E.U.A , D & C; Polypectomy, Biopsy cervix	121	63½	50	150	400	200	1	11	4	17	++	No	No	23	+	Sighing, swallowing. Slight movements towards end
5	E U.A., D & C, Biopsy cervix	113	65	25	118	360	160	1	8	4	12	++	No	No	39	+	Satisfactory
6	E.U A., D & C	157	61	50	154	320	360	1	12	4	12	+	No	?	4	No	Swallowing, moaning, slight movements
7	E.U.A ; D & C, Biopsy cervix	136	60	50	82	360	120	1½	3½	4	9	+++	No	No	15	+	Very slight movements controlled with Dol
8	D & C, E U A.	138	64	50	84	400	1100	1	11	4	20	++	No	No	23	No	Violent movements. Not controlled by 1 5 Gm Dol.
9	D & C; Biopsy cervix, E.U A.	129	65	50	88	400	200	1	6	4	11	+++	No	No	23	+	Satisfactory
10	E.U.A ; D & C	133	64	50	80	400	320	1	9	8	16	+++	No	No	29	No	Mild movement once; controlled by Dol
11	Cystoscopy; Retrograde pyelogram; E.U A , Biopsy cevrix, D & C	133	64	50	96	400	280	½	19	4	26	+++	No (depr)	1′	8	No	Satisfactory

TABLE IV (*cont'd*)

B Induction and Maintenance Requiring Change to Other Agents

Case #	Procedure	Weight (lbs)	Height (inch)	Premedication Meperidine (mgm)	Time before induction (min)	Induction dose (mgm)	Maintenance dose (mgm)	Maintenance started after induction (min)	Duration of anaesthesia (min)	Other agent	Duration of maintenance (min)	Relaxation	Apnoea	Analgesia	Eyes open after last dose dolitrone (min)	Phlebitis	
1	E U A , D & C, Biopsy & caut cervix	146	66½	50	96	400	600	1	15	N_2O-O_2(7 2)-TCE	5	No	No	—	25	No	Violent uncontrollable movements
2	D & C, Biopsy cervix, E U A	122	59	50	85	400	600	1	19	N_2O-O_2(7 2)-TCE	5	No	No	—	41	+	Violent uncontrollable movements
3	D & C, E U A , Cervic polypectomy	147	70	50	84	380	620	1	24	N_2O-O_2(7 2)-TCE	4	+	No	—	17	No	Moderate uncontrollable movements

thiopental This property of Dolitrone is more marked following induction. With prolonged administration the respiratory pattern more closely approaches that of sodium thiopental. Tachypnoea under both agents is marked but more pronounced with sodium thiopental following induction than with Dolitrone; again the respiratory rate with both agents is not markedly different after maintenance for 30 minutes at a steady level

In only three cases was it possible to maintain anaesthesia in an electroencephalographic level comparable for both agents This was most commonly in upper third level In all other cases anaesthesia with Dolitrone required markedly deeper levels in order to make the patient tolerate the endotracheal tube Figure 9 is one example of this. Both tracings are taken in the 18th minute of maintenance The volunteer had received 375 mg of sodium thiopental 2.5 per cent for induction and at the time the tracing was taken he had received 860 mg sodium thiopental 1 per cent He was in upper third electroencephalographic level. At the second sitting 500 mg of Dolitrone 2 5 per cent was required for induction and at the time this tracing was taken 2700 mg. of Dolitrone 2 per cent had been administered Any lighter level of anaesthesia would immediately cause the patient to buck and strain. This tracing shows almost complete absence of brain waves for as long as 18 seconds.

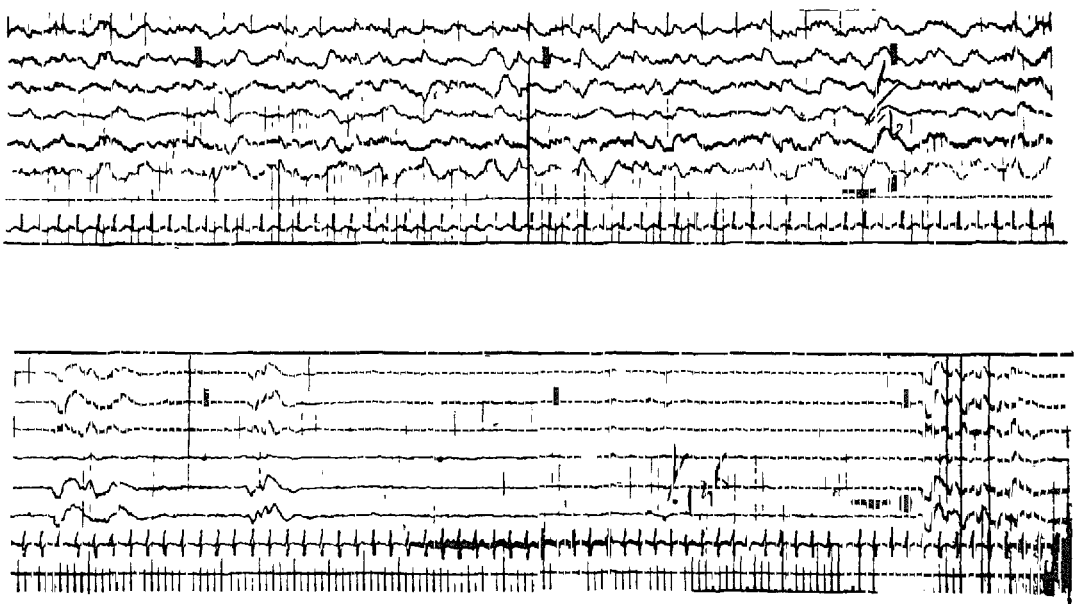

FIGURE 9 Electroencephalogram of volunteer 10 for Na Thiopental (top) and Dolitrone (bottom)—both tracings were taken in the eighteenth minute of maintenance and represent the lightest level at which the endotracheal tube was tolerated

Even with these markedly deeper levels of Dolitrone anaesthesia spontaneous movements of arms and legs quite frequently occurred throughout the administration This was also the case in the very deep level of anaesthesia shown on the electroencephalographic tracing which is illustrated here Only two volunteers did not show these movements at all Although these occasional movements, which consisted of flexion of arms and legs, did not interfere with our experiments, they can be extremely troublesome under actual operating conditions.

In volunteer 6 these movements were so violent that the experiment could not be concluded. The movements consisted of clonic-tonic flexion of arms and legs, mainly limited to the elbows and knees. These were of such intensity as to make smooth maintenance of anaesthesia impossible despite continuous rapid injection of Dolitrone 2 per cent. Yet the same volunteer had been maintained under the experimental conditions on only 1060 mg of sodium thiopental. He had required 560 mg. of Dolitrone 2.5 per cent for induction and even after further injections of up to 1540 mg of 2 per cent Dolitrone for maintenance, the experiment had to be abandoned. This would seem to indicate that Dolitrone is a weak anaesthetic agent with action primarily and almost exclusively upon the cerebral cortex, allowing perhaps preponderance of basic ganglia. This patient also developed severe thrombophlebitis at the site of injection after the experiment, which required physiotherapy because of his inability to fully extend the arm at the elbow The condition resolved without sequelae in the course of ten days

When these volunteers were stimulated after they had been satisfactorily maintained at a steady level of anaesthesia, those under sodium thiopental would usually respond with a slight flexion of the legs which subsided immediately the stimulus was removed As previously mentioned, this stimulus consisted of the insertion of a towel clip at one side of the umbilicus The movement was usually restricted to the leg on the side of stimulation When the same stimulus was applied to individuals under Dolitrone, severe clonic-tonic contraction of both legs at hip and knee would invariably result even under the deepest level of anaesthesia, and was slow to subside after the stimulus had been removed. In fact it tended completely to upset for a time the even maintenance of anaesthesia Both with sodium thiopental and with Dolitrone the electroencephalogram would reveal marked lightening of the level of anaesthesia. In the case of sodium thiopental this would only last as long as the stimulus was applied, whereas with Dolitrone further doses of the drug were needed in rapid succession in order to re-establish the previous level of anaesthesia

Our findings with regard to the wake-up time after sodium thiopental seemed to confirm the animal findings of Thompson, Smith and Werner (1). With two exceptions all individuals reacted to the spoken word much sooner after the conclusion of the experiment with Dolitrone despite the larger total dose of drug administered They also seemed to have less of a hang-over and felt better when they were taken home in the evening

No abnormalities were seen in the electrocardiogram in any experiment with either sodium thiopental or Dolitrone. Neither were there any changes in blood pressure and pulse rates consistent or significant enough to state that there was any marked difference between the two drugs studied. Neither produced marked or prolonged hypotension or significant tachycardia at any time. Post-anaesthetic nausea was not a significant feature with either agent Except for volunteer 6 who developed severe thrombophlebitis no significant postanaesthetic complications developed.

The *clinical use* of Dolitrone confirms our findings in volunteers. Its outstanding advantage is its respiration-sparing properties which are in sharp contra-

distinction to those of sodium thiopental. Double the sleep dose of sodium thiopental if given rapidly almost invariably produces a period of apnoea frequently associated with transitory hypotension. No such hypotension was seen with Dolitrone It must be remembered that, if used for induction alone, Dolitrone is much shorter acting than sodium thiopental and the maintenance agent must be immediately started upon induction. Nitrous oxide maintenance after Dolitrone induction is frequently inadequate since the effect of the induction agent is not carried into the early maintenance period for a sufficiently long time

In the maintenance of anaesthesia Dolitrone is entirely unpredictable and the incidence of unsatisfactory anaesthesia is high However the most disturbing feature is the high incidence of severe and moderate phlebitis which we have encountered with the 2 5 per cent solution When substituting a 2 per cent solution for 2 5 per cent solution the agent becomes even less satisfactory as an anaesthetic agent although the incidence of phlebitis is markedly reduced. We have not attempted to give the agent as a 1 per cent continuous intravenous drip primarily because the 1 per cent solution in distilled water is markedly hypotonic and we have been afraid to use such a hypotonic solution in patients In the light of our clinical experiences it may well have been that some painless induration of the vein at the site of injection developed also in some of our volunteers after Dolitrone If this happened it was not severe enough to cause the volunteers to return and complain about any discomfort, except volunteer 6 who required active treatment for a very painful arm

Another most disturbing feature of Dolitrone is the frequent occurrence of spontaneous movements which can assume most violent proportions and cannot be controlled by the rapid injection of even large doses of the drug They can only be suppressed by a change to other anaesthetic agents.

Analgesia We have seen very little evidence of residual analgesia under the conditions in which the drug has been used by us Comparison of group I with the others of the clinical study seems to indicate that residual analgesia in group I cases may have been due more to nitrous oxide than to Dolitrone or perhaps to a synergism of the two The analgesic and amnesic properties which have been claimed for Dolitrone therefore had to be separately investigated. Since analgesia is a subjective state it was decided that one of us (GMW) should submit to the administration of Dolitrone to decide whether this drug had analgesic properties. No premedication was given. Dolitrone 2 per cent was administered through a Gordh needle in small increments while the subject remained conscious Within 20 seconds of the injection of 1 ml. of 2 per cent Dolitrone there was some tingling in the fingers which spread increasingly throughout the body and was most marked in hands, lips, and tip of tongue. The eyelids became heavy; it was difficult to focus, and some double vision appeared The limbs became heavy but muscle power was retained Both voices and light sensation were markedly increased to the point of unpleasantness Perspiration appeared soon but was not appreciated by the subject until very much later Within a few minutes there was a feeling of nausea which was accompanied by circumoral pallor There was none of the sense of general well-being which is usually associated with the state of general analgesia On the

contrary the prevailing sensation was a most unpleasant one. Deep touch such as squeezing of the calves was appreciated as such but was most unpleasant. All touching of the skin both by the investigators and by the volunteer himself caused marked tingling. Whenever the subject asked that he be tested by pin prick there was a markedly exaggerated painful impression of a very fine needle being thrust through the skin although, unbeknown to the subject, at times only the hub of the needle was used to make contact with the skin. At other times the investigators inserted a towel clip into the subject's arm and this was not noted at all. It would appear that expected painful stimuli were perceived as such in an exaggerated manner whether they were indeed painful or not, whereas truly painful but unsuspected stimuli were not felt at all. At one time tingling of the forehead was replaced by a vice-like pressure on the forehead. This was caused by one of the investigators pressing mildly in the region of the supra-orbital nerve. Analgesia was definitely more marked in the arm used for injection The subject felt an irresistible urge to move from time to time because of the great discomfort he was experiencing during the state of analgesia. The experiment lasted for 20 minutes and during that time a total of 260 mg. of 2 per cent Dolitrone was administered. At the conclusion of the experiment the subject felt a great desire to sleep but after one hour he felt fresh enough to get up and continue with his normal activities. The site of the injection was quite painful and the investigators had noticed hardening of the vein in the forearm while the experiment was still in progress The pain persisted for some four hours and then gradually subsided to a local tenderness. The following morning there was some discolouration but no tenderness although the vein was indurated for some 2½ inches above the site of injection. The subject retained complete recollection of the entire experiment although there was some lack of appreciation of time and the whole experiment seemed somewhat telescoped.

Summary and Conclusions

Dolitrone, a non-barbiturate intravenous anaesthetic agent, has been compared to sodium thiopental in human volunteers. The drug has also been administered to a series of patients undergoing minor surgical procedures In these clinical cases the drug has been evaluated both as an induction and as a maintenance agent. In a further study the analgesic properties of Dolitrone were assessed.

From these, it would appear that Dolitrone has three principle *desirable properties*

1 Because of its marked respiration sparing properties, it could be a useful induction agent It causes practically no apnoea in double the sleep dose and no significant hypotension No cardiac irregularities were noted.

2 Muscle relaxation for such procedures as pelvic examinations under anaesthesia is often satisfactory but unpredictable.

3. Dolitrone has definite analgesic properties although the state of analgesia is subjectively less pleasant than that induced with nitrous oxide, trichlorethylene, or intravenous procaine. It is reasonable to assume that a more profound state of analgesia may be obtained if suitable premedication is given.

We have been unable to demonstrate any amnesic properties of the drug

Against these three advantages are set three overwhelming *disadvantages* of the agent:

1 The high incidence of phlebitis, which ranges from mild to very severe, precludes the use of Dolitrone for anaesthesia or analgesia at the present time, except as a single injection for induction of anaesthesia when phlebitis does not seem to be common. However, one must ask. "Is there a need for another intravenous agent when it must be strictly limited to induction alone?" The incidence of phlebitis could probably be reduced if injection were made into the tubing of a running saline infusion Unfortunately this would entail the administration of undesirably large amounts of normal saline and is therefore not practicable. 5 per cent Dextrose solution which could be given in larger quantities is unfortunately not compatible with the drug.

2 The unpredictability of Dolitrone as a maintenance agent and as far as relaxation is concerned is a serious disadvantage.

3 The frequent occurrence of spontaneous and often uncontrollable movements despite large doses render the agent unsuitable for maintenance of anaesthesia

The drug was so unsatisfactory in clinical use that it was discontinued in each group after it had been used in a relatively small number of cases.

In conclusion, after weighing the advantages and disadvantages of Dolitrone we do not feel that at the present time it can be recommended as a desirable clinical agent. The analgesic properties of Dolitrone are intriguing; whether or not they can be utilized clinically will depend upon the ability of the chemists to evolve a compound less likely to cause venous irritation.

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RÉSUMÉ

Le dolitrone est un agent anesthésique non-barbiturique pour administration intraveineuse, les auteurs l'ont comparé au thiopental sodium chez des volontaires. Ils l'ont également injecté à un certain nombre de malades devant subir de la chirurgie mineure. Au cours de cette étude clinique, le médicament a été évalué aussi bien comme agent d'induction que comme agent d'entretien. Dans une étude ultérieure, les propriétés analgésiques du dolitrone ont été éprouvées.

De tout cela, il résulterait que le dolitrone possède trois qualités principales désirables:

1. Du fait qu'il n'affecte pas la respiration, il pourrait être un agent bien utile pour l'induction. A une dose double de celle requise pour provoquer le sommeil, il cause peu ou pas d'apnée et pas d'hypotension marquée. Nous n'avons pas dépisté d'irrégularités cardiaques.

2. Le relâchement musculaire pour des interventions comme des examens gynécologiques sous anesthésie est souvent suffisant mais inconstant.

3. Définitivement, le dolitrone a un pouvoir analgésique bien que, subjectivement, cette analgésie soit moins plaisante que celle que procure le protoxyde d'azote, le trilène ou la procaine par voie intraveineuse. Quand on a donné une prémédication adéquate, il y a lieu de croire que l'analgésie est plus poussée.

Il ne nous a pas été possible de démontrer si ce médicament peut produire l'amnésie.

Par opposition à ses trois avantages, ce médicament possède trois désavantages importants·

1. La grande fréquence des phlébites, dont la gravité peut aller de bénigne à massive, proscrit, actuellement, l'emploi du dolitrone en anesthésie ou en analgésie à moins qu'il s'agisse de l'injection d'une seule dose pour faire l'induction d'une anesthésie et cela, seulement, si le malade n'a pas tendance à faire des phlébites. Toutefois, on pourrait se demander: "Y a-t-il lieu d'obtenir un autre agent intraveineux dont l'usage se limiterait strictement à l'induction?" La fréquence des phlébites pourrait probablement être diminuée si l'on faisait l'injection de dolitrone dans la tubulure d'un sérum salé déjà installé dans la veine. Malheureusement, cela entraînerait l'administration de grandes quantités de sérum salé ce qui n'est pas pratique et toujours indiqué. Quant au sérum glucosé 5 pour cent qui pourrait être plus indiqué et administré en plus grande quantité, il est incompatible avec le dolitrone

2. L'inconstance du Dolitrone aussi bien dans le maintien de l'anesthésie que dans la production du relâchement musculaire devient un désavantage sérieux

3. L'apparition fréquente de mouvements spontanés et souvent incontrôlables et cela, en dépit de grosses doses, fait que cet agent n'est pas pratique pour le maintien de l'anesthésie

Ce médicament a donné, en clinique, tellement peu de satisfaction que son emploi a été abandonné à différents endroits après usage dans un nombre de cas relativement restreint.

En conséquence, en pesant bien les avantages et les désavantages du dolitrone, nous ne croyons pas, dans le temps présent, pouvoir recommander cet agent comme bienvenu en clinique. Les propriétés analgésiques du dolitrone posent un problème: elles ne pourront pas être employées en clinique à moins que les chimistes réussissent à en extraire un produit moins irritant pour les veines

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