INFLUENCE OF CONTROLLED RESPIRATION ON DOSAGE OF THIO-PENTONE AND D-TUBOCURARINE CHLORIDE REQUIRED FOR ABDOMINAL SURGERY

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In using the anaesthetic sequence D-tubocurarine chloride/thiopentone/nitrous oxide/oxygen, an impression was formed that smaller doses of barbiturate were required when the patient was rendered apnoeic and respiration was manually controlled than when the respiratory excursion was only aided or spontaneous respiration was thought sufficient to ensure full oxygenation (Gray and Rees, 1952). Thiopentone and D-tubocurarine chloride being drugs whose dosage can be accurately measured, it was decided to find out whether manual control of respiration actually does reduce the amount of thiopentone required to produce narcosis.

Experimental Procedure

The average requirements of thiopentone and D-tubocurarine chloride for two comparable series, each of 100 cases (for abdominal surgery), were noted. No patient was included in either series in whom any factor was present which might influence the dose of barbiturate or relaxant required to produce narcosis. These factors included liver dysfunction (Dundee, 1952a), raised blood urea (Richards, Kueter, and Taylor, 1950), severe anaemia (Dundee, 1952b), or acquired tolerance to analgesic or sedative drugs (Dundee and Gray, 1951). Cases in which severe blood loss occurred during operation were also excluded.

All subjects were anaesthetized by the technique recommended by Gray (1948), save that the drugs used were limited to thiopentone, D-tubocurarine chloride, and 50% nitrous oxide and oxygen. In one series of cases apnoea was produced following induction of anaesthesia, and respiration was manually controlled throughout the operation. Spontaneous respiration was allowed to persist, or respiration was aided periodically in the second series of subjects. Premedication was the same for all patients—morphine 1/6 gr. (10 mg.), with atropine 1/100 gr. (0.65 mg.), given 45–60 minutes before induction of anaesthesia. Once anaesthesia was induced, supplementary doses of barbiturate and relaxant were given in amounts not exceeding 50 mg. and 3 mg. respectively, so that at no time did the dose

administered to the patient exceed the requirements by more than these amounts. The series were limited to operations lasting two hours or over. Most patients were anaesthetized personally, and for the remainder, so far as was possible, the same anaesthetist was employed for an equal number of cases from each series. The cases were further balanced so that approximately equal numbers of operations in each series were performed by the same surgeons in the same hospitals.

The weight of all patients was noted before operation and the total amount of drugs administered was recorded in mg./kg. every 15 minutes for two hours. Details of the patients and the operations performed in each series are given in Table I. It will be seen that two series of cases were obtained whose requirements of thiopentone and D-tubocurarine chloride were directly comparable.

Results

Table II shows the result of this investigation, which is represented graphically in Fig. 1. These show that subjects

FIG. 1.—Diagrammatic representation of Table II.

in whom respiration is manually controlled during operation require on the average appreciably less thiopentone than subjects in whom aided or spontaneous respiration is employed. The difference in average amounts of thiopentone administered was found to be statistically significant at 60 minutes (S.E. of difference=0.224), 90 minutes (S.E. of difference=0.314), and at two hours (S.E. of difference=0.381). The potentiation of action of thiopentone that occurs during manually controlled respiration becomes more pronounced as duration of operation proceeds. One feels that if it had been possible to obtain a series of cases in which the operations lasted three to four hours the subjects whose respiration was manually controlled may have required only about half the amount of barbiturate administered to subjects with aided or spontaneous respiration.

The picture obtained with D-tubocurarine chloride is rather different. Despite the fact that this substance in no way potentiates the action of thiopentone (Paulson, Lundy, and Essex, 1949; Gray *et al.*, 1951), it might be argued that the administration of large doses of relaxant will decrease the dose of thiopentone required to produce good operating

TABLE I.—Showing Details of the Two Series of 100 Cases

	Aided or Spontaneous Respiration	Manually Controlled Respiration
Average age	48.4 years	46.9 years
Number of Males	59	70
Number of Females .. .	41	30
Operations:		
Gastrectomy	65	65
Operation on bile ducts ..	10	10
Hysterectomy	6	6
Incisional hernia	6	5
Entero-anastomosis .. .	5	5
Lumbar sympathectomy ..	4	4
Bilateral inguinal hernia ..	3	4
Colectomy	1	1

TABLE II.—Average Doses of Thiopentone and D-tubocurarine Chloride Required at 15-minute Intervals for two Series of Patients Anaesthetized with Thiopentone/D-tubocurarine Chloride/Nitrous Oxide/Oxygen

Time	Thiopentone				D-Tubocurarine Chloride			
	(a) Aided or Spontaneous Respiration		(b) Manually Controlled Respiration		(a) Aided or Spontaneous Respiration		(b) Manually Controlled Respiration	
	mg./kg.	Equivalent for 10-stone Subject mg.	mg./kg.	Equivalent for 10-stone Subject mg.	mg./kg.	Equivalent for 10-stone Subject mg.	mg./kg.	Equivalent for 10-stone Subject mg.
Induction ..	8.51	536.4	7.54	473.2	0.269	16.91	0.316	19.92
15 min. anaesthesia	11.01	693.8	9.16	577.0	0.352	22.19	0.417	26.29
30 "	12.79	806.1	10.44	657.8	0.413	26.04	0.478	30.13
45 "	13.79	868.7	11.10	694.1	0.468	29.48	0.521	32.80
60 "	14.93±0.20	940.6	11.73±0.10	739.0	0.500±0.013	31.47	0.546±0.013	34.42
75 "	15.66	986.7	12.28	773.5	0.533	33.60	0.573	36.11
90 "	16.35±0.29	1,029.9	12.46±0.15	785.1	0.579±0.017	36.47	0.596±0.013	37.19
105 "	17.20	1,083.9	12.52	788.8	0.631	39.74	0.602	37.91
120 "	17.61±0.36	1,109.6	12.81±0.13	806.4	0.657±0.012	41.42	0.605±0.014	38.13

(a) 100 subjects with spontaneous or aided respiration. (b) 100 subjects in whom respiration was controlled throughout the operation.

conditions. For this reason an attempt was made to administer approximately the same doses of D-tubocurarine chloride to the cases in each series. In order to produce apnoea at the beginning of the operation the dose of D-tubocurarine chloride administered to the subjects with aided or spontaneous respiration during the first 45–60 minutes of anaesthesia was found to be significantly greater than that administered to subjects with aided or spontaneous respiration (S.E. of difference at 60 minutes = 0.0161). However, after two hours' anaesthesia the position was reversed, and subjects whose respiration was controlled now required significantly less D-tubocurarine chloride than their counterparts whose respiration was spontaneous or aided (S.E. of difference = 0.0161). An impression was formed that, had an attempt not been made to administer approximately equal amounts of relaxant to both series of cases, this difference would have been more marked. As with thiopentone, it would appear from Fig. 1 that in operations lasting three to four hours the amount of relaxant required when respiration was manually controlled would be very much less than when respiration was periodically aided or spontaneous.

Since the only difference between these two series of cases is the respiratory excursions, it should be possible to relate the differences between manually controlled and aided or spontaneous respiration to the differences in average requirements of thiopentone recorded in Table II. When thiopentone and a relaxant drug are administered and little attempt is made to compensate for respiratory depression, an accumulation of carbon dioxide is inevitable, and if prolonged will result in a decrease in the pH of the blood. Studies on diffusion respiration in dogs (Whitehead *et al.*, 1949) show that, although adequate oxygenation can be maintained for long periods with little or no respiratory movement, this is not accompanied by a corresponding removal of alveolar carbon dioxide. These authors have recorded rises in CO₂ content of arterial blood from 36 vols.% to 75 vols.%, and a fall in arterial blood pH from 7.45 to 6.72 over 45 minutes, during which time arterial oxygen content was barely altered. Provided manually controlled respiration approximates to the patient's normal respiratory excursions, and CO₂ absorption is efficient, the pH of blood in subjects in whom this was performed should remain unchanged throughout the operation. During thiopentone narcosis the amount of drug distributed between plasma and body fat varies with the pH of the blood (Brodie *et al.*, 1950). Decreasing the pH to 6.8 (by inhalation of CO₂) results in a fall in the blood thiopentone level of about 40%. When CO₂ inhalation was stopped the pH rose rapidly to its normal level and was accompanied by a rise in the plasma content of thiopentone.

Changes in Blood pH During Operation

The changes in blood pH which occurred during manually controlled and aided or spontaneous respiration were investigated, using a Muirhead glass electrode battery-operated

pH meter. The findings in 25 cases from each series are shown in Fig. 2. For the sake of simplicity actual figures are not given, but changes from the pre-operative pH of the blood are shown. There is a wide scatter of the readings from each series, due to variations in the respiratory excursions and the efficiency of the soda-lime, but both series of cases show the same tendency. Fig. 2 confirms that a fall in blood pH occurs with aided or spontaneous respiration, but unexpectedly reveals an equally great rise

FIG. 2.—Changes in pH recorded during operation on 25 of each of the two series of subjects referred to in Table I. Changes in pH are recorded as deviations from the pre-operative level.

in pH with manually controlled respiration, indicating hyperventilation in the latter series of cases.

During anaesthesia with thiopentone in man, when adequate ventilation is maintained, the variations in pH (between 7.34 and 7.56) are not enough to affect the plasma concentration of thiopentone (Brodie *et al.*, 1950). In the two series of cases under discussion the average differences resulting from the two types of respiration are much greater—approximately 0.4. From this one would expect that, for equal doses of thiopentone, plasma levels of the drug would be much higher during manually controlled respiration than during aided or spontaneous respiration (Brodie, 1952, personal communication). The concentration of thiopentone in the cerebrospinal fluid (and hence brain concentration) runs parallel to the plasma concentration (Hubbard and Goldbaum, 1950). From this it follows that the duration of narcosis with a fixed dose of thiopentone would be longer with manually controlled respiration than with aided or spontaneous respiration. This is in agreement with the findings of Table II and Fig. 1.

Further Evidence for Potentiation Effect of "Controlled Respiration"

Confirmatory evidence for this was obtained in investigating the effect of hyperventilation with oxygen on the time taken for various subjects to react to a constant stimulus. The investigation was carried out on fit male patients aged between 31 and 49 years, and the constant stimulus employed was the passage of a cystoscope. Selection of subjects and premedication were the same as for the previous two series of cases. Anaesthesia was induced with doses of thiopentone varying between 450 and 700 mg., injected at a fixed rate of 100 mg. in five seconds. In alternate patients a face-mask was applied immediately consciousness was lost, and hyperventilation was carried out with large flows of oxygen (8–10 litres per minute). This proved impossible in some subjects because of difficulty in obtaining an air-tight fit of the face-mask or because of the gases blowing up the stomach. As a result, only 37 out of 102 patients were hyperventilated; the other 65 were allowed to breathe normally.

Cystoscopy was performed immediately the patient was asleep, and the first reaction to this stimulus was taken as

FIG. 3.—Scatter diagram showing times taken for 102 male subjects to react to the stimulus of a cystoscope following varying doses of thiopentone.

the end-point. Duration of narcosis was thus measured from the end of the injection of thiopentone to the first movement of the patient.

Fig. 3 shows the duration of narcosis in subjects who were allowed to breathe spontaneously and in those hyperventilated with oxygen plotted against the dose of thiopentone administered in mg./kg. No direct relation between the dose of thiopentone and the duration of narcosis could be demonstrated in either series, presumably because of acute tolerance to the drug (Mark *et al.*, 1949). However, the results clearly demonstrate a much more prolonged narcosis in subjects who were hyperventilated with oxygen than in those allowed to breathe spontaneously. For the sake of completeness, changes in blood pH were measured in a few cases from each series (Fig. 4), and these show the same picture as Fig. 2.

FIG. 4.—pH changes recorded during cystoscopy in 18 of the cases referred to in Fig. 3.

Discussion

From these investigations it can be concluded that a moderate degree of hyperventilation, such as occurs in manually controlled respiration, results in a prolongation of the action of thiopentone. While the most likely explanation of this phenomenon is the effect of the altered pH of the plasma on the distribution of thiopentone in the body, one cannot be dogmatic and assume that is the sole explanation.

Overventilation for any length of time is accompanied by oliguria and decreased urea clearance (Smith, 1951). In one recorded case of acapnia following hyperventilation the rate of urea clearance was reduced to one-fifteenth of normal (McCance, 1935). It is known that the presence of a high blood urea prolongs thiopentone narcosis (Richards *et al.*, 1950). The possibility exists that during prolonged manually controlled respiration a sufficient rise in blood urea may occur to potentiate the action of the thiopentone and thus reduce the amount of barbiturate required to produce anaesthesia. This possibility was investigated, and

FIG. 5.—Changes in blood urea recorded during operation in seven cases with manually controlled respiration.

Fig. 5 shows actual changes in blood urea recorded during thiopentone/D-tubocurarine chloride/nitrous oxide/oxygen anaesthesia with manually controlled respiration. It can be seen from the results of seven cases investigated that the degree of hyperventilation that occurs during manually controlled respiration has a negligible effect on the blood urea, and in only one case was there any possibility of urea being incriminated as a cause of potentiation of thiopentone. It is interesting to note that in the one case in which a rise in urea was noted an excessive degree of hyperventilation was produced for investigational purposes. It would seem that with controlled respiration as carried out during anaesthesia there are no deleterious effects on kidney function and no marked rise in blood urea.

Loss of consciousness can follow hyperventilation if this is carried to extremes (McCance, 1935; Seevers *et al.*, 1939). A diminution in cerebral blood flow of the order of 30% (part of a general peripheral vasoconstriction) with an average increase of 15% in cerebral oxygen consumption has been reported (Kety and Schmidt, 1946). These would lead to a certain degree of cerebral anoxia, which may be aggravated by the effects of lowering the CO₂ tension on the oxygen dissociation curve of blood. While more oxygen can be taken up by the blood in the lungs, less will be given off to the tissues (Barach *et al.*, 1947). While it is known that potentiation of barbiturate anaesthesia can be accomplished by any means whereby central anoxia is produced (Peterson, Shideman, and Linares, 1950), this could not have played a part in the potentiation of thiopentone observed during manually controlled respiration. In these cases the degree of hyperventilation was so slight that none of the anaesthetists concerned realized that they were in fact hyperventilating the patients until they were told of the pH changes of the blood. Furthermore, using the thiopentone/D-tubocurarine chloride/nitrous oxide/oxygen sequence with manually controlled respiration of the same degree as in the series of cases referred to earlier, Prime and Gray (1952) found peripheral vasodilatation rather than vasoconstriction.

The fact that a patient is not breathing spontaneously will reduce the tone of the intercostals and hence abdominal muscles. If thiopentone/nitrous oxide/oxygen were used without a muscle relaxant, controlled respiration would reduce the amount of barbiturate required to produce satisfactory relaxation. This does not apply directly to the cases described above, but is the probable explanation of the lowered requirements of D-tubocurarine chloride observed at the end of two hours' anaesthesia with manually controlled respiration, as compared with patients who were allowed to breathe spontaneously.

All of the arguments quoted above are applicable to the anaesthetic technique described by Brennan (1952). With doses of 500 mg. of thiopentone for a large healthy adult he was able to produce long periods of narcosis. Undoubtedly he used a higher percentage of nitrous oxide (75%) to obtain a better analgesia, but it is doubtful if this actually resulted (Seevers *et al.*, 1937). Hyperventilation was purposely carried out from the beginning of the operation, and the changes in pH of the blood must have been greater than those recorded in either Fig. 2 or Fig. 4.

Conclusions

1. Subjects anaesthetized with thiopentone/D-tubocurarine chloride/nitrous oxide/oxygen require appreciably smaller amounts of barbiturate when respiration is manually controlled than subjects in whom respiration is aided or spontaneous.

2. More D-tubocurarine chloride is required for the first 45–60 minutes of the operation when respiration is controlled, but after two hours of anaesthesia requirements of relaxant are less than for subjects whose respiration is spontaneous or periodically aided.

3. With this sequence of drugs, aided or spontaneous respiration is accompanied by a fall in the pH of the

blood. Manually controlled respiration results in a rise in blood pH, indicating some degree of hyperventilation.

4. The changes in the pH of the blood, by affecting the distribution of thiopentone in the body, could account for conclusion 1.

5. Hyperventilation with oxygen prolongs the duration of thiopentone narcosis.

6. Other effects of hyperventilation which have been discussed are unlikely to have any potentiating effect on thiopentone.

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A NEW ARTIFICIAL RESPIRATOR

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The increasing use of anaesthetic methods which involve complex intravenous techniques and the deliberate production of a state of apnoea have led to an interest in machines which are capable of ventilating a patient's lungs automatically and so restoring to the anaesthetist the freedom of his hands.

The respirator here described (Fig. 1) was designed for patients anaesthetized for thoracic surgery, and was first subjected to clinical trial at Aintree Hospital, Liverpool, in September, 1949. Since its introduction it has maintained respiration throughout the course of 538 major thoracic operations, of which 432 were cases of lung resection. That the trial has extended into what is, for this type of surgery, a long series of cases, speaks for the acceptance of the machine by surgeon and anaesthetist, and for the absence of complications that could be attributed to its use.

The respirator is of simple construction, the original model being built without special tools in a home workshop. Essentially the mechanism consists of:

1. A three-way tap by means of which the anaesthetic circuit can be connected to a hand-operated breathing-bag, or to a bag inside a glass bottle, at will.