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CHANGES CAUSED BY ANAESTHESIA IN THE BLOOD ELECTROLYTES OF THE DOG

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THERE have been few studies concerning the effects of anaesthesia on the inorganic blood constituents and much of this work has yielded conflicting results. However, a knowledge of such effects is important when assessing changes which are caused by such differing factors as variations in the carbon dioxide tension of the blood or by the use of drugs such as the muscle relaxants.

The effects of anaesthesia on the total plasma calcium concentration were extensively studied by Cloetta and his fellow workers (Cloetta and Thomann, 1924; Brauchli and Schnider, 1929; Cloetta, Fischer and van der Loeff, 1934, 1942) who believed that during narcosis in many species, including man, there was a consistent decrease of up to 10 per cent of the pre-anaesthetic concentration. They also believed that the speed at which this fall occurred depended on the rapidity of action of the anaesthetic agent used. The consistency of the results published by these workers has not, however, been confirmed by other investigators. Eisler, Geness and Dienerstein (1929) and Lipow, Weaver and Reed (1929) reported a variable decrease in the plasma calcium concentration of dogs subjected to ether anaesthesia, while Emerson (1928) and Andrews, Petersen and Klein (1930) observed an increase in concentration. Mollaret, Pocidalo, Lissac and Demongeot (1956) were unable to demonstrate any significant changes in the plasma calcium concentration during diffusion respiration in anaesthetized dogs, but Brown and Prasad (1957) found an increased concentration in dogs inspiring high concentrations of carbon dioxide for prolonged periods. These workers have also studied changes in ultrafiltrable calcium concentrations during carbon dioxide administration. Unfortunately their methods of determination were not sensitive to changes in the ultrafiltrable, but unionized, plasma calcium. This fraction which is normally considered insignificant may greatly increase when there is an accumulation of acid metabolites, such as lactate, in the body.

Reports concerning magnesium are again conflicting. Lipow, Weaver and Reed (1929) and Cloetta, Fischer and van der Loeff (1934) found great variations in the plasma magnesium concentration as a result of various types of anaesthesia. However, Agnoli (1929), Eisler, Geness and Dienerstein (1929), and Marenzi and Gerschman (1933) reported a consistent decrease in magnesium concentration. Changes in the total and ultrafiltrable plasma magnesium concentrations during the administration of carbon dioxide in the respiratory gases of anaesthetized dogs have been studied by Prasad, Flink and Brown (1957).

The early reports of a decreased potassium concentration during anaesthesia in the dog by Lipow, Weaver and Reed (1929) and Eisler, Geness and Dienerstein (1929) have been repeatedly confirmed (Andrews, Petersen and Klein, 1930; Gerschman and Marenzi, 1933a, b; Robbins and Pratt, 1936; Fay, Andersch and Kenyon, 1939a, b; Larson and Brewer, 1939; Brewster, Bunker and Beecher, 1952). The decrease in concentration caused by ether anaesthesia in the dog may be inhibited by 2, 4 dinitrophenol (Larson and Brewer, 1939) or by high epidural nerve block (Brewster, Bunker and Beecher, 1952).

The plasma sodium concentration has been examined in the anaesthetized dog by Lipow, Weaver and Reed (1929), Marenzi and Gersch-

man (1933), and Fay, Andersch and Kenyon (1939a, b), who reported a small but inconsistent decrease in concentration.

The changes in plasma inorganic phosphate during anaesthesia which have been reported are variable. Stehle and Bourne (1924) believed that in dogs ether anaesthesia produced little change, similar findings also being reported about the same time for man (Potter, 1925). On the other hand Bolliger (1926) believed that ether anaesthesia in dogs reduced the concentration of plasma inorganic phosphate, except when partial asphyxia was present. Similar findings were recorded by Eisler, Geness and Dienerstein (1929). Fay, Andersch and Kenyon (1939a), however, found that the mode of administration of ether anaesthesia to dogs was important in this respect, since ether given by open drop caused a decrease, and by closed-circuit methods an increase, in the plasma inorganic phosphate. These workers (1939b) also found an increase during cyclopropane anaesthesia in dogs. An increase in the plasma inorganic phosphate of man during anaesthesia has been reported by Waters and Schmidt (1934) and Foldes, Murphy and Wilson (1950).

Ether anaesthesia always causes a decrease in the blood pH of dogs which is accompanied by a decreased alkali reserve, whether or not a respiratory acidosis is also present (Dripps and Severinghaus, 1955). Cyclopropane has also been shown to cause a decrease in the blood pH of dogs (Fay, Andersch and Kenyon, 1939b).

METHODS

Carotid arterial loops were prepared in healthy young mongrel dogs, weighing 8 to 20 kg.

At the beginning of an experiment, the dog to be used was premedicated with 0.5 mg/kg body weight pethidine hydrochloride and atropine sulphate 0.65 mg. About 1 hour later, one siliconed 19 S.W.G. hypodermic needle was inserted into the carotid artery, a similar needle also being placed in a cephalic vein. The dog was heparinized with a dose of 2 mg/lb. body weight heparin (Roche) and the needles were then connected by 1.5 mm bore polythene tubing to a pH-measuring apparatus (fig. 1) so that a continuous measurement of arterial blood pH could be made, using a Pye "Master" pH meter. Side arms in the polythene tubing near the arterial and venous needles were used for blood sampling and the administration of intravenous injections. At the end of an experiment, protamine sulphate was administered in order to restore normal blood coagulation. Anaesthesia was induced by the intravenous injection of thiopentone sodium (Intraval Sodium) and the dog was intubated with a cuffed Magill tube. The appropriate anaesthetic vapour was then administered from a Boyle's apparatus, using a Water's attachment, with an 8-oz. soda lime canister, and a 1-gallon rebreathing bag.

Blood samples were taken directly under oil, and 0.1 ml samples were then immediately withdrawn for estimation of the total blood carbon dioxide by the method of Conway (1947). The

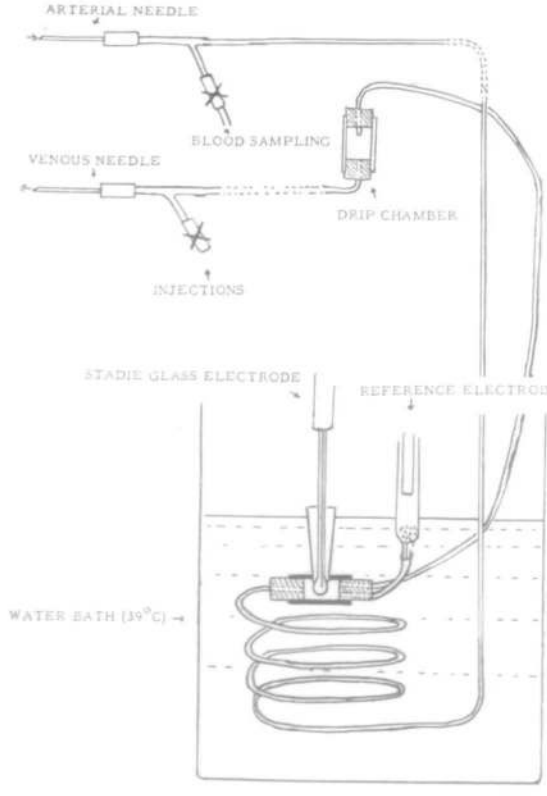

FIG. 1

Apparatus for the measurement of arterial blood pH, and the sites used for blood sampling and the administration of intravenous injections.

blood sample was then centrifuged and the plasma decanted for electrolyte estimations.

Potassium and sodium were estimated with an EEL flame photometer, using suitable dilutions of a standard sclution as a reference. Calcium and magnesium were estimated by precipitation as oxalate and magnesium ammonium phosphate respectively, the precipitates being redissolved in nitric acid and titrated with 0.001N EDTA, using an ethanolamine buffer, pH 10.4 and solochrome black as an indicator.

Plasma inorganic phosphate was estimated by a modification of the method of Simonsen, Westover and Wertman (1947).

EXPERIMENTAL RESULTS

Control experiments.

In order to determine the changes which might occur in the blood electrolytes in a conscious dog, three experiments were carried out in which anaesthesia was not induced. Blood samples were taken every 30 minutes for a period of 2 hours. The results which were obtained in these experiments are shown in figure 2, which indicates the changes which occurred from the control concentrations. These results indicated that although minor changes in concentration might occur, there was no consistent trend.

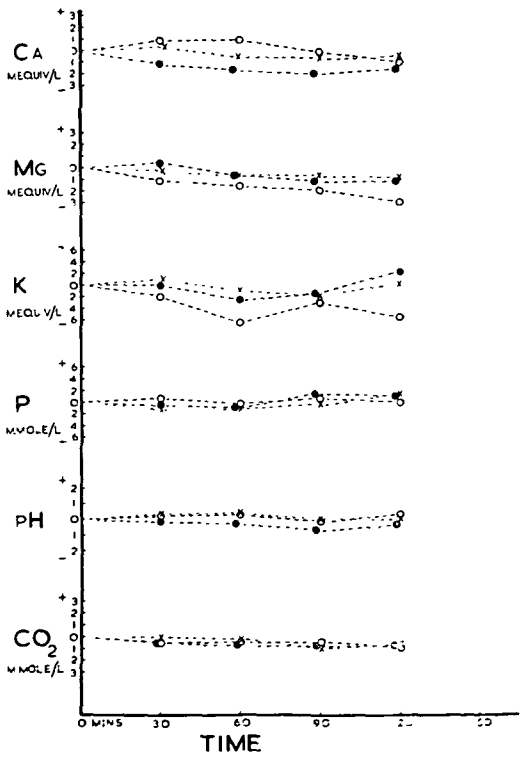

FIG. 2

Premedication only, showing the results of three experiments and indicating variations from the control blood sample taken at 0 minutes.

Thiopentone-ether anaesthesia.

In these and subsequent experiments a control blood sample was taken immediately prior to the induction of anaesthesia. Anaesthesia was induced with just sufficient thiopentone sodium to allow endotracheal intubation and was then deepened to the plane of surgical anaesthesia with ether and oxygen at a flow rate of 4 litres per minute. The results which were obtained in three 2-hour experiments are shown in figure 3.

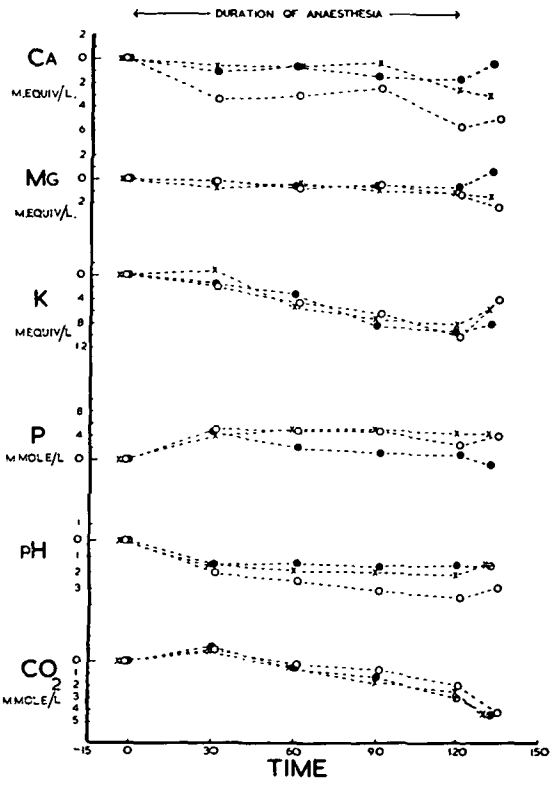

FIG. 3

Thiopentone-ether anaesthesia. Three experiments showing the variations from the control concentrations found prior to the induction of anaesthesia at 0 minutes.

The potassium concentration showed a gradual decrease, the progressive nature of which was in contrast to the changes in concentration of the plasma inorganic phosphate and the blood pH, which were greatest during the first 30 minutes of anaesthesia. The initial increase, followed by a gradual decrease, in the total carbon dioxide content of arterial blood indicated that the depth of anaesthesia might determine the presence or absence of respiratory acidosis during ether anaesthesia in the dog, since it was found difficult to maintain a plane of surgical anaesthesia during the second hour of experimentation. Dripps and Severinghaus (1955) pointed out that most earlier workers had found both a metabolic and respiratory acidosis, whereas recent workers have usually only reported a metabolic acidosis.

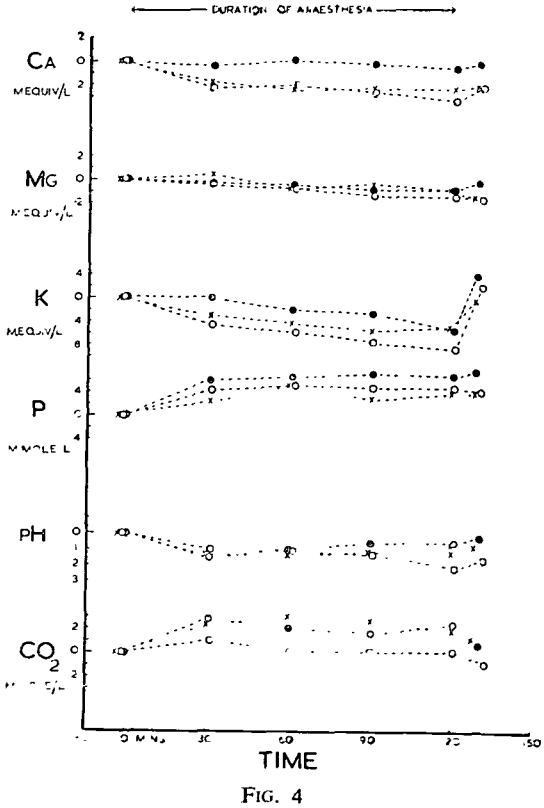

FIG. 4

Thiopentone-cyclopropane anaesthesia. Three experiments showing the variations from the control concentrations found prior to the induction of anaesthesia at 0 minutes.

These results show good agreement with most previous reports. There seems little evidence for a consistent decrease in the plasma concentrations of calcium and magnesium. No significant changes in the sodium concentration, as determined by the flame photometer, were found in these and other experiments in this investigation.

Thiopentone-cyclopropane anaesthesia.

In these experiments thicpentone was again used for the induction of anaesthesia prior to intubation and the administration of cyclopropane. A gas flow rate of 4 litres per minute of oxygen was used in order to minimize the possibility of carbon dioxide retention.

The results of three experiments are shown in figure 4. The chief difference between ether and cyclopropane was shown in the changes in the carbon dioxide content of arterial blood. With cyclopropane the decrease in pH could almost entirely be explained by the increase in carbon dioxide and there was not a significant metabolic acidosis.

Thiopentone-nitrous oxide anaesthesia.

Induction of anaesthesia was achieved by the intravenous injection of thiopentone in larger amounts than were used during the experiments with ether and cyclopropane, since it is difficult to maintain anaesthesia in the dog with nitrous oxide alone. For this reason, too, further injections of thiopentone were given during the course of an experiment when necessary. A flow rate of 2 litres of oxygen and 6 litres of nitrous oxide per minute were used.

Figure 5 shows the results obtained in three experiments. Small but well-defined changes in the electrolyte concentrations were found. The most significant of these were the depression of the potassium and the elevation of the inorganic phosphate concentrations, the greatest changes occurring during the first hour of anaesthesia. The elevation of the carbon dioxide content of the blood largely depended on the amount of thiopentone used, since this influenced the degree of respiratory depression.

It was found that in some cases, where thiopentone had been given by a rapid initial injection of most of the dose ultimately required, there was a transient increase in the pH of the

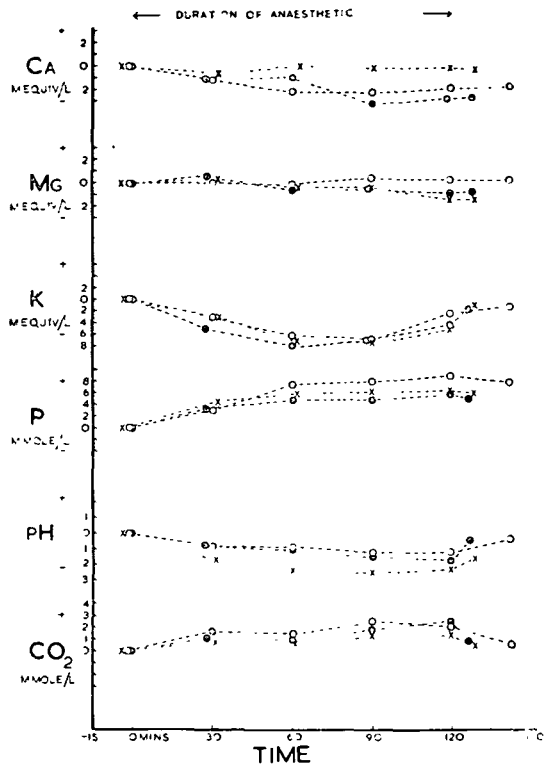

FIG. 5

Thiopentone-nitrous oxide anaesthesia. Three experiments showing the variations from the control concentrations found prior to the induction of anaesthesia at 0 minutes.

blood. This was unexpected and, since the rise was never more than 0.02 pH units, it was at first thought that this was due to a slight drift in the pH meter. However, it was also noted that the increase always coincided with a period of apnoea and that the pH had always returned to the control value, or below, by the time respiratory movements recommenced. It was also found that this change could be reproduced with regularity provided a sufficient amount of thiopentone was given by rapid injection. Further experiments were undertaken which indicated that the increase in pH was not due to the alkalinity of the thiopentone solution or to changes in the buffering capacity of the blood due to a decreased oxygen tension. At present no satisfactory explanation can be given for this phenomenon.

Hydroxydione-nitrous oxide anaesthesia.

The results of two experiments using these agents are shown in figure 6. It was found that dogs required up to 100 mg of hydroxydione sodium (Viadril) per kg body weight and since this drug must be given as a dilute solution, owing to the danger of thrombosis, the amount of injection necessary to produce even light narcosis was too large to be clinically practical in this species. The results obtained showed that there was little change in the blood pH or carbon dioxide content, although the latter was slightly reduced at the end of 2 hours anaesthesia. The only significant change was that of the potassium concentration, which showed the decrease commonly associated with anaesthesia.

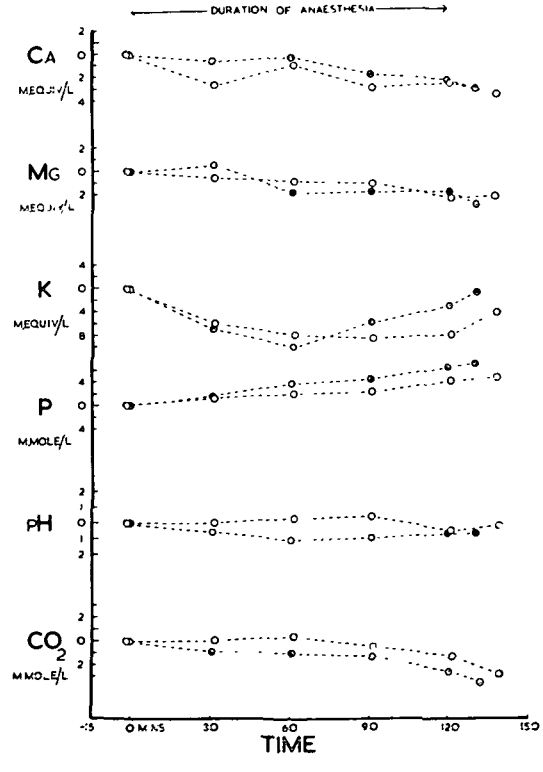

FIG. 6

Hydroxidione-nitrous oxide anaesthesia. Two experiments indicating the variations from the control concentrations found prior to the induction of anaesthesia at 0 minutes.

The effect of carbon dioxide retention during anaesthesia with thiopentone and nitrous oxide.

The inadvertent retention of carbon dioxide has often been blamed for the occurrence of anaesthetic emergencies. Although there have been many reports indicating that respiratory acidosis may occur during clinical anaesthesia in man (Dripps and Severinghaus, 1955), these mainly refer to the use of cyclopropane in closed circuit. There are no reports in the veterinary literature which indicate that respiratory acidosis is a clinical problem, even when pentobarbitone is used as an anaesthetic agent.

The following experiments were, therefore, of interest both to determine the electrolyte changes which might occur during respiratory acidosis and the degree of this which might be found during clinical anaesthesia in this species, using standard medical anaesthetic equipment.

In order to produce carbon dioxide retention, the soda lime canister was omitted from the anaesthetic circuit and the gas flow rate was reduced. A flow rate of 1 litre of oxygen and 1 litre of nitrous oxide per minute was used for the first 20 minutes but at this flow rate the pH never fell by more than 0.3 pH units. In order to produce more severe changes it was necessary to reduce the total gas flow rate to 100 ml of oxygen per minute. At the end of 2 hours anaesthesia the decrease in pH was 0.6—0.8 pH units. It therefore seems unlikely that severe respiratory acidosis may occur during anaesthesia in dogs, when standard medical equipment and the usual total gas flow rates are used.

Figure 7 shows the results obtained in two experiments carried out on the same dog. In the experiment the results of which are plotted by black circles the respiration became very distressed and the degree of carbon dioxide retention was therefore limited. In the other experiment the respiration was depressed when necessary by the injection of small amounts of thiopentone. In the first of these experiments the plasma potassium concentration started to increase earlier and also rose higher by the end of the second hour of anaesthesia than in the second experiment. Although there was a marked difference between the carbon dioxide content of the blood in these two experiments,

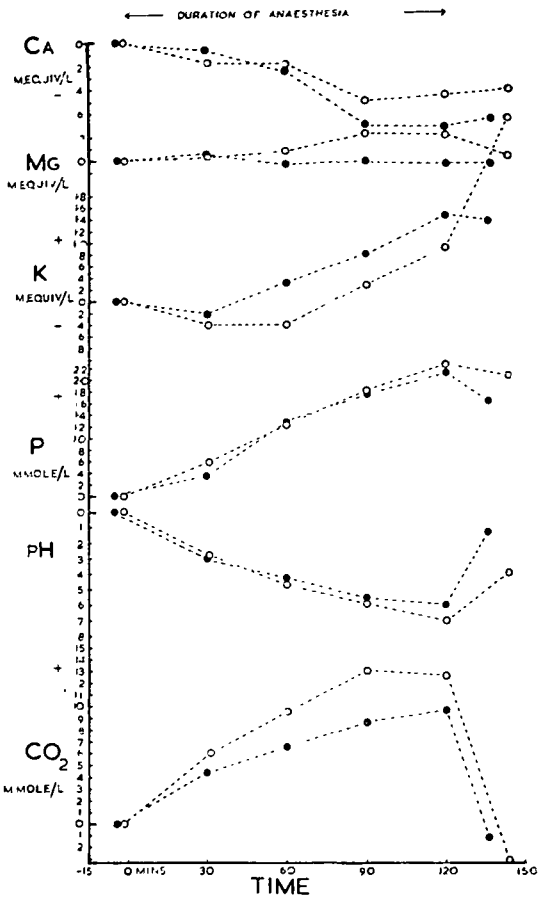

FIG. 7

Thiopentone-nitrous oxide anaesthesia. Two carbon dioxide retention experiments carried out on the same dog. Time in minutes from the induction of anaesthesia.

the fall in pH was very similar. This suggested that there was a greater degree of metabolic acidosis in the first of these experiments.

The plasma calcium concentration had fallen by the end of both these experiments but there was no significant change in the magnesium concentration. The plasma inorganic phosphate concentration was about twice the control concentration by the end of the second hour of anaesthesia.

Since it seemed likely from these experiments that the degree of metabolic acidosis and the increase in potassium concentration might be

related to the degree of respiratory distress, further experiments were carried out to test this theory. Unfortunately in all the other dogs used the respiration never became really distressed although the rate and depth of respiration did show a considerable increase. The results of three such experiments are shown in figure 8 which indicates that a large depression of arterial blood pH can be attained without causing a significant rise in the potassium concentration above the control value.

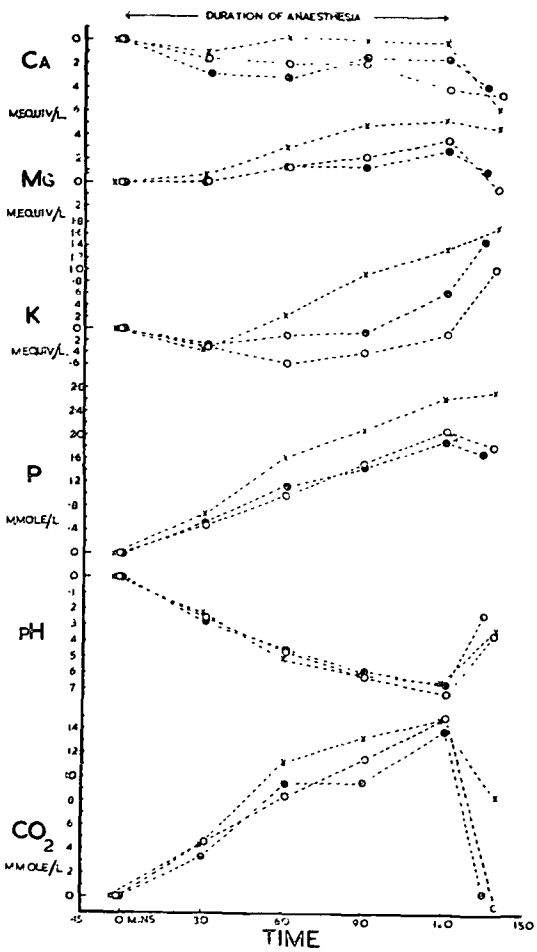

FIG. 8

Thiopentone-nitrous oxide anaesthesia. Three experiments involving the retention of carbon dioxide. Induction of anaesthesia was at 0 minutes.

DISCUSSION

Calcium and magnesium.

The results obtained in this investigation confirm those of other workers who had reported a slight, but inconsistent, decrease in the plasma calcium concentration (Eisler, Geness and Dienerstein, 1929; Lipow, Weaver and Reed, 1929). The plasma magnesium concentration was found to be very stable and it is possible that the variable results of previous investigations may have been due to the methods of estimation.

Plasma inorganic phosphate.

The changes in this ion which have been found during the present investigation agree well with those which have already been reported. Large changes in the plasma inorganic phosphate concentration have been found during respiratory acidosis and alkalosis and this suggests that the main factor concerned in producing changes in concentration is the pH of the blood, as was first suggested by Magee, Anderson and Glennie (1928). This does not necessarily contradict the belief of Foldes, Murphy and Wilson (1950) and Henneman and Vandam (1957) that anaesthetic agents per se may affect the plasma inorganic phosphate as a result of an effect on carbohydrate metabolism, but suggests rather that carbon dioxide tension may be more active in this respect. Whether the plasma concentration of this ion could be used as a measure of respiratory acidosis is doubtful, since in the dog other factors, such as shock, may also cause an increase (Wiggers, 1950).

Potassium.

The plasma potassium concentration appears to be more labile than that of the other blood electrolytes which have been studied. Unless frequent blood samples are taken it may be difficult to assess changes in concentration with accuracy.

This investigation has confirmed the fact that the potassium concentration is decreased by anaesthesia to a degree depending to some extent on the anaesthetic agent used. Thus the decrease during the first hour of anaesthesia was greater when hydroxydione or thiopentone and

nitrous oxide was used than during the use of ether or cyclopropane.

The significance of the decrease in potassium concentration during anaesthesia is not fully known but it seems likely that potassium tends to enter tissue cells due to changes in metabolism. Removal of the kidneys does not affect the fall caused by ether anaesthesia (Gerschman and Marenzi 1933a, b). Larson and Brewer (1939), however, were able to prevent this fall by the administration of 2, 4 dinitrophenol which is now known to uncouple cellular oxidative processes and phosphorylation. Brewster, Bunker and Beecher (1952) believed that the decrease in plasma potassium concentration during ether anaesthesia was of a similar order to that found during prolonged infusion of adrenaline. They found that the fall did not occur when dogs were given a high epidural nerve block prior to the induction of ether anaesthesia. It must be noted, however, that Larson and Brewer (1939) still found a decrease in potassium concentration in adrenal medullectomized dogs, but the method of adrenal medullectomy used by these workers was not described.

Carbon dioxide retention has been found to be associated with an increased potassium concentration in the plasma by the end of the second hour of anaesthesia, but this investigation has shown clearly that it is possible to have a severe respiratory acidosis without an increase above the control concentration. The increase in concentration previously reported by workers such as Sealy, Young and Harris (1954) and Brown (1955) is misleading, since their control samples were always taken after the induction of anaesthesia with thiopentone or pentobarbitone, agents which produce a large decrease in potassium concentration within a few minutes of induction of anaesthesia.

It is possible that there is a threshold concentration of carbon dioxide in the inspired gases above which the potassium concentration of the plasma becomes increased. Such thresholds have already been shown for the stimulation of the adrenal medulla and cortex and the release of potassium from the liver by carbon dioxide (Fenn and Asano, 1956; Tenney, 1956; Richards and Stein, 1957). From the results obtained in this investigation it seems possible that the threshold for the increase in plasma potassium concentration may be affected by the depth of anaesthesia. It must be emphasized that the severity of any changes which may be found is dependent on the length of time for which retention has occurred as well as on the prevailing carbon dioxide tension.

The rise in the plasma potassium concentration which is often found when the carbon dioxide tension in the inspired gases is returned to normal after the administration of high concentrations was thought by Sealy, Young and Harris (1954) to be due to the reflex release of adrenaline, for they showed that this rise could be prevented by the prior administration of piperoxane, an adrenolytic agent. This theory cannot be fully accepted, however, since it has been found that the intravenous infusion of adrenaline causes only a transient increase in the plasma potassium concentration (Brewer, Larson and Schroeder, 1939) and piperoxane does not inhibit this transient rise in concentration, although frequent blood sampling may be necessary to demonstrate its presence (Stevenson, 1959).

Sodium.

Although sodium estimations were carried out in all experiments, the results have not been included since no consistent changes were found. This is of interest, since Arends et al. (1952) and Billings and Brown (1955) reported that the administration of high concentrations of carbon dioxide in the inspired gases of dogs produced a reduction of about 20 per cent in the plasma volume and it therefore might be expected that the plasma sodium concentration would change. Since Giebisch, Berger and Pitts (1955) have found an increase in concentration of up to 10 m.equiv/l. in nephrectomized dogs inspiring high concentrations of carbon dioxide, it is possible that the kidney may have a homeostatic effect in this respect.

Hydrogen-ion concentration.

It is believed that the present investigation is the first in which continuous measurement of the arterial pH has been carried out in conscious dogs. Methods for the continuous recording of pH in acute experiments have been used by

Bjurstedt (1946), Hesser (1949) and Aström (1952).

It is evident from the results of this study and from those already reported in the literature (Dripps and Severinghaus, 1955), that the changes which are found in the arterial blood pH of the dogs during anaesthesia, especially when respiratory acidosis or alkalosis is present, are much greater than those found in man.

The decrease in the blood pH which has been found with increasing concentrations of carbon dioxide in this investigation closely corresponds with the changes which have been previously reported by Spencer et al. (1950), Joels and Samueloff (1956), Mollaret, Pocidalo and Lissac (1956) and Lissac et al. (1958) in dog experiments.

Carbon dioxide.

There has been a tendency to blame changes in the carbon dioxide tension as well as disturbances in "electrolyte balance" for many of the untoward events which may occur during anaesthesia.

While it is true that very high arterial tensions of carbon dioxide have been reported during anaesthesia in man (Dripps and Severinghaus, 1955), by no means all these reports have related to patients who had subsequently died. In most instances the anaesthetic has been cyclopropane, given by closed circuit methods. Where nitrous oxide is used in veterinary anaesthesia it is general practice to use a minimum gas flow rate of 2 to 4 litres per minute even when respiration is controlled and it seems unlikely that serious carbon dioxide retention will occur with this technique even when the soda lime becomes exhausted.

It has been found that recovery from anaesthesia in the dog which has been accompanied by severe carbon dioxide retention may not necessarily be prolonged. Indeed, since carbon dioxide may reduce the amount of thiopentone necessary to maintain a given plane of anaesthesia (Brodie and Hogben, 1957), recovery may be more rapid than usual when the carbon dioxide tension is returned to normal values and anaesthesia terminated. This does not mean that carbon dioxide may be regarded as an aid to anaesthesia but it does confirm the belief of Dripps and Severinghaus (1955) that experimental animals, including dogs, may be able to withstand the effects of prolonged carbon dioxide retention, provided that the pH is not allowed to change too rapidly at the termination of retention, without showing serious side effects.

It must be emphasized that this experimental work was carried out on healthy animals and that the results obtained do not indicate to what degree carbon dioxide retention will affect the metabolic responses of a diseased animal. It is also evident that the length of time for which carbon dioxide is retained is as important as the degree of respiratory acidosis which may be present, in determining the severity of metabolic responses.

SUMMARY

Anaesthesia induced by thiopentone sodium and maintained by ether, cyclopropane or nitrous oxide, produces little change in the total plasma calcium and magnesium concentrations. If respiratory acidosis is severe, the calcium concentration falls either during or shortly after recovery from anaesthesia.

The plasma potassium concentration falls during anaesthesia, although the changes may be only slight during anaesthesia maintained by ether or cyclopropane. No significant change has been noted in the plasma sodium concentration.

The changes in plasma inorganic phosphate are similar in nature to those of the hydrogen-ion concentration.

Except in ether anaesthesia there is an increase in the total blood carbon dioxide content and hydrogen-ion concentration during anaesthesia. In the case of ether anaesthesia the carbon dioxide content of the blood is ultimately reduced although the hydrogen-ion concentration still shows an increase.

ACKNOWLEDGMENTS

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