THE EFFECT ON THIOPENTONE ANAESTHESIA OF GLUCOSE, PHYSOSTIGMINE AND BEMEGRIDE IN DOGS*

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SUMMARY

Observations on induction, duration and recovery after thiopentone, as modified by glucose, physostigmine and bemegride, were made on twelve dogs, every dog acting as his own control. Glucose, together with thiopentone, caused no significant change in induction time, while the duration of anaesthesia and recovery period was prolonged. Physostigmine and bemegride delayed the onset of anaesthesia after thiopentone and shortened the duration and recovery timings, and they antagonized the glucose potentiation of thiopentone anaesthesia. The action of these antagonisms has been discussed as a non-specific one. It is concluded that the duration of surgical anaesthesia with thiopentone can be prolonged by simultaneous intravenous administration of glucose, and this prolongation can be cut short at will by administration of drugs like physostigmine and bemegride.

Thiopentone is one of the most commonly used anaesthetic agents in surgical practice. The drug, however, is mainly used for induction purposes, since prolonged continuous administration of this single anaesthetic agent is neither advocated nor advisable for long surgical operations because of the considerable danger of respiratory depression and fall in blood pressure. Even supplementation by pethidine leads to more respiratory depression. Thus, it is felt that drugs should always be available which are able to minimize the dangers and side effects of thiopentone. Further, if by some means the dose of thiopentone could be reduced without any decrease in its efficiency, the incidence of the ill effects of thiopentone would be greatly diminished.

Barbiturate poisoning, especially with pentobarbitone has been successfully treated with bemegride. The effects of the latter drug have not been completely studied in relation to thiopentone, which is an ultra-short-acting barbiturate, while pentobarbitone belongs to an intermediate group. Bemegride was, therefore, included in this study to observe its effects on the induction, duration and recovery timings of thiopentone anaesthesia.

It has been claimed that bemegride is a specific antagonist to barbiturates. Recent reports, however, throw considerable doubts on this and it is believed that bemegride acts by a mechanism of direct stimulation similar to that of picrotoxin and pentylentetrazol (Hahn, 1960), and the latter drugs were not included in the study.

Physostigmine, on the other hand, is a central nervous system stimulant, which most probably acts by its anticholinesterase activity, rather than by direct stimulation. This drug has not been studied in relation to thiopentone and hence it was thought desirable to study the effect of physostigmine on induction, duration and recovery timings of thiopentone.

Glucose and its intermediate metabolic products have been reported by Lamson, Greig and Robbins (1949) to potentiate the effect of pentobarbitone anaesthesia. They have termed this potentiation “glucose reaction”. This glucose reaction was found by Bester and Nelson (1953) not to influence the induction period. Hence it was proposed to observe whether glucose produced the same effects with thiopentone and, if so, how bemegride and physostigmine could modify this glucose reaction of thiopentone.

It was, therefore, decided to study the effects of bemegride, physostigmine and glucose, on the induction, duration and recovery timings of thio-
pentone, and to study how glucose potentiation of thiopentone anaesthesia could be modified by bemegride and physostigmine to the anaesthetist's advantage.

METHOD

The effect of thiopentone was first observed in twelve dogs and, thereafter, the timings were again noted when thiopentone was administered in combination with glucose, physostigmine or bemegride in the same twelve dogs.

The exact scheme of work was as follows.

Experimental animals.
Healthy medium-sized dogs were used in the series. The weight of the dogs ranged from 8 to 10 kg. Big dogs were not preferred because they were not easy to handle and because of the limited accommodation in the cages. Dogs were selected, because intravenous administration of drugs is easier in this animal than in guineapigs, mice and rabbits (which have been used by different workers).

In all, twelve dogs were used in the present series; each dog was used as his own control. An interval of 7 days was allowed before the same dog was used for another experiment, so that the dog did not develop tolerance to any drug, especially the barbiturates (Virtue and Raster, 1957).

Administration of the Drugs.
The drugs were injected intravenously over a period of 10 seconds into the long saphenous vein, and the induction, duration and recovery times noted. No premedication was given.

Thiopentone.
This was used as a 2.5 per cent solution, because the incidence of phlebitis, breath-holding, and respiratory arrest is greater with the 5 per cent solution. In a preliminary trial thiopentone 10 mg/kg was found to be sufficient to produce surgical anaesthesia with the disappearance of medial and lateral canthus reflexes of the eyes of the dog.

Thiopentone and glucose: the glucose reaction.
In dogs, Lamson, Greig and Robbins (1949), and in rats, Bester and Nelson (1953) had observed the glucose reaction, but these experiments were done with pentobarbitone. Ratcliffe and associates (1949) had shown a similar relationship with thiopentone. Hence it was felt that the glucose reaction should be observed following the simultaneous administration of glucose and thiopentone in dogs. In this study, a 25 per cent solution of glucose was used and a dose of 125 mg/kg was mixed with thiopentone 10 mg/kg. The freshly prepared mixture was administered intravenously.

Thiopentone and physostigmine.
Greig and Mayberry (1951) have reported that previous or simultaneous treatment of a mouse with physostigmine will reduce the delay in onset of anaesthesia by barbitone. This observation is contrary to expectation in view of the central nervous stimulant action of physostigmine. The effect of physostigmine was therefore studied with thiopentone.

The dose for dogs is 0.1 mg/kg body weight intravenously (Hall and Ettinger, 1937). A solution containing physostigmine salicylate 1 mg in 1 ml of sterile water was prepared and autoclaved; the requisite dose according to the weight of the dog was measured by a tuberculin syringe and injected intravenously together with thiopentone, first with and then without glucose. A fresh solution of physostigmine salicylate was prepared each time as the solutions become pink in colour and deteriorate on keeping. A freshly prepared mixture of 10 mg/kg of thiopentone and 0.1 mg/kg of physostigmine was used for administration.

Thiopentone, physostigmine and glucose.
Lamson, Greig and Holidy (1951), reported that physostigmine had no effect on the glucose reaction. Physostigmine has, however, a marked stimulant action on brain activity. In view of these contradictory reports, the effect of physostigmine was observed on the glucose reaction.

Thiopentone 10 mg/kg was mixed with 0.1 mg/kg of physostigmine and 125 mg/kg of glucose solution and the freshly prepared mixture was administered intravenously.

Thiopentone and bemegride.
In some experimental animals, bemegride antagonizes pentobarbitone, thiopentone and barbitone anaesthesia, reducing the sleeping times by half (Shaw et al., 1954). Harris (1955) and Dumont (1958) also give an impression that
patients treated with bemegride seem to awake earlier from thiopentone anaesthesia.

Contrary to the above workers, there have been reports that bemegride has very little or no effect on recovery after barbiturate anaesthesia. Such reports have come from Louw and Sonne (1956), Pedersen (1956), Wyke and Frayworth (1957). Due to these contradictory findings, the effect of bemegride was also observed in our dogs.

Bemegride is supplied as a 0.5 per cent solution in normal saline, and it is quite stable. A dose of 2 mg of bemegride (4 mg/kg) per 5 mg of thiopentone was used in the present study, as has been used by Waine and Dimmore (1958). This was injected with thiopentone, first with and then without glucose, intravenously.

**Thiopentone, bemegride and glucose.**

Having seen the effect of physostigmine on the glucose reaction, it was felt that a similar study should be made with bemegride.

Thiopentone 10 mg/kg was mixed with 4 mg/kg of bemegride (bemegride 2 mg per 5 mg of thiopentone) and with 125 mg/kg of glucose, and this freshly prepared mixture was administered intravenously.

**The times measured.**

Loss of medial and lateral canthus reflexes of the eye was the criterion used for the onset of anaesthesia in dogs (Virtue and Kaster, 1957). "Induction time" was taken as the time from the moment the injection was completed, to the loss of medial and lateral canthus reflexes. The "duration of anaesthesia" was the interval between the disappearance and reappearance of the medial and lateral canthus reflexes. The "recovery time" was taken as the interval between the reappearance of the medial and lateral canthus reflexes and the time when the dog stood on all four legs.

**RESULTS AND DISCUSSION**

The results are summarized in table 1 and fig. 1.

**Glucose.**

When glucose was administered in doses of 125 mg/kg in a freshly prepared mixture with thiopentone, the mean induction period was not significantly changed. This finding is in accordance with that of Bester and Nelson (1953), who administered glucose before, and also simultaneously with, pentobarbitone in rats. Lamson, Greig and Holdby (1951) observed that inter-
FIG. 1

Showing the effects of bemegride, physostigmine and glucose on the induction time, durations of anaesthesia and recovery times on thiopentone anaesthesia in 12 dogs. All times in minutes. For details of dosage see text.

1. Thiopentone.
2. Thiopentone + glucose.
3. Thiopentone + physostigmine.
4. Thiopentone + physostigmine + glucose.
5. Thiopentone + bemegride.
6. Thiopentone + bemegride + glucose.

mediate metabolites, such as lactate, pyruvate and glutamate, reduced the time of onset of anaesthesia after barbitone from 50 minutes to about 17 minutes; while with glucose it was reduced from 50 minutes to 49 minutes. The mean duration of and recovery from thiopentone anaesthesia was found to be very much prolonged, and this was statistically significant. These findings were again in accordance with those of Lamson, Greig and Holidy (1951) and Bester and Nelson (1953).

Physostigmine.
The anticholinesterase drug, physostigmine, when administered in dosage of 0.1 mg/kg was found to increase the induction period of thiopentone from a mean of 1.20 to a mean of 4.50 minutes. This increase was very highly significant statistically. This observation contradicted that of Greig and Mayberry (1951), who reported less delay in the onset of anaesthesia, when physostigmine was administered in dosage of 0.4 microgram per gram of body weight in mice. Their explanation was that by inhibiting cholinesterase activity by drugs, or by depriving this enzyme of its natural substrate, acetylcholine, marked changes in the permeability of erythrocytes and certain other tissues to drugs or ions could be produced (Greig and Holland, 1949; Greig, Holland and Lindvig, 1950). Further, Greig and Mayberry (1951) also observed an increased rate of penetration of barbitone into the brain. They concluded that when physostigmine did this the increased concentration of the barbiturate occurred early, and hence reduced the delay in the onset of anaesthesia. As reported above, the present findings could not confirm this conclusion. It is felt that the effect of a dose of barbiturate expected to produce anaesthesia was counteracted by the direct stimulant effect of physostigmine itself.

Not only was the induction period very significantly prolonged by physostigmine, but the mean duration and recovery timings were greatly shortened. This fact further supports the contention suggested above, that the direct stimulant action of physostigmine significantly counteracts the depressant action of barbiturates. This obvious difference in the present study from that of Greig and Mayberry (1951) may be due to species variation.

Again Lamson, Greig and Holidy (1951) observed that physostigmine had no effect on the glucose reaction. In the present series, however, it was observed that physostigmine not only significantly increased the mean induction period of thiopentone alone from 1.20 minutes to 4.50 minutes, but also significantly increased the mean induction period when it was administered along with thiopentone and glucose from 1.20 minutes to 3.20 minutes. However, it will be evident from the figures that the delay in the onset of anaesthesia after thiopentone with physostigmine, was significantly reduced by glucose from a mean of 4.50 minutes to a mean of 3.20 minutes. This decrease in the prolonged induction time with glucose may be due to the potentiating effect of glucose on the action of thiopentone. The mean
duration of anaesthesia with thiopentone and physostigmine was not significantly altered by glucose. The mean recovery period after thiopentone and physostigmine was not significantly altered by glucose. The mean recovery period after thiopentone and physostigmine was significantly prolonged by glucose, when the drugs were administered in the same mixture. It is thus clear that physostigmine definitely antagonizes the glucose potentiation of barbiturate action as far as duration of anaesthesia is concerned but that its effect on induction and recovery is small.

**Bemegride.**

Bemegride when administered in a dose of 2 mg per 5 mg of thiopentone, was found to reverse the thiopentone effect in all its aspects. For example, induction period was found to be prolonged from a mean of 1.20 minutes to a mean of 5 minutes. The mean duration of anaesthesia and the mean recovery time were shortened from 19.5 minutes to 7 minutes, and from 40.25 minutes to 11 minutes respectively.

Recovery was uneventful except in Dog No. 7, which showed slight convulsions. These findings are in general agreement with those of various other workers in the field such as Shaw and Mercier (1956), Dumont (1956, 1958), La Barre and Desmarez (1956), La Barre and Dumont (1956), La Barre, Dumont and Desmarez (1957).

Contrary to the results of the present series and the observations of the above workers, Louw and Sonne (1956), Pedersen (1956), and Wyke and Frayworth (1957) observed no significant change in the recovery from barbiturate anaesthesia. Even these workers, however, had noticed some lightening of anaesthesia. This apparent contradiction appears to be due to the fact that the latter groups of workers administered various pre-medication drugs in their series and this may have accounted for the difference.

Other workers have reported reactions varying from mild fasciculations to severe convulsions after bemegride was administered in barbiturate poisoning, Shaw and Mercier (1956), Dumont (1956, 1958), La Barre and Desmarez (1956), La Barre and Dumont (1956), and La Barre, Dumont and Desmarez (1957).

Since bemegride is a convulsant agent and a general stimulant of the central nervous system, it may well act against hypnotics by means of a functional antagonism. This antagonism is also noticed against a wide range of hypnotics and central nervous system depressants (Hahn, 1960), and it seems to be nonspecific.

The effect of glucose in the simultaneous administration of thiopentone and bemegride shows that its presence does not alter to any significant extent the induction period, whereas the mean duration and recovery timings are lengthened to a statistically significant level. This shows that the glucose reaction is not very much affected by bemegride, though bemegride could cause awakening of the dogs much earlier.

It is thus concluded that the stage of surgical anaesthesia with intravenous barbiturates can be prolonged without any apparent ill effects by either simultaneous administration of glucose, or by its administration at desired intervals. This prolongation could be nullified at will by the administration of drugs like bemegride and physostigmine.

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**REFERENCES**


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**SOMMAIRE**

Des observations concernant induction, duree et retablissement apres thiopentone et leur modification par du glucose, de la physostigmine et par Bemegride ont ete recueillies par l'auteur apres experience sur 12 chiens, dont chacun servit comme son propre témoin. Le glucose associe au thiopentone ne modifie pas sensiblement le temps d'induction, mais il prolonge le temps de l'anesthesie et celui du retablissement. Physostigmine et Bemegride — apres thiopentone — retardent le debut de l'anesthesie, abrégent la duree de cette derniere ainsi que le temps necessaire pour le retablissement. Ils ont un effet antagoniste au renforcement par le glucose de l'anesthesie au thiopentone. L'action de ces antagonismes a semé, a la discussion, non-spécifique. L'auteur conclut que l'on peut prolonger la duree de l'anesthesie au thiopentone en chirurgie par l'administration intraveineuse simultanee de glucose et que l'on peut couper court a cette prolongation a volonté, par l'administration de medicaments tels que la physostigmine et le Bemegride.

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**ZUSAMMENFASSUNG**