EFFECT OF THIOPENTONE ON MYOCARDIAL FUNCTION

J. H. CHAMBERLAIN, R. G. F. L. SEED AND D. C. W. CHUNG

SUMMARY

In a canine preparation designed to separate myocardial from peripheral cardiovascular effects of the drug, it was found that thiopentone produced minimal depression of the heart. Only in much greater concentrations was significant depression found. It is concluded that the cardiovascular effects of thiopentone i.v. are not a direct effect on the heart.

Thiopentone has well-defined haemodynamic effects. When given i.v. as a bolus, it causes a reduction in systemic arterial pressure and in cardiac output and an increase in systemic vascular resistance. Its effect on central venous pressure is variable, some authors describing no change, an increase or a decrease (Elder et al., 1955; Etsten and Li, 1955; Fieldman, Ridley and Wood, 1955; Flickinger et al., 1961; Conway and Ellis, 1969). Measurements of intrathoracic blood volume (Etsten and Li, 1955; Flickinger et al., 1961) have suggested that this decreases following the administration of thiopentone. The explanation of these findings is that blood has been transferred from the thoracic blood pool to the periphery, resulting in a reduction in venous return (Eckstein, Hamilton and McCammond, 1961) and cardiac output and arterial pressure.

The effect of thiopentone on the heart itself has been less well defined. In particular, there is little evidence on the changes occurring in myocardial contractility at the doses found during anaesthesia with thiopentone. That the heart will be depressed if a sufficiently large dose of thiopentone is given is not in doubt (Woods et al., 1949; Prime and Gray, 1952; Price and Helrich, 1955). These studies showed that, in the isolated heart–lung preparation, cardiac dilatation occurs when thiopentone is introduced. However, they were not performed under physiological conditions; Price and Helrich (1955) reported that successful completion of the experiments required the continuous infusion of noradrenaline. It was only in this last report that an attempt was made to judge the effect on myocardial contractility of thiopentone. Using the Walton Brodie strain gauge arch (Cotten and Bay, 1956; Bendixen and Laver, 1962) for measuring the contractile force of the left ventricle, a reduction in force followed the administration of thiopentone, but large doses were given.

Studies on an intact subject are difficult to interpret. An increase in central venous or left ventricular end diastolic pressure in the face of a decrease in cardiac output would suggest a depression in myocardial contractility. However, the picture is confused by the redistribution of the blood volume which tends to reduce central venous pressure. This confusion is compounded because of reflex changes caused by the intervention itself. A decrease in cardiac output with the resultant decrease in arterial pressure will evoke a sympathetic response which will cause vasoconstriction, enhance the venous return and heart rate, and restore the cardiac output and arterial pressure towards normal. The effect of the anaesthetic itself on the normal operation of these reflexes needs to be taken into consideration also. For these reasons we designed an experiment which enabled us to separate the myocardial and peripheral effects of thiopentone. By the use of intracoronary infusions of thiopentone we aimed to achieve a local concentration of the anaesthetic which was similar to the systemic concentration achieved after an i.v. bolus injection. The effects of intracoronary and i.v. infusions at the same rates were compared.

METHODS

In 19 mongrel dogs anaesthesia was induced with thiopentone 25 mg/kg i.v., and the trachea intubated. Ventilation was controlled with a Starling pump. Anaesthesia was maintained with halothane 0.5% in 67% nitrous oxide in oxygen. Muscle relaxation was achieved by a continuous i.v. infusion of suxamethonium 0.02% in water to avoid any unexpected muscular activity. Both vagi were located in the neck and divided. A central venous catheter was inserted to the external jugular vein and a central aortic catheter via the carotid artery. The chest was opened by a
midline sternotomy; the sympathetic nerve supply to
the heart was interrupted by dividing the branches of
the stellate ganglia. The pericardial sac was opened
and the aortic pad of fat removed before placement of
an electromagnetic flow probe (S.E. Laboratories), the
size of which was chosen to ensure a snug fit around
the ascending aorta. Pacing wires were then clipped
to the right atrial appendage. A catheter tip pressure
transducer (Millar Instruments) was placed in the left
ventricular cavity via the dimple. A branch of the
anterior descending branch of the left coronary
artery was dissected free, and a thin nylon catheter
(0.63 mm o.d.) inserted as shown in figure 1. A previ-
ously measured length of the catheter was moved in a
derivative acceleration $dQ/dt$, left ventricular pressure
and its derivative $dP/dt$, aortic pressure and e.c.g. The
output of the tape recorder was relayed to a multi-
channel pen recorder (Devices M19). Left ventricular
pressure was amplified with a DC amplifier to record
left ventricular end diastolic pressure (LVEDP). In
addition, either the airway pressure or the end-tidal
carbon dioxide concentration was recorded, so that
results could be analysed at the same point during the
respiratory cycle (Chung, Chamberlain and Seed,
1974).

Throughout the course of each experiment blood
gases were monitored hourly and any deviation from
normal was corrected. The body temperature was
retrograde direction so that the tip lay in the main left
coronary artery. Its position was checked at the end of
each experiment and if it was positioned incorrectly
the results were rejected. The distal part of the branch
of the coronary artery used for catheterization was
tied off. In a separate series of experiments with
identical instrumentation, myocardial blood flow was
estimated by the xenon-133 washout technique using
the coronary catheter for injection (McBride and
Ledingham, 1968).

The following were recorded on magnetic tape
(Precision Instrument): aortic blood flow and its
measured with a mercury in glass thermometer in the
rectum and kept constant at $37 \pm 1$ °C with a warm air
blower (Ronson Vent 2000). The central venous
pressure was maintained constant throughout the
study by an i.v. infusion of Hartmann's solution.

**Design of experiment**

The coronary artery catheter was attached to a
constant infusion pump (Braun and Melsungen)
which delivered fluid at a rate of $1.5$ ml.min$^{-1}$.
The coronary plasma flow was assumed to be $55$ ml.
min$^{-1}$ in the left main coronary artery. Mixtures of
THIOPENTONE AND THE MYOCARDIUM

TABLE I. Control values expressed as mean ± SD of haemodynamic variables for various interventions

<table>
<thead>
<tr>
<th>Intervention</th>
<th>LVEDP</th>
<th>Max dP/dt</th>
<th>(Max dP/dt)/TP</th>
<th>Max dQ/dt</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaOH i.c.</td>
<td>7.6 ± 2.4</td>
<td>1605 ± 505</td>
<td>29.0 ± 6.1</td>
<td>5.5 ± 1.7</td>
</tr>
<tr>
<td>Thiopentone i.v.</td>
<td>11.0 ± 2.1</td>
<td>2228 ± 99</td>
<td>33.2 ± 1.6</td>
<td>5.1 ± 0.6</td>
</tr>
<tr>
<td>Thiopentone i.c.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 mg/100 ml</td>
<td>8.1 ± 3.7</td>
<td>2411 ± 247</td>
<td>35.7 ± 4.4</td>
<td>5.0 ± 1.1</td>
</tr>
<tr>
<td>6 mg/100 ml</td>
<td>11.4 ± 2.1</td>
<td>2255 ± 653</td>
<td>32.7 ± 3.2</td>
<td>5.1 ± 1.5</td>
</tr>
<tr>
<td>12 mg/100 ml</td>
<td>11.6 ± 2.6</td>
<td>1969 ± 685</td>
<td>29.9 ± 4.9</td>
<td>5.2 ± 1.6</td>
</tr>
<tr>
<td>18 mg/100 ml</td>
<td>9.8 ± 3.6</td>
<td>1783 ± 438</td>
<td>29.4 ± 4.4</td>
<td>5.2 ± 1.6</td>
</tr>
<tr>
<td>24 mg/100 ml</td>
<td>11.0 ± 2.9</td>
<td>2026 ± 381</td>
<td>32.6 ± 2.1</td>
<td>5.0 ± 0.9</td>
</tr>
</tbody>
</table>

LVEDP = left ventricular end diastolic pressure (mm Hg);
Max dP/dt = maximum left ventricular rate of change of pressure (mm Hg s⁻¹);
TP = total pressure at time of max LV dP/dt;
dQ/dt = rate of change of flow.

When thiopentone in saline were prepared so that on infusion down the coronary artery the concentrations in coronary artery plasma were similar to those found systemically immediately after an i.v. bolus injection and during the maintenance of anaesthesia. The published evidence suggested that a maximum concentration of 24 mg/100 ml will occur after an i.v. bolus injection (Price et al., 1960). For the maintenance of general anaesthesia, Price and Helrich (1955) found that a concentration just in excess of 4 mg/100 ml is required to achieve surgical anaesthesia.

Once a steady state had been achieved control measurements were made and the intracoronary infusion was commenced and continued for 2 min. During the first minute the pen recorder was set to a paper speed of 100 mm s⁻¹. Thereafter fast recordings were made at 1.5 min, and 2 min after the start of the infusion and then at 30 s and 1, 2, 3, 4 and 5 min after stopping the infusion. Various concentrations were used, varying from an equivalent concentration of 3 mg/100 ml to 24 mg/100 ml. The effect of i.v. infusions of these same concentrations were studied also. The effect of an intracoronary infusion of a solution of sodium hydroxide (NaOH) with a pH similar to that of thiopentone was investigated, as was the effect of isotonic saline without thiopentone, at both body and room temperatures.

RESULTS

The control values for the acceptable results occurring in 10 dogs during and following the various infusions are in table I. The percentage changes from these control values for each haemodynamic variable are in figures 2–6. Results were unacceptable in nine dogs, because of misplacement of the catheter, unstable cardiac rhythm or haemodynamic state, or haemorrhage.

Fig. 2. Percent change from control (0%) in stroke volume. “Test period” refers to the 2-min intracoronary infusions and “recovery period” to the 5 min following cessation of infusion, in this and figures 3–6.

Fig. 3. Percent change from control (0%) in max dQ/dt.
decrease in max LV dP/dt, (max LV dP/dt)/TP (TP = total LV pressure at the time of max LV dP/dt), max dQ/dt, peak flow (PF), stroke volume (SV) and mean arterial pressure (MAP). By contrast when the same rate and concentration of thiopentone was given i.v., very little change occurred in any of these indices.

A local coronary blood concentration of 3 mg/100 ml, slightly less than the concentration required systemically to achieve surgical anaesthesia, had very little effect on the myocardium except a small reduction in max dQ/dt and an increase in LVEDP. Concentrations of 12 mg/100 ml and 18 mg/100 ml produced changes similar to those following the highest dose. An infusion of NaOH with a pH of 9.6 caused no change in any of the indices in six dogs. Intracoronary infusion of saline at body and room temperatures produced no effect.

The time at which changes first occurred varied with the concentration of the infusion, being 5 s after the start of the infusion at the highest doses. Depression of max LV dP/dt, and max dQ/dt and increase of LVEDP occurred before any changes in (max LV dP/dt)/TP. The maximal percentage change in each of these indices was similar. Thus, after 2 min of intracoronary infusion at the highest concentration, the percentage changes were: LVEDP +17%, max LV dP/dt -15%, (max LV dP/dt)/TP -14% and max dQ/dt -12%. Alterations in MAP (−7%), PF (−8%) and SV (−10%) were smaller. Most changes had resolved 5 min after stopping the infusion. The persistence of a small depression of max LV dP/dt and max dQ/dt occurred following some of the higher doses. LVEDP had always returned to control values by this time as had (max LV dP/dt)/TP, SV and MAP.

An attempt to demonstrate a dose–response relationship for any of the changes was largely unsuccessful. There appeared to be a clear difference in the magnitude of the response above and below a concentration of 12 mg/100 ml. At this value and above the response appeared maximal. At values of 6 mg/100 ml and less only quite small changes, if any, occurred. The percent changes of the various measurements after 2-min infusion of various concentrations of thiopentone are shown in figure 7. This illustrates both the lack of a linear dose–response relation and also how similar is the magnitude of the changes for each index.

Myocardial blood flow was measured on 24 occasions in four dogs and averaged 82 ml . min\(^{-1}\) per 100 g. No systematic changes were observed over several hours of measurement in any of the animals studied. The haemodynamic measurements for this group were: AP 130±14 mm Hg, LVEDP 2.2±2.7 mm Hg, max LV dP/dt, 2273±305 mm Hg . s\(^{-1}\), (max LV dP/dt)/TP 31.5±4.2 s\(^{-1}\), P.F. 202±44
THIOPENTONE AND THE MYOCARDIUM

FIG. 7. Percent change from control after 2 min of intra-coronary infusion of different concentrations of thiopentone.

ml. s⁻¹, max dQ/dt 5.4 ± 1.4 litre . s⁻¹, heart rate
161 ± 22 min⁻¹. These values are very similar to the control values for the other dogs (table I).

DISCUSSION

The results show clearly that when the myocardium is supplied with blood containing thiopentone in sufficient concentration, its function is depressed. The combination of an increased LVEDP, and a reduced stroke volume and arterial pressure, shows that the heart is failing to empty efficiently. Part passu the depression of max LV dP/dt, (max LV dP/dt)/TP and max dQ/dt indicates a decrease of myocardial contractility. The lack of such changes when the same concentration of the drug is infused i.v., shows quite clearly that factors outside the myocardium are not the cause of these changes.

However, the depression of myocardial function occurred only at concentrations likely to occur transiently following an i.v. bolus injection (Price et al., 1960). When concentrations of 3 mg/100 ml, which are sufficient to produce surgical anaesthesia (Price and Helrich, 1955), were given very little depression occurred and only minimal changes were observed at twice this concentration. Thus myocardial depression is unlikely to be an important factor in the circulatory changes associated with thiopentone anaesthesia.

Certain criticisms may be levelled at this study. First, the presence of a coronary catheter may disturb myocardial function. In general, LVEDP was greater and max LV dP/dt and (max LV dP/dt)/TP less than in a series of dogs prepared similarly by us but without the presence of a coronary catheter (Chung, Chamberlain and Seed, 1974). On the other hand, max dQ/dt and peak flow were similar in both series. In addition, MAP was greater in the catheterized dogs, and this will tend to be associated with an increased LVEDP. We have measured the haemodynamic state before and after placement of the catheter and have not observed any significant immediate deterioration. Animals with an abnormally high LVEDP (> 15 mm Hg) have not been included in this study.

Second, measurements of myocardial blood flow were not made in all the animals in this series. However, the mean flow for the same preparation, found by us in a separate series of experiments, was 82 ml . min⁻¹ per 100 g. The average left ventricular weight of the dogs in this series was 110 g. The concentration of the drug achieved is based on the assumption of a total flow of 90 ml . min⁻¹.

Last, the preparation is not “physiological” in the sense that the dogs were anaesthetized, denervated and open chested. Progressive gradual depression of all cardiovascular indices is not unusual in such preparations. We have examined the changes occurring over a 3-h period in six dogs following the initial preparation and have found that LVEDP increased (7.8–9.4 mm Hg) and max dP/dt (1904–1676 mm Hg . s⁻¹), (max dP/dt)/TP (27.8–25.4 s⁻¹) and max dQ/dt (5.57–5.28 ml . s⁻²) all decreased. These results show only a slight deterioration in myocardial function which would not affect the interpretation of our studies.

Despite these reservations we feel that our conclusion that thiopentone has little, if any, depressant effect on the heart in surgical anaesthetic concentration is, in general, true. A comparison with the data of Prys-Roberts and his associates (Prys-Roberts et al., 1972) concerning the effect of halothane (1%) on a similar preparation highlights this point. These authors found decreases in (max LV dP/dt)/DP of 21% (they used developed pressure (DP) in the denominator (LVP – LVEDP), whereas we used total pressure), and between 33 and 44% in the other indices after up to 30 min of exposure to halothane. This contrasts with our own observations of maximal changes of only 15% at the highest doses. It is possible that continuing our infusion for a longer period would have produced a more profound effect at the high doses, but it seems very unlikely that at the low doses any effect would have occurred at all, and it must be emphasized that the period of exposure of the heart to high concentration of thiopentone, following induction of anaesthesia, is very transient as a result of rapid redistribution of the drug.
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REFERENCES


EFFET DU THIOPENTONE SUR LA FONCTION MYOCARDIAQUE

RESUME

Dans une préparation canine conçue pour séparer les effets cardiovasculaires myocardiques des effets cardiovasculaires périphériques du médicament, on a trouvé que le thiopentone produisait une dépression minimale du coeur. On n'a trouvé de dépression significative que dans les concentrations beaucoup plus fortes. On en a conclu que les effets cardiovasculaires du thiopentone administré par voie intraveineuse ne constituent pas un effet direct sur le cœur.

WIRKUNG VON THIOPENTON AUF DIE MYOKARDIALFUNKTION

ZUSAMMENFASSUNG

In einem Hundepräparat für die Trennung myokardialer von peripheren Herz-Kreislaufwirkungen dieser Droge wurde festgestellt, dass Thiopenton eine minimale Depression der Herzleistung bewirkt. Eine wesentliche Depression wurde nur bei viel höheren Konzentrationen festgestellt. Man schliesst daraus, dass die Kreislaufwirkungen von intravenös verabreichtem Thiopenton keine direkte Wirkung auf das Herz haben.

EFECTOS DE TIOPENTONA EN EL FUNCIONAMIENTO DEL MIOCARDIO

SUMARIO

En una preparación canina, ideada para separar los efectos de la droga sobre el miocardio de aquellos ejercidos sobre la periferia cardiovascular, se encontró que la tiopentona producía una depresión mínima al corazón. Solo se produjo una depresión significativa con concentraciones mucho mayores. Se concluye que los efectos cardiovasculares de tiopentona intravenosa no ejercen un efecto directo sobre el corazón.