The Transient Effect on Muscle Blood Flow of Thiopental Sodium in the Cat

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It is widely agreed that in man hypotension follows rapidly administered intravenous doses of thiopental sodium, regardless of the size of the injection. Moreover, it has been established that this is due to a reduced cardiac output.[1-5] A reduction in venous tone in the limbs has been demonstrated by Prime and Gray[6] and also by Eckstein *et al.*;[7] the latter suggest that thiopental has a direct action on the smooth muscle of the vessel walls. A similar phenomenon has been reported in dogs by Imig and his colleagues,[8] who showed a transient increase in blood flow of the femoral artery associated with a fall in blood pressure following intravenous injections of pentobarbital sodium. In contrast, Burn and Hobbs[9] were unable to detect any alteration in local vascular tone when they injected 10 per cent thiopental into the femoral artery of the dog. They did however show that thiopental produced an increase in arterial tone in the vessels of the perfused rabbit's ear and in isolated arterial strips; Gruber *et al.*[2] also observed vasoconstriction in the perfused rabbit's ear and in the perfused heart. Price and Price[10] report a similar occurrence to that of Burn and Hobbs on isolated strips of rabbit aorta. In none of the studies referred to above has an attempt been made to distinguish the response of the vasculature in the skin from that of the muscle. In this paper, experiments are described in which the direct effects of thiopental on the muscle vascular bed alone were studied.

Method

Cats weighing between 2–3 kg. were anesthetised by injecting a mixture of chloralose (80 mg./kg.) and pentobarbital sodium (6 mg./kg.) into a vein of the fore limb. Blood pressure was recorded continuously throughout all experiments either by a mercury manometer or by a differential transformer transducer attached to a cannula placed in the right common carotid artery. Rectal temperature was maintained at 37–38° C. and measured by means of a mercury thermometer or an electrical resistance thermometer.

Recording of Muscle Contractions. The tibialis muscle was prepared for recording and the limb mounted horizontally on a Brown Schuster myograph stand.[11, 12] The sciatic nerve was dissected free, cut and tied centrally and shielded silver electrodes were placed on the nerve. Contractions were elicited indirectly by square wave pulses of 0.2 m second duration delivered at a rate of 6/minute. The strength of the stimulus was adjusted to that which would elicit maximal excitation of the nerve. The muscle contractions were recorded either on a Sanborn direct writing oscillograph by attaching the muscle to a capacitance strain gauge, or by means of an isometric spring myograph writing on smoked paper.

Recording of Venous Outflow. An incision was made on the medial surface of the thigh in order to expose the femoral artery and vein. With the exception of the artery chosen for intra-arterial administration of the drugs, all branches of the femoral artery supplying the lower limb were ligated and cut, thus excluding skin blood flow. A length of Polythene tubing was passed into the femoral vein directed peripherally, and the blood passed through a drop counting chamber (as described by Hilton[13]) and back into the animal by way of the external jugular vein. The rate of formation of drops was integrated and recorded on the Sanborn oscillograph. Ten minutes before the cannulation of the vein heparin (1,000 units/kg.) was administered intravenously.

Recording of Arterial Inflow. Arterial in-

Received from the Research Department of Anaesthetics, Royal College of Surgeons of England, London, England. Accepted for publication May 6, 1963. Dr. Acheson's present address: 211 Highland Street, New Haven, Connecticut.

flows were recorded on a smoked drum using a density flow meter,[14] and in these studies the muscle was perfused with a Vane constant pressure pump [15] so as to eliminate any effects which might be due to a fall in blood pressure. The artery was prepared in the same way as described in the previous section.

Administration of Drugs. In the perfusion experiments the drugs were administered into the cannula as it entered the femoral artery supplying the lower limb, or else intravenously. In other experiments drugs were injected either intra-arterially or intravenously. For the intra-arterial injections, a needle cannula was tied into the central end of a branch of the femoral artery, and injections were made rapidly in a retrograde direction into the artery. The volume of the drug injected never exceeded 0.3 ml. and was given within 10 seconds. Intravenous injections were made into a cannula placed in the femoral vein of the opposite hind limb and washed through with 0.9 *N* saline (w/v).

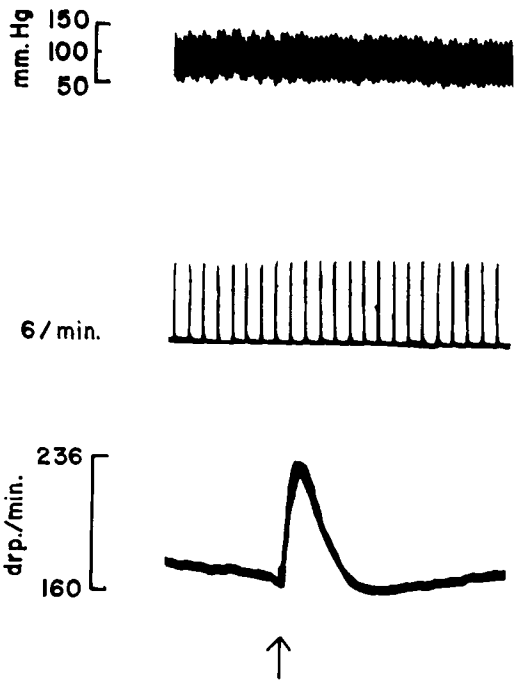

FIG. 1. Records of blood pressure (top), tibialis twitch tension (center) and venous outflow (bottom) in response to intra-arterial injection of 2 per cent thiopental sodium (1 mg./kg.) indicated by arrow. Note that there was an increase in venous outflow which was of 50–60 seconds duration followed by a brief decrease; the twitch tension increased slightly but the blood pressure remained constant.

Results

In order to study the direct effect of thiopental sodium on the muscle blood flow, the intra-arterial route of administration was selected. In this way very small doses of thiopental could be given which had no effect on the animal's blood pressure.

Venous Outflow Studies

Intra-arterial Injections. In these experiments intra-arterially administered thiopental (1 mg./kg. 2 per cent solution) resulted in a rapid increase in blood flow. Control injections of saline were made repeatedly during every experiment; the effect produced was always an insignificant one. In addition, control injections of soluble barbital, buffered to an alkalinity comparable to that of thiopental sodium (*p*H 10.4) were also injected. This was to determine whether the alkalinity of the solution in itself might affect the blood flow through the muscle. The procedure was also ineffectual.

The increase in flow caused by intra-arterial thiopental was so rapid in onset that it occurred before the injection was completed and gradually declined during the following 50–60 seconds. Subsequently there was a period of slightly diminished blood flow of variable duration, before the flow returned to its pre-injection level. A typical record in response to 1 mg./kg. is shown in figure 1. At this level of dosage there was no change in blood pressure.

When the dose of thiopental was increased to 2 mg./kg. there was a greater increase in blood flow. However, this was accompanied by a fall in blood pressure of 50 mm. of mercury which persisted for about 20 minutes; however, the duration of the increased flow was similar to that obtained at a dose level of 1 mg./kg. (fig. 2). Thiopental always caused an increase in flow which could be related to the rate of flow before injection of the drug (fig. 3).

Intravenous Injections. Thiopental (6–10 mg./kg. intravenously) resulted in an immediate diminution in venous outflow. At the

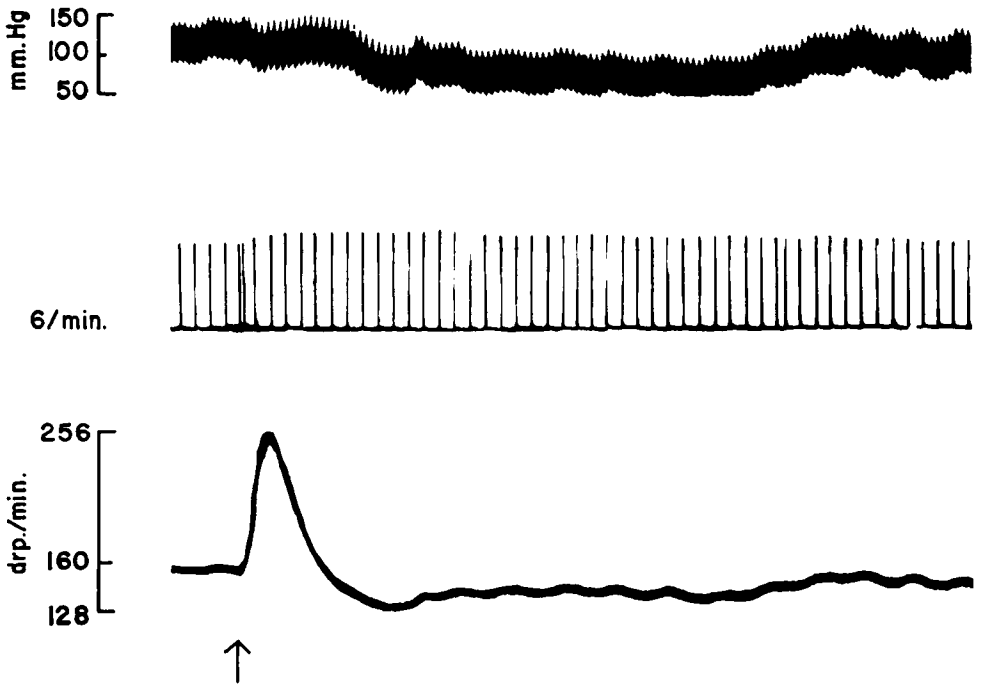

FIG. 2. The change in the tracings shown in figure 1 in response to 2 mg./kg. thiopental sodium given intra-arterially. The changes in blood flow and twitch tension are more marked than those shown in figure 1; note that there is now a fall in blood pressure.

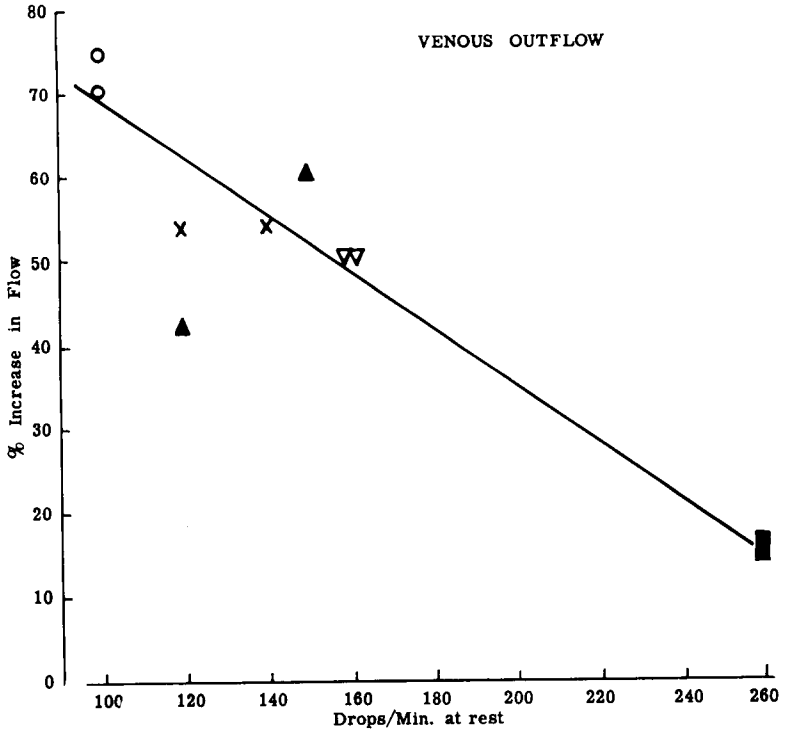

FIG. 3. The relationship between the percentage increase in venous outflow elicited by 1 mg./kg. thiopental sodium given intra-arterially, and the initial blood flow (5 cats).

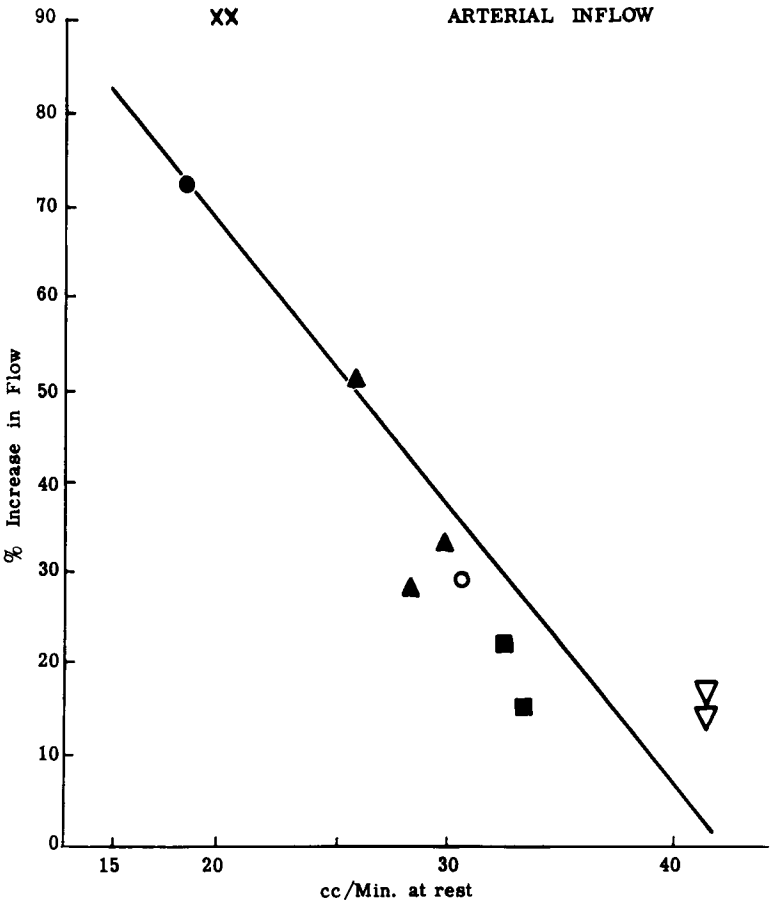

FIG. 4. The relation between percentage increase in arterial inflow and the initial blood flow (6 cats).

higher dose levels the blood pressure fell significantly and a complete cessation of flow occurred; the blood pressure was then between 50 and 60 mm. of mercury. Artificial ventilation was required at these dose levels.

Arterial Inflow Studies

Intra-arterial Injections. As in the previous experiments, there was an immediate increase in flow which lasted from 50–60 seconds. Once again the magnitude of the effect was related to the initial flow rate (fig. 4). However, the increase in flow was not followed by a diminished blood flow, and only in this respect did the results differ from those obtained with venous outflow recordings. Typical records using doses of 1 mg./kg. and 2 mg./kg. are shown in figures 5 and 6.

Intravenous Injections. Thiopental sodium administered intravenously at the dose level 6 mg./kg. resulted in no alteration in flow rate other than that which was consistent with the volume of solution which was injected; however, the systemic blood pressure fell from 70 mm. to 40 mm. and took some 30 minutes to re-establish itself. At the dose level of 10 mg./kg. there was a progressively increasing reduction in flow and a fall in blood pressure which was once more prolonged. At both of these dose levels it was necessary to ventilate the cat artificially.

Muscle Contractions

Thiopental sodium caused an increase in the twitch tension of the tibialis anterior muscle. The effect was seen more clearly with intra-arterial than with intra-venous injections. The increase in tension was immediate and persisted for a variable duration. There was a linear relation between the log of the dose

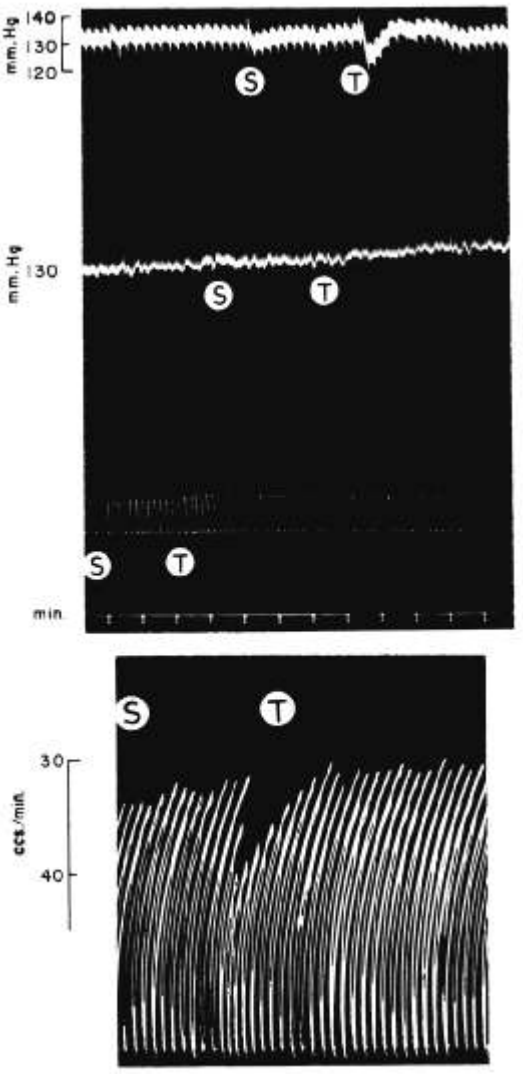

FIG. 5. The response of perfusion pressure (top) blood pressure (second) twitch tension (third) and arterial inflow to intra-arterial doses of normal saline (S) and thiopental sodium (T) in a dose of 1 mg./kg.

of thiopental and the percentage increase in twitch tension (fig. 7). The increase in tension appeared to be independent of the blood flow through the muscle since it occurred whether or not there was an increased or a decreased flow and whether or not there was an associated fall in blood pressure.[16]

Discussion

It will be seen from the results of these experiments that thiopental sodium causes an increase in muscle blood flow when administered intra-arterially. The increase in flow was not due to the alkalinity of the solution (*p*H 10.4). The rapidity of the onset of the action of thiopental is highly suggestive of a direct vasodilator action on the vessel wall as postulated by Eckstein *et al.*,[7] but this effect is a transient one. Kinmonth and Shepherd,[17] basing their conclusions on direct microscopy, described a 30 second contraction of the femoral artery wall of the rabbit after intra-arterial

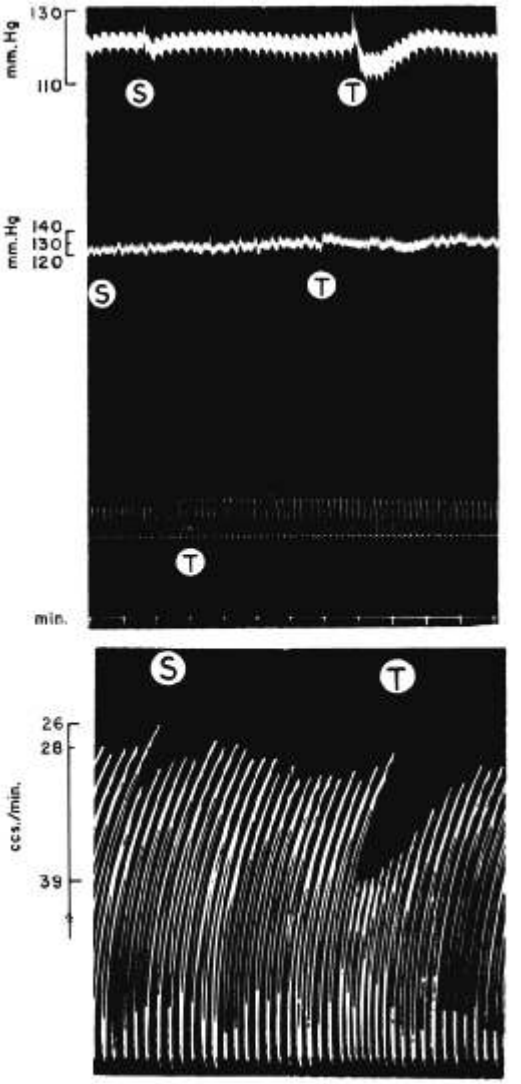

FIG. 6. The response of the variables shown in figure 5 to intra-arterial thiopental sodium in a dose of 2 mg./kg.

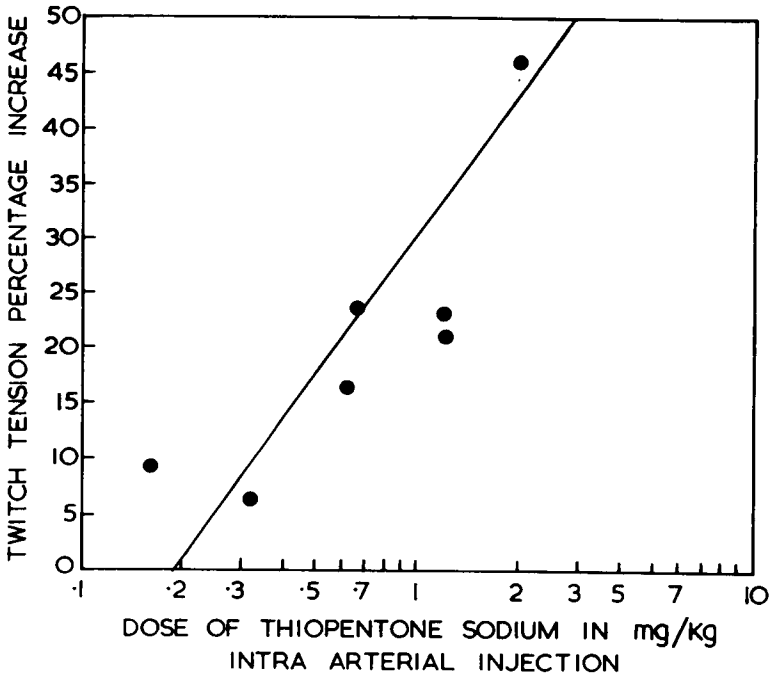

FIG. 7. The relation between the logarithm of the dose of thiopental sodium and the percentage increase in twitch tension.

injection of thiopental in a 5 per cent solution. This contraction was followed by a dilation lasting one minute. While the increase in flow observed in the present study is quite consistent with the dilation which they describe, at no time was there a period of decreased flow preceding it. However, the fact that they used a more concentrated solution might possibly explain the discrepancy between the two results. With intravenous injections of thiopental the effect produced is more difficult to interpret. Under these conditions an increased flow was never observed. This may be explained by a simultaneous diminution of cardiac output or vascular changes elsewhere or both which mask the direct action of thiopental on the muscle blood vessels. When the muscles of the lower limb were perfused at a constant pressure and a dose of thiopental was administered intravenously which produced no change in blood flow, a fall in blood pressure resulted. This hypotension lasted up to 30 minutes. The present results showed that the dilator effect of thiopental on muscle blood vessels lasted for only one minute. This result differs from that reported by other workers. Imig and his colleagues in their studies on the femoral artery blood flow in the dog found a significant increase in flow following intravenous injection of pentobarbital sodium. This effect lasted up to two minutes, and there was an associated fall in blood pressure which persisted up to fifteen minutes. As their experiments were conducted on conscious animals using an electromagnetic flowmeter, it is likely that skin flow was included in their measurements and could account for their slightly more prolonged period of increased blood flow. In addition, the plethysmographic studies of Prime and Gray[6] and the more recent ones of Eckstein and his colleagues[7] also include skin flow and thus may explain the prolonged period of vasodilatation which they observed. As the dilator effect of thiopental on muscle blood vessels is so transient, it cannot explain the prolonged period of vasodilatation which they observed. (As the dilator effect of thiopental is so transient on muscle blood vessels where the vasomotor tone is low, it cannot explain the prolonged hypotension caused by the drug.) It seems possible from the results reported above that there is a more prolonged dilatation in skin vessels. These together with an effect on other vascular areas which may be a direct action on smooth muscle or indirect

action through nervous pathways, may explain the hypotension which occurs as a result of intravenous injections of thiopental sodium.

Summary

A transient increase in muscle blood flow follows the administration of thiopental sodium given by intra-arterial and intravenous injection in the cat.

It is therefore suggested that the hypotension which is known to be caused by this drug is not, as previous authors have believed, a consequence of increased muscle blood flow.

The apparent discrepancies between the present findings and the work of others are discussed.

I am grateful to the late Professor Ronald Woolmer and Professor Gustav Born for their encouragement and for providing the facilities for this research. Of the many people who discussed the problem with me I should like in particular to acknowledge my indebtedness to Dr. John Vane. The work was supported by a grant from the Medical Research Council of Great Britain.

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