Effect of Hemorrhage on Plasma Thiopental Concentrations

Norman A. Bergman, M.D.

Broom et al. proposed that thiopental exhibits ultra-short action after moderate doses not because of rapid metabolism but because of rapid localization of the drug in body fat. Price et al. pointed out that uptake of thiopental by adipose tissue is not sufficiently rapid to account for speedy recovery of consciousness after administration of this drug. A dynamic concept of the distribution of thiopental in the body was presented according to which all body tissues, nervous and non-nervous, compete for thiopental. After administration of thiopental prompt loss of consciousness is due to the high proportion of the cardiac output which goes to the brain and rapid recovery of consciousness is explained by disappearance of thiopental from the central blood pool and rapidly perfused vital tissues, including brain, as less well perfused tissues take up the drug. Concentration of thiopental in adipose tissue occurs much later. Rate of disappearance of thiopental from plasma is a function of both blood flow to the various tissues and capacity of these tissues to take up thiopental from blood. These theses have been verified by experiment and by theoretical calculations. Goldstein and Aranow also concluded that the depressant action of thiopental on the nervous system is terminated by accumulation of thiopental in regions which are perfused more rapidly than body fat depots. True rate of metabolism of thiopental, 6 per cent of the total dose per hour in the dog, is too slow to affect plasma levels of thiopental appreciably in the immediate post-administration period.

A corollary to the above described dynamic concept of the distribution of thiopental in the body is that factors which alter peripheral blood flow should also change rate of disappearance of thiopental from plasma. The present report describes experimental determination of the effect of decreased peripheral blood flow due to oligemia following hemorrhage on plasma thiopental concentration in dogs.

Methods

Unpremedicated dogs were anesthetized with diethyl ether in oxygen through a well fitting canine mask using a closed circuit with carbon dioxide absorption. An endotracheal tube was inserted and catheters were placed in the femoral artery and into the inferior vena cava via the femoral vein in each animal. The nine control animals were permitted to awaken without further manipulation. The nine experimental animals were subjected to rapid hemorrhage of 25–30 ml. blood/kg. of body weight before being permitted to awaken. Upon recovery from inhalation anesthesia, as judged by attempts to make a purposeful movement, each animal received 25 mg./kg. of thiopental sodium as a 2 per cent solution given intravenously over a two minute interval. On appearance of respiratory depression mechanical positive pressure breathing with air was instituted and continued until spontaneous ventilation was deemed adequate. Venous blood samples were withdrawn from a 20 cm. catheter passed via the femoral vein five minutes following termination of thiopental injection and at predetermined intervals thereafter over the next 90 minutes. These samples were centrifuged and the plasma analyzed for thiopental concentrations using the technique of Brodie et al. In our laboratory, recovery
of thiopental acid added to plasma in amounts of 25 mg./liter was greater than 92 per cent.
Blank plasmas run through the analytical procedure had negligible optical densities at 305 mg.

In certain dogs arterial blood samples were withdrawn simultaneously with venous blood samples. Blood pH was measured on arterial samples using a glass electrode (Instrumentation Laboratory Inc., Boston, Mass.). Arterial blood pressure was monitored throughout the experiments. Dogs becoming reactive before termination of the experiment were lightly reanesthetized with diethyl ether. Differences in mean values for plasma thiopental concentrations and blood pH at corresponding time intervals following thiopental administration between control dogs and dogs subjected to hemorrhage were examined for statistical significance using Student's t test.6

Results

Blood pressures of all dogs, both control and hemorrhaged, had returned to near preadministration levels within ten minutes following thiopental administration. Arterial blood pressures in the two groups were comparable. No difference in duration of unconsciousness following thiopental administration between the two groups was noted. Further experimental results are reported in table 1 for control animals and in table 2 for animals subjected to hemorrhage. Mean values for plasma thiopental concentration were significantly lower in dogs subjected to hemorrhage than in control dogs at corre-

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Table 1. Plasma Thiopental Concentrations (mg./liter) and Blood pH at Intervals Following Thiopental Administration—Control Dogs

Table 2. Plasma Thiopental Concentrations (mg./liter) and Blood pH at Intervals Following Thiopental Administration—Dogs Subjected to Hemorrhage
sponding intervals following thiopental administration ($P < .05$ at 5 minutes and $P < .005$ at all other time intervals) (fig. 1). Mean values for blood pH were significantly lower in dogs subjected to hemorrhage than in control dogs at 5, 10, 15 and 30 minutes ($P < .05$) but no significant difference in mean values for blood pH occurred at 60 and 90 minutes.

Discussion

Fifty per cent mortality occurred in splenectomized dogs when blood volume was reduced to 61 per cent of prebleeding volume by rapid hemorrhage. In the present study dogs were subjected to rapid hemorrhage of 25–30 ml. blood/kilogram body weight. Hemorrhage of this magnitude reduced circulating blood volume to 70–75 per cent of prebleeding value and was associated with definite physiologic responses. These included lowering of arterial blood pressures, tachycardia, and significant compensatory fluid shift in splenectomized dogs.

Decreased peripheral blood flow following hemorrhage would be expected to slow removal of thiopental from the central blood pool. On hemodynamic considerations only, it was predicted that following administration of thiopental, plasma concentrations of this drug would be greater in an individual made hypovolemic by hemorrhage than in a normal individual. Findings of the present study are contrary to this prediction. Plasma thiopental concentrations were significantly lower during the ninety-minute interval immediately following administration of the drug in dogs which had been subjected to hemorrhage than in control dogs. Following hemorrhage, therefore, changes in factors which determine plasma thiopental concentration in addition to magnitude of peripheral blood flow also occur. Possible explanations for findings of the present study might include sequestration of thiopental in poorly perfused vascular beds, alterations in blood-tissue partition ratios for thiopental produced by changes in intracellular composition and composition of blood, or decreased thiopental carrying capacity of blood caused by hypoproteinemia with resulting loss of thiopental binding sites.

Decreases in plasma thiopental concentrations in dogs during respiratory acidosis produced by carbon dioxide inhalation were observed and were explained by changing blood-tissue partition ratios with alterations in relative proportions of dissociated and undissociated forms of thiopental. The magnitude of these changes was approximately a 10 per cent decrease in plasma thiopental concentration for each 0.10 unit decrease in blood pH. In the present study several conditions were encountered which are known to alter blood pH. Significant metabolic acidosis may occur during administration of diethyl ether to dogs and during the oligemic state. Changes in alveolar ventilation incident to changes in depth of anesthesia and other factors may cause respiratory acidosis and alkalosis. In the present study mean values for blood pH at corresponding intervals during the first hour following thiopental administration were 0.08 to 0.10 pH units lower in dogs subjected to hemorrhage than in control dogs. On the basis of Brodie’s data this magnitude of pH change can account for only a small portion of
observed differences in plasma thiopental concentration. In addition, findings of significant
differences between mean values for plasma thiopental concentrations between control dogs
and hemorrhaged dogs at 90 minutes following thiopental administration when blood $pH$ was
identical in the two groups eliminate changes in blood $pH$ as an important factor contributing
to experimental results. Little information is available, however, concerning changes
in intracellular $pH$. It is recognized that intracellular $pH$ during respiratory acidosis pro-
duced by the freely diffusible substance carbon dioxide might differ considerably from
intracellular $pH$ during metabolic acidosis of comparable degree. $^{13}$ $pH$ gradients across cell
membranes might exert a significant influence on partition of thiopental between blood and
tissues.

Summary

Plasma thiopental concentrations in the first ninety minutes following thiopental adminis-
tration were significantly lower in dogs which had been subjected to a hemorrhage of 25–
30 ml blood kilogram body weight than in control dogs. This finding is contrary to the
prediction that decreased peripheral blood flow following hemorrhage should slow disappear-
ance of thiopental from plasma. Following hemorrhage, changes in other factors deter-
mining plasma thiopental concentration in addition to magnitude of peripheral blood flow
also occur.

Abbott Laboratories Inc. provided the thiopental acid which was used as the standard in thiopental
determinations in this study.

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