Hemodynamic effects of barbiturates and benzodiazepines

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Intravenous administration of a short-acting barbiturate is the most common method for the rapid and pleasant induction of anesthesia. Recently, benzodiazepine derivatives such as diazepam have achieved popularity as an alternative for induction and maintenance of anesthesia. Often the reason for selecting a specific barbiturate or benzodiazepine is the likely hemodynamic changes that will follow intravenous administration of that drug. This review summarizes hemodynamic changes that occur after intravenous administration of barbiturates or benzodiazepines to patients with and without underlying heart disease.

Barbiturates

Hemodynamic effects of short-acting barbiturates (thiopental, thiamylal, methohexital) used for induction of anesthesia may be due to (1) direct myocardial depression, (2) peripheral venous pooling with decreased left ventricular diastolic filling and stroke volume, and (3) decreased sympathetic nervous system outflow from the central nervous system.[1]

Direct myocardial depression reflected by reduced myocardial contractility is readily demonstrated with the use of isolated heart preparations after even moderate doses of barbiturates.[1] In man

negative inotropic effects may be obscured by baroreceptor-mediated reflex responses. Decreased tone of systemic capacitance vessels leading to peripheral venous pooling, decreased venous return, left ventricular diastolic filling, and stroke volume is implied by the demonstration of increased venous forearm distensibility following thiopental administration to human subjects.[2] This peripheral venous dilatation might also obscure any tendency for the central venous pressure to increase secondary to direct myocardial depression. The impact of reduced central nervous system sympathetic outflow is likely to be transient due to reflexly mediated increases in peripheral sympathetic nervous system activity.

Filner and Karliner[3] have measured circulatory responses one minute after the rapid intravenous administration of thiopental, 5 mg/kg, to six healthy volunteers (*Table 1*). Compared with measurements of awake patients, the only statistically significant change following thiopental was an average 20 beats/min increase in heart rate. An index of myocardial contractility ($1/PEP^2$) was not changed, suggesting that direct myocardial depression did not occur in these patients. The most likely explanation for the findings was a baroreceptor-mediated increase in peripheral sympathetic nervous system activity.

Table 1. Hemodynamic effects of thiopental (mean ± SD)

	Awake	After thiopental 5 mg/kg
Heart rate, beats/min	63 ± 8	83 ± 4*
Mean arterial pressure, torr	93 ± 6	93 ± 17
Cardiovascular index, l/min/m^2	3.7 ± 0.1	4.3 ± 0.8
PA_{O_2}, torr	8.2 ± 3.8	10.0 ± 5.6
Systemic vascular resistance, dynes · sec · cm^{-5}	981 ± 220	837 ± 230
$1/PEP^2$, msec	87 ± 12	82 ± 20

* $p < 0.01$ compared with control.

Table 2. Hemodynamic effects of thiopental (mean ± SE)

	Control	Thiopental, equivalent to 1.0 MAC
Heart rate, beats/min	80 ± 4	100 ± 4*
Systolic blood pressure, torr	136 ± 8	117 ± 4*
Diastolic blood pressure, torr	73 ± 3	68 ± 3
Left ventricular ejection time, sec	0.42 ± .006	0.43 ± .008
Pre-ejection period, sec	0.12 ± .005	0.13 ± .005
$1/PEP^2$, msec	80 ± 8	58 ± 5*

* $p < 0.025$ compared with control.

The importance of reflexly mediated responses in minimizing circulatory changes after barbiturates were administered intravenously must be remembered when these drugs are given to patients with attenuated baroreceptor activity. Conceivably, such patients would be less able to compensate for direct myocardial depressant and peripheral vasodilating effects of barbiturates. Baroreceptor responses (specifically the heart rate response to changes in blood pressure) are blunted in elderly patients, those with a history of essential hypertension, and patients receiving antihypertensive or beta-adrenergic blocking drugs. Inhalation anesthetics also greatly depress baroreceptor activity. Rapid intravenous administration of barbiturates might cause profound hypotension in these patients.

The cardiovascular effects associated with plasma thiopental concentrations necessary to prevent movement in response to surgical stimulation were studied in ten healthy patients scheduled for elective surgery.[4] Circulatory changes included an increase in heart rate of 20 beats/min; decrease in systolic blood pressure, 19 torr; and a decrease in $1/PEP^2$ of 27% (*Table 2*). The most likely

explanation for the circulatory changes after thiopental was thought to be decreased preload secondary to peripheral venous pooling. The change in systolic time intervals (left ventricular ejection time, pre-ejection period and $1/PEP^2$) most likely represented a minimal decrease in myocardial contractility. Similar circulatory changes have been observed following 4 mg/kg of thiopental given as a bolus intravenously to patients with and without underlying heart disease.[5] In contrast, depression of myocardial contractility as evidenced by systolic time intervals was significantly greater during administration of halothane, 0.65%, about 0.8 MAC. Enflurane, about 0.8 MAC, produced reductions in $1/PEP^2$ similar to those observed following administration of thiopental.[6] The similar or greater depression of systolic time intervals during halothane, 0.8 MAC, or enflurane anesthesia suggested that these drugs produced more direct myocardial depression than thiopental, which was administered in a dose roughly equivalent to 1.0 MAC for inhalation anesthetics.

The rapid onset and short duration of intravenous barbiturates make these drugs useful for treating acute hypertension that may follow direct laryngoscopy and intubation of the trachea, surgical skin incision, or splitting of the sternum before cardiopulmonary bypass. The amount of oxygen required for the myocardium is reduced by negative inotropic effects of barbiturates most likely when tachycardia is blunted, e.g., patients receiving propranolol. This characteristic may be particularly advantageous for patients with coronary artery disease and good left ventricular function.

The minimal hemodynamic effects of barbiturates are ideal for induction of anesthesia in healthy patients and in those with coronary artery disease. Although supporting data are not available, it is a clinical impression that profound decreases in blood pressure after barbiturates are most likely to occur in the presence of hypovolemia. Also patients with blunted baroreceptor responses are theoretically more vulnerable to exaggerated circulatory responses after receiving barbiturates. Hypotension may be minimized in susceptible patients by administering small doses of barbiturate, 50 mg/min intermittently, rather than the same dose as a bolus.[1] A slow infusion rate is more likely to permit sufficient time for compensatory reflex responses to offset direct myocardial depression and peripheral pooling that follow administration of barbiturates.

Benzodiazepines

Diazepam. Although classified as a minor tranquilizer, this benzodiazepine derivative is widely used to induce anesthesia. Much of this popularity, particularly in patients with heart disease and poor left ventricular function, is due to the minimal hemodynamic and ventilatory changes produced by diazepam.[7] Doses required for induction of anesthesia usually produce mild degrees of ventilatory and cardiovascular depression equivalent to that observed during natural sleep. It is an unsubstantiated clinical impression that the incidence and severity of cardiovascular depression with diazepam are less than those with short-acting barbiturates administered to produce an equivalent degree of central nervous system depression. Despite these minimal responses, it is important to remember that an occasional patient may experience dramatic decreases in blood pressure or profound ventilatory depression after as little as 2.5 to 10 mg of diazepam.[8, 9]

The hemodynamic effects of diazepam, 0.5 mg/kg, administered intravenously for 10 minutes to induce anesthesia in awake patients before elective aortocoronary saphenous vein bypass graft operations have been studied in ten patients given morphine and scopolamine as premedication.[10] The only statistically significant hemodynamic change at the conclusion of diazepam infusion was an 11-torr reduction in mean arterial pressure (*Table 3*). Prakash et al[11] reported similar decreases in blood pressure associated with a modest reduction in systemic vascular resistance after diazepam, 0.6 mg/kg, given intravenously.

Nitrous oxide is often added to the anesthetic maintenance drugs to insure adequate amnesia and analgesia. Previous studies have demonstrated that addition of 50% nitrous oxide to background morphine, 1 mg/kg, in patients with coronary artery disease resulted in significant reductions in blood pressure and cardiac output, while systemic and pulmonary vascular resistance and pulmonary artery occluded pressure increase.[12,13] In contrast, the addition of 50% nitrous oxide following the administration of diazepam, 0.5 mg/kg, did not produce any changes except a 2.4-torr increase in right atrial pressure (*Table 3*).[10] Based on these observations, nitrous oxide may be added to diazepam to insure adequate anesthesia with minimal detrimental changes in the systemic and pulmonary circulation. This contrasts with the undesirable hemodynamic changes that occur when nitrous oxide is added to morphine in patients with similar underlying heart disease.

A major disadvantage of diazepam used for induction of anesthesia is its

Table 3. Hemodynamic effects of diazepam and diazepam-nitrous oxide (mean ± SE)

	Awake	Diazepam	Diazepam N_2O
Heart rate, beats/min	66 ± 3	68 ± 2	65 ± 2
Mean arterial pressure, torr	102 ± 3	91 ± 3*	91 ± 3*
Cardiovascular index, l/min/m^2	2.8 ± 0.1	2.7 ± 0.1	2.5 ± 0.1*
PA_0, torr	11.5 ± 1.1	10.6 ± 1.2	11.9 ± 1.2
Right arterial pressure, torr	8.1 ± 1.2	7.2 ± 0.2	9.6 ± 1.4†
Pulmonary artery pressure, torr	18.4 ± 1.4	16.3 ± 0.9	17.0 ± 0.2
Systemic vascular resistance, dynes · sec · cm^{-5}	1391 ± 97	1344 ± 120	1377 ± 128
Pulmonary vascular resistance, dynes · sec · cm^{-5}	101 ± 11	95 ± 9	97 ± 15

* < 0.05 compared with awake.
† < 0.05 compared with diazepam.

Table 4. Changes after administration of midazolam, diazepam, and thiopental

	Midazolam	Diazepam	Thiopental
Mean dose to produce loss of lid reflex, mg	12	26	212
Induction time, min	2.6	2.6	1.3
Mean arterial pressure decrease > 25%*	2/25	0/24	0/26
Heart rate increase > 25%*	4/25	7/24	3/26
Burning with injection*	7/25	16/24	5/26
Postoperative phlebitis*	0/25	4/24	0/26

* Number of patients.

long duration of action (beta half-time >40 hours).[14] Also, the poor solubility of diazepam in water requires preparation in organic solvents that may cause pain when injected intravenously and produce phlebitis.

Midazolam. This is a newly synthetized short-acting (beta half-time 1.7 hours) water-soluble benzodiazepine with central nervous system properties similar to diazepam.[14] It is about 1.5 times as potent as diazepam. Water solubility eliminates the need for organic solvents and decreases the incidence of burning with intravenous injection as well as postoperative phlebitis (*Table 4*).[15] Heart rate and mean arterial pressure changes are minimal and similar to those observed after the administration of diazepam (*Table 4*). Therefore, midazolam may be preferable to diazepam when induction of anesthesia with a benzodiazepine derivative is needed.

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