CATECHOL AMINE LEVELS DURING LIGHT AND DEEP ANESTHESIA

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Anesthetic agents are known depressants of many of the body's physiological functions. Of particular concern to the anesthesiologist is the depression of the cardiovascular system produced by these agents. As with other disturbances of normal physiology, the body attempts to compensate for this abnormal condition. One method of overcoming the cardiovascular depression would be an increased production of epinephrine and norepinephrine, for the stimulating effects of the catechol amines on the cardiovascular system are well recognized. Recent animal and human investigation indicate the possibility that these amines may be one of the compensatory mechanisms whereby the body attempts to overcome the depressant effects of the anesthetic agents.[1-5] In a previous report, however, in an effort to assess the significance of catechol amines under clinical conditions, we were unable to detect significant increases in the plasma catechol amines during light surgical anesthesia with ether, halothane (Fluothane) thiopental-nitrous oxide and cyclopropane.[6]

This report will present the findings of further studies on plasma catechol amines under clinical conditions during deep surgical anesthesia. For completeness and comparison, the results obtained during light surgical anesthesia also are presented.

Method of Study

The patients, most of whom were adults undergoing a variety of elective surgical procedures, comprised the investigative material of this study (table 1). All patients had normal physical findings and laboratory studies and were in good health except for the condition requiring their admission to the hospital. The anesthetic agents employed were cyclopropane, thiopental-nitrous oxide, ether, and halothane.

TABLE 1

Surgical Procedures

Site of Operation	Light Anesthesia	Deep Anesthesia	Spinal
Face, Eye, and Nose	5	5	
Neck (Thyroid and Radical Neck)	3	6	
Breast	12	11	
Pulmonary		2	
Liver and Gall Bladder	4	5	
Spleen		2	
Stomach	3	2	2
Colon	5	4	2
Uterus and Adnexa	8	4	3
Extremities	7	2	2
	47	43	9

The patients received preoperatively an appropriate dose of meperidine (50–100 mg.) and either atropine or scopolamine (0.2–0.4 mg.), according to their age, weight, and physical status one hour to one and a half hours prior to their arrival in the operating room. On arrival in the operating room, a control sample of blood was withdrawn. Light surgical anesthesia (lower plane 1) was administered for one hour at which time another sample of blood was obtained.

In the deep surgical anesthesia group (upper plane 4), light surgical anesthesia was administered for one hour; then fifteen minutes prior to withdrawing the second sample of blood, deep surgical anesthesia was produced. Depth of anesthesia was judged solely on the basis of changes in eye signs and respiratory patterns.

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In both groups of patients, blood for analyses was obtained from a large antecubital vein, and the surgical procedure was in progress at the time the second sample of blood was secured.

Cyclopropane was administered by the closed circle technique with ether, halothane, and nitrous oxide administered by the semi-closed circle technique. Thiopental was given intravenously in a 0.4 per cent continuous drip method. Respiratory exchange was assisted in all patients to avoid accumulation of carbon dioxide.

The administration of cyclopropane, ether and halothane was preceded by a sleeping dose of intravenous thiopental. If endotracheal intubation was indicated, this was performed after the administration of succinylcholine chloride. For abdominal operations requiring muscle relaxation, a continuous drip of succinylcholine chloride was utilized.

Spinal anesthesia between the fourth and sixth sensory level in 9 patients was included. The level of spinal anesthesia was obtained, either by the single injection or the continuous technique.

The concentration of plasma catechol amines in the blood samples was determined by utilizing the method of Weil-Malherbe and Bone, as modified by Richardson.[7]

The patient's anesthesia record and post-anesthesia course were reviewed for any findings which might be related to changes occurring in the concentration of plasma catechol amines.

TABLE 2

DISTRIBUTION OF PATIENTS

Agent	Light Anesthesia	Deep Anesthesia
Halothane (Fluothane)	12	10
Ether	12	10
Thiopental-Nitrous Oxide	11	12
Cyclopropane	12	11
Spinal	9	—

RESULTS

Ninety-nine patients were studied: 47 during light surgical anesthesia, and 43 during deep surgical anesthesia (table 2). As previously mentioned, 9 patients received spinal anesthesia. The age range of these patients was 7 to 78 years, with a mean age of 47. The distribution between male and female was approximately equal. The concentration of total plasma catechol amines in the control specimens varied from 0.88 μg. per liter to 4.67 μg. per liter, with an average concentration of 2.47 μg. per liter. These concentrations are within the normal range for the laboratory technique mentioned.

Light Surgical Anesthesia. Ether produced the largest increase in total plasma catechol amines at the end of one hour of anesthesia. Halothane showed the next largest increase,

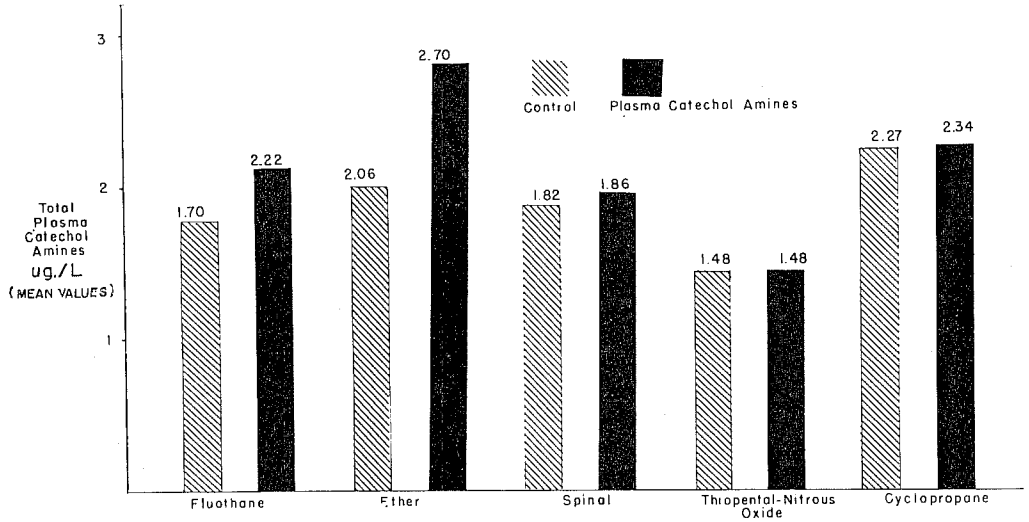

FIG. 1. Total plasma catechol amines in light anesthesia.

TABLE 3

MEAN PLASMA LEVELS OF EPINEPHRINE AND NOREPINEPHRINE AFTER ONE HOUR OF LIGHT SURGICAL ANESTHESIA

(Figures in Parentheses Represent Range of Concentrations)

	Epinephrine, μg./liter		Norepinephrine, μg./liter	
	Control	Anesthesia	Control	Anesthesia
(Halothane) Fluothane	0.27 (0.00–0.48)	0.52 (0.15–1.14)	1.42 (0.84–4.32)	1.70 (0.62–3.32)
Ether	0.32 (0.07–0.74)	0.72 (0.20–1.58)	1.74 (0.72–3.13)	1.98 (0.53–5.60)
Spinal	0.35 (0.15–0.68)	0.41 (0.19–1.10)	1.37 (0.79–1.92)	1.46 (0.62–1.90)
Thiopental Sodium-Nitrous Oxide	0.34 (0.10–0.84)	0.35 (0.00–0.98)	1.05 (0.39–3.16)	1.16 (0.00–2.90)
Cyclopropane	0.49 (0.21–0.95)	0.50 (0.07–1.42)	1.78 (0.91–3.63)	1.83 (0.26–3.78)

with spinal, thiopental-nitrous oxide and cyclopropane anesthesia producing little change (fig. 1). Halothane and ether, in light general anesthesia, produced a suggestive increase in the epinephrine fraction, but with little or no increase noticed in the norepinephrine fraction. Thiopental-nitrous oxide and cyclopropane anesthesia did not produce measurable change in either fraction (table 3). However, neither the increase in concentration of the total plasma catechol amines nor the changes in concentration of epinephrine or norepinephrine observed with halothane and ether proved to be statistically significant.

A majority of the patients responded in a manner which was clinically satisfactory. However, significant hypotension occurred in 8 patients—two with each agent (table 4). The most severe hypotension occurred in 2 patients receiving thiopental-nitrous oxide anesthesia, and in one of these patients catechol amines were not detectable at the end of one hour of anesthesia.

TABLE 4

TOTAL PLASMA CATECHOLS AFTER ONE HOUR OF ANESTHESIA IN PATIENTS WITH HYPOTENSION

(Two Patients with Each Agent)

	μg./liter Control	μg./liter One Hour Anesthesia
Halothane (Fluothane)	1.10	1.24
Ether	2.00	1.75
Thiopental-Nitrous Oxide	0.77	0.41
Cyclopropane	3.37	2.57

Deep Surgical Anesthesia. In contrast to the results obtained during light surgical anesthesia, cyclopropane produced a rise in the concentration of total plasma catechol amines; whereas halothane did not produce a change. Ether produced a rise in the total plasma catechol amines and as in light surgical anesthesia, no change was observed with thiopental-nitrous oxide (fig. 2). The fraction of catechol amines reflecting these changes with ether and cyclopropane was norepinephrine, with little change occurring in the epinephrine fraction (table 5). The increases in total plasma catechol amines observed with ether and cyclopropane are statistically significant ($p < .05$).

Hypotension occurred in 17 patients in deep anesthesia. Ether anesthesia produced hypotension in 8 patients; and the catechol amines, during this period of deep anesthesia, were significantly increased over the control levels. In those patients who became hypotensive during thiopental-nitrous oxide anesthesia, there was a marked decrease in circulating catechol amines. However, with

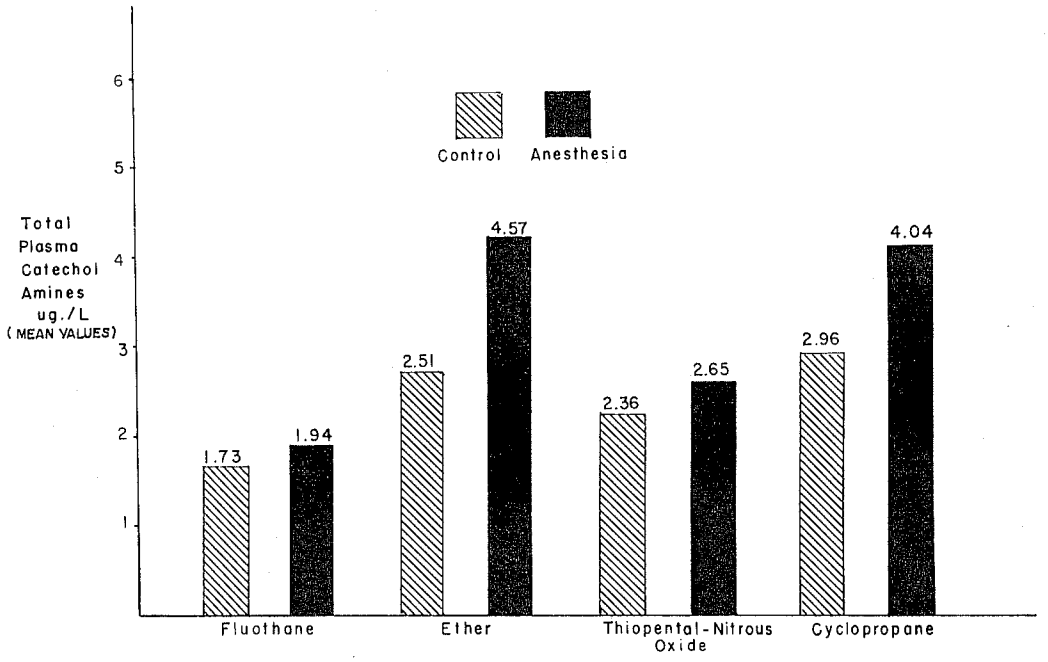

FIG. 2. Total plasma catechol amines in deep anesthesia.

TABLE 5

MEAN PLASMA LEVELS OF EPINEPHRINE AND NOREPINEPHRINE IN DEEP ANESTHESIA

(Figure in Parenthesis Represents Range of Concentration)

	Epinephrine, μg./liter		Norepinephrine, μg./liter	
	Control	Anesthesia	Control	Anesthesia
Ether	0.44 (0.13–1.23)	0.67 (0.05–1.63)	2.07 (1.30–3.56)	3.90 (1.57–8.50)
Cyclopropane	0.44 (0.20–0.72)	0.60 (0.18–1.16)	2.52 (1.25–4.32)	3.44 (2.21–4.84)

TABLE 6

PLASMA CATECHOLS IN DEEP ANESTHESIA IN PATIENTS WITH HYPOTENSION

Agent	Patients	Control	Anesthesia
Cyclopropane	2	2.41	2.72
Thiopental Sodium-Nitrous Oxide	2	2.80	1.54
Halothane (Fluothane)	5	1.96	1.84
Ether	8	2.90	4.27

halothane and cyclopropane there was little change (table 6).

The influence of spinal anesthesia on the plasma levels of catechol amine was not remarkable (fig. 1).

There were no patients in either group, light or deep surgical anesthesia, who became hypertensive during the period of study.

DISCUSSION

The specificity and sensitivity of the ethylenediamine method of Weil-Malherbe and Bone, as modified by Richardson, have been questioned by certain investigators.[8, 9] Others have verified and correlated this method with biological methods.[10, 11] The validity and reliability of the quantitative technique have been reviewed recently in detail by Manger and associates.[12] In our own laboratory, predictable increases or decreases in plasma catechol amines have occurred in accordance with the conditions imposed.[13] Further, the method has been clinically accurate in the diagnosis of pheochromocytoma. Under these circumstances and in view of the fact that the patients in this series had normal blood chem-

ical analyses, the objections to the method appear questionable in our minds.

The statistically significant increase in the catechol amines occurring with cyclopropane and ether in deep surgical anesthesia corroborates the findings of other investigators.[2-5]

The absence of increased levels of catechol amines under spinal anesthesia confirms the impressions presented in other studies.[14] The suggestion that the lack of increase of these amines with thiopental-nitrous oxide and halothane could account for the increased frequency of hypotension with these agents is also substantiated.[5]

That patients tolerate light surgical anesthesia better than deep surgical anesthesia is apparent from this study. Although both groups of patients were clinically the same, more than twice as many became hypotensive under deep surgical anesthesia. This could be accounted for on the basis that although some agents, such as ether and cyclopropane, can produce a significant increase in catechol amines, this increase is not enough to overcome the depressing effects of the anesthetic agents on the cardiovascular system in some patients. During light surgical anesthesia the depressing effects of the anesthetic agents are less, and the maintenance of near normal levels of catechol amines with all agents is enough to overcome these depressing effects in a majority of the patients. On the basis of studies in animals on the influence of anesthetics on the peripheral vascular bed and myocardial contractile force, this appears to be a reasonable conclusion.[2, 15]

The marked increase in catechol amines, both in normotensive and hypotensive patients, noticed with ether probably reflects the sympathomimetic property of this agent.

Summary

The changes in concentration of plasma catechol amine levels were investigated in surgical patients receiving general anesthesia consisting of halothane, ether, thiopental-nitrous oxide and cyclopropane. Nine patients received spinal anesthesia. In the general anesthesia group, the concentration of catechol amines was investigated both in light and deep surgical anesthesia.

During light surgical anesthesia, no significant rise in the catechol amines with any agent was detected. In the deeper planes of anesthesia, however, ether and cyclopropane produced a statistically significant increase in the catechol amines, with the other two agents producing no change. The fraction reflecting this increase was norepinephrine.

In those patients who became hypotensive, thiopental-nitrous oxide failed consistently to produce an increase and, in fact, a decrease in the circulating catechol amines was noted.

No change in catechol amine levels occurred with spinal anesthesia.

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HANDICAP ANESTHESIA In a missionary hospital at Shikarpur, West Pakistan, the following is described as the method used for the administration of general anesthesia for eye surgery: Drop chloroform is given first with the use of a face mask. Intubation is carried out. The rubber tube is then connected to an ordinary kitchen funnel. This is covered with a small Turkish face cloth, upon which chloroform is again dropped. It is claimed that in spite of tremendous handicaps, excellent results may be obtained if technique is carefully adjusted to field conditions. (*Pritikin, R.: Mass Ophthalmic Surgery Under Handicaps in Pakistan, J. International Col. Surgeons 31: 335 (March) 1959.*)

PAIN RELIEF Subarachnoid alcohol block was performed in 106 patients with intractable pain due to malignant disease. Fifty per cent obtained complete relief and 33 per cent obtained partial relief. The usual technique for spinal anesthesia was modified by careful positioning of the patient and other precautions so as to limit the action of the alcohol to the dorsal nerve roots. More predictable results were thus obtained, with fewer of the distressing complications (paralyses, paresthesias, and vesical and intestinal dysfunction) that may be produced by older methods. Ten spinal cords were examined at subsequent autopsies. The most constant finding was demyelinization of the dorsal roots of the spinal nerves, with extention peripherally to the dorsal root ganglia and centrally into certain tracts within the cord. (*Hay, R. C., Yonezawa, T., and Derrick, W. S.: Control of Intractable Pain in Advanced Cancer by Subarachnoid Alcohol Block, J. A. M. A. 169: 1315 (March 21) 1959.*)

MALPRACTICE In a 341-page report of a two year study in five California hospitals Bloom found: (1) The organization and performance of the medical staff had a direct bearing on the number of malpractice suits. (2) The low-suit hospitals were better managed than the high-suit hospitals. (3) The quality of medical work performed in low-suit hospitals was judged superior to that of high-suit hospitals. (4) Patients were more critical of their care in the high-suit hospitals. Recommendations were that physicians should be less reluctant to call attention to sub-standard practices of their colleagues and undertake a study for the purpose of suggesting indicated changes in hospital administration, staff organization, accreditation methods, work quality evaluation and control, and staff requirements. (*Good Organization Means Fewer Lawsuits, Mod. Hosp. 91: 59 (Oct.) 1958.*)

MATERNAL MORTALITY In this follow-up study of the maternal mortality associated with anesthesia in Bronx County, New York, the maternal mortality has dropped from 1.3 per 10,000 live births in 1946–1951 to 0.5 for the period 1952–1957. While no cases of spinal shock were reported during the latter period, asphyxia, massive collapse and cardiac arrest continued to occur. Most of these maternal deaths due to anesthesia were considered preventable. Further decrease in mortality from aspiration asphyxia is only possible through the combined efforts of the obstetrician and the anesthetist. The need for competent anesthesia personnel is emphasized. (*Klein, M. D., and Clahr, J.: Maternal Mortality Associated with Anesthesia, Obst. & Gynec. 13: 32 (Jan.) 1959.*)