PLASMA CATECHOLAMINES BEFORE DURING AND AFTER NEUROLEPTANESTHESIA OR NITROUS OXIDE–HALOTHANE ANESTHESIA

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ABSTRACT

Plasma levels of epinephrine (E) and norepinephrine (NE) were measured by sensitive high–speed ion-exchange chromatography in patients undergoing major operations under neuroleptanesthesia (NLA) or N_2O-halothane anesthesia (GOH). Intravenous thiamylal decreased E and increased NE in most patients. NLA decreased both E and NE, while GOH decreased E and tended to increase NE. E and NE were inclined to increase during surgery compared with their preoperative values (under anesthesia); an exception was the value of NE under GOH. The most prominent increases in E and NE were frequently observed during the recovery period. E decreased but NE still maintained its high value on the day following the operation. There were no significant correlations between catecholamine levels and mean arterial pressure or heart rate. Compared to the values found in healthy subjects, preanesthetic E levels in our patients were quite high, probably due to psychological stress. (KEY WORDS: Epinephrine, norepinephrine, thiamylal, neuroleptanesthesia, nitrous oxide–halothane anesthesia, surgery, sympathoadrenal response.)

The effects of anesthetic drugs on sympathoadrenal activity have been estimated by measuring plasma catecholamine (CA) levels in animals[1,2] and man.[3,4] However, contro-

versial results have been reported. For instance, halothane has been found to decrease[1-3] or to increase plasma norepinephrine (NE) levels after induction.[4] In addition, previous studies have failed to document consistent changes in plasma CAs during surgery,[5-8] seemingly due to the differences in anesthetic depth[9] or methods employed, and to the extent of surgical stress.

The present study was undertaken to explore the differential effects of droperidol -fentanyl-nitrous oxide anesthesia (NLA) and halothane-nitrous oxide anesthesia (GOH) on human plasma levels of epinephrine (E) and NE during preoperative, surgical and recovery periods in the patients. The effects of sleeping doses of thiamylal on these CAs were also studied. In addition, in order to evaluate the psychological stress of the patients awaiting anesthesia and surgery, measurements of plasma CAs in healthy subjects were carried out for the purpose of comparison.

METHODS EXPERIMENT I

Twelve surgical patients A. S. A. physical status I to II and without nervous or endocrine abnormalities, were premedicated with hydroxyzine (2 mg/kg) and atropine (0.5 mg) intramuscularly 30 minutes (8: 00 a. m.) before the scheduled induction of general anesthesia (8: 30 a. m.). The patients undergoing elective intra-abdominal surgery lasting 3-4 hrs were randomly assigned to one of two groups: nitrous oxide-fentanyl -droperidol anesthesia (NLA) and nitrous oxide-halothane anesthesia (GOH). Informed consent was obtained from each patient prior to the study.

An intravenous catheter was inserted into a forearm vein for the administration of drugs and fluids. An intraarterial catheter was also inserted into a radial artery for monitoring arterial pressure and for drawing 5-ml blood samples to measure blood gases and plasma levels of epinephrine (E) and norepinephrine (NE). Arterial blood samples were obtained immediately before the induction of anesthesia (control), immediately after induction with thiamylal sodium (3-5 mg/kg, intravenously) and before the endotracheal intubation (thiamylal), just before (anesthesia), 20-30 (early) and 60-80 minutes (late) after the start of the operation, immediately before the termination of surgery (end), 30-60 minutes after transfer to the recovery room and in the morning of the following day.

All patients were intubated endotracheally with the aid of succinylcholine chloride (1 mg/kg) and ventilated mechanically. Patients in the NLA group received droperidol, (0.2 mg/kg) and fentanyl (6 μg/kg) through inhalation of 60% nitrous oxide (N_2O) after the intubation. Fentanyl (0.1 mg) was supplemented intravenously every 30 minutes thereafter.

Patients in the GOH group inhaled 1.5% halothane for the first 10 minutes and then 1.0% halothane with 60% N_2O throughout anesthesia. Intravenous pancuronium provided muscle relaxation for mechanical ventilation in both groups. Ventilation volume was adjusted so as to eliminate hyper-or hypoventilation. At the end of the operation, neostigmine (1.0-2.5 mg) preceded by atropine (0.5-1.5 mg) was injected intravenously to

reverse the neuromuscular blockade.

For the measurement of plasma levels of E and NE, blood samples were rapidly placed in chilled collection tubes containing disodium edetate and reduced gluthathione and centrifuged at 4℃ for 15 minutes. Forty-four μl of 9 N perchloric acid were added to each milliliter of plasma. The supernatants were assayed for catecholamines by sensitive high-speed ion-exchange chromatography with a fluorometric detector.[10] The sensitivity of this assay was 20 pg for both E and NE. Recoveries from plasma containing 1000 pg of catecholamine standards were 93.6±0.7 (mean±SE, n=7) and 74.4±2.2% for E and NE, respectively.

Core temperature was monitored via a rectal temperature probe. Mean arterial pressure (MAP) and heart rate (HR) were also recorded. Standard statistical methods, including paired or nonpaired t tests, and the chi square tests for paired observations, were used, and significance was defined as $P \leqq 0.05$.

<div align="center">Experiment II</div>

This study was made for the purpose of comparing the preanesthetic levels of catecholamines in surgical patients with those in normal subjects. Sixteen healthy normotensive subjects (eight male volunteers from our Department, 26-47 years of age, and eight female volunteers from the Operating Unit, 22-45 years of age) were the subjects of this study. At about 8: 00 a. m. on the day of the observation, they were put on a table in the supine position for at least 20 minutes before the blood sampling. Five ml of venous blood were withdrawn from a forearm vein and analyzed for E and NE with the same methods as described above. Immediately after blood sampling, MAP and HR were also checked.

<div align="center">Results Experiment I</div>

Plasma levels of E and NE in all patients tested are summarized in Table 1. There were no significant correlations between plasma E and NE values, tested in all patients, during the wakeful state before anesthesia (correlation coefficient, r=0.446). To estimate the differential effects of the anesthetics and surgery, percent changes from the control values were calculated for both methods of anesthesia (Table 2).

Sleeping doses of thiamylal decreased E significantly. In contrast, NE was increased (though insignificantly) by thiamylal in most subjects (8 of 10) (Table 1, 2).

Plasma E was decreased by both NLA and GOH in all patients. Plasma NE was decreased significantly by NLA (p<0.05), while it was increased by GOH in most subjects (Table 1, 2). The differences between the mean changes caused by NLA and those by GOH were significant (Table 2).

Plasma E tended to increase during surgery with both methods of anesthesia compared to the preoperative values (under anesthesia), but not significantly in comparison with the preanesthetic values (control). Significant increases in E were noted during the

Table 1. Plasma levels of E and NE in response to anesthesia and surgery in individual patients

	Case	Age	Sex		Control	Thiamylal	Anesthesia	early	Surgery late	end	Recovery room	Next day morning
NLA	1	65	F	E	549	600	127	1068	293	421	362	374
				NE	451	469	287	508	649	1063	442	457
	2	28	M	E	594	282	147	311	831	272	967	147
				NE	116	117	54	472	644	481	357	376
	3	38	M	E	44	29	23	217	53	70	82	25
				NE	67	37	19	68	146	53	176	150
	4	43	F	E	781	415	385	497	485	479	1245	281
				NE	158	186	118	134	189	159	442	74
	5	71	M	E	136		88	273	121	195	250	161
				NE	106		107	179	108	113	157	200
	6	71	F	E	356	149	20	423	390	317	461	100
				NE	20	106	20	129	100	97	157	120
GOH	7	44	M	E	224	412	15	274	182	489	1938	207
				NE	66	74	81	130	97	165	348	415
	8	69	F	E	366	146	71	230	230		426	
				NE	115	194	211	218	262		283	
	9	38	F	E	197		58	222	85	229	318	170
				NE	77		147	117	108	76	167	246
	10	31	M	E	462	510	383	1646	737	520	418	193
				NE	116	209	178	206	184	169	240	325
	11	42	M	E	200	75	38	227	763	128	46	
				NE	62	70	127	102	115	80	30	
	12	48	M	E	226	156	70	74	67	61	158	61
				NE	160	115	80	100	111	156	155	72

pg/ml

NLA = Neuroleptanesthesia (Nitrous oxide-fentanyl-droperidol);
GOH = Nitrous oxide-halothane anesthesia; Control = Before anesthesia

Table 2. Percent changes (mean ± standard error) in plasma E, NE and hemodynamics (MAP and HR) in response to anesthesia and surgery

		Control	Thiamylal	Anesthesia	early	Surgery late	end	Recovery room	Next day morning
E	NLA	100	$64 \pm 12^*$	$37 \pm 9^{***}$	187 ± 66	96 ± 14^s	96 ± 19^s	$148 \pm 18^*$	$55 \pm 14^*$
	GOH	100	88 ± 27	$35 \pm 11^{***}$	133 ± 47	120 ± 49	106 ± 33	220 ± 130	62 ± 16
			$(76 \pm 15^*)$						
NE	NLA	100	182 ± 88	$69 \pm 12^*$	256 ± 92	272 ± 83	237 ± 72	314 ± 100	248 ± 81
	GOH	100	129 ± 20	$151 \pm 23 \rceil \dagger$	$157 \pm 20^*$	155 ± 22	144 ± 28	224 ± 68	318 ± 120
			(156 ± 43)						
MAP	NLA	100	82 ± 19	85 ± 8	102 ± 10	101 ± 8^s	99 ± 8	87 ± 9	
	GOH	100	82 ± 16	90 ± 7	85 ± 9	85 ± 9	89 ± 10	88 ± 8	
			(82 ± 17)						
HR	NLA	100	98 ± 2	92 ± 5	100 ± 6^s	104 ± 10	103 ± 9	107 ± 8	
	GOH	100	99 ± 2	108 ± 14	110 ± 10	110 ± 10	109 ± 5	101 ± 3	
			(99 ± 2)						

Significantly different from the preanesthetic base-line (Control)
($^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$)
Significantly different from the preperative value (Anesthesia)
($^sP < 0.05$, $^{ss}P < 0.01$, $^{sss}P < 0.001$)
Significantly different between the two groups (NLA and GOH)
($\dagger\ P < 0.05$)
Inside parentheses in the thiamylal column are means ± SE, calculated in all subjects.

recovery phase from NLA. Decreases of E were observed on the first postoperative day in comparison with control values (significant in the NLA group, but insignificant in the GOH group).

Plasma NE tended to rise in response to surgery under both methods of anesthesia, but a significant rise was demonstrated only at the early phase of surgery under GOH (Table 2). In contrast with E, NE tended to maintain its high value even until the next morning.

MAP increased significantly during the late phase of surgery under NLA but not under GOH in comparison with the preoperative value (during anesthesia). HR also increased significantly during the early phase of surgery only under NLA. However, there were no significant correlations between the mean changes of CAs and those of MAP or HR during the procedures.

There were no statistically significant differences in age, sex, the duration of anesthesia or surgery between the NLA and GOH groups. Neither arterial pH nor $Paco_2$ differed significantly between the NLA and GOH groups at each corresponding sampling time.

<div align="center">EXPERIMENT II</div>

Resting forearm venous E and NE levels in each healthy subject are shown in Table 3. Venous NE levels in female subjects were higher than those in males (P<0.01). No differences between males and females could be found in venous E levels. The regression analysis of venous NE versus E values in all subjects showed no significant correlations (r=0.130). There were no relationships between these CA levels and age.

The comparison of these venous CA levels in healthy subjects with arterial CA levels in the surgical patients during wakefulness revealed that arterial E levels in the patients were significantly higher than those in the healthy subjects (p<0.001). There were no significant differrences between the patients and healthy subjects in plasma NE levels.

Table 3. Plasma levels of E and NE in healthy male and female subjects

Male				Female			
Case No.	Age(yr)	E(pg/ml)	NE (pg/ml)	Case No.	Age (yr)	E (pg/ml)	NE (pg/ml)
1	29	108	262	1	29	95	334
2	34	253	398	2	28	86	263
3	26	48	257	3	35	54	314
4	29	103	203	4	32	132	380
5	33	61	88	5	45	51	262
6	32	142	140	6	22	56	369
7	30	275	98	7	29	51	202
8	47	20	72	8	35	51	107
Mean±SE	33±3	80±16	170±29	Mean±SE	32±3	63±7	264±31**

**Significantly different between the groups (male and female) (P<0.01)

DISCUSSION

The depressive and augmentative effects of thiamylal on plasma E and NE, respectively, as demonstrated in most subjects, may indicate that the drug causes an inhibitory effect on adrenal activity[11] and a facilitatory effect on peripheral sympathetic activity in man.[4/12)13]

The depressant effects of NLA on both plasma E and NE in most subjects may indicate that NLA blocks sympathoadrenal activities in man. Sympathomimetic effects of N_2O in humans have been demonstrated by Smith et al.,[14] but not by others.[4)8)15] A review of these reports reveals that the inhalation of N_2O may have a slight sympathomimetic effect in man, at least transiently. The addition of 60% N_2O might have had some stimulant effects on sympathetic activities in the present study. Nevertheless, the addition of droperidol-fentanyl had depressant effects on both plasma E and NE. Therefore, the depressant effects of NLA on plasma CA are thought to be produced by droperidol-fentanyl.

Several authors[16-18] reported that fentanyl prevented increases of plasma E and NE levels during intubation and surgery dose-dependently. Recently, Brown et al.[8] have also demonstrated that Innovar ® (droperidol+fentanyl) tend to decrease plasma E and NE. Our data almost coincide with their results. They have attributed these plasma CA changes to the effects of fentanyl on sympathetic activities. However, the effects of an adjuvant neuroleptic, droperidol, on plasma CA must also be considered. In particular, the α-adrenergic blocking action of droperidol might contribute to the changes of plasma CAs.[19]

The effects of halothane on plasma E and NE have been studied, but followed by controversial results. The earlier reports, using the old trihydroxy-indole method, suggested that halothane did not cause significant changes in plasma E, NE or total CAs in man or dogs.[20-22] More recent studies, using radioenzymatic assay, have demonstrated that halothane attenuated plasma E and NE in animals.[1)2] In contrast, Joyce et al.[4] have recently shown that halothane and GOH caused an increase in plasma NE 15 minutes after induction and a subsequent return to control at 45-60 minutes in seven unpremedicated patients. Our study has demonstrated that plasma NE increases in a majority of the patients (5/6) even at 30 minutes after the inhalation of halothane mixed with 60% N_2O.

Even if the residual effects of thiamylal might persist at 30 minutes after GOH in the present study, the converse changes of NE with NLA suggest that the sympathoadrenal effects of GOH are distinct from those of NLA. Further, the lack of significant correlations between plasma CA levels and hemodynamic changes suggests that these changes of plasma CAs caused by the two methods of anesthesia originate from the pharmacological actions of the anesthetics on the sympathoadrenal systems rather than from reflex responses to hemodynamic variables.

The apparent reciprocal suppression and augmentation of plasma E and NE obsear-ved during GOH suggest that the sympathetic nervous pathway to the adrenals may be distinct from the pathway to the peripheral nerves in man.[3] Divergent adrenomedullary and peripheral sympathetic pathways would also explain the dissociation of E and NE levels observed during hypoglycemia,[23][24] several kinds of stress[25] and anesthesia.[3] Circulating E is derived from adrenomedullary cells, whereas plasma NE levels are thought to result primarily from an overflow of NE released at the sympathetic nerve terminals.[3][26] These two circulating CAs, therefore, may change depending upon the rates of release, reuptake and metabolism. Previous studies have shown that reuptake and metabolism are hardly affected by anesthetics,[27][28] while the releases of CAs are profoundly affected.[29]

Thus, the results of plasma E and NE levels observed during anesthesia are probably related to changes in release from adrenomedullary cells and sympathetic nerve endings, respectively, rather than to changes in reuptake or metabolism of the CAs.

Both plasma E and NE tended to increase during surgery (Table 2) in the present study. These data are in general agreement with other reports.[3][5][6][8] However, a significant increase as compared with the controls was demonstrated only in the NE value during the initial stage of GOH (Table 2). This increase of NE is more likely due to the effects of halothane rather than to the stress of surgery, since there were almost no changes of the hormone compared to its preoperative value (during GOH). In compari-son with the preoperative values, significant increases were noted in the E values at the late and end stages of surgery during NLA. This might be due to three factors : high preanesthetic values of plasma E; profound decrease caused by NLA; and the relative lightness of anesthesia during the late phase of surgery. The high value of plasma E in patients anticipating anesthesia and surgery was demonstrated in the comparison study with healthy subjects. These trends of sustained increases of plasma CAs in the early postperative period have also been observed by other investigators.[3][5]

Plasma CA changes in response to surgery have been studied by several investiga-tors. Increases in both of these hormones,[3][6][8] increases in E alone[5] or no changes in the hormones[16][17] have been reported during surgery. A more detailed review of these previous studies reveals that the anesthetic depth (or dose)[9] and/or the extent or variety of surgery might account for the differences among the above reports. Except for the NE value under GOH, in the present experiment there were no significant changes in these hormones during surgery with either method of anesthesia as compared with the control. Although there were no significant differences between the NLA and GOH groups in NE levels during surgery, the hormone tended to increase more during surgery under NLA than under GOH (Table 2). This may be one of the causes of hypertension sometimes noted during surgery under NLA. By contrast, under GOH, plasma NE levels remained almost unchanged during surgery as compared with those just before surgery. In this study, both CA levels (particularly the E level) tended to peak in the recovery

room.

Up to now, there have been no available data on plasma CA levels during postoperative days. The present results indicate that plasma E maintains a high level even on the day following surgery in some patients (Table 1), although the values were about half the control levels (Table 2). Thus, these obsearvations suggest that the greatest endocrine stress response occurs in the preoperative and early postoperative periods.

Perry et al.[1] investigated the relationships between each of the hemodynamic variables (blood pressure, heart rate, cardiac output) and plasma CA in dogs by determining the correlation coefficient for each anesthetic (halothane, isoflurane, cyclopropane) and for the differences between anesthetics. They could not find any remarkable relationship. On the other hand, Halter et al.[3] demonstrated a significant correlation between MAP and plasma E and NE. The absence of a remarkable correlation between hemodynamic variables and plasma CA in this study may be related to the fact that other factors influence these variables and that circulating CAs are not always a valid index of hemodynamic changes.[12]

Venous CA levels in healthy subjects are comparable to those found in the recent data by Halter et al.,[30] who used the single isotope enzymatic assay. The significantly high levels of venous NE with females, demonstrated in the present study, may suggest that α-sympathetic activation is more dominant in females at this morning hour than in males. No correlations between plasma CAs and sex or hemodynamics have been found in previous reports.[12] Whether this sex difference concerning venous NE is specific to this particular morning hour could not be ascertained in the present study. Our aim in Experiment II was to examine the sympathoadrenal status of the surgical patients lying on the operating table awaiting anesthesia and surgery by comparing their plasma levels of CAs with those in the healthy subjects at the same time of day. Although some differences in the arterial-venous concentration of E (about 50 pg/ml) have been reported,[30] mean arterial E levels in the NLA and GOH groups before anesthesia were about 300 and 200 pg/ml more, respectively, than those in the healthy subjects. These remarkably high levels of arterial E in our patients could not be explained by the arterial-venous differences of E. Therefore, these high levels of E in our patients before anesthesia might be caused by the response to the stress of the environment and/or expectation of anesthesia and surgery. Furthermore, these data from the patients reveal that our premedication was insufficient for controlling their psychological stress.

Thus, the present results may indicate that the sympathoadrenal system is profoundly facilitated during pre-and postanesthetic periods as well as during surgery in terms of plasma CA concentrations.

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