EFFECTS OF DROPERIDOL-PENTAZOCINE-N₂O ANAESTHESIA ON ADRENOCORTICAL FUNCTION IN MAN

T. OYAMA, M.D., M. TAKIGUCHI, M.D. AND K. SATO*

THE EFFECTS of neuroleptanalgesia and anaesthesia on cardiovascular, respiratory and metabolic functions have been studied extensively. However, reports concerning its effect on adrenocortical activity have been scant. Oyama and Takiguchi have recently observed that neuroleptanaesthesia with dehydrobenzperidol (droperidol), pethidine, and nitrous oxide did not significantly stimulate adrenocortical function, but could not block adrenocortical stimulation during surgical intervention and after operation.¹

Since neuroleptanaesthesia (NLA) reduces cardiovascular sensitivity to catecholamines,^{2,3} it seems to be important from the homeostatic point of view to know whether or not NLA blocks the normal adrenocortical response to surgical or anaesthetic stress.

The present study was undertaken to investigate the effect of NLA produced with droperidol, pentazocine, and nitrous oxide on adrenocortical function, as judged by its influence on the free cortisol level in the plasma in 19 patients, and to compare the results with the effects of anaesthesia plus surgery. Pentazocine is a potent non-narcotic analgesic.^{4,5}

METHOD

Nineteen patients, ranging in age from 16 to 58 years, who were free from endocrine, hepatic, and renal disease, were the subjects of the study (Table I). They were given pentobarbital 100 mg by mouth 1½ hours before operation, and pethidine 35 mg and atropine 0.5 mg intramuscularly 1 hour before operation.

Anaesthesia was induced with droperidol 0.15 mg/kg given by intravenous injection followed six minutes later by intravenous pentazocine 1–1.2 mg/kg. This was supplemented with nitrous oxide (6 L/min) and oxygen (2 L/min). Suxamethonium 40 mg was given intravenously for endotracheal intubation. General anaesthesia was maintained with nitrous oxide (3.5 L/min) and oxygen (1.5 L/min). Subsequent doses of pentazocine 30 mg were injected intravenously as indicated by elevation of arterial blood pressure or pulse rate, movement, lacrimation, or increase in respiratory rate. Tubocurarine (15–30 mg) was injected in divided doses to obtain muscle relaxation during abdominal surgery. Respiration was assisted or controlled intermittently throughout the procedure.

The operations lasted an average of 2 hours and 30 minutes (50 min to 5 hr 40 min), the average duration of anaesthesia being 3 hours and 37 minutes (2 hr 10 min to 6 hr 45 min). The average dose of droperidol was 8.5 mg (6.3–10.0

*Department of Anaesthesia, Hirosaki University School of Medicine, Hirosaki, Aomori-Ken, Japan.

TABLE I
PATIENTS, OPERATIONS AND DOSAGE OF DROPERIDOL AND PENTAZOCINE

No.	Age	Sex	Operations	Duration of op. (hr)	Duration of anaesth. (hr)	Droperidol (mg)	Pentazocine (mg)
1	43	M	Tumor extirp. from thigh	2:55	3:50	9.3	150
2	32	F	Plastic ope. of cicatrices	3:50	4:45	9.8	105
3	49	F	Oophorectomy	3:05	4:35	8.0	105
4	20	M	Skin grafting	3:45	4:30	10.0	120
5	30	F	Fixation of uterus	1:45	2:40	6.3	105
6	21	M	Skin grafting	1:25	3:00	10.0	150
7	16	F	Skin grafting	1:15	2:10	8.0	90
8	18	M	Osteotomy	1:25	2:13	10.0	150
9	45	M	Laminectomy	50	3:40	8.3	150
10	19	F	Tumor extirp. from neck	1:30	2:25	7.5	90
11	29	F	Adhesiotomy	1:45	2:40	7.5	105
12	17	F	Extirp. of haemangioma	2:15	3:35	7.5	105
13	40	F	Hemithyroidectomy	2:40	3:40	9.0	150
14	44	F	Nephro lithotomy	2:00	3:10	7.5	90
15	58	F	Cholecystectomy	2:10	3:10	8.8	150
16	47	F	Hysterectomy	2:20	3:10	8.8	150
17	18	M	Colectomy	5:40	6:45	10.0	210
18	44	F	Hysterectomy	3:45	4:30	7.5	150
19	28	M	Decompress. of facial n.	3:15	4:15	7.5	120
Mean				2:30	3:37	8.5	129

mg) and of pentazocine 129 mg (90–210 mg). The period of anaesthesia alone, before operation, was at least 45 minutes in each case.

Blood samples were obtained at the following times: (1) 8.30 am, just prior to induction; (2) 15, 30, and 45 minutes after anaesthesia alone; (3) 15 and 30 minutes, 1 hour and 2 hours after the start of operation; (4) when the patient had fully awakened in the recovery room. One ml of venous blood was obtained in a heparinized syringe, and centrifuged within 30 minutes. The free cortisol (17-hydroxycorticosteroid = 17-OHCS = hydrocortisone) in 0.05 ml of plasma was determined according to the method of competitive protein binding radio-stereoaassay utilizing H³-corticosterone of Murphy,⁶ with a Beckman liquid scintillation counter. The recovery rate of cortisol by our method was 95 per cent, and the duplicate error on the same sample was ± 1.5 mcg/100 ml.

RESULTS

Table II and Figure 1 show the effect of a droperidol-pentazocine-N₂O anaesthesia alone on plasma cortisol levels. The mean plasma free cortisol levels at 8.30 am just prior to induction in the 19 patients was 15.7 ± 0.9 mcg/100 ml of plasma. It increased slightly but insignificantly to 15.7 ± 1.1 and 16.5 ± 1.5 mcg/100 ml at 15 and 30 minutes after the anaesthesia alone, but was elevated significantly ($p < 0.02$) to 21.1 ± 2.0 mcg/100 ml after 45 minutes of anaesthesia alone. It increased significantly ($p < 0.001$) to 24.9 ± 2.0 , 29.9 ± 1.6 , 30.4 ± 1.6 , 33.4 ± 2.2 mcg/100 ml at 15 and 30 minutes, 1 hour and 2 hours after the start of operation respectively. It was still high at 30.6 ± 2.0 mcg/100 ml in the recovery room when the patients were considered to have awakened adequately.

TABLE II
EFFECT OF DROPERIDOL-PENTAZOCINE-N₂O ANAESTHESIA ON PLASMA
FREE CORTISOL LEVELS (mcg/100 ml)

Sub- jects	Time (min)								
	Preind.	Anaesth. 15'	30'	45'	Op.15'	30'	60'	120'	RR
1	20.5	19.5	19.5	28.5	31.5	34.0	32.5	38.0	39.0
2	11.0	5.0	15.0	22.0	27.5	27.5	27.0	30.5	29.0
3	23.0	17.0	10.0	12.5	18.5	22.5	22.0	25.0	23.0
4	19.0	14.0	27.5	37.0	37.5	37.5	39.0		34.0
5	18.0	18.0	10.0	16.0	12.0	26.0	29.0	23.0	18.5
6	17.5	18.0	11.0	12.0	7.5	23.5	25.0		13.0
7	7.0	9.0	3.5		14.0	21.0	31.0		30.0
8	10.0	13.5	5.0	20.0	20.0	40.5	36.0		35.0
9	18.0	14.0	25.5	28.5	41.0	38.0	32.0		26.0
10	10.5	10.0	10.5	6.5	24.0	26.0	24.5		10.5
11	15.0	24.0	18.0	26.5	22.0	37.0			37.5
12	18.0	18.0	18.0	17.0	24.0	36.0	30.0	43.5	33.5
13	17.0	18.5	14.0	20.5	26.5	24.0	26.5	27.0	30.5
14	21.5	24.0	24.5	24.5	29.0	34.5			31.5
15	14.0	16.5	23.0	35.0	40.0	37.0	34.0	37.0	40.0
16	18.5	23.0	20.5		25.5	31.0	42.5	41.0	41.0
17	13.0	7.5	17.0	19.5	23.5	22.5	25.5	28.0	40.0
18	10.5	15.0	27.0		25.0	35.5	42.5	41.0	41.5
19	17.0	15.0	15.0	13.5		15.0	18.5		28.0
Mean	15.73	15.76	16.55	21.15	24.94	29.94	30.44	33.40	30.60
SE	0.97	1.17	1.58	2.03	2.06	1.63	1.60	2.25	2.04
p		NS*	NS*	0.02	0.001	0.001	0.001	0.001	0.001

*Statistically not significant.

DISCUSSION

The present study demonstrated that the neuroleptanaesthesia (NLA) consisting of droperidol, pentazocine, and nitrous oxide, for a period of 45 minutes, significantly stimulated adrenocortical activity, as judged by the plasma free cortisol level.

NLA using pentazocine could not block adrenocortical stimulation during and after operation as was the case with NLA employing pethidine.^{1,7} It is interesting to note that plasma cortisol levels attained during surgery under the droperidol-pentazocine-nitrous oxide anaesthesia were higher than those obtained when droperidol-pethidine-nitrous oxide was used.¹¹ This was not due to the magnitude of surgical stress.

It is well known that an increase in plasma cortisol levels is seen during operation under general anaesthesia.⁸ The new intravenous anaesthetic agents such as ketamine⁹ and gamma-hydroxybutyrate,¹⁰ cause a preoperative rise. On the other hand, thiopental and the nonbarbiturate ultrashort-acting agent, propofol, have the least stimulating effect on adrenocortical activity.¹¹

The adrenocortical stimulation by this NLA, as judged by the elevation of the cortisol level, resembles those of gamma-hydroxybutyrate and ketamine. Both these agents tend to increase arterial blood pressure during anaesthesia. We would suggest that adrenocortical stimulation by NLA with droperidol and pentazocine might account for the increased arterial blood pressure.

Plasma Free Cortisol Levels During Droperidol-Pentazocine-N₂O Anesthesia and Surgery

FIGURE 1

It is known that cortisol is essential for maintenance of the normal cardiovascular response to stress.¹² Thomas and Brockman¹³ and Spink and Vick¹⁴ hypothesize a possible additive function of cortisol to catecholamine. Lillehei and coworkers¹⁵ and Schumer and Sperling¹⁶ demonstrated that cortisol increases cardiac output in animals and in man.

Droperidol is a derivative of butyrophenone, possessing sedative, antiemetic and alpha-adrenergic blockade properties. Pentazocine (Talwin®) is a powerful

non-narcotic analgesic, which is a derivative of benzomorphan having a chemical structure similar to Nalorphan, a morphine antagonist. The analgesic potency of 35 mg of pentazocine is equivalent to that of 75–100 mg of pethidine or 10 mg of morphine.

Neuroleptanaesthesia produced by droperidol, pentazocine and nitrous oxide appears to have many advantages over other techniques. These include stability of cardiovascular status, rapid induction and recovery and good postoperative analgesia. It may therefore be recommended for poor risk patients. In our experience, approximately 47 per cent of patients did not require any analgesic within 24 hours postoperatively. This technique is considered to be contraindicated in children and in patients with asthma, or impairment of liver or kidney function.

SUMMARY AND CONCLUSION

A study was undertaken to evaluate the effect of neuroleptanaesthesia (NLA), produced by droperidol-pentazocine-nitrous oxide on adrenocortical function, as judged by its influence on plasma free cortisol levels, in 19 patients undergoing operation.

NLA alone for 45 minutes stimulated adrenocortical function significantly. Adrenocortical stimulation was further accentuated during surgery and in the postoperative period. A possible relationship between the tendency to arterial hypertension caused by droperidol-pentazocine-nitrous oxide and adrenocortical activity is also discussed.

RÉSUMÉ

Cette étude voulait évaluer les effets de la neuroleptanesthésie (NLA) sur la fonction corticosurrénalienne; la neuroleptanesthésie (NLA) était produite par l'association droperidol-pentazocine et protoxyde d'azote; pour ce faire, nous avons étudié chez 19 opérés, l'influence de la NLA sur les taux de cortisol plasmatique libre.

Durant 45 minutes, la NLA, agissant seule, a stimulé la fonction corticosurrénalienne de façon significative; au cours de l'opération et des suites opératoires, nous avons constaté une stimulation additionnelle de la cortico-surrénale. Nous avons également discuté la relation possible entre la tendance à l'augmentation de la tension artérielle causée par l'association dropéridol-pentozocine et protoxyde d'azote et l'activité cortico-surrénalienne.

REFERENCES

1. OYAMA, T. & TAKIGUCHI, M. Effect of Neuroleptanaesthesia on Adrenocortical Function in Man. *Brit. J. Anaesth.* 42: 425 (1970).
2. CORRSSEN, G.; DOMINO, E. F.; & SWEET, R. B. Neuroleptanalgesia and Anaesthesia. *Anesth. & Analg.* 43: 748 (1964).
3. ZAUDER, H. L.; DEL GUERCIO, L. R. M.; FEINS, N.; BARTON, N.; & WOLLMAN, S. Hemodynamics during Neurolept Analgesia. *Anesthesiology*. 26: 266 (1965).
4. SADOVE, M.; BALAGOT, R. C.; & PECORA, F. N. Pentazocine - A New Nonaddicting Analgesic. Preliminary Single-Blind Study. *J.A.M.A.* 189: 199 (1964).
5. NORRIS, W. & TELFER, A. B. M. The Sedative Properties of Pentazocine (Fortral). *Brit. J. Anaesth.* 40: 341 (1968).

6. MURPHY, B. E. P. Some Studies of the Protein-Binding of Steroids and Their Application to the Routine Micro and Ultramicro Measurement of Various Steroids in the Body Fluids by Competitive Protein-Binding Radioassay. *J. Clin. Endocr. & Met.* 27: 973 (1967).
7. OYAMA, T.; TAKIGUCHI, M.; TAKAZAWA, T.; & KIMURA, K. Effect of Meperidine on Adrenocortical Function in Man. *Canad. Anaesth. Soc. J.* 16: 282 (1969).
8. VANDAM, L. D. & MOORE, F. D. Adrenocortical Mechanism Related to Anesthesia. *Anesthesiology*. 21: 531 (1960).
9. OYAMA, T.; MATSUMOTO, F.; & KUDO, T. Effects of Ketamine on Adrenocortical Function in Man. *Anesth. Analg.* 49: 697 (1970).
10. OYAMA, T.; KUDO, T.; SHIBATA, S.; & MATSUMOTO, F. Effects of Gamma-Hydroxybutyrate on Plasma Hydrocortisone Concentration in Man. *Anesth. & Analg.* 47: 350 (1968).
11. OYAMA, T.; KIMURA, K.; TAKAZAWA, T.; & TAKIGUCHI, M. Effects of Propanidid on Plasma Cortisol Concentration in Man. *Anesth. & Analg.* 49: 39 (1970).
12. WILLSON, R. F. & FISHER, R. R. The Hemodynamic Effects of Massive Steroids in Clinical Shock. *Surg. Gynec. Obstet.* 127: 769 (1968).
13. THOMAS, C. S. & BROCKMAN, S. K. The Role of Adrenal Corticosteroid Therapy in Escherichia Coli Endotoxin Shock. *Surg. Gynec. Obstet.* 126: 61 (1968).
14. SPINK, W. W. & VICK, J. A. Evaluation of Plasma, Metaraminol and Hydrocortisone in Experimental Shock. *Circ. Res.* 9: 184 (1961).
15. LILLEHEI, R. C.; LONGERBEAM, J. K.; BLOCK, J. H.; & MANAX, W. C. The Nature of Irreversible Shock, Experimental and Clinical Observations. *Ann. Surg.* 160: 682 (1964).
16. SCHUMER, W. & SPERLING, R. Shock and Its Effects on the Cell. *J.A.M.A.* 205: 215 (1968).