Journal of Surgical Oncology 20:192–196 (1982)

The Relation Between the Status of Adaptive System and the Number of Postoperative Complications in Patients With Gastrointestinal Cancer: The Effect of Phenazepam

M.N. OSTROUMOVA, MD, N.N. SIMONOV, MD, V.K. KOVALEV, MD, AND M.I. BERNSTEIN, MD
From the N.N. Petrov Institute of Oncology, U.S.S.R. Ministry of Public Health, Leningrad

The decrease in 11-hydroxycorticosteroids concentration caused by 0.5 mg of dexamethasone administered at 11 pm was studied in 91 primary patients suffering from gastrointestinal cancer. In dexamethasone-resistant patients postoperative complications developed in 65% of colon cancer patients and in 42% of stomach cancer patients. In dexamethasone-sensitive patients the complications were observed in 24% and 12% of patients, correspondingly. The elevation of hypothalamic threshold of sensitivity to the inhibiting effect of glucocorticoids, revealed by the dexamethasone suppression test, was considered to be a result of a combined action of age, the tumor itself, and pronounced emotional stress during the preparation for operation. The derivative of benzodiazepin—phenazepam—when administered before the operation in colon cancer patients improved the results of the dexamethasone suppression test and decreased the number of postoperative complications.

KEY WORDS: **colon cancer, stomach cancer, postoperative complications, emotional stress, hypothalamus, dexamethasone test, benzodiazepine**

INTRODUCTION

Neuroendocrine hypothalamopituitary-adrenal complex is the principal part of the adaptive system. The value of the hypothalamic threshold of sensitivity to the inhibiting effect of glucocorticoids characterizes the effectiveness of regulation acording to the negative feedback mechanism. When the level of glucocorticoids is raised, their effect on the corresponding receptors in the brain lowers the secretion of hypothalamic corticotropin-releasing factor (CRF). As a result, ACTH secretion is lowered and corticosteroid level is normalized. The lymbic-hypothalamopituitary complex threshold of sensitivity to the action of glucocorticoids is not a permanent magnitude. According to the law of deviation of homeostasis formulated by V.M. Dilman, the elevation of hypothalamic threshold takes place with aging, which at first provides the increase in the capacity of homeostatic systems during organism development and later on contributes to the formation of age-associated disease dysadaptosis, or in the terms used by the author at present, hyperadaptosis [Dilman, 1978, 1979]. Besides, the prolonged elevation of hypothalamus threshold of sensitivity may occur under the conditions of organism adaptation to an unusual situation, for instance, under chronic stress, or metabolic disorders caused by a malignant tumor progression [Bishop and Ross, 1970; Dilman, 1971, 1978, 1979; Dilman et al, 1979a,b; Saez, 1974]. Thus, the resistance of central neuroendocrine structures to the inhibition according to the negative feedback mechanism may lead to the overloading of homeostatic regulation, damage of adaptive reactions, and pathologic changes.

It is natural that an oncological patient hospitalized for treatment into the special clinic should endure a stressful situation. Strong emotional tension when making out a patient's diagnosis and waiting for the operation, in a number of cases, causes the acute attacks of

Accepted for publication October 29, 1981.

Address reprint requests to M.N Ostoumova, MD, N.N. Petrov Institute of Oncology, USSR Ministry of Public Health, Leningrad, USSR.

0022-4790/82/2003-0192$02.00

chronic diseases, especially cardiovascular pathology, psychogenic disturbances, and formation of depressive-like states [Simonov and Gnezdilov, 1978; Leme-Lopes, 1973], which indicates the impairment of organism system of adaptation. As a result, the difficulties arise in preparation of patients for the operation, and the risk of postoperative complications and death increases [Simonov and Gnezdilov, 1978; Druss et al, 1968; Gnezdilov et al, 1977]. However, these disorders do not acquire a pronounced clinical form. That is why it is of importance to assess objectively the subclinical stage of dysadaptosis caused by malignant tumor, age, and therefore progressing emotional stress, during the preparation of patients for the operation.

For this purpose the dexamethasone suppression test was used in patients with gastrointestinal cancer, the results of the test being considered with regard to the course of postoperative period. It turned out that the patients resistant to the inhibiting effect of dexamethasone developed a greater number of postoperative complications. The elevation of hypothalamic threshold of sensitivity to the inhibiting effect of glucocorticoids is known to be a characteristic feature of the patients suffering from endogenous mental depression [Carrol et al, 1976]. We have shown formerly that in patients with the alarm-depressive syndrome the inhibition by dexamethasone is increased due to the administration of tranquilizers – diazepam and phenazepam [Nuller and Ostroumova, 1980]. Therefore, in a number of colon cancer patients the effect of phenazepam was examined for the study of the means of the prophylaxis of postoperative complications.

MATERIALS AND METHODS

Sensitivity to dexamethasone was tested in 55 colon cancer patients and 36 stomach cancer patients (49 men, 42 women; average age 54). The control group consisted of 30 clinically healthy subjects (11 men, 19 women; aged 45–64, average age 51). In addition, a group of subjects without malignant tumors who had been hospitalized into the Institute of Oncology, was examined (24 subjects: 10 men, 14 women; aged 39–65, average age 52).

Dexamethasone was administered per os at the dosage of 0.5 mg at 11 pm; 11-hydroxycorticosteroid levels (11-HOCS) were determined by fluorimetric method [De Moor et al, 1960], and blood was sampled after fasting, at 9 am on the day of dexamethasone administration and at the same hour on the day after dexamethasone administration. The patients were considered dexamethasone-resistant if their blood level of 11-HOCS was lowered after dexamethasone by less than 40% or still exceeded 10 μg%.

All the patients under study were subjected to radical surgical treatment. In colon cancer patients the proctectomy was produced by means of abdominoanal resection or abdominoperineal extirpation, thus considering the surgical intervention approximately the same in both operations. In stomach cancer patients subtotal resection was produced; only two patients were gastrectomized. Parenteral feeding was not introduced after the operation.

Colon cancer patients were informed of the possible formation of the unnatural anus. The complications of "medium" severity were considered suppuration of the operative wound, cystitis, urethritis, urinary bladder atonia, flaccid healing of perineal operative wound, and thrombophlebitis. Peritonitis (without anastomosis sutural disjunction), focal pneumonia, myocardial infarction, pelvic fat phlegmons, fecal fistulization, and sepsis were considered "severe" complications. During the period of preparation for the operation 24 colon cancer patients were treated with phenazepam at the dosage of 1 mg 2–3 times a day for 7 days. The dexamethasone test was performed before and after the treatment.

RESULTS

As shown in Table I the results of dexamethasone test in patients with gastrointestinal cancer did not essentially differ from those in the hospital control group, ie, the subjects without malignant tumors who had been hospitalized into the oncological clinic. Stomach cancer patients at Stages III–IV of the disease showed a greater resistance to the inhibiting action of dexamethasone than those at Stages I–II (11-HOCS level after dexamethasone was 10.7 ± 0.62 and 6.4 ± 1.40 μg%, correspondingly, $P < 0.01$). However, all the patients examined in our Institute manifested a greater resistance to the inhibiting effect of dexamethasone as compared to those examined under ambulatory conditions. This means that in patients with malignant tumors the sensitivity to dexamethasone is most likely disturbed due to emotional stress caused by hospitalization into the specialized oncological clinic.

The analysis of the data during the course of the postoperative period showed that in patients with complications the sensitivity to dexamethasone before operation was lower than in those with a favorable postoperative course. The most pronounced changes were revealed in patients with "severe" complications resulting in death. Figure 1 shows the data on the incidence and severity of complications in the subjects with both good and unsatisfactory results of the dexamethasone suppression test. A considerably larger number of complications was observed in the patients resistant to dexamethasone action before the operation: All the terminal cases related to "severe" complications, had fallen into this group. Exceptions were three terminal cases, due to hemorrhage from a large vein during operation, pulmonary artery embolism on the day following the operation, and peritonitis resulting from sutural disjunction of in-

TABLE I. The Results of Dexamethasone Test in Patients with Gastrointestinal Cancer and in Control Subjects

Group	No. of cases	11-HOCS level (μg%) Basal	After dexamethasone	Inhibition (%)
Ambulatory control	30	14.8 ± 1.1	5.0 ± 0.9	−66
Hospital control	24	12.3 ± 0.9	8.0 ± 0.0	−35
Colon cancer				
The whole group	55	15.8 ± 0.6	9.8 ± 0.2	−38
Stage I	3	21.1 ± 4.4	6.5 ± 2.4	−70
Stage II	5	12.8 ± 1.1	6.4 ± 0.9	−50
Stage III	38	16.0 ± 0.9	11.0 ± 0.9	−31
Stage IV	9	15.9 ± 1.7	7.9 ± 1.0	−50
Without complications	27	15.6 ± 0.9	8.2 ± 1.1	−47
With complications (a + b + c)	25	15.7 ± 1.0	12.0 ± 1.2	−24
(a) "Medium"	8	16.7 ± 2.0	12.6 ± 3.0	−25
(b) "Severe"	9	16.7 ± 1.8	10.6 ± 1.7	−36
(c) Death cases	8	13.7 − 2.6	12.9 ± 2.0	−6
Stomach cancer				
The whole group	36	15.7 ± 0.7	9.5 ± 0.8	−39
Stage I	5	12.5 ± 2.8	5.8 ± 2.4	−54
Stage II	4	14.6 ± 1.3	7.3 ± 1.7	−50
Stage III	22	16.6 ± 1.1	10.5 ± 1.3	−37
Stage IV	5	15.9 ± 2.0	11.9 ± 2.5	−25
Without complications	23	15.7 ± 1.0	8.8 ± 1.2	−44
With complications (a + b + c)	10	15.8 ± 1.7	11.1 ± 2.0	−30
(a) "Medium"	5	18.4 ± 2.1	11.3 ± 3.3	−38
(b) "Severe"	2	12.4 ± 7.2	10.8 ± 6.3	−13
(c) Death cases	3	13.5 ± 4.9	10.9 ± 3.7	−19

TABLE II. The Results of Dexamethasone Test Before and After Phenazepam Administration in Colon Cancer Patients Before the Operation

	Dexamethasone-resistant patients					Dexamethasone-sensitive patients				
		11-HOCS level (μg%)					11-HOCS level (μg%)			
Group	No. of cases	Basal	After dexa-methasone	Inhibition (%)	No. of complica-tions (%)	No. of cases	Basal	After dexa-methasone	Inhibition (%)	No. of complica-tions (%)
All patients	31	16.5 ± 0.9	12.2 ± 0.8	−26	65	21	15.5 ± 0.9	5.3 ± 0.5	−66	24
Patients before phenazepam administration	15	19.5 ± 2.6	16.9 ± 1.9	−13	–	9	19.6 ± 1.9	6.0 ± 0.5	−69	–
Patients after phenazepam administration	15	16.2 ± 1.3	11.5 ± 1.3 $P < 0.05$	−29	33	9	16.7 ± 1.6	6.4 ± 0.8	−62	22

terintestinal anastomosis. It is obvious that these complications, to a considerably smaller extent, depended on the status of a patient before the operation. All three previously mentioned patients showed good dexamethasone test results.

Tranquilizers were used for the treatment of colon cancer patients. As we thought, such tumor localization induced in patients the most pronounced alarm state, which is caused by traumatic operation abruptly disturbing the function of the intestine [Simonov and Gnezdilov, 1978; Druss et al, 1968; Gnezdilov et al, 1977]. Table II shows that in dexamethasone-sensitive patients, phenazepam did not influence the results of dexamethasone test and the number of postoperative complications. On the contrary, in dexamethasone-resistant patients the drug essentially improved the results of the test and decreased the number of postoperative complications (see Fig. 1).

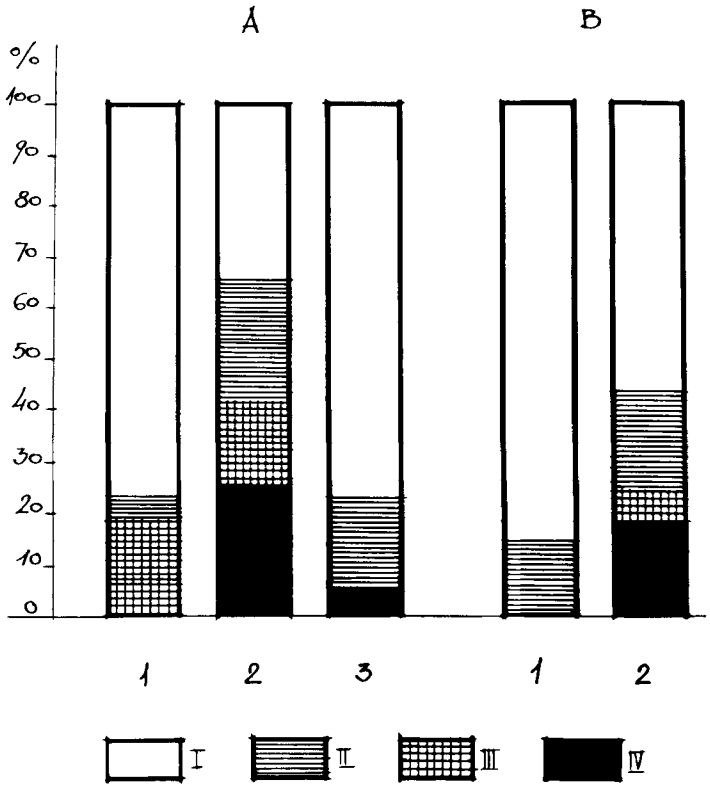

Fig. 1. The number of postoperative complications in patients with gastrointestinal cancer according to the results of dexamethasone test: The effect of phenazepam. (A) Colon cancer patients; (B) stomach cancer patients; (1) dexamethasone-sensitive patients; (2) dexamethasone-resistant patients; (3) dexamethasone-resistant colon cancer patients after treatment with phenazepam; (I) without complications; (II) "medium" complications; (III) "severe" complications; (IV) deaths.

DISCUSSION

During the preparation of patients for the operation, approximately half of gastrointestinal cancer patients have shown resistance to the inhibiting effect of dexamethasone. This is evidence for the impairment of regulation by feedback mechanism, which, according to the classification by Dilman, relates to the central type of homeostatic failure [Dilman, 1974, 1978]. An age-associated process leading to regular disturbances of homeostasis is the basis of the elevation of hypothalamic threshold of sensitivity to the inhibiting effect of glucocorticoids [Dilman, 1978, 1979; Dilman et al, 1979a]. We have also found that some localizations of tumors increase the resistance of patients to dexamethasone as compared to the corresponding control age group [Dilman, 1974; Dilman et al, 1979b; Ostroumova et al, 1978; Ostroumova et al, 1979; Bishop and Ross, 1970; Saez, 1974]. A number of studies show that the resistance to dexamethasone effect correlates with unfavorable prognosis in cancer patients [Bishop and Ross, 1970; Saez, 1974]. A similar phenomenon is observed in stomach cancer patients who show more pronounced disturbances of dexamethasone test results at Stages III–IV of the disease, than at Stages I–II. The correlation is found between lipid and carbohydrate disturbances on the one hand, and insufficient decrease in 11-HOCS level on the other, after the administration of dexamethasone in endometrial cancer patients [Ostroumova et al, 1979]. It is quite possible that both factors, age and metabolic background caused by tumor growth, produce their effect on the results of dexamethasone test in the patients suffering from gastrointestinal cancer.

It is also of interest that the elevation of hypothalamic threshold of sensitivity to the inhibiting action of glucocorticoids is characteristic for the patients with endogenous mental depression [Carrol et al, 1976; Nuller and Ostroumova, 1980]. An important role in its pathogenesis is played by the deficiency of neuromediators—serotonin and noradrenaline—in the central nervous system [Coppen, 1967; Maas, 1975; Shildkraut, 1965]. The excessive emotional stress causes the exhaustion of monoamines in the brain on the one hand [Bliss and Zwanzinger, 1966; De Pasquale et al, 1977] and provokes depres-

sive fits on the other [Nuller, 1976]. A comparison of these data allows us to suggest that the resistance of the hypothalamus to the inhibition by glucocorticoids should be a result of monoaminergic processes' deficiency in the brain, caused by strong emotional stress or other reasons, in particular, protein deficiency registered in stomach cancer patients. The practice of the treatment of depressive patients shows that sensitivity to dexamethasone is essentially improved by the administration of either L-tryptophan and L-Dopa (serotonin and noradrenaline precursors), or tranquilizing drugs—diazepam and phenazepam [Ostroumova et al, 1978; Nuller and Ostroumova, 1980].

In dexamethasone-resistant patients suffering from colon cancer, phenazepam not only improves the results of the dexamethasone test, but also decreases a number of postoperative complications. Strong emotional stress endured by these patients before the operation seems to be an important component of homeostatic regulation deficiency. Thus, pharmacological correction of hypothalamic threshold of sensitivity in oncological patients during preoperative period is indispensable for the prophylaxis of certain pathological states under the conditions of chronic stress.

REFERENCES

Bishop MS, Ross EJ (1970) Adrenocortical activity in disseminated malignant disease in relation to prognosis. Brit J Cancer, 24: 719–725.

Bliss EL, Zwanzinger J (1966) Brain amines and emotional stress. J Psychiat Res 4, 1P:189–198.

Carrol BJ, Curtis GC, Mendels J (1976) Neuroendocrine regulation in depression. 11. Discrimination of depressed from nondepressed patients. Arch Gen Psychiat, 33:1051–1058.

Coppen A (1967): The biochemistry of affective disorders. Brit J Psychiat 113:1237–1264.

De Moor P, Steno O, Raskin M, Hendriks A (1960): Fluorimetric determination of free plasma 11-hydroxycorticosteroids in man. Acta Endocrinol 33:297–307.

De Pasquale A, Costa G, Scapagnato C (1977): Noradrenalina e serotonina cerebrali dopo stressa andigeno nel ratto: Influenza della resina di "Cannabis." Riv Farmacol Ter 1:71–78.

Dilman VM (1971): Age-associated elevation of hypothalamic threshold of feedback control and its role in development, aging and disease. Lancet 1:1211.

Dilman VM (1974): "Endocrinological Oncology." Leningrad: "Medizina" Publication.

Dilman VM (1978): Aging, metabolic immunodepression and carcinogenesis. Mech Aging Develop 8:153–173.

Dilman VM (1979): Hypothalamic mechanisms of aging and of specific age pathology. V. A model for the mechanism of human specific age pathology and natural death. Exp Gerontol 14:287–300.

Dilman VM, Lapin IP, Oxenkrug GF (1979a): Serotonin and aging. In Essman B (ed): "Serotonin in Health and Disease." vol. 5, pp 111–212.

Dilman VM, Ostroumova MN, Tsyrlina EV (1979b): Hypothalamic mechanisms of aging and of specific age pathology. 2. On the sensitivity threshold of hypothalamo-pituitary complex to homeostatic stimuli in adaptive homeostasis. Exp Gerontol 14: 175–181.

Druss RG, O'Connor JF, Prudden JF, Stern LO (1968): Psychological response to colectomy. Arch. Gen Psychiat 18:53–59.

Gerasimenko VN, Borisov IV (1974): Psychotherapy in oncological practice. Clin Med 9:48–50 (in Russian).

Gnezdilov AV, Alexandrin GP, Simonov NN, Evtuikhin AI, Bobrov YuF (1977): The role of stress factor in the postoperative course of patients with rectal cancer. Surg Oncol 9:517–523.

Leme-Lopes G (1973): Depression states and cancer. In: "Masked Depression." Vienna: Stutgart, pp 212–213.

Maas JW (1975): Biogenic amines and depression. Arch Gen Psychiat 32:1357–1363.

Nuller YuL (1976): Some pathogenic mechanisms relating to the classification of manic-depressive psychoses. J Neuropathol Psychiat 5: 717–723 (in Russian).

Nuller YuL, Ostroumova MN (1980): Resistance to inhibiting effect of dexamethasone in patients with endogenous depression. Acta Psychiat Scand 61:169–177.

Ostroumova MN, Krylova NV, Vishnevski AS (1979): Regulatory disturbances of adrenal cortex function in endometrial cancer patients. Prob Oncol 5:62–63 (in Russian).

Ostroumova MN, Tsyrlina EV, Nuller YuL, Smirnov VM, Petushkov EP, Dilman VM (1978): Age-associated dynamics of regulation in adaptive homeostat and age-associated pathology. Human Physiol 4:625–635 (in Russian).

Saez S (1974): Corticotrophin secretion in relation to breast cancer. In Stoll BA (ed): "Mammary Cancer and Neuroendocrine Therapy." London: Butterworths and Co., pp 101–122.

Simonov NN, Gnezdilov AV (1978): Therapy of psychogenic disturbances in patients with gastrointestinal cancer. Materials of All-Union Symposium "Modernization of the Methods of Medical Rehabilitation of Cancer Patients." Leningrad: pp 77–79.

Shildkraut JJ (1965): The catecholamine hypothesis of affective disorders. Amer J Psychiat 122:509–522.