

# EFFECT OF INTRAVENOUS INFUSION OF SODIUM BICARBONATE ON ELECTROENCEPHALOGRAM AND ERYTHROCYTE ULTRASTRUCTURE IN CANCER PATIENTS

I. G. Davydova, V. L. Kassil',  
N. T. Raikhlin, and N. A. Filippova

UDC 616.006-052.616.831-073

**KEY WORDS:** malignant tumors, electroencephalogram, alkalosis, erythrocytes, ultrastructure.

It was shown previously [1, 2] that the reaction of the electroencephalogram (EEG) to respiratory alkalosis, induced by voluntary hyperventilation with a fall of  $p\text{CO}_2$  of the blood, is distorted in patients with malignant tumors in various situations.

According to observations made during a study of the effect of hypocapnia on CNS function, hyperventilation is always accompanied by worsening of the EEG, as a rule with the appearance of slow waves [5-8]. As our own studies have shown, in patients with malignant neoplasms respiratory alkalosis was accompanied by normalization of the abnormal background EEG. Differences also were found in the EEG changes depending on the extent of spread

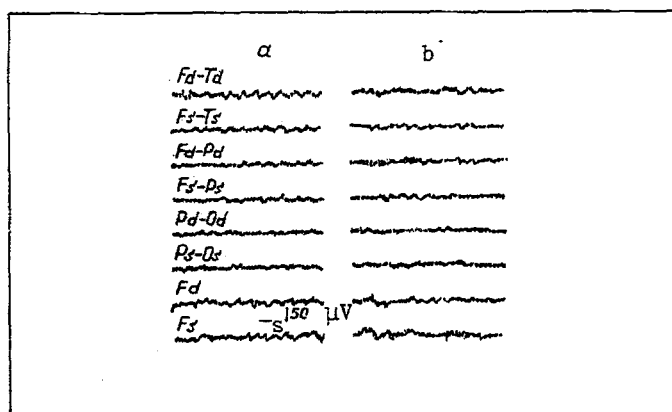


Fig. 1. EEG of patient P, a man aged 64 years (diagnosis: carcinoma of the stomach  $T_3N_0M_0$ ): a) before infusion of sodium bicarbonate; in capillary blood pH 7.35; BE = -1.7 mmoles/liter; EEG shows polymorphic flat slow activity, most marked in central and frontal derivations; b) after infusion of sodium bicarbonate; in capillary blood pH 7.44; BE = +3.9 mmoles/liter; normalization of EEG with appearance of well-marked alpha-rhythm. EEF derivations: FT) fronto-temporal; FT) fronto-parietal; PO) parieto-occipital; F) frontal with reference electrode attached to the ear; d, s) right and left hemispheres.

Oncologic Research Center, Moscow. (Presented by Academician N. N. Trapeznikov, Academy of Medical Sciences. Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 113, No. 4, pp. 352-355, April, 1992. Original article submitted July 8, 1991.



**Fig. 2.** Ultrastructure of erythrocytes in control and in cancer patients with no distant metastases: a) erythrocytes of patient K, a man aged 22 years (diagnosis: hydatid cyst of the liver) before infusion of sodium bicarbonate: relatively monomorphic with homogeneous contents and a smooth membrane, 9000 $\times$ ; b) erythrocytes of patient T, a man aged 64 years (diagnosis: carcinoma of stomach T<sub>3</sub>N<sub>0</sub>M<sub>0</sub>) before infusion of sodium bicarbonate: erythrocytic aggregate, 5000 $\times$ ; c) erythrocytes of the same patient: condensation of the juxtamembranous layer around perimeter of erythrocytes, 15,000 $\times$ ; d) erythrocytes of same patient after infusion of sodium bicarbonate; widening of spaces between erythrocytes in aggregate, 6000 $\times$ .

TABLE 1. Time Course of Blood Gases and Acid-Base Balance during Investigation

Stages of investigation	Patients with malignant neoplasms (n = 23) (M ± m)				Control group (n = 4)			
	pH	pCO <sub>2</sub> , mm Hg	BE, mmoles/liter	pO <sub>2</sub> , mm Hg	pH	pCO <sub>2</sub> , mm Hg	BE, mmoles/liter	pO <sub>2</sub> , mm Hg
Before infusion of sodium bicarbonate	7.41±0.008	37.8±0.96	0.19±0.13	72.9±2.1	7.34—7.39	43.0—46.2	+0.2—+2.0	60.0—69.5
At end of infusion	7.48±0.006*	40.9±0.7	6.3±0.55*	68.9±1.6	7.43—7.45	41.8—49.1	+4.2—+4.5	74.7—77.2
At end of hyperventilation	7.56±0.011*	29.0±0.8*	4.4±0.75*	76.8±2.5	7.45—7.48	23.0—26.0	-3.8—+1.4	75.0—79.0

Note. Asterisk indicates data for which  $p < 0.05$  compared with initial values.

of the tumor [3]. The results can be explained by the presence of generalized intracellular acidosis in cancer patients, which can be temporarily abolished or reduced (depending on the stage of the disease) by artificial respiratory (gaseous) alkalosis of the blood.

The aim of this investigation was to study the time course of the EEG in cancer patients, in whom a state of temporary metabolic (nongaseous) alkalosis was created. Considering that metabolic alkalosis was created in the blood, it was considered desirable to undertake a parallel study of erythrocyte ultrastructure.

## METHODS

Altogether 23 patients with malignant tumors in various situations and of different histogenesis (carcinoma of the stomach — 16; of the liver — 2; pancreas, sigmoid colon, ampulla of Vater, larynx, and leiomyosarcoma of the stomach — 1 of each) were studied. No metastases were found in 9 patients, in 10 metastases were located in regional lymph nodes, and in 4 patients distant metastases were present. The average age of the patients was  $52.1 \pm 2.6$  years; there were 11 men and 12 women. In all cases the diagnosis was confirmed histologically. The control group consisted of 4 patients with benign diseases: hydatid cyst of the liver, chronic pancreatitis, retroperitoneal keratoma, chemodectoma of the neck. Their ages varied from 18 to 36 years and there were two men and two women. Patients with tumors and accompanying diseases of the CNS and respiratory organs, and also with diseases of the blood system were not investigated. All subjects received 4.2% sodium bicarbonate solution by intravenous drip in a dose of 3-4 ml/kg over a period of 10-12 min. After the end of infusion, the patients breathed deeply for 4 min at a rate of 16-18 cycles/min and with a tidal air value close to the vital capacity of the lungs. Before the beginning of injection of sodium bicarbonate and at its end, as well as during the period of hyperventilation, values of pO<sub>2</sub>, pCO<sub>2</sub>, and the acid-base balance (ABB) of the capillary blood were determined by the micro-Astrup method on an ABC-1 apparatus (Radiometer, Denmark) or AVL-940 automatic gas analyzer (Switzerland); the EEG was recorded on an 8-channel ink-writing electroencephalograph (Nihon Kohden, Japan).

In 8 patients (5 with malignant neoplasms and 3 from the control group) erythrocyte ultrastructure was studied in peripheral blood taken from the cubital vein. The blood cells were fractionated in a Ficoll—Verografin density gradient ( $\rho = 1.077$ ) at 400 g for 30 min [4]. The residue was fixed for 1 h in 2.5% glutaraldehyde solution in phosphate buffer (pH 7.2-7.4). After dehydration the material was embedded in Epon-812. Sections were cut on an LKB-111 ultramicrotome (Sweden), stained with lead citrate and uranyl acetate, and examined and photographed in the JEM-1200 electron microscope (JEOL, Japan).

## RESULTS

All patients tolerated injection of sodium bicarbonate easily and without complications, but some patients with malignant tumors noted an improvement in their general state and "clarity in the head."

The time course of the gas partial pressures and ABB of the blood of the patients tested is illustrated in Table 1. Injection of sodium bicarbonate led to a significant shift of pH and of the base excess (BE) toward the alkaline side in all subjects, i.e., they developed metabolic alkalosis.

An electroencephalographic study of one of the four patients in the control group revealed no abnormality, one patient had moderate diffuse changes in background activity, and the other two patients had local as well as diffuse changes. The EEG showed no change in electrical activity of the brain after injection of sodium bicarbonate with time.

The EEG of patients with malignant tumors was characterized by multiple disturbances of brain electrical activity (Fig. 1a). These include disturbances of the alpha-rhythm in all patients, the presence of slow theta- or theta- and delta-waves (21 of 23 cases — 91.3%, including 10 in whom slow waves were combined with fast and pointed waves), a high frequency of interhemispheric asymmetry (18 of 23 cases — 78.3%), and absence of metastases in the brain. These changes were evidence of disturbances in the diencephalic or mesencephalic region and of diffuse and local cortical changes. Changes in the background EEG in patients with a distant metastases were much more marked. After infusion of sodium bicarbonate, all patients of this group showed a positive trend of brain electrical activity, characteristics of the alpha-rhythm improved, the number of slow waves decreased, and interhemispheric asymmetry became less marked (Fig. 1b). With the same shift of pH toward the alkaline side, normalization of the EEG was more pronounced in patients with absence of distant metastases.

Incidentally, during voluntary hyperventilation after the end of sodium bicarbonate injection the dynamics of the EEG in patients with malignant tumors became normal (negative) in character, although before infusion, hyperventilation led to improvement of brain electrical activity in 69.6% of these same patients, no trend was observed in 21.7%, and only in 8.7% was hyperventilation accompanied by a negative (normal) trend of the EEG, associated with better tolerance of deep hypocapnia.

As already mentioned, the erythrocytes of 8 patients were subjected to electron microscopy, accompanied by a control group of 3 cases. Erythrocytes in the control group were moderately polymorphic and consisted mainly of rod-shaped discs with a smooth edge. Often the erythrocytes were biconcave with homogeneous contents and a smooth membrane. They lay some distance apart, or were in contact with a small part of their surface (Fig. 2a). After infusion of sodium bicarbonate no visible changes occurred in the erythrocytes.

Investigation of the erythrocytes of cancer patients with no distant metastases revealed a considerable number of erythrocytic aggregates of different sizes and shapes (Fig. 2b). On the whole the erythrocytes were characterized by marked polymorphism: there were many cells with asymmetrical smoothing of their concave outline, with an uneven surface, and with an asymmetrically curved pole. Many erythrocytes showed considerable condensation of juxtamembranous material around their whole perimeter (Fig. 2c). After infusion of sodium bicarbonate a tendency was observed for separation of the erythrocytes in the aggregates to take place (Fig. 2d); condensation of the juxtamembranous layer disappeared from some erythrocytes, whereas in others the thickness of this condensation was reduced or it was no longer prominent around the whole perimeter of the cell.

In cancer patients with distant metastases the general picture differed only a little from that described above: erythrocytic aggregates were observed, erythrocytes of the most varied shape were found, and the juxtamembranous layer was condensed in many cells. After infusion of sodium bicarbonate no significant changes were observed in the picture, although a tendency toward disaggregation of the erythrocytes could be detected.

The creation of temporary metabolic alkalosis was not accompanied by any changes in the EEG or erythrocyte ultrastructure in patients of the control group, but caused improvement of the parameters studied in patients with malignant neoplasms. These findings are in agreement with a previous hypothesis [1-3], that patients with cancer have intracellular metabolic acidosis, which is generalized in character. Creation of metabolic alkalosis in the blood leads to temporary restoration of normal brain electrical activity and normal erythrocyte ultrastructure in cancer patients.

#### LITERATURE CITED

1. I. G. Davydova and V. L. Kassil', *Dokl. Akad. Nauk SSSR*, **285**, No. 3, 724 (1985).
2. I. G. Davydova and V. L. Kassil', *Dokl. Akad. Nauk SSSR*, **289**, No. 4, 1016 (1986).

3. I. G. Davydova and V. L. Kassil', *Metastasization of Malignant Tumors: New Approaches* [in Russian], Kiev (1987), pp. 41-42.
4. A. Boyum, *Scand. J. Clin. Lab. Invest.*, **21**, No. 1, 77 (1968).
5. H. Davis and W. Wallace, *Arch. Neurol. Psychiat.*, **47**, No. 4, 606 (1942).
6. O. Förster, *Abl. ges. Neurol. Psychiat.*, **38**, 289 (1924).
7. R. Gerard, *Am. Neurol. Ass.*, **62**, No. 1, 49 (1936).
8. F. A. Gibbs, D. Williams, and E. L. Gibbs, *J. Neurophysiol.*, **3**, No. 1, 49 (1940).