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# TREATMENT OF PRIMARY BRAIN TUMORS WITH SEHYDRIN[1]

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Abstract. *The results of Sehydrin administration in 46 patients with malignant and 6 patients with benign tumors of the brain are presented. Pronounced therapeutic effect for the whole group was 63.5% and 73%, if partial regression of neurological symptoms in the entire brain and separate foci is considered. The percentages for patients with malignant tumors only were 61 and 71.1, respectively. Since Sehydrin has virtually no significant untoward side-effects, it is considered a most safe medication for the management of brain tumors. It is recommended in cases of inoperable tumor and for post-operative adjuvant chemotherapy with a view toward extending the patient's survival time and improving the quality of life.*

The treatment of primary central nervous system tumors still represents a very difficult challenge. Neither adjuvant chemotherapy after surgery plus radiation treatment nor cytostatic [cytotoxic] therapy for inoperable cancer result in positive response or prolong survival time. The principal reasons for low efficacy in the treatment of brain tumors are: impenetrability of the blood-brain barrier by most cytostatics; the cytostatics have low lipophilic activity; and the specific blood circulation of most brain tumor tissues. As a result, in many cases the systemic use of cytostatics in "active" concentrations is not effective for penetration into tumors. Also important is that most brain tumors are low-grade and of low sensitivity to cytostatics. According to the most complete literature reviews, only few cytostatics from the nitrosourea group--CCNU (lomustine), BCNU (carmustine), HCNU (nidran)--as well as natulan (5), which can penetrate the blood-brain barrier, are effective in the treatment of primary brain tumors. Even attempts to combine some of the most active medications (natulan + lomustine + vincristine) are not successful (6). Generally, gliomas (with the exception of rare epiphyseal tumors that can be treated with cisplatin, bleomycin and others) are the most resistant to cytostatics, including natulan and nitrosourea derivatives (3,7).

But even small, so-called "active," cytostatic effects are obtained by persistant use of large dosages that cause too severe side effects--vomiting, myelodepression, etc. Therefore an effective treatment for inoperable brain tumors or for prevention of recurrence represents an actual problem that is still unresolved. Our investigations purposed to increase the effectiveness of brain tumor therapy by use of Sehydrin. Previous data on the effect of Sehydrin on tumors of different sites (10.8%

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[1]The medication hydrazine sulfate, following approval for clinical use, was named Sehydrin by the special nomenclature commission of the Pharmacology Committee, dated January 8, 1990.

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antitumor effect, 40% tumor stabilization effect, 46.6% symptom normalization effect) had demonstrated the feasibility of use of this drug in terminal patients (2). However, Sehydrin had never before been administered in patients with primary brain cancer. We were encouraged by the fact that Sehydrin was neurophilic and had been demonstrated to be most effective in peripheral neuroblastoma. From the beginning we hypothesized a positive response to Sehydrin based on a specific mechanism of action (different from other drugs)--monoamine oxidase inhibition that caused production of adrenalin, serotonin and other mediators (1,4).

Clinical investigations were performed at the Neurosurgical Department of the Scientific Research Institute of Experimental Medicine (St. Petersburg), the A. L. Polenov Neurosurgical Institute (St. Petersburg), the Department of Neurosurgery of the Mariinskaya Hosptial (St. Petersburg), and at the Vilnius Institute of Oncology (Lithuania).

Methods and Materials. Sehydrin was used as a drug in patients with primary inoperable brain tumors and also as a preventive for recurrence after surgery. 52 patients from ages 6 to 62 years were investigated. Most of them (46 out of 52) had high-grade malignancies with recurrence after surgery. The usual life expectancy of such patients is no more than 6 months after surgery. Partial tumor resections prior to Sehydrin therapy were carried out in 38 patients with glioblastoma and malignant astrocytoma. All these patients had acute neurotoxic and neurological symptoms--increased intracranial pressure, seizures, severe headaches, sensory and motor disorders. Five out of 6 patients with non-malignant tumors also had similar symptoms after surgery.

Sehydrin was administered in 60 mg enteric-coated tablets 3 times daily for 30-40 days (in all 5.4 grams to 7.2 grams per course). Children 6 to 12 years old were given 30 mg 3 times daily (2.7 grams to 3.6 grams per course). Repetitive courses (a total of 5 to 20) were given to patients with primary inoperable cancer (anaplastic astrocytoma, glioblastoma and others) and also to patients with a clinical absence of progressive disease or to patients with significant positive effect, with drug-free intervals of from 2 to 4 weeks. Sehydrin at the same dosage basis was also used as adjuvant therapy after surgery with or without radiation.

Because of an absence of significant side effects of Sehydrin, there was no need for special laboratory control studies. But in order to obviate toxic side effects, it was necessary for patients taking Sehydrin to avoid the use of alcohol and barbiturates (even in small dosages).

To evaluate both therapeutic effects and side effects during the course of Sehydrin administration, the patients' psychoneurological status, electroencephalogram, electrocardiogram and, from time to time, brain tomography and spinal fluid pressure and contents were examined. Routine analyses of blood, urine and kidney function were also performed.

One of the most important criteria for drug evaluation (recommended by the 2nd Conference of Neurosurgeons, USSR) was the effect of Sehydrin on survival time. It was considered that a treatment is successful if a cancer patient's survival was prolonged more than 6 months after diagnosis. Also evaluated were the course of rehabilitation (clinical improvement) and the period of rehabilitation without recurrence.

Therapeutic Effect of Sehydrin on Malignant and Non-Malignant Brain Tumors

| Tumor Type | No. of Patients | Regression of Neurological Symptoms | | No Effect or with Tumor Progression |
|---|---|---|---|---|
| | | Complete | Partial | |
| Glioblastoma | 38 | 24 | 3 | 11 |
| Undifferentiated astrocytoma | 4 | 2 | 1 | 1 |
| Malignant meningioma | 4 | 2 | 1 | 1 |
| Astrocytoma (benign) | 3 | 3 | | |
| Ependymoma (benign) | 1 | 1 | | |
| Meningioma (benign) | 1 | | | 1 |
| Acoustic neuroma, giant (benign) | 1 | 1 | | |
| Totals | 52 | 33 | 5 | 14 |
| % | (100) | (63.5) | (9.6) | (26.9) |

Results and Discussion. Significant therapeutic effect (complete regression of neurological symptoms) in the entire group of brain tumor patients occurred in a high percentage of patients, 63.5%--increasing to 73.1% if partial regression of neurological symptoms is included (see Table). For patients with malignant tumors (46 patients) the response rates were similar--60.8% and 71.7%, respectively. These results are superior to those for the nitrosourea compounds.

In 38 patients with glioblastomas Sehydrin administration resulted in at least tumor stabilization and tumor regression in 27 (71%). Regression of symptoms and improvement in the general well-being were observed as follows: a decrease in headaches and dyspepsia, and a partial restoration of cranial nerve function as well as sensory and motor function. Survival time was increased from 9 to 16 months (average, 13±0.6 months)--twice the survival as after usual surgery. Eight (30%) of those 27 patients survived more than 19 months and one patient--more than 30 months. Sehydrin therapy was ineffective in only 11 of 38 patients with malignant glioblastomas; these patients died from tumor progression in 4 to 5 months after surgery.

patients had regression of symptoms lasting 11 months, with the institution of 2 courses of Sehydrin; another patient (who had tumor progression after surgery, radiation and chemotherapy) obtained 18 months of regression of symptoms, with 5 courses of Sehydrin. In a group of 6 patients with non-malignant tumors, 5 had complete response (tumor regression and regression of neurological symptoms) lasting 5 years, as a result of 8 courses of Sehydrin with a 5 to 7 month interval between courses (one patient with progressive ependymoma of the inferior IVth ventricle that recurred 11 years after surgery and 4 courses of radiation therapy, had a complete response).

Initial manifestations of response to Sehydrin therapy were already apparent by the second week of treatment, with significant improvement in the general condition and varying degrees of symptomatic regression.

The following clinical examples serve to illustrate the effects of Sehydrin treatment on central nervous system (brain) tumors.

Case 1. Patient S., a 10-year old male, was treated at the Polenov Neurosurgery Institute, with a diagnosis of ciliary protoplasmic astrocytoma of the left subcortical ganglions, with penetration into the IIIrd (left-sided) ventricle. On surgery (craniotomy of the fronto-temporal area), only part of the tumor was removed. After surgery, the patient received 8 courses of Sehydrin without complications or side effects, over a period of 5 years. The neurological status--regression of symptoms, EEG analysis and the patient's overall condition indicated an absence of tumor progression during all this time. (He was able to continue his studies in high school.)

Case 2. Patient R., a 57-year old female, was treated at the Neurosurgical Department of the Mariinskaya Hospital, with a diagnosis of recurrent glioblastoma of the right parietal region. She exhibited acute symptoms of brain damage, with especially severe headaches, as a result of tumor progression. Four courses of Sehydrin therapy resulted in a significant improvement in the patient's general condition, in particular, regression of headaches, which permitted surgery to remove the recurrent tumor. At operation the encapsulated tumor was removed. There were no symptoms of tumor recurrence, or side effects, during a period of 9 months after 2 prophylactic, postoperative courses of Sehydrin therapy.

Case 3. Patient K., a 48-year old female, was treated at the Neurosurgical Department of the Scientific Research Institute of Experimental Medicine. At the time of admission she was in very critical condition with acute disorders of the psyche (frontal lobe origin). Her symptoms included hypertensive headache, ataxia, psychic disorders--which had sharply increased in the months previously. Because of progressive symptoms, surgery was performed (craniotomy of the left fronto-temporal lobe, partial decompression and tumor excision). Microscopic analysis of the tumor proved it to be a malignant (undifferentiated) astrocytoma. Following surgery, the patient's condition remained very critical: acute psychic disorders, hallucinations and psychomotor excitement. Sehydrin treatment was started on the 4th day after surgery at the usual dosage regimen. Within 2 days the first manifestations of regression of psychic disorders were noted, hallucinations and headaches disappeared, the patient commenced contact with people and a sense of orientation appeared. In the next days sleep, mood and appetite began to normalize. From the 10th day of Sehydrin treatment the patient's psychic status and mood completely normalized. On the 24th day of Sehydrin therapy she left the clinic in good condition. The patient

was observed over the next 10 months, during which time repeated courses of Sehydrin were administered; no recurrences were noted.

It has become obvious that Sehydrin has many advantages over presently used nitrosourea compounds (not only by virtue of therapeutic effects but also because of an absence of side effects, even after multiple, repeated courses). No myelodepression was observed. Routine electrocardiographic and laboratory tests in various studies revealed no disorders in liver, kidney, cardiovascular and endocrine function as a result of Sehydrin therapy. Also no digestive tract disorders were noted, and only 5% of patients had nausea only at the beginning of courses.

Therefore, Sehydrin can be considered a most safe medication for the treatment of brain tumors (malignant and non-malignant). It is advisable to use Sehydrin treatment for both inoperable tumors and for adjuvant chemotherapy following radical or palliative surgery, in order to prolong patient survival and to improve the quality of life for this category of patients.

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