Treatment of Meningeal Leukemia With Pyrimethamine

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Pyrimethamine, a substituted pyrimidine with potent folate antagonistic properties, was given orally to treat two episodes of meningeal leukemia in a long-term survivor with acute myeloblastic leukemia. Remissions of seven and at least 6 mo duration were obtained on the two occasions. Spinal fluid concentrations of pyrimethamine were 10–25% of the simultaneous plasma concentrations. Considerations regarding lipid solubility, body distribution, and easily reversible toxicity of pyrimethamine suggest that further therapeutic trials are warranted, especially in childhood lymphoblastic leukemia.

Since the work of Farber, folic acid antagonists, particularly methotrexate, have attained a recognized place in the therapy of certain neoplastic disorders, especially in choriocarcinoma in the female and acute lymphoblastic leukemia in childhood. With improved survival in childhood-type acute lymphoblastic leukemia, meningeal leukemia has become a significant cause of morbidity in the disease, occurring despite control of the leukemia in bone marrow and peripheral blood, and tending to occur more frequently in longer survivors. The mainstay of therapy for meningeal leukemia at present is intrathecal administration of methotrexate, because neither methotrexate nor other cytotoxic agents in common use are capable of crossing the blood-brain barrier to any significant extent. External irradiation of the central nervous system has also been used. There are obvious shortcomings to each of these forms of therapy.
Pyrimethamine, a substituted pyrimidine used in the chemoprophylaxis and therapy of malaria and in the therapy of toxoplasmosis, acts as a folic acid antagonist. That pyrimethamine may cross the blood-brain barrier is indicated by its accumulation in the brain of rhesus monkeys, and by demonstration of its central nervous system toxicity in man and animals. Therefore, investigation of the effectiveness of oral pyrimethamine in meningeal leukemia appeared worthwhile. Our experience with one patient whose clinical course made him uniquely suitable for such a trial constitutes the basis for this report.

CASE REPORT

A 36-yr-old man was found to have subleukemic acute myeloblastic leukemia in 1964. A complete peripheral blood and bone marrow remission, obtained with 6-mercaptopurine (6-MP) and prednisone, was maintained with 25–50 mg 6-MP daily until early 1969, when transient episodes of generalized headache occurred, associated with variable neurological signs and symptoms, including visual and speech defects, vomiting, hemiparesis, and hemihypesthesia. Meningeal leukemia was considered, but was not further pursued because of the transient nature of the episodes. Admission to the University of Alabama Hospital became necessary in July 1969, because of bilateral leg pain for 6 wk and leg weakness for 24 hr. Physical examination revealed bilateral papilledema, diminished deep tendon reflexes, and marked lower extremity weakness with inability to walk. Hemogram and bone marrow examination were normal.

Neurosurgical evaluation including ventriculograms demonstrated communicating hydrocephalus with adhesive arachnoiditis. Ventricular fluid contained 156 WBC/cu mm, 96% of which were blasts, many containing Auer rods. Fluid protein was 83 mg/100 ml, and glucose was 90 mg/100 ml. A synthetic subcutaneous reservoir with ventricular shunts was inserted, and methotrexate, 0.2 mg/kg body weight, was administered via the reservoir every other day. After four doses of methotrexate by this route the shunts became infected, requiring removal of the reservoir and institution of antibiotic therapy. The bacterial meningitis was successfully treated, but mental deterioration with agitated psychotic behavior ensued. Lumbar puncture became very difficult, and therapy with oral pyrimethamine was instituted, 75 mg daily for 4 days, then 100 mg daily. After 5 days of pyrimethamine therapy, hallucinations and mental confusion had cleared, and after 8 days the patient became fully ambulatory. At discharge, after 11 days of pyrimethamine, the spinal fluid contained 16 WBC/cu mm; 13 lymphocytes, two blasts, and one neutrophil. CSF glucose was 68 mg/100 ml and protein was 485 mg/100 ml.

Symptomatic thrombocytopenia necessitated termination of pyrimethamine therapy and administration of folinic acid after 26 days of therapy. Papilledema cleared, and the patient remained without symptoms with normal hemograms for 7 mo.

In February 1970, readmission to the hospital became necessary after the patient had a major motor seizure, followed by confusion, vomiting, and headache. Physical findings were limited to fever, somnolence, combativeness, and moderate nuchal rigidity without papilledema. Spinal fluid was cloudy and xanthochromic and contained 1380 WBC/cu mm, 95% of which were blasts, many containing Auer rods (Fig. 1). Spinal fluid protein was 320 mg/100 ml; glucose was 69 mg/100 ml. Hemogram was normal. Pyrimethamine (300 mg initially, then 150 mg daily) was given orally.

Within a few hours after the initial dose of pyrimethamine, the patient's mental status showed significant improvement. He became afebrile within 24 hr, and a course of continued improvement followed, allowing discharge after 9 days of therapy. After 15 days of therapy, leukopenia and thrombocytopenia necessitated terminating pyrimethamine therapy and giving parenteral folinic acid. A subsequent 5-day course of pyrimethamine, 200 mg daily, was given for headache. Moderate thrombocytopenia resulted, and intramuscular folinic acid was again given. Maintenance therapy with 6-MP, 25 mg daily, was continued throughout the course of therapy.

The patient remained in robust health, with normal hemograms and bone marrow
examinations, for 6 mo. He then entered a relapse of the leukemia in the peripheral blood and bone marrow. He died in December 1970. No autopsy was obtained.

Figure 2 represents the course of events during and after the second course of therapy with pyrimethamine. The spinal fluid was never entirely free of leukemic cells.

**ASSAY METHODS AND RESULTS**

Pyrimethamine concentration in plasma and spinal fluid was estimated by means of a modification of procedures previously reported\(^{10,11}\) using *Streptococcus faecium* ATCC No. 8043. A standard curve is established by inoculating the bacteria in autoclaved tubes containing Difco folate assay medium, to which has been added a constant excess concentration of folic acid and varying known concentrations of pyrimethamine. Bacterial growth after 16-18 hr incubation at 37°C is monitored by optical density measurement at 650 nm. Bacterial growth is inversely proportional to pyrimethamine concentration. Standard curves are highly reproducible, and the assay is usable at concentrations of pyrimethamine as low as 10 ng/ml.

Relationships of pyrimethamine dose and plasma and spinal fluid concentration of the agent are indicated in Fig. 3. In general, spinal fluid pyrimethamine concentration was 10–25% of the corresponding plasma concentration. No evidence of accumulation of the drug in spinal fluid after repeated dose was found. Pyrimethamine was also cleared rapidly from the plasma, although there is other evidence of persistence of the drug, presumably in tissue.\(^{11}\)

**Fig. 2**—Relationships of pyrimethamine dose, hemograms, and spinal fluid findings during and after the second course of therapy.
Pyrimethamine [2,4-diamino-5-(p-chlorophenyl)-6-ethylpyrimidine] is one of a group of substituted pyrimidines known to be folic acid antagonists. Its main use has been in the chemoprophylaxis and therapy of malaria and in the therapy of toxoplasmosis, usually in combination with a sulfonamide. Although the effects of pyrimethamine upon the hematopoietic and other systems resemble those of methotrexate, its only use as a cytotoxic agent has been in the therapy of polycythemias.

Like methotrexate, pyrimethamine inhibits dihydrofolate reductase (DHFR), the enzyme responsible for reduction of oxidized folate compounds to the biologically active tetrahydroderivatives, the form of all the known folate coenzymes. The degree of binding of DHFR by pyrimethamine is not as great as that of methotrexate, which has been variously termed "non-competitive," "stoichiometric," or "pseudoirreversible." The extreme degree of DHFR binding by methotrexate, inhibiting formation of all folate coenzymes, must diminish the specificity of methotrexate for neoplastic cells, and probably accounts for the prolonged severe toxicity of methotrexate.

The toxic effects of pyrimethamine and methotrexate are similar. Both produce diarrhea, gastrointestinal ulceration, alopecia, and megaloblastosis with pancytopenia and bleeding. Pyrimethamine in severe intoxication (doses of 350-625 mg in children) also produces convulsions. However, the hematological and gastrointestinal toxicity of pyrimethamine is readily reversible at any time by the administration of folinic acid, whereas folinic acid must be given before or shortly after an overdose of methotrexate if toxicity is to be prevented or ameliorated.

Another important difference between methotrexate and pyrimethamine concerns body distribution of the agents. Penetration of methotrexate into cells and compartments depend upon the presence of a transport system for oxidized folates. It is well recognized, in particular, that methotrexate does not cross the blood-brain barrier in therapeutic amounts when given in tolerable oral or parenteral doses. Pyrimethamine, which is not charged at physiologic pH, is readily lipid-soluble, and is apparently capable of free entry into all cells and body compartments. Ability of pyrimethamine to traverse the blood-brain barrier is indicated by evidence already cited, and was demonstrated in the patient reported here.

Significant transport into the spinal fluid of pyrimethamine in this patient is indicated not only by the assay data obtained, but also by reduction in spinal...
fluid population of cells generally regarded as relatively resistant to folate antagonists. Methotrexate is usually not very effective in adult acute myelogenous leukemia involving blood and bone marrow, whereas it is usually effective when given intrathecally in meningeal myelogenous leukemia. The explanation for this discrepancy probably is the much higher drug concentration attained in spinal fluid after intrathecal injection than can be attained in plasma after tolerable oral or parenteral doses. Thus, the explanation for relative resistance of myeloblastic leukemia cells to methotrexate is more likely to be poor penetration of the drug into the cells, rather than inherent resistance of the cells to the drug. In this respect, pyrimethamine should have a distinct advantage over methotrexate.

Reference to Fig. 4, which is a plot of plasma vs. spinal fluid concentration of pyrimethamine, raises the question of a threshold of plasma concentration below which no drug enters the spinal fluid, and above which transport is readily accomplished. A limited number of observations on a single patient do not establish that a threshold exists, however. Further investigations in this regard are in progress. If a threshold exists, a different dosage schedule utilizing a large single dose rather than divided doses may be advantageous in further trials of therapy.

Although effective transport of pyrimethamine across the blood-brain barrier was demonstrated in this patient, experience with antibiotics and other drugs has indicated that substances normally excluded by the blood-brain barrier may penetrate the barrier in the presence of inflammation. Blood-brain barrier penetration by pyrimethamine in subjects with normal meninges remains to be established, and is under study.

Meningeal leukemia is a significant problem in childhood acute lymphoblastic leukemia, particularly now that prolonged survival is possible. The complication occurs even in the presence of peripheral remission. The usual

**Fig. 4.**—Comparison of plasma and spinal fluid concentrations of pyrimethamine, suggesting a "threshold" effect.
explanation for this occurrence is the inability of commonly used agents, other than prednisone, to penetrate the blood-brain barrier, producing a "reservoir" of leukemia cells immune to attack by usual methods of therapy. It should be noted that this view is not universally accepted. A further consideration is that the folate concentration of spinal fluid is about three times the plasma concentration. It is enticing to speculate that the spinal fluid thus provides a unique environment favoring growth of leukemic cells.

Attempts to eradicate reservoirs of cell by prophylactic intrathecal administration of methotrexate or aminopterin, or by external irradiation, or both, have not been successful in producing longer remissions or in decreasing the incidence of meningeal leukemia. BCNU [1,3-bis(chloroethyl)-3-nitrosourea], an experimental alkylating agent capable of crossing the blood-brain barrier, has been used successfully to produce remission in meningeal leukemia, but this drug has serious delayed bone marrow toxicity.

A drug, such as pyrimethamine, which is readily absorbed from the gastrointestinal tract, that can enter virtually every cell and body compartment, that has potent folate antagonistic properties, and that produces reasonable and readily reversible toxicity should provide a useful addition to the chemotherapeutic armamentarium in leukemia, particularly in acute lymphoblastic leukemia of childhood, in which folate antagonists are of demonstrated usefulness. Consideration should be given to the use of pyrimethamine in meningeal leukemia when intrathecal therapy is not feasible. Further study is indicated to determine the long-range effects of pyrimethamine as an antileukemic agent, with particular emphasis on its potential for controlling or preventing late meningeal complications.

REFERENCES

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