Parenteral nitrogen mustard for inflammatory arthritis

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■ A patient with progressive psoriatic arthritis refractory to methotrexate therapy was treated empirically with intravenous nitrogen mustard, or HN2. His response to therapy was compared with the responses of five rheumatoid arthritis patients treated with the same regimen. At 14 days after therapy was begun the patient with psoriatic arthritis showed significant improvement, at least comparable to that observed in the rheumatoid arthritis group. Intravenous HN2 therapy may be an alternative to methotrexate for progressive psoriatic arthritis.

INDEX TERMS: ARTHRITIS; NITROGEN MUSTARD ▯ CLEVE CLIN J MED 1990; 57:643–646

METHOTREXATE is considered by many to be the drug of choice for severe progressive psoriatic arthritis (PSA).[1] However, the therapeutic alternatives are less clear when methotrexate therapy is unsuccessful.

We report a case of chronic, progressive psoriatic arthritis (PSA) resistant to oral and parenteral high-dose methotrexate. The arthritis improved after intravenous nitrogen mustard (HN2) therapy. We compare this patient's response to HN2 to the response observed in five unselected patients with rheumatoid arthritis (RA) treated with the same regimen.

CASE REPORT

The index patient was a 40-year-old white male with a 19-year history of PSA. He had been treated with oral methotrexate since July 1976 in dosages ranging from 7.5 mg to 12.5 mg each week. Methotrexate therapy had been initiated after the patient responded inadequately to therapeutic doses of nonsteroidal anti-inflammatory drugs. At the start of methotrexate therapy, the patient demonstrated seven swollen or painful joints and a painful right heel. Two months after starting methotrexate, 7.5 mg per week, the swollen and tender joint count was zero and the right heel was no longer painful.

During the next 7 years, the methotrexate dosage remained constant at 7.5 mg per week and joint symptoms were well controlled. The active joint count ranged from zero to two. However, in December, 1983, the skin rash became more prominent and the swollen and tender joint count rose to five. Joint manifestations remained unchanged despite an increase in the oral methotrexate dosage to 12.5 mg each week. Liquid oral methotrexate, 10 mg to 25 mg each week, was started in July 1984 to treat the worsening psoriatic rash. In January 1985, after unsatisfactory response to 25 mg per week of liquid methotrexate, intramuscular methotrexate was added to the regimen, 35 mg to 50 mg every 4 to 6 weeks.

The patient continued to have significant cutaneous

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TABLE 1
INDEX PATIENT RESPONSE TO HN2 THERAPY

Disease activity measured	Days after start of treatment 0	6	14	53	Percent improvement
Swollen/tender joint count	24	25	19	6	+62
Duration of morning stiffness (hours)	4	2.5	1	0.75	+75
Grip strength (mmHg)	R L 42 >300	R L 60 >300	R L 102 >300	R L 150 >300	+58*
Visual analogue scale (cm)†	9.0	6.7	4.3	2.3	+52
Westergren sedimentation rate (mm/h)	103	106	116‡	45	−12

*Right hand only
†10 = pain as severe as it can be, 0 = no pain
‡Day 8

manifestations as well as joint symptoms throughout 1985 and 1986. In 1987, oral prednisone, 10 mg to 25 mg per day, was added, but in July 1988 the rash was prominent and the number of swollen and tender joints continued to increase. It now numbered 24 and involved the hands, knees, feet, and right hip.

The patient was hospitalized for intravenous HN2 treatment. He tolerated the treatment well, experiencing only nausea and emesis on the first day, as expected. These effects did not recur with later treatment. During hospitalization, he experienced some improvement in the signs and symptoms of PSA.

MATERIALS AND METHODS

Five patients with RA were treated with the same HN2 protocol that was used for the PSA patient. This population consisted of three males and two females with a mean age of 53.2 (range, 43 to 61) years and median disease duration of 12 (range, 5 to 192) months. Prior medications included nonsteroidal anti-inflammatory drugs in all patients and hydroxychloroquine, 200 mg or 400 mg per day, for patients 1 and 3, respectively. Patient 4 had responded poorly to parenteral gold and was allergic to d-penicillamine. Patient 5 had not responded to either parenteral gold or oral cyclophosphamide. All patients were receiving prednisone in a mean daily dose of 11.0 mg (range, 5 to 20) when HN2 was initiated.

As in the index patient with PSA, disease parameters were prospectively evaluated in the five RA patients. The assessment included duration of morning stiffness, active joint count (number of joints that were swollen or tender), grip strength using a modified cuff on a standard sphygmomanometer inflated to 20 mmHg, and a visual analogue pain scale.[2] Measurements were performed at the same time each day for each patient. Two RA patients were evaluated only during hospitalization. Three were evaluated both in the hospital and 1 to 3 weeks after discharge. The patient with PSA was evaluated during hospitalization and through the succeeding 53 days post-hospitalization.

Intravenous HN2 was chosen empirically; our previous experience with the drug indicated its beneficial effect in the treatment of severe RA.[3] For all six patients, HN2 was given as a 1- to 3-mg intravenous bolus over 5 minutes with 10 units of ACTH in 250 cc of 5% dextrose in water. The combination was administered daily for 7 to 9 days to a total dose of approximately 0.3 mg/kg.

RESULTS

The index patient's response to HN2 is recorded in *Table 1*. One week after hospital discharge and 14 days after the initiation of intravenous HN2, there was noticeable clinical improvement. At that time, oral methotrexate was reinstituted at 12.5 mg per week and azathioprine, 50 mg per day, was added. At day 53, very significant improvement was noted. The white cell count, which was 11,320 cells/mm^2 prior to HN2 therapy, fell to a low of 6,880 cells/mm^2 on day 14. Leukopenia was not seen. The platelet count at day 14 was 255,000.

Table 2 summarizes the changes in measures of disease activity and white blood cell count in the five RA patients. Although the data suggest inefficacy, this may be a result of reduction in the daily prednisone dosage from 20 mg to 10 mg in patient 2, and from 10 mg to 7.5 mg in patient 3.

Three patients were seen 1 to 3 weeks after hospital discharge (*Table 3*). Although mean morning stiffness reverted to baseline, the joint count, grip strength, and Westergren sedimentation rate showed clinically significant improvement. The white blood cell count fell

slightly, as expected, but no patients experienced leukopenia. The platelet count rose in two patients and fell less than 20% in three patients. One patient experienced nausea without vomiting after the first dose of HN2. No other adverse effects were noted—including infection, mild ulcers, and alopecia.

TABLE 2
RHEUMATOID ARTHRITIS PATIENTS' RESPONSE TO HN2 THERAPY

Patient #	1		2		3		4		5		Percent mean improvement
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
Swollen/tender joint count	21	16	22	19	2	9	24	7	26	21	+24
Duration of morning stiffness (hours)	0	1.75	2.5	0.75	0.1	0.1	6	0	2	2	+55
Combined grip strength (mmHg)	210	108	60	126	256	186	40	60	46	50	–13
Visual analogue scale (cm)*	3.1	1.6	4.2	2	3†	2	6	4.6	9	8	+28
Westergren sedimentation rate (mm/h)	116	93	123	101	93	75	40	–	77	68	+25
White blood cell count ($\times 10^3/mm^2$)	11.5	13.5	9.2	7.1	12.7	11.5	8.6	6.0	10.1	10.4	–6.9

*10 = pain as severe as it can be, 0 = no pain
†Obtained on day 4 of treatment

TABLE 3
EFFICACY OF HN2 ON FOLLOW-UP

Patient #	1		2		4		Mean		
	Pre	F/U	Pre	F/U	Pre	F/U	Pre	F/U	Change (%)
Swollen/tender joint count	21	12	22	4	24	1	22.3	5.6	+74.6
Duration of morning stiffness (hours)	0	1.5	2.5	.75	6	6	2.83	2.75	–2.8
Combined grip strength (mmHg)	210	262	60	250	40	122	103.3	190.2	+84.1
Westergren sedimentation (mm/h)	116	75	93	57	40	38	93	56.6	+39
White blood cell count ($\times 10^3/mm^3$)	11.5	8.2	9.2	6.2	8.6	12.3	9.8	8.9	–8.8

Pre = Prior to HN2 Therapy
F/U = 1 to 3 weeks after hospital discharge

DISCUSSION

The medical literature is of little help when methotrexate therapy fails for the patient with severe, progressive psoriatic arthritis. Azathioprine has been reported to be useful in two uncontrolled series.[4,5] A single-case report described the sequential use of cyclophosphamide, HN2, and 6-mercaptopurine in a patient with clearly diagnosed PSA.[6] Joint symptoms did not improve after the first treatment, which included an intravenous bolus of 20 mg HN2, nor after a second treatment 7 months later. Scherbel reported 12 patients with "psoriasis and rheumatoid arthritis" who were given intravenous HN2, 1 to 3 mg, with 10 units of ACTH daily for 5 to 7 days.[7] Of the 12 patients, 10 experienced some reduction of joint pain.

HN2 experience with rheumatoid arthritis

The medical literature is more extensive concerning the treatment of RA with HN2. Five separate uncontrolled series report the effects of HN2 given in a variety of doses and schedules.The first was reported by Jimenez-Diaz, who treated 32 patients with intravenous bolus doses of HN2, 4 mg to 6 mg daily for 3 or 4 days.[8] Most patients experienced some benefit after the second dose. "Very good" or "good" responses were seen in 26 patients (81%). Phillips and co-workers obtained the same results in five patients given 0.1 mg/kg HN2 each day for 4 days.[9]

In contrast, Cohen and associates treated four patients with RA and one patient with RA and osteoarthritis using the same protocol, but interpreted the trial as a failure.[10] Treatment was limited by severe nausea and vomiting after the second dose of HN2, so that only 0.2 mg/kg was given. Despite the author's conclusion, four of five patients described immediate subjective improvement and the mean erythrocyte sedimentation rate fell from a pretreatment value of 774 mm/h to a post-treatment value of 534 mm/h.

Paul and colleagues devised a treatment protocol that was apparently influenced by Cohen's description of toxicity. They premedicated 17 patients with pentobarbital, amobarbital, and meperidine, and then administered 0.1 mg/kg HN2 each day for 4 days.[11] Only 7 of 17 patients experienced vomiting. Improved joint range of motion and decreased joint pain were described in 16 of 17 patients. These benefits persisted for 12 weeks.

Scherbel modified the dosing schedule in a prospective study of 17 patients.[7] In this trial, 10 patients received 0.1 mg/kg on alternate days and 7 patients received 0.05 mg/kg each day. All 17 also received 10 units of ACTH. The total HN2 dose was 0.4 mg/kg. All patients improved within 2 to 7 days from the start of therapy, but at the 6-month follow-up, 15 had relapsed. This report also described the results of a similar treatment protocol in 221 patients evaluated retrospectively. In this group, 204 patients (92.3%) experienced "excellent" or "good" improvement. Nausea was reported by 88 (40%) and vomiting by 22 (10%).

Three controlled trials of HN2 therapy for RA have been published. Kitt and associates compared seven RA patients who received three doses of HN2 (0.1 mg/kg/d) to four control patients who received placebo.[12] After 3 to 5 weeks of follow-up, the seven treated patients showed greater improvement in all clinical and laboratory disease parameters. When 15 additional patients were treated with the same protocol, all showed some improvement immediately after treatment. All 22 patients were then followed for at least 6 months. Some patients maintained improvement up to 18 months.

In another trial, intravenous HN2, 0.1 mg/kg, was compared with intravenous methylprednisolone, one 1-g pulse per week, for 3 weeks. The patients were evaluated regularly during treatment and for 9 months thereafter. The degree and duration of response to HN2 was similar to the response to methylprednisolone.

Segal and associates studied nine patients with RA who experienced a flare in disease activity.[3] The patients were randomized to receive either intravenous methylprednisolone, 1 g for 3 consecutive days, or intravenous HN2, 1 mg to 3 mg daily for 10 days to a total dose of 0.3 mg/kg. Although both groups showed improvement, the methylprednisolone pulse benefit lasted only 5 days. The benefits of HN2 treatment were sustained throughout the 59 days of the study. These authors concluded that both methylprednisolone pulse and intravenous HN2 were of benefit in RA flares, but that the benefit of HN2 was of longer duration.

Psoriatic compared to rheumatoid arthritis

The immediate response (day 6) to HN2 in our patient with PSA was less gratifying than the response seen in patients with RA. Although the duration of morning stiffness declined from 4 hours to 2.5 hours, only modest improvement was seen in the grip strength and visual analogue scale, and the joint count and Westergren sedimentation rate worsened. This relatively modest effect on PSA compared to RA was probably documented by Scherbel in 1957.[7] Of 221 RA patients treated with HN2, 73% experienced an "excellent" response and 20% a "good" or "fair" response. Of 12 patients with "psoriasis and rheumatoid arthritis", none experienced an "excellent" response and in 83% the response was "good" or "fair."

At 14 days, our patient had clinically significant improvement in the joint count, duration of morning stiffness, grip strength, and visual analogue scale. These results were at least comparable to the improvement seen in RA patients. Further improvement at day 56 may have been due in part to the reinstitution of oral methotrexate, 12.5 mg/wk, and the addition of azathioprine, 50 mg/d.

These data suggest that intravenous HN2 may be a therapeutic alternative to methotrexate for severe, progressive PSA. Controlled studies may be indicated.

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