Inosiplex for Localized Herpes Zoster in Childhood Cancer Patients: Preliminary Controlled Study

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By multiple criteria, inosiplex—a reputed stimulator of virus-sensitized lymphocytes—had no demonstrable therapeutic effects in a preliminary controlled study of patients with localized herpes zoster and cancer. Lymphocytes from the six drug-treated patients were no more responsive to varicella-zoster antigen and phytohemagglutinin than were lymphocytes from seven patients who received a placebo.

Inosiplex (*p*-acetamidobenzoic acid salt of inosine-dimethylaminoisopropanol acid in a 1:3 molar ratio) is presently under investigation as an antiviral agent with broad-spectrum effects. Based on results obtained with *in vitro* systems (12), laboratory animals (9, 11), and human volunteers (4), the drug's mechanism of action appears to involve a stimulation of the cellular immune system, in particular the "activated lymphocytes" that have been previously sensitized to foreign viral protein. Evidence that impaired cellular immunity can prevent or delay recovery from viral infections has come from studies by Blanden in an animal model (1-3) and in patients with congenital abnormalities of the immune system (6, 10).

Herpes zoster infection provides an excellent model for evaluating the therapeutic efficacy of inosiplex. Patients with zoster have had a previous exposure to varicella-zoster virus (VZV) because of earlier episodes of varicella and therefore should have a population of sensitized lymphocytes. Moreover, the extent of zoster infection can be readily determined from counts of cutaneous lesions. In the present study, inosiplex treatment was evaluated on the basis of four principal determinants: (i) progression of lesions within the dermatome after the beginning of drug therapy, (ii) maximum percentage of dermatome involvement, (iii) skin dissemination and the associated viremia, (iv) responsiveness of lymphocytes to VZV antigen and phytohemagglutinin (PHA) *in vitro*.

Contingent on informed written consent, 13 children with cancer and herpes zoster were randomly selected by a double-blind technique to receive either oral inosiplex (six patients) or a placebo with an identical appearance and taste (seven patients). To be enrolled in the study,

patients had to have papulovesicular lesions in a typical dermatome distribution, with the onset of lesions occurring within 72 h of enrollment. All patients were receiving anticancer chemotherapy or irradiation (or both) when they developed zoster, but did not receive treatment for their malignancies during the course of the study.

Inosiplex was supplied by Newport Pharmaceutical Co., as 500-mg scored tablets. The calculated dosage for each patient was 1.5 g/m² per day; the drug was administered in six doses at 3-hour intervals from 8 a.m. to 11 p.m., and the last dose of each day was doubled. The final administered dose was determined by "rounding off" to the nearest multiple of 250 mg, resulting in an administered daily dosage ranging from 1.8 to 2.7 g/m². Doses were repeated if vomiting occurred within 1.5 h after drug administration. A total of 30 doses was established as the minimum required course. For patients who developed new dermatome lesions beyond 5 days, therapy was continued until 1 day after the progression of lesions within the dermatome had stopped or until 10 or more new lesions were seen outside the dermatome on 2 successive days (drug failure).

As reported earlier (8), the progression of dermatome lesions was determined daily from serial color photographs. Three physicians not involved in the management of the patients independently evaluated the photographs as to duration of new lesion formation and the maximum percentage of dermatome involvement.

Lymphocyte transformation in response to VZV antigen and PHA *in vitro* was assessed before the first dose of drug (day 0) and again on days 3 and 6 during the study. The assay procedure has been described fully in a previous

report (13). Additional laboratory studies included serial hemograms, urinalysis, chest roentgenograms, blood urea nitrogen, uric acid, blood sugar, and liver function tests. Serum immunoglobulins and complement-fixation titers to VZV antigen were determined for each patient during the acute- and convalescent-phases of infection. Vesicle fluids and heparinized blood samples were obtained serially for virus isolation in cultures of human foreskin fibroblasts (7). Negatively stained specimens from the one patient, without a VZV isolate, were examined by electron microscopy for the presence of herpesvirus particles.

The two study groups were comparable in age distribution (median ages: 9.5 versus 12 years) and types of malignant diseases. With one exception, all patients were free of clinically detectable cancer when they entered the study. The time of onset of zoster lesions before enrollment was similar for both groups (Fig. 1). On the day of enrollment absolute lymphocyte counts in the inosiplex-treated patients ranged from 576 to 1,742 (median, 951) and from 160 to 1,890 (median, 704) in controls. VZV was isolated from the vesicle fluid of 12 patients, all of whom had a $\geq$ fourfold rise in complement-fixation titer or a convalescent titer of $\geq$ 1:32 to VZV. The only child without a viral isolate had a convalescent complement-fixation titer of 1:32, herpesvirus particles in negatively stained specimens of vesicle fluid, and a positive in vitro lymphocyte response to VZV antigen within 4 days after the onset of infection.

Inosiplex had no important influence on the course of infection, as judged by the criteria

FIG. 1. Response of localized herpes zoster in children receiving inosiplex or a placebo of identical taste and appearance. The actual total daily dosage of the drug is indicated for each patient.

established for this study. New lesions continued to appear for a median of 3.5 days (range, 0 to 5 days) after the beginning of drug treatment, compared with 4 days (range, 0 to 6 days) for the control group (Fig. 1). After 2 days of therapy, the proportion of patients with continued progression of dermatome lesions was essentially the same in both groups (4/6 versus 4/7). Zoster involvement of more than 50% of the dermatome was seen in three drug-treated patients compared with two patients who were receiving the placebo. Moderate-to-severe skin dissemination, defined as 2 or more consecutive days of 10 new lesions outside an infected dermatome, was noted for three patients receiving inosiplex and for three receiving the placebo. VZV was isolated from the blood of three patients with widely disseminated lesions, one of whom was receiving inosiplex. The course of infection was not related to drug dosage (Fig. 1).

As shown in Table 1, inosiplex did not enhance lymphocyte responsiveness to VZV antigen or PHA. To the contrary, by day 3, the drug appears to have prevented or delayed lymphocyte responses as compared with results obtained in the placebo group. By day 6, this effect was not apparent with VZV antigen but still persisted with PHA. By this time, all but three patients in the study had at least one positive response; two of these nonresponders became responsive later in the convalescent phase (data not shown).

The adverse effects of drug treatment were minimal. Inosiplex did not produce vomiting or other gastrointestinal complications. Liver function tests were within normal limits in both study groups. One child with an initial leukocyte count of 2,600 cells/mm³ developed leukopenia (1,000 cells/mm³) by day 5 of inosiplex therapy, but this reduced count returned to the original level within 2 days. Two patients receiving the drug had transient serum uric acid levels of 8.3 mg/dl (normal range, 2.5 to 6 mg/dl). The remaining laboratory studies were not indicative of drug-induced abnormalities.

By the four criteria of this evaluation, inosiplex had no discernible therapeutic effects. The progression of new dermatome lesions after initiation of therapy, the extent of skin dissemination, and the maximum percentage of dermatome involvement were essentially the same in both study groups. Cellular immunity, as determined by lymphocyte responsiveness to VZV antigen and PHA, was not enhanced by drug treatment (Table 1); in fact, the numbers of positive responders on days 3 and 6 were lower than the control group.

Admittedly this is a small controlled study and may have been insufficient to establish a lack of drug efficacy. A much larger number of

TABLE 1. *Lymphocyte transformation in vitro*

Group	Antigen	No. of patients with a positive response ^a		
		Day 0	Day 3	Day 6
Inosiplex (N = 6)	VZV	1	1	4
	PHA	5	2	2
Placebo (N = 7)	VZV	2	6	5 ^b
	PHA	5	4	6 ^b

^a Lymphocyte stimulation index greater than 2.0 (13).

^b Only six patients were tested.

patients would need to be studied to obtain statistically significant differences. If, for example, the true proportion of patients with continued progression of dermatome lesions after 2 days were 0.70 in the placebo group but only 0.30 in the inosiplex group, then at least 38 patients (19 in each group) would be required to be reasonably certain of obtaining a significant result (5). However, the drug had no apparent therapeutic value in any of the four categories evaluated, indicating that further study was not warranted.

Insufficient dosage would provide an alternative explanation for the observed lack of therapeutic efficacy, but if corrected to the adult body surface area (1.73/m²) the dose range in this study (3.1 to 4.7 g/day) is comparable to that reported for clinical trials of inosiplex in adults (14, 15).

The basis for an antiviral effect of inosiplex has been attributed to stimulation of activated lymphocytes previously sensitized to foreign viral protein (9). Hence, in this study, drug failure could be related to deficient lymphocytes in patients who had received chemotherapy or irradiation. For this reason, the results do not preclude further evaluation of the drug in normal hosts with herpes zoster.

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