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Antiviral Treatment of Chronic Hepatitis B Virus Infection: Pharmacokinetics and Side Effects of Interferon and Adenine Arabinoside Alone and in Combination

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In an uncontrolled trial, 29 patients with chronic hepatitis B virus infection were treated with 93 courses of adenine arabinoside at doses ranging from 2.5 to 15 mg/kg per day. Most patients were treated concomitantly with human leukocyte interferon. Significant, but transient, neurotoxicity was seen with adenine arabinoside therapy in 44% of all courses. Manifestations of toxicity were mainly neurological and ranged from pain syndromes to tremors and, rarely, seizures. Suppression of numbers of lymphocytes was also noted. All effects were reversible with time. The extent of toxicity was dependent upon the dosage of adenine arabinoside. Treatment with interferon appeared to potentiate the occurrence of toxicity with adenine arabinoside. Arabinofuranosylhypoxanthine serum levels increased in a dose-dependent manner and tended to accumulate in interferon-treated hepatitis patients during a course of therapy. Elevated blood levels and drug accumulation were associated with toxicity in a significant fashion. Human leukocyte interferon was administered to 38 patients in 113 separate courses. Interferon side effects were rapidly reversible upon cessation of therapy. These included initial fever, myalgias, and hair loss as well as suppression of granulocytes, platelets, and lymphocytes in the blood.

As antiviral chemotherapy is established as a clinically useful modality, the spectrum of treatable disease expands, and the manifestations of toxicity are more likely to appear. As experience with a drug grows, modification of therapy on the basis of known risk factors, pharmacokinetic predictions, and drug monitoring become feasible. Clinical trials with adenine arabinoside (9-β-D-arabinofuranosyladenine; vidarabine) have been underway since 1974, and drug toxicity has been observed infrequently (10). The toxic reactions have included nausea, vomiting or diarrhea (or both), leukopenia, and thrombocytopenia in patients with cancer receiving very high doses (1 g/m^2 per day), (G. P. Bodey, J. A. Gottlieb, K. B. McCreadie, and E. J. Freireich, Proc. Am. Assoc. Cancer Res. 15:129, 1974), mild hypokalamia (9), and the syndrome of inappropriate secretion of antidiuretic hormone (14). Tremors have also been noted (11, 15). Severe adenine arabinoside toxicity has been implicated in four neurological deaths after therapy for cytomegalovirus infection in renal transplant recipients (S. C. Marker, K. E. Groth, and R. J. Howard, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 18th, abstr. no. 519, 1978). Toxicity was seen in our patients early in the therapeutic trials and was reported on in a preliminary communication (16). As a result, a program for drug level monitoring was established, and toxicity was carefully recorded. Additional data are presented here, and toxicity is correlated with treatment regimen risk factors and drug levels. Pharmacokinetic parameters are also presented and discussed. Our studies suggest a relationship between toxicity and elevated plasma drug levels. Drug accumulation may occur and may also be related to toxicity. Possible risk factors are identified and may be modifiable.

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MATERIALS AND METHODS

Patients and therapy. Between November 1975 and December 1979, 40 patients with chronic hepatitis B virus infection, with normal renal function before therapy, were selected for treatment with antiviral chemotherapy as described in the first paper in this

series (16a). Briefly, human leukocyte interferon was administered daily or twice daily by subcutaneous injection. Doses ranged from 2.0×10^6 to 20×10^6 U daily. Adenine arabinoside was administered at 4- to 6-week intervals in daily 12-h intravenous infusions of 2.5 to 15.0 mg/kg per day in warmed 5% dextrose in water at a concentration up to 450 mg/liter. Courses of administration ranged from 1 to 21 days. Most patients received adenine arabinoside for 7 to 10 days per course. All patients were hospitalized during therapy with adenine arabinoside or high-dose interferon (10×10^6 to 20×10^6 U/day). Twenty-seven of the 40 patients received both drugs simultaneously at some time during their treatment regimen, accounting for 77 of 93 adenine arabinoside courses and 77 of 113 interferon courses. Courses were considered combined when administration of adenine arabinoside and interferon occurred simultaneously.

Toxicity monitoring. Hospitalized patients were visited by a physician daily and examined for neurological or other problems. Outpatients were seen weekly. Toxicity was monitored by history and examination and recorded on a toxicity tally sheet. Since this therapeutic trial was uncontrolled, toxicity was ascribed to one or the other drugs during combination therapy, based upon similar events, within the same trial, using either drug alone.

Blood studies. Blood was obtained before therapy and serially during therapy and after for complete blood counts, platelet counts, and blood chemistry. In addition, interferon assays were performed by methods previously described (13). Adenine arabinoside and arabinofuranosylhypoxanthine plasma levels were performed on blood collected in EDTA and pentostatin (CI-825; Parke Davis & Co., Detroit, Mich.) for analysis by high-pressure liquid chromatography (5), by Arlyn Kinkel at Parke Davis & Co. Early (day 2) and late (day 7) levels were obtained before (trough) and just after (peak) adenine arabinoside infusions on 21 patients.

RESULTS

Adenine arabinoside side effects. The side effects encountered with adenine arabinoside are summarized in Table 1. They fall into three major groups: central nervous system related, possibly peripheral nervous system related, and gastrointestinal.

The most severe toxicity was in one patient, aged 56, who developed tremor, ataxia, encephalopathy, myoclonic seizures and coma with a superimposed aspiration pneumonia. This patient's course, which was previously reported (16), occurred early in our therapeutic trials, before the potential toxicity of this drug was understood and before drug levels were monitored. The episode was precipitated by dehydra-

TABLE 1. Neurological side effects encountered with adenine arabinoside

Symptoms	No. affected/ total[a]	(% affected)
Possibly peripheral nervous system related		
Pain syndromes	36/93	(39)[b]
Arthralgia	2/93	(2)
Extremity pain (myalgia)	36/93	(39)
Dysesthesia	5/93	(5)
Jaw pain	8/93	(9)
Abdominal pain	9/93	(10)
Itching	4/93	(4)
Central nervous system related		
Ataxia	11/93	(12)
Dysgraphia	5/93	(5)
Tremor (Intention)	15/93	(16)
Encephalopathy	1/93	(1)
Myoclonic seizure	1/93	(1)
Coma	1/93	(1)
Psyche changes		
Bizarre dreams	1/93	(1)
Depression	8/93	(8)
Gastrointestinal		
Diarrhea	10/93	(11)
Nausea and vomiting	23/93	(25)
Abdominal pain	9/93	(10)
Weight loss	15/29	(52)
Greater than 5% of pretreatment body weight	10/29	(34)
Greater than 10% of pretreatment body weight	5/29	(17)

[a] The total number treated was 29 patients (weight loss) or 93 treatment courses (all others).
[b] Twenty-four moderate; 12 severe.

tion secondary to vomiting and poor fluid intake, during which there was a rise in blood urea nitrogen to 42 mg/100 ml. The patient recovered fully from his neurotoxicity over 4 to 6 months.

Central nervous system-related symptoms included, in addition to those described, ataxia (12%) which was always short lived (1 to 5 days), occurred always 1 to 2 days after cessation of therapy, and was never associated (when found alone) with other sequelae. Dysgraphia occurred in 5% of courses, and was usually short lived (1 to 2 weeks posttherapy). It occasionally progressed to an objective intention tremor. Eight of 12 episodes of severe prolonged pain (discussed below) were preceded by tremor. Psyche changes ranged from bizarre nightmares to prolonged depression requiring antidepressant therapy. One patient threatened suicide. All mood changes abated within 3 to 5 months. Twenty-nine electroencephalograms were performed on 12 patients under study. Results correlated poorly to the clinical manifestations and were considered unhelpful.

Side effects possibly related to peripheral nervous system damage were also seen. One very distressing side effect, the prolonged pain syndrome, occurred in 38% of patients. The pain syndromes varied from a mild fleeting discomfort during or after therapy to severe prolonged pain requiring narcotics, bedrest, and cessation of work for more than 1 month and persisting up to 6 months after therapy was stopped. Five of six patients developed extremity pain with localized, but often changing, myalgias and shooting pains in the hands and feet. Occasionally, decreased reflexes were noted.

Arthralgias were seen concomitantly in two patients and were once associated with a modest joint effusion. Jaw pain, usually localized over the temporomandibular joint, and exaggerated by chewing, but occasionally by salivation alone, was a problem in 9% of courses. Abdominal pain, which often began with bloating and nausea during therapy, but occasionally progressed to more severe, generalized abdominal distress, without abnormal physical findings, was seen in 10% of courses. Four patients suffered a self-limited (1- to 4-week) period of diffuse pruritus, not associated with a visible rash, change in bilirubin, or relief with standard antipruritic agents. Electromyelography studies, creatine phosphokinase, aldolase, Dane particle-associated polymerase, Clq, total serum complement, rheumatoid factor, antinuclear factor and erythrocyte sedimentation rate were examined during these episodes. No correlation to clinical toxicity was found.

Side effects related to gastrointestinal dysfunction included diarrhea, nausea, vomiting, and weight loss. These effects appeared strictly related to dose and were alleviated by discontinuation of therapy.

Hematological parameters were monitored in all patients undergoing therapy, and results are summarized in Fig. 1. A significant depression of circulating lymphocytes occurred (nadir 48% of pretreatment levels) before the addition of interferon. This effect was not dose related. This effect was not long lasting, but recovery was delayed by concomitant interferon.

Adenine arabinoside pharmacokinetics. After patient treatment courses were completed 148 plasma samples were sent for analysis of adenine arabinoside and its major metabolite, arabinofuranosylhypoxanthine. Adenine arabinoside was not detected in any sample. Arabinofuranosylhypoxanthine was detectable in all patients just after the infusion (peak).

Figure 2 shows the peak plasma levels of arabinofuranosylhypoxanthine obtained at different dosages of adenine arabinoside. Mean early peak plasma arabinofuranosylhypoxanthine levels were 2.04 ± 0.59 (standard deviation [SD]) μg/ml and 2.07 ± 0.41 (SD) μg/ml on 5 and 7.5 mg/kg per day, respectively, rising to 4.32 ± 1.07 μg/ml at 10 mg/kg per day and 5.02 ± 1.83 (SD) μg/ml at 15 mg/kg per day, demonstrating a dose level correlation. In addition, there was evidence for accumulation of peak drug levels late in the treatment courses in the interferon-treated patients. Mean levels rose to 3.23 ± 1.90 (SD), 3.93 ± 2.77 (SD), 6.09 ± 1.87 (SD), and 7.98 ± 0.93 (SD) μg/ml for doses of 5, 7.5, 10, and 15 mg/kg per day respectively. Comparing these early and late peak levels in patients on combination therapy, then, accumulation is statistically significant ($P < 0.05$ (15 mg/kg per day), $P < 0.01$ (7.5 mg/kg per day), $P < 0.1$ (10 mg/kg per day), $P < 0.001$ (15 mg/kg per day)) by Student's t test.

Figure 3 shows a comparison of the levels from our patients treated at a dose of 10 mg/kg per day to patients treated at the University of Alabama for viral infections other than hepatitis B. The latter did not receive interferon. Infusion parameters were similar, and dosages were identical. Drug administration lasted for 10 days (compared with 7 days for the hepatitis B patients). Higher early and late peak levels were seen in interferon-treated patients ($P < 0.001$) by t test).

Levels after 12 h without drug (trough) averaged 0.27 ± 0.35 (SD) μg/ml (range, 0 to 1.1 μg/ml). Comparing trough levels, no evidence for accumulation was found.

Adenine arabinoside: pharmacodynamics. In our patient population, toxicity was observed in patients treated with combination therapy at lower dosages than when adenine arabinoside was used alone. In fact, significant neurotoxicity

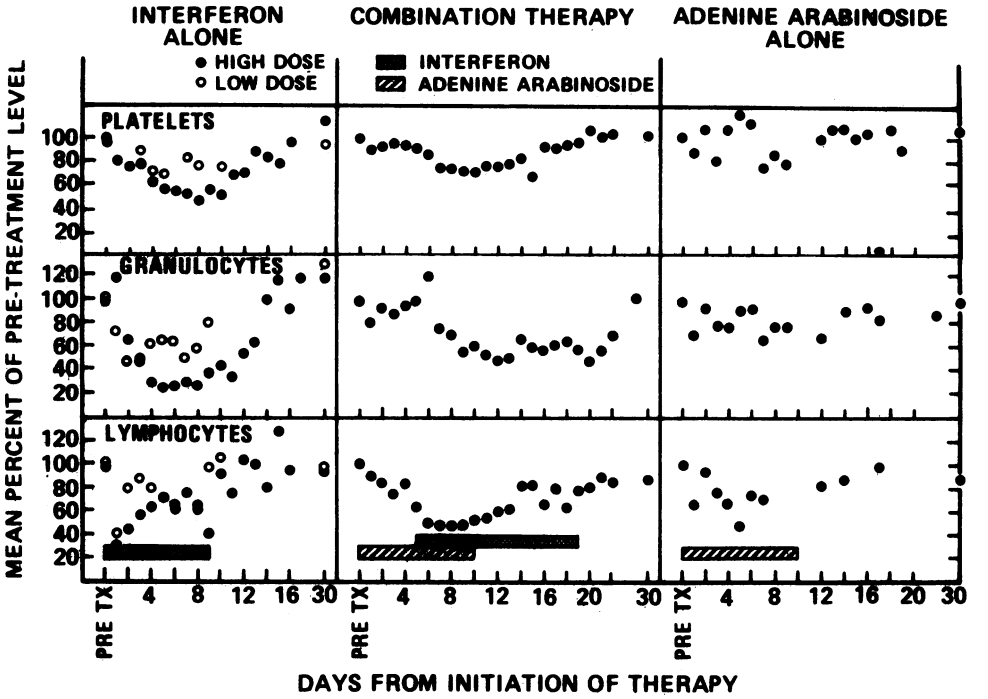

FIG. 1. Hematological effects of therapy. Hematological values for patients receiving high-dose (●) and low-dose (○) interferon alone (defined in text), combination therapy, and adenine arabinoside alone are plotted as a mean of percentages of pretreatment values for all patients tested on any specific day. Pretreatment values, treatment values, and posttreatment values up to 30 days after initiation of therapy are shown.

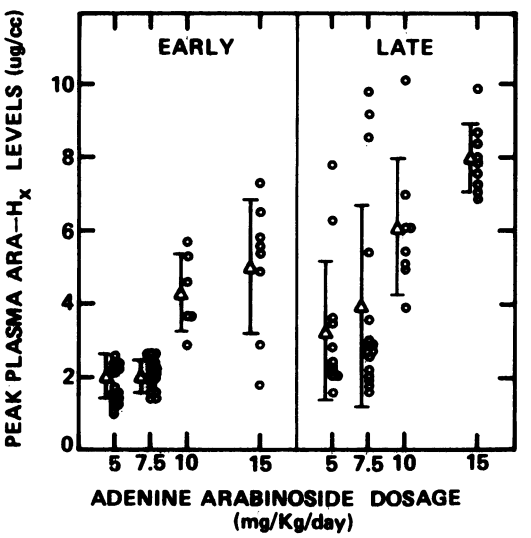

FIG. 2. Dosage of adenine arabinoside compared with arabinofuranosylhypoxanthine (ARA-H_x) levels in patients on combination therapy. Arabinofuranosylhypoxanthine values just after adenine arabinoside infusions (peaks at various dosages are compared from day 2 [early] and day 7 [late] of a 7-day course of therapy). The means ± 1 SD are displayed to the left of the individual values for each dose used.

did not appear at low doses in the group treated with adenine arabinoside alone, where toxicity was never seen below 120 mg/kg per course. However, there was a 32% incidence of neurotoxicity with dosage ranges of only 20 to 40 mg/kg per course when interferon was added, and 100% toxicity was observed with dosages over 120 mg/kg per course ($P < 0.001$). Analysis of all individual treatment courses demonstrates not only the differences between two treatment regimens, but also a continuously increasing incidence of toxicity with increasing adenine arabinoside dose.

The major manifestations of significant neurotoxicity were then analyzed according to plasma levels. Since drug accumulation may be the major factor in the increased incidence of toxicity in this study, late peak plasma levels were compared among the nontoxic and toxic subgroups (Fig. 4). Elevated late peak plasma arabinofuranosylhypoxanthine levels were associated with each type of toxicity seen (P values by t test shown). The severe pain syndrome was consistently associated with high levels, and this complication was never observed with a level lower than 7 μg/ml. This observation was corroborated by giving lower doses in repeat courses of therapy to patients with significant neurotoxicity. Of the 19 patients who had signifi-

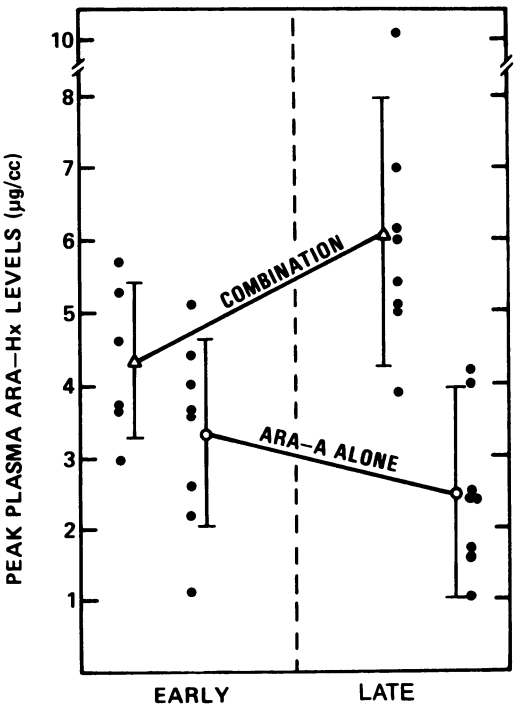

FIG. 3. Accumulation and increased plasma levels with combination therapy. Peak arabinofuranosylhypoxanthine levels found in patients without hepatitis treated with adenine arabinoside alone are compared with levels in hepatitis B-infected patients treated with human leukocyte interferon and adenine arabinoside (combination), after equivalent pharmacokinetic sampling. All patients displayed were being treated with 10 mg of adenine arabinoside per kg per day. Means ± 1 SD are displayed to the left of the individual values. The data from patients without hepatitis were obtained by R. Buchanan and R. Whitley, and assays were performed by A. Kinkel in a manner identical to other observations reported here. Early and late times of sampling are defined as in Fig. 2.

cant neurotoxicity, 12 underwent a repeat course at a lower dose without toxicity and thereby continued with therapy.

Adenine arabinoside: risk factors. Predictable risk factors for toxicity were sought retrospectively. Renal dysfunction is not analyzable in our group since we did not accept any patient with renal failure before therapy. Table 2 summarizes the effect of age on toxicity with combination therapy. The data in this table again demonstrate that toxicity was dose dependent. Furthermore, younger patients were less likely to develop toxicity in either dosage range. ($P < 0.04$ by the trend test of Armitage [1]). Liver function tests, including serum glutamic oxalacetic transaminase, bilirubin, albumin, and alkaline phosphatase were examined for a possible influence on both drug accumulation and toxicity. Serum glutamic oxalacetic transaminase elevations of greater than 375% of normal were associated with an 80% incidence of toxicity versus 39% for those with lesser enzyme elevation.

Interferon: side effects. Interferon side effects are shown in Table 3. Initial fever was seen in 40% of treatment courses. All patients were pretreated with acetaminophen. Temperature elevations usually occurred within 4 h of the first injection and only occasionally recurred on subsequent treatment days in patients receiving high doses of interferon (10×10^6 to 20×10^6 U/day). No recurrence after day 1 was noted at lower doses. Fever was often associated with chills. Fatigue and malaise were seen in 29% of courses and were a problem only with prolonged courses of high-dose interferon. Symptoms cleared within a few days of discontinuation of the drug. Twenty-five percent of patients experienced diffuse myalgias similar to a "flu-like illness." These also disappeared quickly after discontinuation of the drug. Hair loss was observed in five patients (21%), although it was clinically obvious in only three (8%). The loss occurred in males and females and followed a typical hereditary baldness pattern. This usually began late in therapy after prolonged or high-dose interferon. Nausea and vomiting were occasionally seen with high-dose interferon courses (8%), but were not a significant problem. Mild depression was also observed in a few

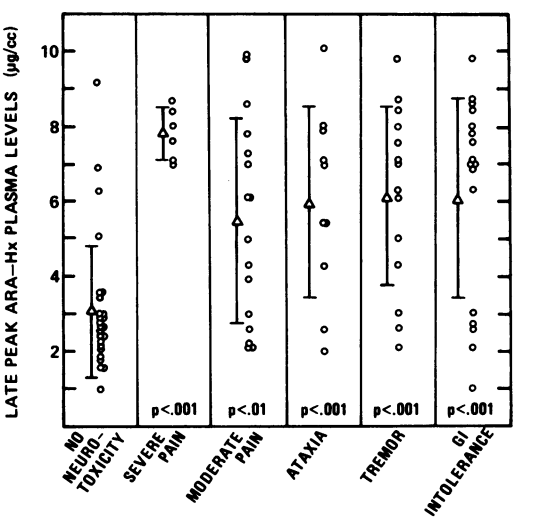

FIG. 4. Relationship of individual toxic courses to plasma arabinofuranosylhypoxanthine levels. Peak plasma levels drawn at the end of the treatment course are grouped according to the type of toxicity encountered (definitions in text). The means ± 1 SD are plotted to the left of the individual values. *P* values calculated by *t* test comparing the nontoxic group to the different toxic groups are also shown.

TABLE 2. Effect of age on neurotoxicity with combination therapy

Age	Toxic courses/total (%) by ara-A[a] dosage range (mg/kg/course):	
	20 to 80	80 to 230
≥50	8/14 (57)	2/2 (100)
40 to 49	4/15 (27)	6/6 (100)
<40	10/39 (26)	11/17 (65)
Trend test *P* value	0.0375	0.0314

[a] ara-A, Adenine arabinoside.

patients (3%) treated with interferon. Mild weight loss was a factor in 11% of patients. All of the latter effects rapidly disappeared upon stopping interferon therapy.

Interferon had a dose-related suppressive effect on platelets and granulocytes. High-dose interferon (10×10^6 to 20×10^6 U/day) was associated with a nadir of 48% of pretreatment levels of platelets and 26% of pretreatment levels of granulocytes. Low-dose interferon had a similar, but less severe, suppressive effect. No bleeding or infectious complications of these effects were seen despite occasional suppression of granulocytes below 1,000/mm^3 or platelets below 100,000/mm^3. Recovery to pretreatment levels was rapid and virtually complete within 5 days of discontinuation of interferon.

Interferon: pharmacokinetics. Peak circulating interferon activity titers were measured 4 h after subcutaneous injection in all patients. A total of 643 titers were performed. Serum levels were found to be dose dependent. At the lowest dose given in this study (0.3×10^4 U/kg), 7 of 20 (35%) titers fell into the measurable range (10 U) with a mean of 8.1 U (standard error [SE], 2.1). As the dose increased to 2.3×10^4 U/kg, 21 of 26 (81%) peak titers fell into the measurable range with a mean of 30.7 U (SE, 4.1). All levels fell into the measurable range at interferon doses of 2.9×10^4 U/kg or greater. Mean titers were 51.6 U (SE, 4.2) at doses of 4×10^4 to 5×10^4 U/kg, 79.7 U (SE, 7.2) at doses of 8.5×10^4 to 10×10^4 U/kg, 113 U (SE, 13.2) at doses of 10×10^4 to 15×10^4 U/kg, and 459.9 U (SE, 94.7) at doses of 15×10^4 to 20×10^4 U/kg. The maximum recorded peak interferon titer in this study was 2,000 U in a patient receiving 17×10^4 U/kg.

DISCUSSION

Because this mode of therapy was new, these clinical trials were uncontrolled, and doses and format of administration were variable. Despite this, striking differences between types of therapy and the associated adverse effects became clinically apparent.

Thrombocytopenia and granulocytopenia, which have been previously encountered with adenine arabinoside (6), were not seen in our patients. Neurotoxicity, including tremors and convulsions, was first seen in association with adenine arabinoside therapy in preclinical trials with rhesus monkeys at doses of 25 mg/kg per day (10). Early clinical trials with this compound, however, were apparently free of significant toxicity at 15 mg/kg per day (10). We saw neurological side effects with administration of high doses of adenine arabinoside alone; however, our overall incidence of 44% significant toxicity was surprising since it included some patients receiving low daily doses of drug. The data herein show that hepatitis B-infected patients, also undergoing therapy with interferon, have a significant tendency to drug accumulation. This is in marked contrast to previously published findings in patients without hepatitis B virus infection who were not treated with interferon (4). Furthermore, those being treated concomitantly with interferon appeared subject to significant toxicity at lower doses than patients with similar underlying disease not receiving interferon. There should be further testing of the possibility that hepatic disease also plays a role in our patients' apparent increased risk of adenine arabinoside toxicity. However, it is important to note that in our study the elevated blood levels seen with drug accumulation are also highly correlated to the severity of toxicity.

TABLE 3. Interferon side effects (non-hematological)

Symptom	No. affected/total[a]	(% affected)
Initial fever (38°C or greater)	45/113	(40)[b]
Fatigue and malaise	33/113	(29)
Diffuse myalgia	9/38	(24)
Hair loss	8/38	(21)
Nausea and vomiting	3/38	(8)
Depression	3/38	(8)
Weight loss		
Greater than 5% of pretreatment weight	4/38	(11)
Greater than 10% of pretreatment weight	0/38	(0)

[a] The total number treated was 38 patients or 113 treatment courses.
[b] Of 45 patients, 11 had fever to 39°C.

Conversely, then, toxicity may be preventable, while still allowing long-term use of this drug.

Studies have not been performed to date in which therapy could be modified on the basis of plasma drug level data. The data in Fig. 4, however, imply that drug monitoring would be useful for future studies. The nontoxic patients were those who did not accumulate the drug and who had late peak plasma arabinofuranosylhypoxanthine levels ranging from 1.0 to 3.6 μg/ml (87%), whereas the toxic patients had corresponding plasma levels with means ranging from 5.5 (moderate pain) to 7.8 μg/ml (severe pain). This would leave room for a reasonably wide therapeutic ratio if doses could be adjusted on the basis of blood levels in individual patients. Drug monitoring will be mandatory in those patients with a tendency to accumulate, i.e., interferon-treated chronic hepatitis B virus-infected patients and patients with renal dysfunction. However, overall clinical experience with this drug is relatively small at present, and therefore risk factors for drug accumulation are by no means complete. We may be missing other factors which have not been analyzed for lack of drug level data. Dosage nomograms might be constructed in the future, if this information were prospectively sought in a larger trial. The largest group of patients treated with adenine arabinoside were those with herpes simplex encephalitis (17), where little to no toxicity has been encountered. However, unmasking neurological toxicity in this group being treated for devastating neurological disease could be most difficult indeed. Certainly, in light of our patient with renal dysfunction and a previous report of four neurological deaths secondary to adenine arabinoside in patients with renal dysfunction (Marker et al. 18th ICAAC, abstr. no. 519), administration of this drug to these patients will be inappropriate without drug monitoring capability. Yet, postrenal transplant patients represent an important group of patients predisposed to serious cytomegaloviral and other herpes viral infections which are susceptible in vitro to this compound. While the correlation of serum glutamic oxalacetic transaminase elevation and toxicity appears significant on the surface, enzyme elevations were found to be dose dependent. Since toxicity is dose dependent, a firm conclusion cannot be established regarding serum glutamic oxalacetic transaminase as a risk factor. No correlations of this type could be made with other parameters of liver function. Age as a risk factor and other potential risk factors to toxicity, including liver disease, require further investigation.

The accumulation seen in the presence of interferon is not explained, yet speculations can be made. Interferon inducers have been shown to inhibit the P-450 drug metabolizing enzyme system in mice (16). No cause-effect relationship can be drawn here, since the known metabolic breakdown of this drug does not appear to involve this system (5). However, metabolic pathways not yet described for this agent may exist. Furthermore, both stimulatory and inhibitory effects of interferon on other enzyme systems have been observed (for a review, see reference 2). In addition, a possible interaction at the target organ level might also exist.

Interferon has a reversible suppressive effect on granulocytes and platelets, which has been previously reported (7). A trend toward lymphocyte suppression has also been previously described (3). The other side effects with interferon, including reversible hair loss, have been previously described (8, 12).

By measuring serum interferon activity, we were able to predict the dose necessary to achieve significant titers in every patient (2.9×10^4 U/kg) and to establish a dose-dependent relationship. However, there was significant variation in absolute levels from patient to patient and from lot to lot. No relationship was established between titer and therapeutic effect or toxicity. The variability encountered may represent fluctuations in cell culture conditions, serum factors which might influence interferon's antiviral action or its stability, and other factors which play a role in the reproducibility of any bioassays performed on a week to week basis. Future development of interferon assays not based on biological activity, such as radioimmunoassay, should enhance our understanding of the pharmacokinetics of interferon.

Future clinical investigations with combination antiviral therapy must be pursued not only in hepatitis B virus infection, but also in other settings, in an attempt to increase the therapeutic effect of a single agent. However, toxicity is also shown to increase significantly when adenine arabinoside and interferon are combined. Prevention of toxicity with careful drug level monitoring might be accomplished. Older patients and patients with renal or hepatic dysfunction must not be treated in future studies until drug monitoring during therapy becomes available. Our current investigations suggest that a combination of therapies does not enhance toxicity if the drugs are given consecutively rather than concurrently.

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LITERATURE CITED

1. **Armitage, P.** 1971. Statistical methods in medical research. John Wiley & Sons, Inc., New York.
2. **Baglioni, C.** 1979. Interferon-induced enzymatic activities and their role in the antiviral state. Cell **17**:255–264.
3. **Billiau, A., P. de Somer, V. G. Edy, E. De Clercq, and H. Heremans.** 1979. Human fibroblast interferon for clinical trials: pharmacokinetics and tolerability in experimental animals and humans. Antimicrob. Agents Chemother. **16**:56–63.
4. **Buchanan, R. A., A. W. Kinkel, C. A. Alford, and R. J. Whitley.** 1980. Plasma levels and urinary excretion of vidarabine after repeated dosing. Clin. Pharmacol. Ther. **5**:690–696.
5. **Glazko, A. J., T. Chang, J. C. Drach, D. R. Mourer, P. E. Borondy, H. Schneider, L. Croskey, and E. Maschewske.** 1975. Species differences in the metabolic disposition of adenine arabinoside, p. 111–133. *In* D. Pavan-Langston, R. A. Buchanan, and C. A. Alford (ed.), Adenine arabinoside: an antiviral agent. Raven Press, New York.
6. **Gottlieb, J. A., and G. P. Bodey.** 1974. Possible bone-marrow depression by ara-A therapy for disseminated herpes zoster. N. Engl. J. Med. **290**:914.
7. **Greenberg, H. B., R. B., Pollard, L. I. Lutwick, P. B. Gregory, W. S. Robinson, and T. C. Merigan.** 1976. Effect of human leukocyte interferon on hepatitis B virus infection in patients with chronic active hepatitis. New Engl. J. Med. **295**:517–522.
8. **Ingimarsson, S., K. Cantell, and H. Strander.** 1979. Side effects of treatment with long-term interferon. J. Infect. Dis. **140**:560–563.
9. **Koplan, J. P., K. A. Monsur, S. O. Foster, F. Huq, M. M. Rahaman, S. Huq, R. A. Buchanan, and N. A. Ward.** 1974. Treatment of variola major with adenine arabinoside. J. Infect. Dis. **131**:34–39.
10. **Kutz, S. M.** 1975. Toxicology of adenine arabinoside, p. 145–147. *In* D. Pavan-Langston, R. A. Buchanan, and C. A. Alford (ed.), Adenine arabinoside: an antiviral agent. Raven Press, New York.
11. **Lauter, C. B., E. J. Bailey, and A. M. Lerner.** 1976. Microbiologic assays and neurologic toxicity during uses of adenine arabinoside in humans. J. Infect. Dis. **134**:75–79.
12. **Merigan, T. C.** 1977. Pharmacokinetics and side effects of interferon in man. Tex. Rep. Biol. Med. **35**:541–547.
13. **Merigan, T. C., D. F. Gregory, and J. K. Petralli.** 1966. Physical properties of human interferon prepared *in vitro* and *in vivo*. Virology **29**:515–522.
14. **Ramos, E., R. F. Timmons, and S. C. Schimpff.** 1979. Inappropriate antidiuretic hormone following adenine arabinoside administration. Antimicrob. Agents Chemother. **15**:142–144.
15. **Ross, A. H., A. Julia, and C. Balakrishnan.** 1979. Toxicity of adenine arabinoside in humans. J. Infect. Dis. **133**:A192–A198.
16. **Sacks, S. L., J. L. Smith, R. B. Pollard, V. Sawhney, A. S. Mahol, P. Gregory, T. C. Merigan, and W. S. Robinson.** 1979. Toxicity of vidarabine. J. Am. Med. Assoc. **241**:28–29.

16a. **Scullard, G. H., R. B. Pollard, J. L. Smith, S. L. Sacks, P. B. Gregory, W. S. Robinson, and T. C. Merigan.** 1981. Antiviral treatment of chronic hepatitis B virus infection. I. Changes in viral markers with interferon combined with adenine arabinoside. J. Infect. Dis. **143**:772–783.

17. **Whitley, R. J., S. J. Soong, R. Dolin, G. J. Galasso, L. T. Ch'ien, and C. A. Alford, et al.** 1977. Adenine arabinoside therapy of herpes simplex encephalitis. N. Engl. J. Med. **297**:289–294.