Toxicity and Pharmacokinetics of a Pyrrolizidine Alkaloid, Indicine N-Oxide, in Humans


ABSTRACT

Indicine N-oxide (NSC 132319), the first pyrrolizidine alkaloid to be studied as an antitumor agent in humans, was administered to 29 patients with advanced cancer by 10-min infusion daily for five consecutive days in planned escalations ranging from a daily dose of 0.15 to 3.0 g/sq m. At all doses tested, plasma concentrations of indicine N-oxide exhibited a biphasic decline best approximated by a two-compartment open model. At daily doses up to 1.5 g/sq m, the distributive and postdistributive half-lives of plasma elimination ranged from 0.8 to 3.7 min and from 90.6 to 171.7 min, respectively. Total body clearance ranged from 3.6 to 6.2 ml/min/kg. At the highest dose tested, 3 g/sq m, a striking, and as yet unexplained, increase in the half-life of the initial distribution phase and a decrease in total body clearance were noted. Approximately 40% of the administered dose of indicine N-oxide was eliminated in the urine within 24 hr as unmetabolized drug and 2% as the free base indicine. Dose-limiting toxicity of the drug was reversible leukopenia and/or thrombocytopenia. Repetitive courses of indicine N-oxide had a cumulative effect on the severity of myelosuppression, and prior treatment with a nitrosoarene enhanced the hemopoietic toxicity of indicine N-oxide. Other toxicities included mild nausea and vomiting during treatment, reversible increases (±20% of pretreatment values) in serum creatinine in 11 of 43 courses, and transient alterations in serum glutamic-oxaloacetic transaminase. No objective responses were noted, but five patients with advanced gastrointestinal cancer had stability of disease for at least four months. For subsequent studies of drug activity in patients with solid tumors, we would recommend 3.0 g/sq m daily for five days repeated every five weeks. Indicine N-oxide should be used with great caution, or not at all, in patients treated previously with nitrosoarenes or other drugs known to produce cumulative bone marrow toxicity.

INTRODUCTION

Pyrrolizidine alkaloids are distributed widely in nature, the tertiary bases and the N-oxides occurring in the plant families of Compositae, Leguminosae, and Boraginaceae (3). At least 150 pyrrolizidine alkaloids naturally occurring as the free base and over 30 occurring as the N-oxide have been described (13). In humans, ingestion of grain contaminated with plant material containing pyrrolizidine alkaloids or consumption of infusions of the leaves of certain plants ("bush tea") has produced severe acute hepatotoxicity in the form of venooculsive disease (12). The effects of chronic ingestion of pyrrolizidine alkaloids in humans are unknown (12).

The ability of many pyrrolizidine alkaloids to cause an unusual chronic liver disease in grazing animals (3, 12), characterized by centrilobular necrosis and markedly enlarged hepatocytes with increased DNA content, prompted extensive study of their chemical and toxicological properties. Antimitotic and mutagenic activity and ability to produce chromosomal breakage suggested that the alkaloids might possess antitumor activity (3, 12). Many pyrrolizidine alkaloids are active in experimental tumor models (3, 5, 12, 13), but acute and chronic toxicities, especially hepatic toxicity, diminished enthusiasm for their clinical evaluation (9, 12, 17, 18). Hepatotoxicity and carcinogenicity appear to be associated with metabolism of the alkaloids to reactive pyrrolic compounds, the dehydropyrrolizidines (1, 3, 6, 9, 10). It has been assumed that antitumor activity is also a consequence of metabolism to dehydropyrrolizidines. The N-oxides of pyrrolizidine alkaloids are generally less toxic and have less antitumor activity than the free bases when given parenterally (5, 10). Given p.o., the N-oxides produce toxicity comparable to that of the free bases, presumably because of reduction of the N-oxide to the free base by gut flora and subsequent metabolism to dehydropyrrolizidines by the liver (6, 10, 13).

Indicine N-oxide (Chart 1), the major pyrrolizidine alkaloid in Heliotropium indicum Linn. (Boraginaceae) (11), produces little hepatotoxicity in rodents and is active against Walker 256 carcinoma, murine leukemias P388, L1210, and P1534, and the B16 melanoma (7, 11). Large animal toxicity studies of indicine N-oxide (4, 16) revealed reversible alterations in hepatic function (increases in SGOT3 and serum glutamic-pyruvic transaminase and in bromsulphalein retention) but no histological evidence of liver injury. Other toxicities included bone marrow hypoplasia, nephrosis, emesis, and bloody diarrhea. Although the reasons for the apparently low hepatotoxicity of indicine N-oxide compared to that of other pyrrolizidine alkaloids (and their N-oxides) are not known, indicine N-oxide seemed to be the most appropriate compound of this group for clinical study.

To determine a pharmacologically active but clinically tolerable dose of indicine N-oxide and to look for evidence of antitumor activity in humans, the drug was administered to advanced cancer patients. A 5-day schedule was chosen because indicine N-oxide had marked route and schedule dependency in the P388 system, maximum activity occurring when given daily for 9 days. The starting dose was 150 mg/sq m daily for 5 days, which is one-third of the lowest toxic dose in the rhesus monkey (4).

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1 The abbreviation used is: SGOT, serum glutamic-oxaloacetic transaminase.
2 To whom requests for reprints should be addressed.
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MATERIALS AND METHODS

Patients. All patients had histologically proven advanced carcinoma, for whom either previous therapy had failed or no other form of therapy offered reasonable hope of cure or significant palliation. Patients with severe malnutrition, persistent vomiting, recurrent gastrointestinal bleeding, serum creatinine > 1.5 mg/dl, any increase in direct reacting serum bilirubin, or previous radiation therapy to either the entire pelvis or lumbosacral spine were excluded. Therapy was deferred at least 4 weeks after any previous major surgical procedures, radiotherapy, or chemotherapy (6 weeks for patients receiving nitrosoureas). All patients were ambulatory and received treatment as outpatients. The median age of patients was 57 years with a range of 31 to 78. Eleven patients had colorectal carcinoma; 5 had adenocarcinomas of unknown origin; 3 had pancreatic carcinomas; 3 had gastric carcinomas; 3 had lung carcinomas; and 1 each had carcinoma of the liver, gallbladder, esophagus, and parotid. Nine patients had no prior therapy, 1 had radiotherapy only, 15 had chemotherapy only, and 4 had chemotherapy and radiotherapy.

Clinical Studies. The following studies were obtained within 3 days prior to initiation of therapy: WBC, hemoglobin, platelet count, differential WBC count, urinalysis, serum creatinine, SGOT, alkaline phosphatase, direct and total bilirubin, electrocardiogram, and chest X-ray. Weight, symptomatic status, and performance status were assessed on the first day of therapy. All parameters, as well as a complete physical examination, were repeated at 3-week intervals. WBC and platelet counts were obtained twice weekly, and SGOT and serum creatinine were obtained once weekly as long as the patient remained on the study. Patients were entered on the study in groups of 3 and observed for a minimum of 3 weeks counting from the last day of treatment before new patients were entered at the next dosage level. Courses were repeated at 6-week intervals provided patients remained stable or improved. Patients having no toxicity following their initial course of treatment were eligible for treatment at the next dosage level. Written informed consent was obtained from each patient.

Lyophilized indicine N-oxide, supplied by the Division of Cancer Treatment, National Cancer Institute, Bethesda, Md., was dissolved in distilled water to a concentration of 100 mg/ml, and the appropriate dose was given without further dilution by i.v. injection over 3 to 4 min daily for 5 consecutive days. Daily dose levels studied were 0.15, 0.3, 0.45, 0.675, 1.0, 1.5, 2.25, 2.7, and 3.0 g/sq m.

Assays. Indicine N-oxide and indicine were measured in plasma and urine by a gas chromatographic method with a 63Ni electron capture detector as previously reported (2). Venous blood samples were obtained on Days 2, 3, 4, and 6. Blood samples were withdrawn into evacuated heparin-containing tubes. Plasma was separated after low-speed centrifugation and stored at -70°C until assay. A urine sample was collected prior to treatment, then as frequently as patients could void following treatment for up to 6 hr, and finally as a single sample until 24 hr after treatment. Conjugates of indicine N-oxide and indicine in urine were determined after hydrolysis in 0.5 N HCl at 100°C for 1 hr or after incubation with β-glucuronidase (Boehringer Mannheim, Indianapolis, Ind.), 20 units/ml at pH 4.5 for 12 hr at room temperature.

Pharmacokinetic analyses were conducted by using the NONLIN computer program. The biexponential decline in the plasma concentrations of indicine N-oxide was fitted by nonlinear least-square regression analysis without weighting to the equation C = Ae^-t+ Be^-t. C is the plasma concentration of indicine N-oxide at time t after the administration of indicine N-oxide; A and B are the intercepts at t = 0, and α and β are the fast and slow disposition rate constants.

RESULTS

Clinical Toxicology. Dose-limiting toxicity was myelosuppression (Table 1). After initial courses of treatment at daily doses up to 1.5 g/sq m, there was little myelosuppression. The first 3 patients receiving their initial treatment with indicine N-oxide at daily doses of 2.25 g/sq m had moderate leukopenia accompanied in 2 instances by thrombocytopenia. Each of these patients had previously been treated with a nitrosourea. At 2.7 g/sq m, 2 of 3 patients previously treated with a nitrosourea had severe leukopenia and thrombocytopenia. The most severely toxic patient, whose WBC remained below 1,200/μl and whose platelet count was below 50,000/μl for over 4 weeks, had received previously 5 courses of trans-1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea (110 mg/sq m) at 10-week intervals as part of a combination regimen also including 5-fluorouracil and ICRF 159. trans-1-(2-Chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea had been discontinued 8 months prior to indicine N-oxide treatment. The other patient with myelosuppression (WBC, 2,500/μl; platelets, 33,000/μl) had received previously only one course of chlorozotocin at 200 mg/sq m. The third patient had no myelosuppression despite extensive previous therapy with multiple nonnitrosourea drugs and one treatment with 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea at 70 mg/sq m.

Table 1. Structural formula of indicine N-oxide.
Because of excessive hematological toxicity at a daily dose of indicine N-oxide at 2.7 g/sq m in patients previously treated with nitrosoureas, we escalated the daily dose to 3.0 g/sq m only in patients not previously treated with a nitrosourea. Two patients treated at this dose had moderate leukopenia (2800 and 3800 WBC/µl) without thrombocytopenia. For all courses, the median day nadir of leukopenia (WBC < 4,100/µl) was Day 19 (range, 11 to 33), and the median day nadir of thrombocytopenia (platelets < 130,000/µl) was Day 18 (range, 14 to 32). The median day to recovery from leukopenia was Day 25 (range, 15 to 46), and the median day to recovery from thrombocytopenia was Day 34 (range, 21 to 43).

There was a suggestion that repetitive courses of indicine N-oxide produce cumulative bone marrow toxicity. Four patients receiving multiple courses at a daily dose ≤ 2.25 g/sq m had definite but mild myelosuppression following their third or fourth course (Table 2, Patients 1 to 4). No patient not treated previously with a nitrosourea had leukopenia or thrombocytopenia after the first course of drug at doses ≤ 2.7 g/sq m (Table 1).

Other toxicities were not of major clinical importance. Mild to moderate nausea and vomiting occurred at all doses, although these symptoms were more frequent at the highest dose. Six of 8 courses at 3.0 g/sq m were associated with mild to moderate nausea (accompanied in 2 instances by vomiting) usually on the first 2 or 3 days of treatment. Hepatic toxicity as detected by increases in SGOT was infrequent, mild, and reversible. Only 3 of 44 evaluable courses were associated with transient elevations in SGOT. Four patients had documented progression of known hepatic neoplastic diseases and could not be evaluated for drug-induced changes in hepatic function.

Reversible increases in serum creatinine (<50% greater than pretreatment value) occurred after 9 of 46 evaluable courses. Two other patients with known ureteral obstruction developed progressive renal insufficiency during treatment with indicine N-oxide. One of these had 2 courses of indicine N-oxide at a daily dose of 2.25 g/sq m. Serum creatinine rose to 1.6 mg/dl during the first course, returning to 1.3 mg/dl at 6 weeks. During the second course, serum creatinine rose to 1.7 by the eighth day and reached 2.4 mg/dl by Day 42. The second course of treatment was associated with greater hematological toxicity than was the first course (platelet count, 39,000 versus 105,000), suggesting that impaired renal function increases the hematological toxicity of indicine N-oxide.

Ten of 37 courses at daily doses ≤ 2.25 g/sq m were associated with decreases in serum hemoglobin of between 1 and 2.4 g/dl over the first 5 days of treatment. At higher doses, however, anemia did not occur, and in no instance was hemolysis documented.

Pharmacological Studies. Plasma elimination of indicine N-oxide was determined in 3 patients each at daily doses ranging from 0.45 to 3.0 g/sq m (Chart 2). The data for each dose level were approximated best by a 2-compartment model with elimination from the central compartment. At doses of 0.45, 0.675, 1.0, and 1.5 g/sq m, the means of the constants characterizing the model were: k12 (forward distribution rate constant), 0.60 ± 0.17 min⁻¹ (S.E.); k21 (backward distribution rate constant), 0.11 ± 0.05 min⁻¹; k10 (elimination rate constant), 0.14 ± 0.05 min⁻¹; V1 (volume of the central compartment), 159 ± 68 ml/kg; and V2 (volume of peripheral compartment), 655 ± 37 ml/kg (Table 3). At the highest dose, 3.0 g/sq m, the half-life of the distributive phase was longer and the total body clearance was lower than at lower doses.

At least one patient at each dose level up to 1.5 g/sq m daily had pharmacokinetic studies repeated on the fifth day of drug

### Table 2

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<th>Lowest platelet count (x10³/µl)</th>
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<td>3.1</td>
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</table>

Chart 2. Plasma concentrations of indicine N-oxide following i.v. administration of indicine N-oxide at the following doses: x, 450 mg/sq m; •, 1000 mg/sq m; ■, 1500 mg/sq m; ▲, 3000 mg/sq m. Points, mean from 3 patients.
Table 3
Pharmacokinetic parameters for indicine N-oxide

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<th>Dose (g/sq m)</th>
<th>Half-life (min)</th>
<th>Apparent volume of distribution</th>
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<td>Distributive phase</td>
<td>Postdistributive phase</td>
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<tr>
<td>0.45</td>
<td>3.7 ± 1.2a</td>
<td>171.7 ± 35.7</td>
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<tr>
<td>0.675</td>
<td>1.1 ± 0.6</td>
<td>120.7 ± 65</td>
</tr>
<tr>
<td>1.0</td>
<td>1.7 ± 1.1</td>
<td>101.8 ± 50.5</td>
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<tr>
<td>1.5</td>
<td>0.9 ± 0.2</td>
<td>90.6 ± 24.5</td>
</tr>
<tr>
<td>3.0</td>
<td>40.3 ± 30.0</td>
<td>85.6 ± 41.8</td>
</tr>
</tbody>
</table>

a Mean ± S.E. of 3 patients.

administration. No differences in pharmacokinetic parameters were noted between the first and fifth days of treatment. At a daily dose of 3.0 g/sq m, there was accumulation of indicine N-oxide over the first 2 days of treatment, reaching a peak of approximately 18 µg/ml 24 hr after the second dose and remaining at that level 24 hr after each subsequent dose.

Indicine, the free base of indicine N-oxide, was detected in plasma after administration of indicine N-oxide at doses of 1.0 g/sq m or greater, but it could be quantitated with precision only after the highest dose, 3.0 g/sq m. The initial plasma concentration of indicine fell rapidly over the first 15 min, then rose reaching a peak value of approximately 10 µg/ml at about 1 hr, and remained relatively constant over the next 4 hr, while the plasma concentration of indicine N-oxide declined from a peak concentration of 350 µg/ml to 70 µg/ml at 4 hr.

Indicine N-oxide and indicine were detected in the urine of patients receiving indicine N-oxide at all dose levels. As shown in Chart 3, the urinary excretion of indicine N-oxide and indicine over 24 hr was variable, although there was a correlation between the amount of each component excreted and the dose of indicine N-oxide administered. Approximately 40% of the total dose of indicine N-oxide was recovered within 24 hr in the urine as parent compound and approximately 2% of the total dose as indicine. (The preparations of indicine N-oxide administered to patients contained less than 0.05% indicine.) Approximately 10% of indicine N-oxide in the urine was in the form of a nonglucuronide conjugate. About 18% of indicine in the urine was in the form of a glucuronide conjugate, and approximately 33% was as other (acid-labile) conjugates.

Therapeutic Effect. No objective responses were noted. Two patients with carcinoma of the colon had stability of disease for approximately 6 months, and 1 patient with carcinoma of the colon has remained stable for more than 6 months. A fourth patient with carcinoma of the esophagus had symptomatic improvement after 2 courses of indicine N-oxide but progressed at 3.5 months. Two other patients with carcinoma of the pancreas have remained stable for more than 5 and 6 months, respectively.

DISCUSSION

The major toxic effect in humans of indicine N-oxide given by slow i.v. injection daily for 5 consecutive days is myelosuppression. The severity of myelosuppression is enhanced in patients who have had prior treatment with nitrosoureas. The effect of prior treatment with other drugs on toxicity of indicine N-oxide could not be assessed. Although toxic nephrosis and abnormalities in liver function were consistently noted in large animal toxicity studies, at the dosages used in this study significant impairment of hepatic and renal function was not seen.

The effects of the pyrrolizidine alkaloids on hematopoietic function have not been systematically studied (3, 11). Anemia associated with liver disease has been reported in animals of many species chronically exposed to the alkaloid (12), but there is little information concerning effects on leukocyte and platelet production. Sundareson (19) reported hepatocellular damage and a decrease in the number of hematopoietic cells in the livers of fetal mice exposed to senecionine in vitro. Levin and Novachenko (5) noted hepatic injury and pancytopenia associated with marked erythroblastosis and delayed granulocytic maturation in the bone marrow of adult rats given weekly injections of heliotrine for 1 to 8 months. Our findings that...
indicine N-oxide produces marked myelosuppression in humans without concomitant hepatotoxicity, raise the possibility that hematological toxicity is mediated by a mechanism other than that responsible for hepatoxicity.

The hepatotoxic effects of the pyrrolizidine alkaloids (and their N-oxides when administered p.o.) have been attributed to their metabolism to pyrrolic compounds capable of alkylation (3, 6, 10). Indicine N-oxide, by analogy to the N-oxides of many other pyrrolizidine alkaloids, can only be dehydrogenated to W-oxide, by analogy to the W-oxides of many other pyrrolizidine alkaloids. This metabolism to pyrrolic compounds capable of alkylation (3, 6, 10). Indicine N-oxide, present in the plasma and urine of our patients treated with indicine N-oxide, the concentrations of indicine were only a few percentages of the concentrations of indicine N-oxide. Since the cytotoxic activity of indicine N-oxide is no greater and is probably less than the activity of an equimolar dose of indicine N-oxide (against murine P388 leukemia implanted i.p. in C57BL x DBA/2 F1 mice), we consider it unlikely that the cytotoxicity of indicine N-oxide is dependent upon metabolism to indicine and subsequent formation of pyrrolic intermediates (14).

We had an opportunity to study only 3 patients at each dose level of indicine N-oxide. The striking increase in the half-life of the distribution phase and the decrease in total body clearance at 3.0 g/sq m compared to values at lower doses (Table 3) suggest dose-dependent kinetics. The large S.E. of the means of pharmacokinetic parameters at all doses indicated considerable variability among patients, making it impossible to be certain of this point. Additional studies of metabolism and elimination of indicine N-oxide, including fecal and biliary excretion, are planned.

We have demonstrated the presence of small amounts of indicine N-oxide and indicine (~2% of total dose) in the bile of rabbits over 24 hr following i.v. administration of indicine N-oxide (15). Since only 40% of the total dose given to humans (65 to 85% in rabbits) can be accounted for by urinary excretion, significant hepatic elimination in humans is a distinct possibility. Thirteen of our patients had abnormal plasma concentrations of hepatic enzymes, but none had severe impairment of liver function (no increase in direct reading bilirubin). There was no discernible relationship between these abnormalities in hepatic function and drug toxicity or pharmacokinetic parameters.

Indicine N-oxide should be evaluated for antitumor activity in Phase II studies. It is the first pyrrolizidine alkaloid N-oxide to be studied in humans and lacks the acute hepatotoxic effects associated with other alkaloids of remarkably similar structure. Limiting toxicity is dose-dependent reversible myelosuppression, although repetitive courses have a cumulative effect on the severity of leukopenia and thrombocytopenia. Patients previously treated with nitrosoureas are more sensitive to the myelosuppressive activity of indicine N-oxide. We recommend a daily dose of 3.0 g/sq m for 5 consecutive days by slow i.v. injection (3 to 5 min) for patients not previously treated with a nitrosourea. Although a few patients will not have recovered fully from myelosuppression until the sixth week, the majority can be retreated every 5 weeks. The toxicity of indicine N-oxide in patients with impairment of renal and/or hepatic function remains to be studied.

In subsequent early Phase II studies, we have used a dose of 2.25 mg/sq daily for 5 days in patients with prior nitrosourea therapy. Three of 4 patients adequately observed have severe myelosuppression. Based on these findings, we recommend that indicine N-oxide either not be used or be given in greatly reduced dose to patients treated previously with nitrosoureas or other agents known to produce cumulative bone marrow toxicity, e.g., mitomycin C.

REFERENCES

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