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Somnolence, hypotension, and metabolic acidosis following high-dose teniposide treatment in children with leukemia*

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Summary. This report describes an unexpected adverse effect in three children receiving teniposide at 3–5 times the conventional dosage (i.e. 200 mg/m^2) plus cytarabine as part of continuation therapy for acute lymphocytic leukemia. Pharmacokinetic studies in each patient had demonstrated high teniposide clearances, and thus the increased dosage requirements were necessary to attain plasma concentrations similar to those expected for patients with average drug clearance. At 3–4 h after the beginning of the 4-h simultaneous infusions of teniposide and cytarabine, these patients experienced somnolence, hypotension, and metabolic acidosis. The adverse events were associated with elevated teniposide plasma concentrations during the infusions compared with those in patients receiving similar doses without toxicity, and clinically significant ethanol concentrations, presumably from the teniposide formulation. Blood concentrations of cremophor and histamine, which are also constituents of the teniposide formulation, were not measured. In addition, concomitant therapy with antiemetic agents in patients who may have been mildly volume-depleted due to emesis may also play a contributory role. Prolonging the infusion time for patients receiving teniposide doses above 500 mg/m^2 will avoid excessive teniposide and ethanol plasma concentrations and minimize the risk of this potentially serious side effect.

Introduction

Teniposide is an effective drug for the treatment of pediatric malignancies, including acute lymphocytic leukemia [5, 17]. Previous studies from this institution have demonstrated substantial pharmacokinetic variability for teniposide, a relationship between response and drug concentrations, and the ability to adjust dosage regimens to achieve targeted concentration profiles [18, 19]. Thus, for patients with drug clearances that are 2–3 times higher than the median population values, dosages are proportionally increased to achieve similar concentration profiles to those achieved in patients with average population clearances. While the primary dose-limiting toxicities of teniposide are myelosuppression and mucositis, hypersensitivity reactions have been reported [8]. In the context of a clinical study evaluating the control of pharmacokinetic variability, unusually high dosages of teniposide were administered, and an unexpected acute adverse event involving somnolence, hypotension, and metabolic acidosis was observed in three children.

Patients and methods

The 3 patients described in this report are among 120 consecutive children enrolled on the current St. Jude Children's Research Hospital protocol (TOTAL-XII) for newly diagnosed acute lymphocytic leukemia (ALL). Clinical remission of leukemia had been achieved following 6 weeks of induction therapy with a combination of prednisone, vincristine, daunorubicin, L-asparaginase, teniposide, and cytarabine. The teniposide and cytarabine during induction were given as three fixed doses of 200 and 300 mg/m^2, respectively, and there were no pharmacokinetic studies at this time. Patients then began post-remission continuation therapy, which consisted of daily 6-mercaptopurine (75 mg/m^2) p.o. and weekly methotrexate (40 mg/m^2 i.v. or i.m.) for 2 years. During the first year, the 6-mercaptopurine and methotrexate therapy was interrupted every 6 weeks by either high-dose methotrexate (weeks 1, 13, 25, 37, 49) or teniposide plus cytarabine (weeks 7, 19, 31, 43, 55). Patients were randomized to receive either fixed dosages of methotrexate (1500 mg/m^2), teniposide (200 mg/m^2), and cytarabine (300 mg/m^2) or pharmacokinetically adjusted dosages to achieve a target area under the concentration-time curve (AUC), defined as values between the 50th and 90th percentiles predicted for patients receiving fixed doses of each drug. The patients described in this report were randomized to the adjusted-dose group. Only the teniposide and cytarabine doses given as post-remission-induction therapy were adjusted. Teniposide and cytarabine were administered simultaneously as 4-h infusions on days 1 and 3 of

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each scheduled course. Blood samples were collected at 1.5, 3.5, 8, and 20 h after the start of each infusion. Plasma was assayed for cytarabine and teniposide by high-performance liquid chromatography, using ultraviolet and electrochemical detection, respectively [21, 22]. Pharmacokinetic parameters were determined by fitting a two-compartment model to each patient's data, using Bayesian estimation [19]. Whole-blood ethanol concentrations were obtained with the 1.5-h and 3.5-h samples and measured by gas chromatography. All teniposide dosages were administered as a 1 mg/ml solution in 5% dextrose in water for injection. Teniposide at 1 mg/ml concentration has been shown in our laboratory to be stable by visual inspection and assay for up to 24 h at room temperature. Teniposide was supplied by Bristol Laboratories through the National Cancer Institute and contained the following constituents per 50 mg ampule: teniposide 50 mg, benzyl alcohol 150 mg, *N*, *N*-dimethylacetamide 300 mg, polyoxyethylated castor oil (cremophor) 2.5 g, maleic acid qs pH 5.1, and ethanol 40% (w/v).

To assess potential contributing factors, age, sex, antiemetic regimen, concomitant intrathecal therapy, teniposide and cytarabine dosage, teniposide and cytarabine plasma concentrations during infusion, teniposide and cytarabine AUC, teniposide volume of distribution and clearance, liver, and renal function tests were evaluated for all children treated according to this protocol with teniposide dosages ≥ 500 mg/m^2. Statistical differences among these potential factors were assessed using the Mann-Whitney test.

Results

Case reports

Case 1. A 2-year-old girl received her third course of treatment with cytarabine at 590 mg/m^2 and teniposide at 648 mg/m^2. The highest dose of teniposide during previous courses was 614 mg/m^2. Diphenhydramine 1 mg/kg and promazine 1.25 mg/kg were administered i.v. prior to chemotherapy. Based on data from course 2, the estimated systemic clearance for teniposide was 36 ml min^{-1} m^{-2} and that for cytarabine, 965 ml min^{-1} min^{-2}. Within 5 min after completion of the 4-h cytarabine and teniposide infusions, she became dusky, pale, and unresponsive. A blood pressure of 93/66 mmHg, heart rate of 144 beats/min and respiratory rate of 32 breaths/min were noted. Oxygen saturation was 84% by pulse oximetry and oxygen administration by mask was begun. Aggressive hydration, methylprednisolone, and diphenhydramine were administered. Blood pressure fell to 70 mmHg by palpation within 35 min after the end of the infusions. Laboratory values obtained 1 h after the event were: sodium 126 mEq/l, potassium 2.4 mEq/l, chloride 99 mEq/l, bicarbonate 13 mEq/l, and glucose 271 mg/dl. The patient remained unresponsive for approximately 45 min. Two hours after the initial event, the patient was lethargic, but responsive, with a blood pressure of 95/60 mmHg. At that time venous blood gases showed pH 7.30, pO_2 33 mmHg, pCO_2 32 mm Hg, and bicarbonate 15.9 mEq/l. The patient's blood pressure returned to normal approximately 10 h after the event began. Plasma ethanol concentrations obtained 30 min before and 2 h after the event were 80 mg/dl and 10 mg/dl respectively. Serum electrolytes and venous blood gas values were normal 12 h after chemotherapy and there were no apparent sequelae. The patient subsequently received teniposide 270 mg/m^2 and cytarabine 450 mg/m^2 over 4 h without reaction.

Case 2. A 10-year-old girl received her fifth course of treatment with cytarabine at 230 mg/m^2 and teniposide at 893 mg/m^2. The highest previous teniposide dose was 805 mg/m^2. Diphenhydramine 1 mg/kg and prochlorperazine 0.08 mg/kg were administered i.v. prior to chemotherapy. Based on data from course 4, the estimated systemic clearance for teniposide was 57 ml min^{-1} m^{-2} and that for cytarabine was 650 ml min^{-1} m^{-2}. Approximately 2 h after the start of the teniposide and cytarabine infusions, the patient was noted to be drowsy, nauseous, and vomiting. At 3.5 h into the infusion the patient was noted to be diaphoretic, unresponsive, and hypotensive. The infusions were stopped and the blood pressure was 62 mmHg on palpation, heart rate 112 beats/min, and respiration was irregular. The pO_2 by pulse oximeter was 96%. Lactated Ringer's solution and hydrocortisone 500 mg were administered i.v. Oxygen was administered by face mask. The patient remained unresponsive for approximately 60 min. On admission to the ICU her blood pressure was 101/69 mmHg, heart rate 131 beats/min, and respiratory rate 18 breaths/min. She was lethargic but responsive. Laboratory values obtained 1 h after the event were: sodium 126 mEq/l, potassium 2.6 mEq/l, chloride 95 mEq/l, bicarbonate 20 mEq/l, and glucose 335 mg/dl. The venous blood gas showed pH 7.29, pCO_2 45 mmHg, pO_2 58 mmHg, and bicarbonate 21.5 mEq/l. Whole-blood ethanol concentrations obtained immediately before the event and 2 h after were 130 mg/dl and 60 mg/dl, respectively. Serum electrolytes and venous blood gas values were normal within 12 h and there were no apparent sequelae. The patient subsequently received teniposide 720 mg/m^2 and cytarabine 230 mg/m^2 over 8 h without reaction.

Case 3. A 3-year-old white girl received her third course of treatment with cytarabine at 210 mg/m^2 and teniposide at 567 mg/m^2 over 4 h. The highest previous teniposide dose was 556 mg/m^2. Diphenhydramine 1 mg/kg and promazine 1.25 mg/kg were administered i.v. prior to chemotherapy. Based on data from course 2, the estimated systemic clearance for teniposide was 28 ml min^{-1} min^{-2} and that for cytarabine was 265 ml min^{-1} min^{-2}. Approximately 3.75 h into the infusion, the patient was noted to have mottled skin, in addition to which she had grunting respirations and was severely somnolent with a blood pressure that was difficult to determine. The teniposide and cytarabine infusions were stopped and normal saline, hydrocortisone 100 mg, and epinephrine 0.1 mg were administered i.v. Oxygen was administered by face mask and the patient was transferred to the ICU with a blood pressure of 104/73 mmHg, heart rate 162 beats/min, and respiratory rate 13 breaths/min. Laboratory values obtained 1 h after the event were: sodium 136 mEq/l, potassium 2.7 mEq/l, chloride 104 mEq/l, bicarbonate 9 mEq/l, and glucose 379 mg/dl. Venous blood gases at that time showed pH 7.07, pCO_2 32 mmHg, pO_2 44 mmHg, and bicarbonate 9.3 mEq/l. Whole-blood ethanol concentrations obtained 10 min prior to the event and 1.5 h post event were 60 mg/dl and 30 mg/dl, respectively. Normal saline, sodium bicarbonate, and dopamine (10 μg kg^{-1} min^{-1}) were required for treatment of persistent hypotension. Serum electrolytes, venous blood gas values, and blood pres-

Table 1. Disposition of teniposide ≥500 mg/m² and cytarabine in three courses in which somnolence, hypotension, and metabolic acidosis and 16 courses in which no reaction occurred. Teniposide concentrations during infusion and teniposide AUC were significantly greater in the courses in which a reaction occurred. No reaction group includes courses from the three children described in the text. Median (range)

	Reaction	No reaction
Number of children	3	5
Number of courses	3	16
Age (years)	3.5 (2–10)	7(2–17)
Teniposide dosages (mg/m² over 4 h)	648 (567–893)	658 (511–840)
Teniposide mean peak concentration (μM)*	93 (77–116)	59 (40–80)
Teniposide AUC (μM·h)**	974 (478–1125)	395 (265–668)
Cytarabine dosages (mg/m² over 4 h)	230 (200–590)	429 (230–675)
Cytarabine mean peak concentration (μM)	7 (4–20)	9 (5–15)

* $P = 0.0086$; ** $P = 0.029$

sure returned to normal within 12 h and the dopamine infusion was discontinued. The patient was then discharged with mild residual somnolence. The patient subsequently received teniposide 523 mg/m² and cytarabine 220 mg/m² over 8 h without reaction.

When comparing the characteristics of patients receiving teniposide dosages greater than 500 mg/m², the peak teniposide plasma concentrations were significantly higher in patients experiencing these adverse effects than in 5 patients receiving similar dosages (16 courses) with no adverse effects (median 93 μM vs 59 μM; $P = 0.0086$) (Table 1). The teniposide AUC was also significantly greater in the group experiencing this adverse effect (median 974 μM·h vs 395 μM·h; $P = 0.029$). The high teniposide plasma concentrations implies increased concentrations of other components in the teniposide formulation (e.g. ethanol, cremophor), although cremophor concentrations and histamine release were not measured. No other variables were found to be different between the two groups of patients.

Discussion

The occurrence of somnolence, hypotension, and metabolic acidosis in these three patients receiving high dosages of teniposide was associated with high plasma concentrations of teniposide and ethanol. They received teniposide dosages that were 3–5 times higher than conventional dosages (200 mg/m²), due to previous high teniposide clearance. However, the plasma concentrations during and shortly after the end of the infusions were higher than predicted and were significantly higher than those measured in other courses of teniposide at dosages of greater than 500 mg/m² without adverse effects. The measured values ranged from 77–116 μM. By 4 h after the end of the infusion, teniposide concentrations had fallen to less than 40 μM in all cases, within the 50–90th percentiles as predicted by the pharmacokinetic model for each subject.

In one of the three subjects, teniposide clearance was determined while the patient was receiving anticonvulsant therapy that was subsequently discontinued. The clearance estimate was substantially lower and the AUC much higher than that determined with concomitant anticonvulsant therapy. This suggests the possibility of anticonvulsant induced teniposide clearance that we will investigate in further studies.

Previously reported adverse reactions to teniposide include urticaria, angioedema, pruritus, hypotension, and anaphylactoid/anaphylactic reactions have not been shown to be related to concentration [8]. Hypersensitivity reactions to teniposide have been attributed to the parent compound or an excipient in the teniposide formulation [14]. A recent review reported an incidence of hypersensitivity reactions of 3.6% to 6.5% in teniposide-treated patients but serious hypotension or altered sensorium were infrequent complications [14]. Reactions can occur during or after teniposide infusions regardless of previous teniposide exposure. Kellie et al. [8] reported a 5.8% incidence of hypersensitivity reactions among 2549 doses of teniposide administered to 108 children with acute lymphocytic leukemia, with flushing, chills, maculopapular rash, pruritus, or periorbital edema reported most frequently. Six children had severe reactions (bronchospasm, cyanosis, hypotension), but the majority of the reactions were grade I–II (by National Cancer Institute criteria [13]) and occurred during infusions of teniposide. The three patients described in the present report had received 6–10 doses of teniposide prior to their adverse event, with no apparent difficulties. The absence of symptoms upon rechallenge, the paucity of constitutional symptoms of allergic reaction (rash, urticaria, angioedema) and the relatively late occurrence of the event make hypersensitivity reactions less likely.

Cytarabine was given to all patients but was not likely to have contributed to the adverse effects observed. Cytarabine has been given at doses 5 times higher than those used in this protocol, with no reports of symptoms similar to those reported here [7]. In addition, both dose and measured cytarabine concentrations were lower in the patients with the adverse effects (Table 1).

Due to poor solubility in water, the current teniposide formulation contains 2.5 g of polyoxyethylated castor oil (cremophor) and 40% (w/v) ethanol per 50 mg teniposide. The usually recommended concentrations for administration of teniposide is not to exceed 0.4 mg/l. For higher doses, especially when given over short infusion times, we have used a concentration of 1 mg/l and shown it to be stable for up to 24 h. This is necessary to keep the volume of fluid infused within tolerable amounts. Although this pharmaceutical formulation is typically diluted in various amounts of intravenous solutions prior to infusions, over 25 g/m² cremophor and over 20 g/m² ethanol are administered when teniposide dosages exceed 500 mg/m².

Cremophor has been implicated as a probable cause of anaphylactoid reactions following administration of cremophor-containing medications [1, 11, 23]. Cardiopul-

monary effects of cremophor include a marked and sustained decrease in systemic blood pressure, pulmonary pressures, and cardiac output, with increased pulmonary vascular resistance [4]. The reaction is associated with an increase in plasma concentrations of histamine and catecholamines [4, 10].

Ethanol causes cardiovascular toxicity, central nervous system depression, and direct vasodilation. Signs of ethanol intoxication may be noted at levels above 50 mg/dl in children [9]. Ethanol concentrations exceeded 60 mg/dl in all three patients at the onset of signs and symptoms and were sufficiently elevated to have contributed significantly to the toxicities observed. In addition, ethanol-induced diuresis could have contributed to the electrolyte abnormalities seen in the three patients, although the dilutional effect of greater then 125 ml m^{-2} h^{-1} of 5% dextrose in water was also a plausible cause [2, 3, 15, 16].

To estimate the maximum teniposide infusion rate (mg m^{-2} h^{-1}) which would yield ethanol dosages likely to produce blood concentrations above 50 mg/dl, simulations were performed with previously reported ethanol pharmacokinetic parameters [6]. Teniposide dosages ≥ 500 mg/m^2 contain 20 g/m^2 of ethanol and are likely to produce blood ethanol concentrations ≥ 50 mg/dl, if the infusion duration is less than 4 h. For this reason, teniposide doses ≥ 500 mg/m^2 are now administered as an 8-h infusion, with hourly monitoring of vital signs. These slower infusion rates minimize the likelihood of clinically significant ethanol concentrations as well as transiently elevated teniposide plasma concentrations. Three subsequent patients receiving teniposide doses of 700–800 mg/m^2 over 8 h had no detectable ethanol concentrations (i.e. ≤ 10 mg/dl) during or following infusions of teniposide, and no acute adverse effects have been observed. The AUC values obtained for the patients receiving the 8-h infusions were all within the target range. In addition, teniposide has been administered at similar or higher doses by continuous infusions over 24–72 h without unexpected systemic adverse effects [18, 19].

Additive central nervous system depressant activity following concomitant ethanol and phenothiazine medications has been described [12, 20]. This results in impaired psychomotor function, as well as excessive sedation, hypotension, and respiratory depression. Additionally the alpha-1 blockade effect of phenothiazine can result in impaired compensatory vasoconstriction. All three children received phenothiazines prior to chemotherapy as antiemetic therapy and had symptoms and signs consistent with phenothiazine effects. However, virtually all children treated according to this protocol received concomitant phenothiazines and teniposide. Therefore, it is uncertain whether phenothiazines played any role in the complications of these patients.

In conclusion, the syndrome of somnolence, metabolic acidosis, and hypotension following the administration of high-dose teniposide and cytarabine in three children with acute lymphocytic leukemia was associated with transiently elevated teniposide plasma concentrations, teniposide AUC, and clinically significant ethanol concentrations. Ethanol intoxication, cremophor toxicity, and transiently excessive teniposide concentrations could each contribute to these complications. Prolonging the infusion time and close monitoring are recommended for patients receiving teniposide doses above 500 mg/m^2.

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