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Clinical report

Plasma pharmacokinetics of etoposide (VP-16) after i.v. administration to children

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The pharmacokinetics of etoposide (VP-16), a semi-synthetic derivative of podophyllotoxin, were studied in 16 pediatric patients (median age 8.3 years; range 4 months to 22 years) including two girls with Down's syndrome (DS). The drug was administered as infusions (1–3 h) in a wide range of doses (9–322 mg, corresponding to 32–210 mg/m^2). The area under the plasma concentration versus time curve (AUC), dose normalized by the body surface area, was independent of age, while AUC normalized by the dose in mg/kg increased with increasing age of the patients. The interpatient variability of AUC, normalized for the dose in mg/m^2, was 23% (CV) compared to 32% (CV) normalized for the dose in mg/kg. The terminal half-life time was 4.1 h (median value; range 2.0–7.8 h). The pharmacokinetics of etopside in children with DS and chromosomally normal children were very similar with regard to systemic drug exposure and plasma half-life time. From the pharmacokinetic point of view it was therefore not necessary to make any dose modifications in the two girls with DS. The two DS patients did not experience any enhanced degree of toxicity from their etoposide treatments. The results support that dosing of etoposide to children should be based on body surface area. [© 2000 Lippincott Williams & Wilkins.]

Key words: Children, dosing, Down's syndrome, etoposide, pharmacokinetics, VP-16.

Introduction

Etoposide (VP-16), a semi-synthetic derivative of podophyllotoxin, is widely used in pediatric oncology. It acts by interaction with DNA topoisomerase II and has activity against a large number of malignancies, as a single agent or in combination regimens. Children with Down's syndrome (DS) have at least a 10- to 30-fold increased risk of leukemia, both lymphocytic and myeloblastic, as compared to chromosomally normal children (NDS).[1,2] Children with DS experience a higher rate of therapy complication of their antineoplastic treatment as compared to NDS.[3] The aim of the present investigation was to study dosing of i.v. etoposide infusions to children and to evaluate if there exists a pharmacokinetic rationale for not using standard doses of etoposide to children with DS. The etoposide pharmacokinetics were studied in a wide range of doses after i.v. administration to 16 patients, aged 4 months to 22 years, including two girls with DS.

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Patients and methods

Patients

The study was approved by the Local Ethics Committee. Oral informed consent was obtained from the parents and, when appropriate, also from the children prior being included into the study.

Sixteen patients (nine females and seven males) participated in the present study. One male patient was sampled twice, 4 weeks apart. The median age of the patients was 8.3 years (range 4 months to 22 years). Their diagnoses included acute lymphocytic leukemia, Ewings's sarcoma, medulloblastoma, rhabdomyosarcoma and teratoma. Two girls with DS, aged 3 and 7.4 years, were included in the study.

Treatment schedule

Etoposide was given as a part of treatment protocols togeather with other antineoplastic agents including carboplatin, cisplatin, cytosinarabinoside, epirubicin, ifosphamide, lomustine, methotrexate (MTX) and vincristine. The administered doses of etoposide were within the range 9–322 mg, corresponding to 32–210 mg/m^2.

Drug administration

An IVAC Model 561 Infusion Pump (Medical Instrument Systems Scandinavia, Täby, Sweden) was used for i.v. administration of etoposide, using infusion times within the range 1–3 h. The infusion pump was neither temporarily stopped nor was the infusion rate changed during the administration of the drug.

Sampling procedure

Blood (3 ml) was drawn from a central venous access immediately prior to, and at 1, 2, 6, 8 and 12 h after the end of infusion. In four of the patients, who received etoposide as a 2 h infusion, additional samples were collected at 0.5, 1, 1.75 and 20 h after the start of the infusion. In these four patients, blood was drawn from a peripheral vein during infusion. Blood was collected into heparinized glass test tubes (Vacutainer® Hemogard®; Becton Dickinson, Meyland Cedex, France). The plasma fraction was isolated by centrifugation, transferred into microcentrifuge tubes and stored at −70°C until analysis.

Analytical procedure

Etoposide in plasma was determined by reversed-phase liquid chromatography.[4]

Pharmacokinetics

The pharmacokinetics of etoposide were evaluated by compartment analysis. Initial estimates were obtained from the JANA stripping program.[5] The final estimates of the pharmacokinetic parameters were obtained from the PC-NONLIN program (version 2.0).[6] The reciprocal of measured plasma concentrations were used as weights in the iterative procedure.

The optimal pharmacokinetic models were established by visual inspection of the fitted plasma concentration time curves and from the weighted squared residuals using the *F*-ratio test.[7]

Statistics

The Mann–Whitney *U*-test was used for the comparison of values from two independent populations. Correlation was established by the Spearman rank correlation test. Dispersion of data from two populations was compared by the Bartlett's test for equal variances. $p<0.05$ was considered as statistically significant.

Results

The plasma concentration versus time profile of etoposide was described either by the one- or two-compartment model. The interpatient variability of the area under the plasma concentration versus time curve (AUC) was 6-fold. AUC was not only dependent on the dose in mg/m^2 ($p<0.0001$), but also on the absolute dose in mg (p= 0.0056), as established by multiple linear regression including age, sex, dose in mg and dose in mg/m^2 as independent variables.

In the entire patient population AUC, dose normalized by the body surface area, was independent of age (Figure 1). In contrast, AUC normalized by the dose in mg/kg increased with increasing age of the patients, $p<10^{-3}$ (Figure 2).

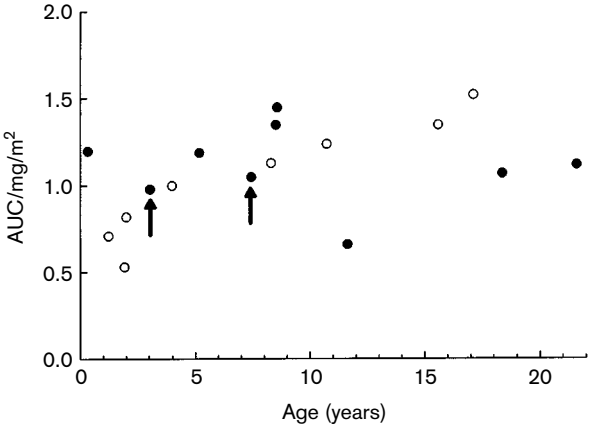

Figure 1. AUC, dose normalized by body surface area as a function of age. AUC is expressed as μg·h/ml. Closed symbols: females; open symbols: males; arrows: data from children with DS. R_s=0.4562; p=0.07.

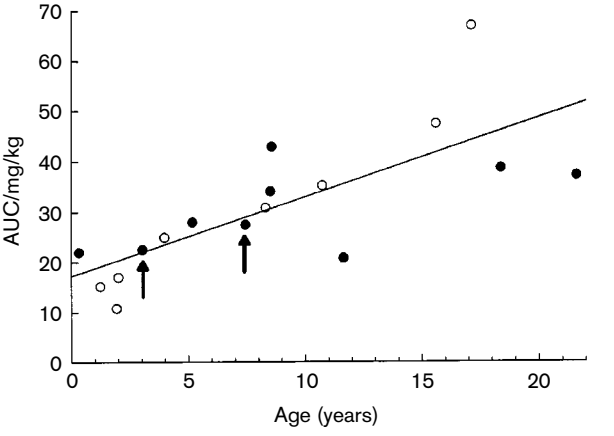

Figure 2. AUC, dose normalized by body weight as a function of age. AUC is expressed as μg·h/ml. Closed symbols: females; open symbols: males; arrows: data from children with DS. R_s=0.8113; $p<10^{-4}$.

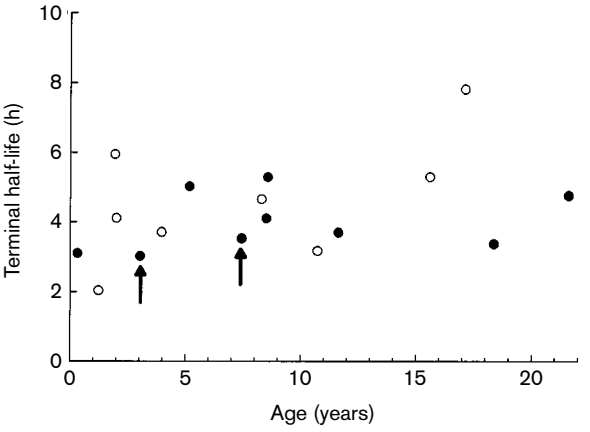

Figure 3. Terminal half-life and age. Closed symbols: females; open symbols: males, arrows: data from children with DS. R_s=0.3529; p=0.17.

In females neither AUC/mg/m^2 nor AUC/mg/kg were dependent on age (Figures 1 and 2). In males AUC/mg/m^2 as well as AUC/mg/kg increased with increasing age (Figures 1 and 2), $p<10^{-3}$ and $p<10^{-3}$, respectively.

There was no difference in AUC/mg/m^2 or AUC/mg/kg between males and females. The terminal half-life ($t_{½}$) was not age dependent (Figure 3), with a median value of 4.1 h (range 2.0–7.8 h). The $t_{½}$ did not differ between males and females, but the interpatient variability of $t_{½}$ was higher among the males, p=0.026.

In the two children with DS neither the dose-normalized AUC values nor the $t_{½}$ values of etoposide deviated from data observed in the NDS patients (Figures 1–3).

Discussion

Most antineoplastics have a narrow therapeutic index. Despite adjustment of doses for body surface area there remains widespread variability in both clinical and pharmacokinetic outcome for patients. The sources of this variability are unclear and cast doubt on the usefulness of normalization for body surface area as a means of optimizing treatment for individual patients. In adults, normalization of the dosage of antineoplastic drugs using body weight or body surface area is actually of very limited value to predict drug exposure, expressed as AUC, as a consequence of the large interpatient pharmacokinetic variability.[8,9]

The pharmacokinetics of etoposide in children, administered as i.v. infusions over periods of 1 h to several weeks using a wide range of doses have extensively been studied.[10–16] Etoposide plasma clearance in children shows marked interpatient variability and dosing based on body surface area or in infants body weight does not compensate for interindividual differences.[16] Pharmacokinetically guided dosing is feasible, but is likely to be of most benefit in patients with abnormalities of renal or hepatic function, or in children previously exposed to cisplatin.[17] Also, there is no established therapeutic interval, which is a prerequisite for therapeutic drug monitoring.

Initially, we used an extensive sampling protocol including nine blood samples for evaluation of the etoposide pharmacokinetics in the children. In these patients the plasma concentration–time curves were described by the two-compartment model in accordance with earlier findings. However, calculations revealed that the use of only five blood samples drawn at 1, 2, 6, 8 and 12 h post-infusion resulted in AUC values comparable (101.3 ± 13.5%; mean value ± SD) with the AUC values obtained by the more extensive sampling protocol, but with the plasma concentration–time curve described by the one-compartment model.[15] For ethical reasons this less extensive sampling protocol was used in the remaining patients.

The results in the present study support the assumption that dosing of etoposide to children should be based on BSA.[16] Our results from multiple regression analysis also indicated that the pharmacokinetics of etoposide in children is dose dependent, but the increase in AUC/mg/m^2 with increasing dose was not statistical significant using correlation analysis. BSA normalized AUC values showed a very low interpatient variability (CV=23%), despite the large range of doses used in the present study. AUC normalized values based on body weight increased with increasing age of the patients and had a considerably higher interpatient variability (CV= 32%) (Figure 2). Thus dosing of etoposide to children based on body weight is less feasible. The gender differences in age dependency of normalized AUC values observed in Figures 1 and 2 indicate that there might be a need for dose adjustments based on age in males. In particular, risks for underdosing of young males must be considered.

The $t_{½}$ values reported in the present study are in close agreement with earlier observations.[18] No gender differences of the etoposide terminal half-life was observed in children, but in adults a shorter half-life has been observed in women.[19] This difference, as well as the observation of a larger interpatient variability of terminal half-life in males, reported in the present study, are, however, unlikely to be of clinical importance.

Patients with DS have enhanced sensitivity to toxic effects not only of antineoplastics, but also of several other drugs.[20] Thus, it has been observed that patients with DS have a decreased tolerance to MTX and often develop severe symptoms of bone marrow and gastrointestinal toxicity.[21–23] Altered MTX pharmacokinetics with higher plasma concentrations and lower plasma clearance was observed in two children with DS, which might have contributed to the higher incidence of MTX-associated toxicity observed,[22] whereas a pharmacokinetic difference has been contested by other investigators.[23] Prolonged renal MTX excretion has also been noticed in children with DS treated for acute lymphoblastic leukemia, despite normal renal function tests.[24] Increased sensitivity of doxorubicin associated with a lowered clearance was observed in one of the patients with DS participating in the present study (data not shown).

The pharmacokinetics of etopside in children with DS and NDS are very similar with regard to systemic drug exposure and plasma half-life (Figures 1–3). From the pharmacokinetic point of view we can therefore conclude that it was not necessary to make any dose modifications in the two girls with DS. The two DS patients did not experience any enhanced degree of toxicity from their etoposide treatments.

Acknowledgments

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