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Research Paper

The Systemic Absorption of Etoposide after Intravaginal Administration in Patients with Cervical Intraepithelial Lesions Associated with Human Papillomavirus Infection

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Purpose. The purpose of this study was to determine the systemic absorption and the release of etoposide in cervical tissue administered via a vaginal ovule to women diagnosed with cervical intraepithelial lesions associated with human papillomavirus (HPV).
Methods. Fifteen women with low- and high-grade intraepithelial neoplasia confirmed by colposcopic test received a 50-mg intravaginal etoposide dose three times a week for 3 weeks. At the end of the study period, paralleled with the last ovule administered, blood samples were collected over a period of 24 h, and *in situ* cervical samples were obtained at 3 and 10 h after drug administration. Etoposide concentrations were determined in plasma and in *in situ* cervical samples using the high-performance liquid chromatography method with electrochemical detection.
Results. Pharmacokinetic analyses of plasma data indicated low or lack of systemic exposure of etoposide after the vaginal administration. Nevertheless, high concentrations of etoposide were found in all *in situ* cervical samples, indicating that etoposide could be released from its pharmaceutical formulation.
Conclusions. The results of the study suggest that the etoposide administered as intravaginal ovule is safe and tolerable and apparently could be a suitable option in patients with cervical intraepithelial neoplasia. Clinical results and the true impact on HPV infection and evolution of dysplasia need to be confirmed.

KEY WORDS: etoposide; human papillomavirus; intraepithelial dysplasia; vaginal ovule.

INTRODUCTION

Cervical carcinoma is a major gynecological cancer in several low-income countries. Although detection routine screening programs have been implemented since 1975, an increased rate of new cases has also been detected (1,2). Human papillomavirus (HPV) has been proposed as an etiological factor in the pathogenesis of this cancer (3–6). Viral replication produced after infection is a characteristic in proliferative benign lesions. Cervical condyloma induced by HPV is associated with the development of both squamous cell and adenocarcinoma of cervix cancer. To date, there have been several studies suggesting that some drugs, such as 5-fluorouracil, bleomycin, and etoposide, have significant keratolytic effects on a wide spectrum of lesions produced by HPV (7,8).

Etoposide is a semisynthetic derivative of epipodophyllotoxin with significant *in vitro* and *in vivo* antineoplastic action, acting through the inhibition of DNA topoisomerase II activity (9,10). It is used against a wide variety of tumor types, including small-cell lung cancer, testicular cancer, non-Hodgkin's lymphoma (11), and breast cancer (12,13).

Good results have also been reported in patients with cervical carcinoma after using etoposide. Kobayashi and Kawashima (14) demonstrated that etoposide (oral dose of 50 mg/day, administered during 14 consecutive days followed by a 2-week discontinuation) during 8 months was effective in a patient with recurrent cervical cancer. Recent reports on oral etoposide in patients with cervical cancer support these findings (15–17). In addition, it was shown that administration of 50-mg/day etoposide for 21 consecutive days did not produce severe side effects. Thus, oral administration of etoposide for 21 days resulted effective in cervical cancer.

There are few studies on topical administration of antineoplastic drugs via a vaginal ovule formulation in cancer patients. The application of these antineoplastic drugs by vaginal administration has been used more commonly for treatment of cervical dysplasia (7,18,19). In this work, the use of etoposide administration via vaginal ovule in patients with cervical intraepithelial lesions was planned.

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Although the majority of these studies have evaluated efficacy of vaginally administrated drugs, it is also important to know the systemic absorption because a large amount of antineoplastic drugs shows adverse effects after oral or intravenous (i.v.) administration. Adverse effects include thrombocytopenia, neutropenia, gastrointestinal toxicity (nausea, vomiting), abdominal discomfort, diarrhea, anorexia, paresthesias, alopecia, low blood pressure, mucositis, anemia, headache, and fatigue. These side effects would not be acceptable to patients with any type of cancer.

On the other hand, drug absorption from vaginal administration could vary depending on dissolution properties of the formulation and retention or residence time in the vagina (20,21). In addition, there is little information available on the biopharmaceutics of vaginal dosage forms. Therefore, a systemic absorption study of etoposide is necessary for evaluating the amount of drug that could be delivered from its pharmaceutical formulation. Consequently, the purpose of this work was to evaluate the systemic absorption of etoposide and its release in cervical tissue after intravaginal dose in patients with cervical intraepithelial lesions HPV infection associated.

MATERIALS AND METHODS

Subjects

A prospective, single-arm trial with 30 women was carried out with the following criteria: intraepithelial neoplasia, HPV+, 20–60 years old, and 64 ± 12 kg of body weight. Among these, 15 consecutive women were selected to perform pharmacokinetic evaluation. The study was carried out according to the tenets of the Declaration of Helsinki promulgated in 1964 and approved by the Ethics and Scientific Committee of the National Institute of Cancerology in México City. Before their inclusion, all study subjects signed an informed consent. Each volunteer underwent a complete physical examination including pelvic examination, patient history, vital signs, electrocardiogram, and routine laboratory tests prior to and during each visit. Diagnosis of HPV was established with clinical, histopathologic, and hybrid capture system techniques. No subject was taking any medication at the time of the study, excluding oral contraceptives.

Study Variables

Clinical, biochemical, HPV, pelvic, and colposcopic tests were evaluated at each visit. Conization with histopathologic review was performed at the end of study.

In this article, the main biodisposition characteristics of the pharmaceutical formulation used are reported.

Drugs and Reagents

Etoposide was obtained from Laboratorios Lemery, S.A. de C.V. (México City). Chromatographic-grade acetonitrile and methanol were obtained from E. Merck (Darmstadt, Germany). All other reagents were of analytical grade. High-quality water employed to prepare solutions was obtained with the use of a Milli-Q Reagent Water System (Continental Water Systems, El Paso, TX, USA).

Drug Administration and Sample Collection

Patients received a 50-mg vaginal etoposide dose (prepared as gelatin capsules and provided by Laboratorios Lemery S.A. de C.V.) every 3 days for 21 days. Upon final administration, blood samples were collected at 0, 0.25, 0.50, 0.75, 1.0, 1.5, 2.0, 4.0, 6.0, 8.0, 10.0, and 24 h after drug application. Plasma was separated by centrifugation and was immediately frozen at −20°C until etoposide analysis.

Plasma etoposide concentrations were determined using a high-pressure liquid chromatographic method (HPLC) previously published (22). Briefly, 0.5 ml of plasma was extracted with a mixture of dichloromethane/ether; organic phase was dried under nitrogen and reconstituted with a 100-μl mobile phase. Mobile phase consisted of acetonitrile/acetate buffer 50:50 (v/v). Waters Chromatography HPLC system (Milford, MA, USA) was used with rehodyne manual injector, 600S pump, Symmetry C18 column and electrochemical detector.

To establish whether etoposide applied via vaginal administration was released from its pharmaceutical formulation and, in consequence, exposed to epithelial tissue, cervical swabs were collected with cytobrush at 3 and 10 h after drug application, and total etoposide amount was determined by HPLC as in plasma samples.

Table I. Biochemical Characteristics of Participating Patients

	Basal	Visit 1	Visit 2	Visit 3	Visit 4	Final	Significance
White blood cell	6.5 ± 1.7	6.4 ± 2.0	8.9 ± 11	6.6 ± 2.0	8.7 ± 13	6.6 ± 1.9	0.5731
Neutrophils (10^9/l)	62 ± 10	62 ± 10	61 ± 15	64 ± 10	58 ± 15	61 ± 11	0.5831
Hemoglobin (g/dl)	12 ± 1.4	12 ± 1.4	12.6 ± 1.3	12.2 ± 1.5	12.4 ± 1.5	12.6 ± 1.4	0.9297
Platelets (mm^3)	279 ± 71	268 ± 87	281 ± 71	308 ± 76	300 ± 76	275 ± 80	0.4370
Creatinine (g/dl)	0.85 ± 0.20	4.5 ± 17	0.81 ± 0.13	1.15 ± 1.54	0.84 ± 0.19	0.85 ± 0.18	0.3749
Calcium (mg/100 ml)	9.5 ± 0.6	9.5 ± 1.2	9.6 ± 0.6	9.6 ± 0.5	9.6 ± 0.7	9.8 ± 0.6	0.9224
Urea nitrogen (mg/100 ml)	26 ± 7.0	28 ± 7.0	26 ± 8.0	25 ± 6.0	25 ± 6	27 ± 6.0	0.7138
Bilirubin (mg/dl	0.54 ± 0.3	0.46 ± 0.2	0.47 ± 0.2	0.48 ± 0.2	0.70 ± 1.0	0.50 ± 0.2	0.5833
Lactate dehydrogenase (U/l)	284 ± 51	268 ± 48	273 ± 52	266 ± 47	280 ± 50	271 ± 48	0.8366
Albumin (g/dl)	4.1 ± 0.24	4.14 ± 0.36	4.27 ± 0.344	4.20 ± 0.23	4.24 ± 0.27	4.28 ± 0.26	0.3103
Aspartate aminotransferase (U/l)	20 ± 7.0	23 ± 11.7	23 ± 13.0	22 ± 10.8	26 ± 13.7	26 ± 13.0	0.5706
Alanine aminotransferase (U/l)	18.8 ± 10.2	19.2 ± 10.7	17.8 ± 8.7	17.4 ± 6.7	19.9 ± 9.9	19.0 ± 10.2	0.9644

Table II. Response to Treatment Among Total Study Population (Number of Patients)

Extension of human-papillomavirus-associated lesion upon colposcopic examination[a]	Basal	Final
Without lesion	0	6[b]
<25	12	14[b]
26–50	16	10
51–75	2	0
>75	0	0

[a] Expressed as percentage of the observed cervix.
[b] Patients without lesion or with lesions <25% increased after the treatment due to regression of larger pretreatment lesions.

RESULTS

Table I shows the biochemical characteristics of study patients. All patients had normal levels of the following parameters before and in every visit made for clinical evaluation: white blood cell count, neutrophils, hemoglobin, platelets, serum creatinine, electrolytes (including calcium), blood urea nitrogen, and normal hepatic function (as defined by serum levels of total bilirubin, lactate dehydrogenase, albumin, aspartate aminotransferase, and alanine aminotransferase). During the study, any side effect (myelosuppression, headache, nausea, vomiting, anorexia, alopecia, etc.) and compliance after vaginal etoposide administration were recorded.

Because of the fact that the probable systemic absorption and the release in cervical tissue after intravaginal dose of etoposide was the main purpose of the study, clinical outcome and treatment results will be published elsewhere. Briefly, among the 30 studied patients, we found 83.3% overall response (complete and partial response). Table II shows the clinical results as percentage of the observed cervix of the number of patients that presented lesions at pretreatment and final times. It is worth mentioning the fact that there were no lesions greater than 50% of the observed cervix at the end of the treatment, and consequently, there was a greater proportion of patients without lesions or with lesions of less than 25%. No evidence of progression was noted.

In accordance with drug absorption data, only three patients showed detectable levels of etoposide in plasma samples. Comparing plasma etoposide concentrations after the 50-mg vaginal etoposide dose, it was found that these concentrations were much lower than those found in plasma samples drawn from two patients with cancer 1 h after the 50-mg oral etoposide dose (Fig. 1). Cervical samples showed high levels of etoposide, demonstrating that etoposide was released from its pharmaceutical formulation and remained at least 10 h in the cervical tissue (Fig. 2).

Figures 3 and 4 show chromatographic separation of etoposide and internal standard from both plasma and cervical samples. Retention times for internal standard (2-acetamidophenol) and etoposide were 4.0 and 8.0 min, respectively. No interfering peaks occurred at these times.

DISCUSSION

Cervical cancer continues to be the major cause of cancer mortality in women in developing countries and represents approximately 25% of cancer-related deaths in Mexican women (23). Some studies have demonstrated a relationship between HPV, cervical intraepithelial neoplasia, and invasive carcinoma of cervix. Additionally, it has been predicted that

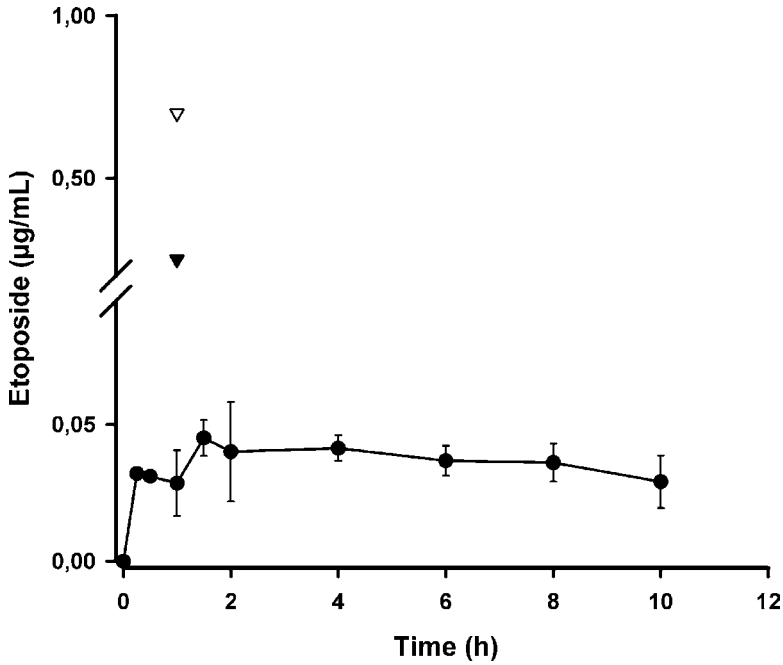

Fig. 1. Plasma etoposide concentrations observed in three patients with cervical intraepithelial lesions receiving a 50-mg vaginal dose (●); data are presented as mean ± standard deviation. Cancer patients receiving an oral 50-mg dose of etoposide; ▼, patient 1; ▽, patient 2.

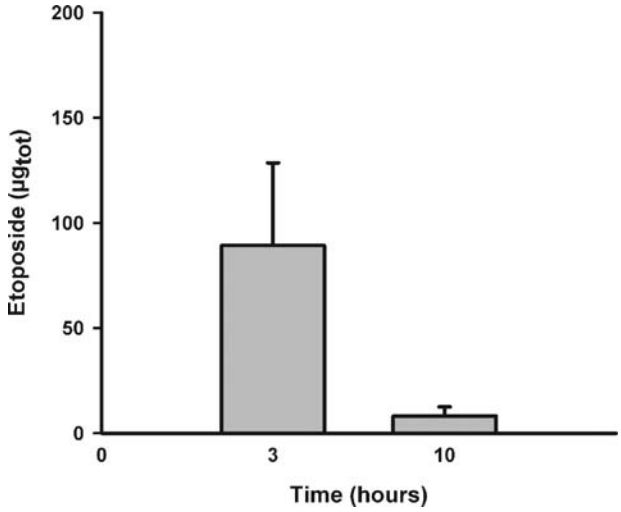

Fig. 2. Etoposide concentration in cervical swab samples from six patients with cervical intraepithelial lesions receiving an etoposide intravaginal administration of 50 mg. Data are presented as mean ± standard error of mean.

within 10 years, 66% of all dysplasia—without medical intervention—would progress to carcinoma *in situ*. It is important to bear these data in mind to be able to search for new alternatives for cervical dysplasia treatment before progression to malignant lesions.

Conization and cryotherapy techniques have been the treatment of choice to eradicate cervical dysplasias associated with HPV lesions (24). However, these methods are so invasive that newer treatments are currently under investigation to improve intraepithelial neoplasia management.

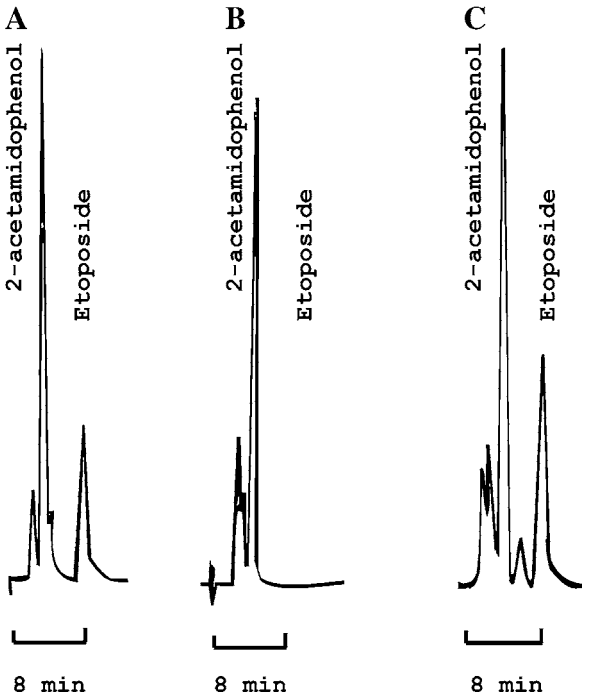

Fig. 3. Typical chromatogram of human plasma extracts. Plasma spiked with 0.5 μg/ml of etoposide and 0.05 μg/ml of internal standard (2-acetamidophenol; A). Plasma sample drawn from a patient 2 h after a 50-mg vaginal etoposide dose (B). Plasma sample drawn from a patient 1 h after a 50-mg oral etoposide dose (C).

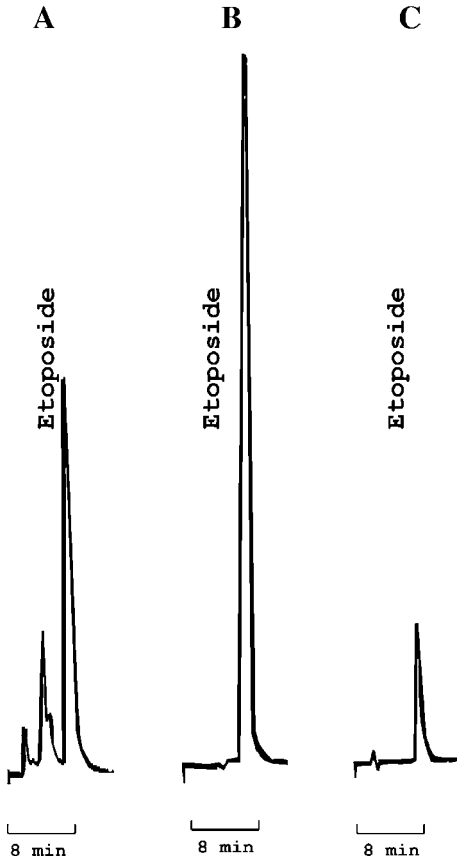

Fig. 4. Typical chromatogram of human vaginal extracts. Solution spiked with 80 μg of etoposide (A). Cervical samples collected from a patient 3 h (B) and 10 h (C) after a 50-mg vaginal etoposide dose.

Application of antineoplastic drugs by vaginal administration has been used for the treatment of cervical dysplasia (19,25,26). In this work, the vaginal administration of etoposide was studied as a new alternative for cervical dysplasia. The safety and tolerability of etoposide were determined from a vaginal ovule administration to women with diagnosis of cervical intraepithelial lesions associated with HPV.

This study demonstrated low systemic absorption of etoposide from vaginal administration; etoposide concentrations reached levels of approximately 0.02–0.06 μg/ml. This indicated that amount of absorbed etoposide remained lower than that of a therapeutical oral dose. There are many studies on the oral pharmacokinetics of etoposide. Although a clear therapeutic plasma concentration window has not yet been established, there is evidence suggesting that antitumor activity can be achieved at plasma concentration of approximately 0.5–1.0 μg/ml (27,28). It is also widely accepted that plasma levels of approximately 10 μg/ml are associated with side effects (29,30). In an early study of oral etoposide carried out with Mexican women, maximum concentration reported was approximately 2.0 μg/ml at 0.5–1 h (31). In accordance with our data, no patients showed plasma concentrations around this value after vaginal administration. With the data obtained with two cancer patients, etoposide concentration at 1 h after oral dose of 50 mg was 0.5 μg/ml, indicating that the

method employed here can be used confidently for detecting plasma levels of etoposide.

When total amount of etoposide was determined in cervical samples, these were absolutely higher than those found in plasma. This indicated that etoposide was not absorbed into the systemic blood circulation from vaginal administration. Nonetheless, etoposide could be delivered from its pharmaceutical formulation and be exposed to cervical tissue at least during 10 h. In addition, no systemic side effects and local necrosis occurred because of vaginal administration of etoposide at the used dose.

CONCLUSION

Results presented in this study suggest that etoposide administration via intravaginal ovules is safe to use and tolerable in patients with cervical dysplasia. Moreover, it shows advantages compared with oral or i.v. administrations because the intravaginal administration represents a noninvasive method and can be self-applicable. In addition, it can be considerably less aggressive and cheaper than other treatments utilized in cervical neoplastic lesions. It can also represent an alternative cervical method to elude conization and cryotherapy.

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