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Short Communication

Modified high-performance liquid chromatographic method for the determination of ganciclovir in plasma from patients with severe renal impairment

R. BOULIEU*, N. BLEYZAC and S. FERRY

Institut des Sciences Pharmaceutiques et Biologiques, Laboratoire de Pharmacie Clinique, 8 Avenue Rockefeller, 69373 Lyon Cedex 08 (France) and Hôpital Cardiovasculaire et Pneumologique, Service Pharmaceutique, B.P. Lyon-Montchat, 69393 Lyon Cedex 03 (France)*

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ABSTRACT

Using the rapid and sensitive high-performance liquid chromatographic (HPLC) method previously described for the analysis of ganciclovir in plasma, we have observed an interfering peak which co-elutes with the peak of ganciclovir in plasma samples from heart-transplant patients with severe renal insufficiency. A slight modification of this method allows the separation of the two peaks. The modified HPLC method, presented in this paper, is suitable for the accurate determination of ganciclovir in plasma from patients with severe renal impairment.

INTRODUCTION

Ganciclovir is a nucleoside analogue that exhibits antiviral activity against viruses of the herpes group, including cytomegalovirus [1]. Ganciclovir is an effective therapy for cytomegalovirus infection in immunocompromised patients, such as patients with acquired immunodeficiency syndrome or immunosuppressive therapy following organ transplantation [2].

Recently, we have developed a high-performance liquid chromatographic (HPLC) method [3] for the determination of ganciclovir in plasma. The method was used for drug monitoring in heart-transplant patients under ganciclovir theraphy for severe cytomegalovirus infection.

When using this method for the analysis of plasma samples from patients with severe renal impairment, we have observed on the chromatograms an interfering peak that coelutes with the peak of ganciclovir. Thus, in this paper, we present a slight modification of the previous method for accurate analysis of ganciclovir in plasma from patients with severely impaired renal function.

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EXPERIMENTAL

Chemicals

Ganciclovir was purchased from Syntex (Paris, France), 9-methylxanthine (internal standard) was from Fluka (Buchs, Switzerland), and potassium dihydrogenphosphate, orthophosphoric acid and perchloric acid were obtained from Merck (Nogent/Marne, France).

Chromatographic conditions

The chromatographic apparatus consisted of the following components: a Model 420 pump equipped with a Model 430 variable-wavelength detector (all from Kontron, St. Quentin les Yvelines, France), a Model 712 WISP sample processor (Waters, St. Quentin les Yvelines, France) and a D2000 Chromato-integrator (Merck).

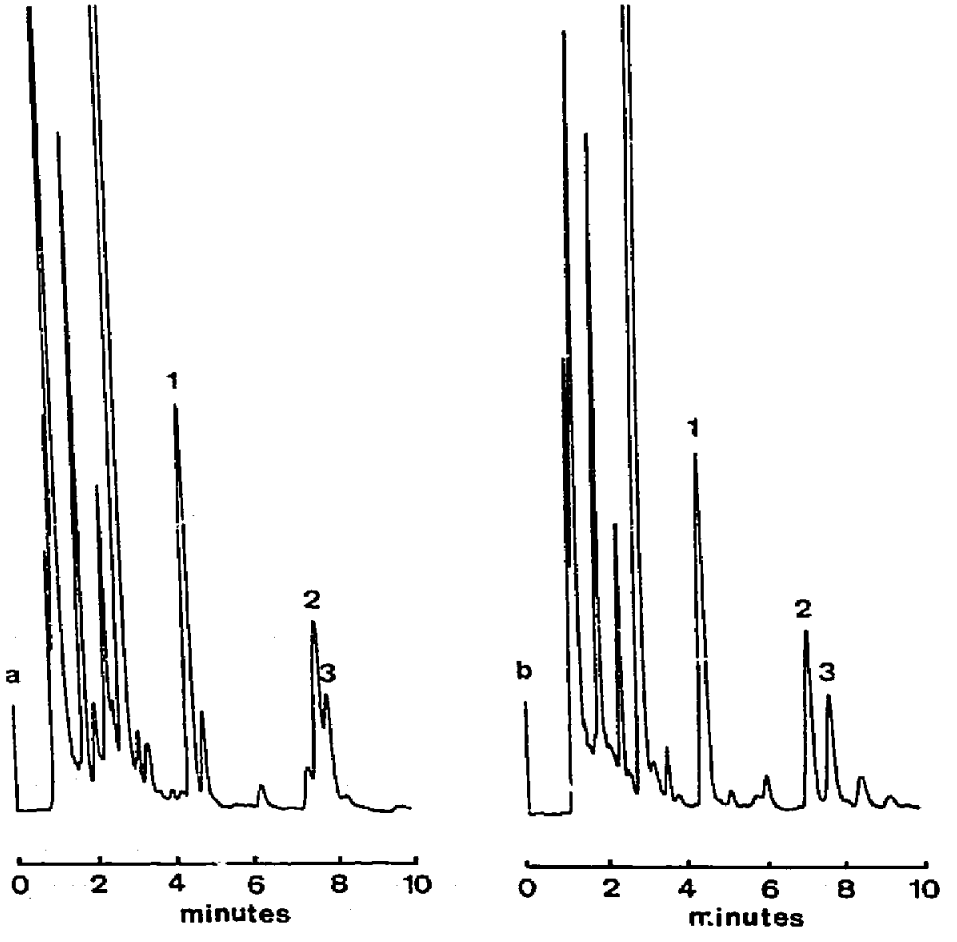

Fig. 1. Chromatograms of a plasma sample from a heart-transplant patient with severe renal insufficiency under ganciclovir therapy (1.25 mg/kg per day): (a) pH of the mobile phase adjusted to 5.25; (b) pH of the mobile phase adjusted to 3.50. Peaks: 1 = 9-methylxanthine (internal standard); 2 = ganciclovir; 3 = unknown interfering peak.

The chromatographic system consisted of Hypersil ODS (3 μm) as stationary phase and 0.02 *M* potassium dihydrogenphosphate as mobile phase with the pH adjusted to 3.50. The flow-rate was 1.5 ml/min and the detection wavelength was 254 nm.

Sample preparation

Blood samples were collected in heparinized tubes and deproteinized by perchloric acid according to the previous method [3].

RESULTS AND DISCUSSION

The chromatograms of a plasma sample from a heart-transplant patient with severe renal insufficiency are shown in Fig. 1. The modification of the pH of the mobile phase from 5.25 to 3.50 allowed the separation of the two peaks. At pH 3.50, ganciclovir is resolved from the unknown interfering peak whereas at pH 5.25, the two peaks coeluted. The interfering peak was found only in plasma samples from patients with renal impairment. The peak height does not seem to be correlated with the degree of renal insufficiency. Further investigations are needed for the identification of this compound.

The calibration curve was linear up to 30 mg/l. The minimum detectable amount, defined as a signal-to-noise ratio of 4, was 0.5 ng. The intra-day and inter-day coefficients of variation ($n = 10$) were found to be 3.0 and 2.9%, respectively, at a concentration of 1.0 mg/l, and 2.5 and 0.7% at a concentration of 7.50 mg/l.

Under the conditions used, there was no interference with the compounds of interest by related endogenous compounds, such as uric acid, hypoxanthine, xanthine, guanine and guanosine, or by drugs, such as acyclovir, allopurinol, oxypurinol, azathioprine, 6-mercaptopurine, caffeine and theophylline.

In conclusion, the modified HPLC method presented in this paper is suitable for the accurate determination of ganciclovir in plasma from patients with severely impaired renal function.

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