Comparison *in vitro* felodipine release rate from the original *versus* generic product with controlled release of the drug

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Key words: *felodipine; dissolution study; controlled release; comparison.*

Summary. *After patent protection of original brand is over, there are a lot of generic products occurring on the pharmaceutical market. It may be the way to reduce the price, but on the other hand, one should expect the same quality and almost identity with original brand, because the development of generic drugs is based on pharmacological properties of the original brand. The aim of this study was to compare the similarity of two products with controlled release of felodipine – generic product Presid® and original brand Plendil® – which are commercially available in Czech Republic, based on in vitro dissolution testing. The dissolution test in three dissolution media of increasing pH (1.2, 4.5, and 6.5) for the simulation of physiological pH within the gastrointestinal tract confirmed controlled release of felodipine from the original product Plendil ER 5 mg and Plendil ER 10 mg during the period of 24 hours. The release of felodipine from generic products Presid 5 mg and Presid 10 mg was not controlled for 24 hours as it is indicated in the information leaflet. In the generic products, felodipine release was controlled just for 12 or 18 hours and in this respect did not show similarity with the original brand. Since patients take the drug just once a day in the morning, the controlled release of felodipine, which lasts only 12 to 18 hours, can cause insufficient blood pressure control especially in the most critical morning hours and higher cardiovascular risk.*

Introduction

Felodipine is a calcium antagonist that selectively reduces smooth muscle contractile activity in resistance vessels. Effects on other smooth muscles and myocardium only occur when plasma concentrations of felodipine are much more higher than therapeutic levels. Treatment with felodipine reduces arterial blood pressure by reducing systemic vascular resistance (1). Decreased resistance has been measured in the coronary, renal, hepatic and muscular vascular beds (2). When using calcium antagonists in the patients with heart failure, felodipine and amlodipine proved the most beneficial effects.

Felodipine is used in the treatment of all forms of hypertension and in prophylactic treatment of angina pectoris (stable and vasospastic form) (3, 4). Hypertension is the most important (however reversible when treated) risk factor for most cardiovascular diseases. It is also strongly associated with ischemic stroke, myocardial infarction, end-stage renal disease, and heart failure. Myocardial infarction, sudden cardiac death, ischemic stroke, unstable angina pectoris show a clear circadian variation, exhibiting a peak in the morning hours. This pattern results from the stress arising from tasks and duties of the forthcoming day. Increased vascular tone, arterial pressure, and coagulability – all of them may play their important role. Elevations in plasma cortisol levels are among the best-established endogenous morning changes, and they could enhance coronary-arterial sensitivity to the vasoconstrictor effects of catecholamines. Finally, blood viscosity rises in the morning hours, and the tissue plasminogen activator does not show sufficient increase to compensate for the above-mentioned risks. This imbalance might result in relative attenuation of fibrinolysis that would thus promote a hypercoagulable state. This might increase the risk of otherwise innocuous mural thrombi, which, due to attenuation of mentioned fibrinolysis, can cover minute plaque fissures, grow, and become occlusive in a vessel. Cardiovascular events have a peak incidence in the morning hours as they occur mostly between 6 AM and noon (5). It seems to be necessary to manage smooth blood pressure control within all 24 hours, especially in the morning hours (6, 7).

After patent protection of original branded drug

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expires, there are a lot of generic products occurring on the pharmaceutical market. It may be the way to reduce the price, but on the other hand, one should expect the same quality and almost identity with original brand, because the development of generic drugs is based on pharmacological properties of the original brand. This experimental study compares the drug release of original brand Plendil® ER 5 (10) mg and generic product Presid® 5 (10) mg based on dissolution test. Drug information leaflet of Presid® indicates the continuing felodipine release for the period of 24 hours that enables application of the drug once per day in the morning. As far as a peak incidence of cardiovascular events in the morning hours is concerned, it seems to be vital to maintain the drug release continually for 24 hours.

Materials and methods

For the preparation of dissolution media and standard felodipine solution, purified water and chemicals of analytical grade were used. All methods were used in accordance with European Pharmacopoeia and regulations binding on drugs manufacturers. Cetyltrimethylammonium bromide was used as a solubiliser of very poorly soluble felodipine as it is recommended due to more accurately measurement of very poorly soluble drug release (8).

Preparation of dissolution medium (pH 1.2): 2.0 g of sodium chloride and 4.0 g of cetyltrimethylammonium bromide were dissolved in 500 mL of purified water; 80.0 mL of 1 M hydrochloric acid were added, and the solution was diluted to 1000.0 mL with purified water (7, 8).

Preparation of dissolution medium (pH 4.5): 6.8 g of potassium dihydrogen phosphate and 4.0 g of cetyltrimethylammonium bromide were dissolved in purified water and diluted to 1000.0 mL with purified water (7, 8).

Preparation of dissolution medium (pH 6.5): 41.2 mL of 1 M sodium dihydrogen phosphate, 39.2 mL of 0.5 M disodium hydrogen phosphate, and 4.0 g of cetyltrimethylammonium bromide were mixed and filled up with purified water to 1000.0 mL (9).

Preparation of standard felodipine solution: 50.0 mg of felodipine were dissolved in ethanol (200.0 mL); 5.0 mL of this solution were diluted with dissolution medium to 200.0 mL.

Commercially available products were obtained from pharmacies (Table).

The dissolution tests were carried out from November 2002 to March 2003 in accordance with the recommendations of Czech Pharmacopoeia 2002, European Pharmacopoeia 4.0, and USP XXVI in the paddle apparatus (Sotax AT 7 Smart, Switzerland) at a stirring rate of 100 rpm at 37°C. Six tablets of each product were transferred into a release vessel containing 500 mL of dissolution medium. At predetermined times, 10 mL of the bath volume were automatically withdrawn and filtrated. Felodipine concentrations of the samples were determined using UV spectrometry at a wavelength of 362 nm and appropriate background correction (absorption at 450 nm) because of adjuvants in felodipine tablets. At predetermined times, the amount of the released felodipine was measured which allowed us to calculate the mean rates of the released felodipine per the period of time (in mg/hrs).

The mean values of release rates with their standard deviations from six measurements are presented in Fig. 1–3. Statistical significance was tested using Student's t test for unpaired samples, at a significance level of $P<0.05$.

Results and discussion

Dissolution tests. According to the recommendations for dissolution studies, the similarity of two drugs should be proved by dissolution study *in vitro* in three types of media. The first one is to simulate the conditions in stomach (pH from 1 to 2), the second one the transition between stomach and small intestine (pH about 4.5), and the third one conditions in the small

Table. **Studied products**

Name	Batch	Shelf life up to
Plenil® ER 5 mg	CL 6575	11/2004
Plenil® ER 10 mg	CK 8114	10/2004
Presid® 5 mg	3A105092	05/2003
Presid® 5 mg	3A202103	02/2005
Presid® 10 mg	3A105091	05/2003
Presid® 10 mg	3A105201	12/2004

intestine (pH approximately 6.8) (7, 8). In this study, three dissolution media of increasing pH values (1.2, 4.5, and 6.5) were used to simulate the physiological pH within the gastrointestinal tract.

The present study revealed no discrepancies between the real and declared contents of felodipine in a tablet. The nominal content of original brand Plendil® ER was slightly higher in some dissolution media similarly as original Modip® in Petersen dissolution study (9). Although the measured absorbance was corrected up to background, this correction was not probably sufficient to remove the influence of background at all. Still, and despite the mentioned drawback, this method is officially used (9).

The evaluation of dissolution study should be done in accordance with the recommendations of the European Agency for the Evaluation of Medicinal Products for the similarity factor F_2. If the value of the factor is above 50, the dissolution profiles are more than 90% identical and are considered similar. For determination of the similarity factor F_2, at least three measured values of released amount of the drug should be used: the first one should be within limits of 20–30%, the second one about 50%, and the third at least 80% of released drug. The calculation of similarity factor can include only one value exceeding 85% of the released drug (7, 8). Plendil® as an original brand should be regarded as standard. In this case, however, the felodipine content in Plendil® exceeded the declared value and that is why the similarity factor comparison is not acceptable. For this reason, the rate of drug release is more appropriate. The mean drug release rate for each time interval was calculated.

The characteristics of the controlled release of felodipine in the original brand Plendil ER 5 mg and Plendil ER 10 mg were confirmed during 24 hours in all dissolution media. Drug release was evident also in the last period, between 18 and 24 hours (Fig. 1–3).

The generic drugs, Presid 5 mg and Presid 10 mg, showed only limited controlled release of the drug.

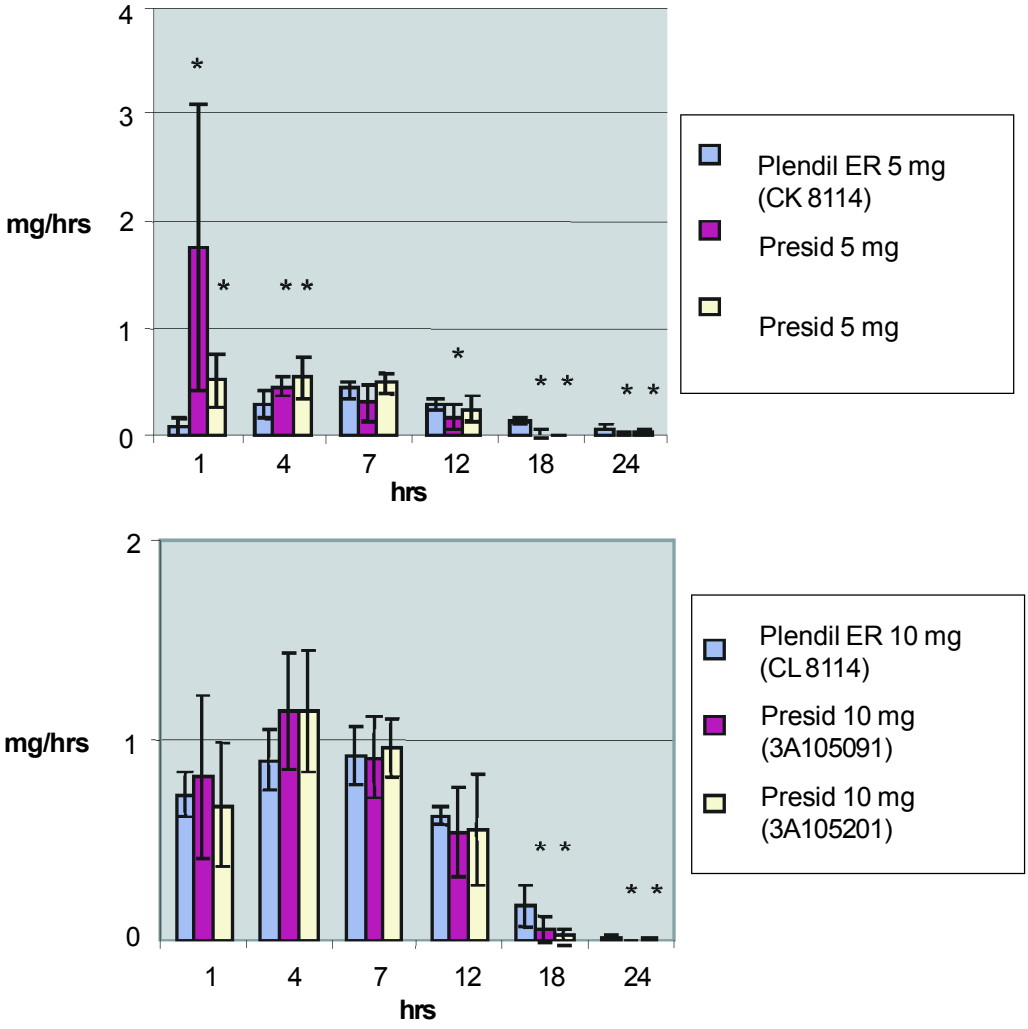

Fig. 1. **Release rate of felodipine in dissolution medium pH 1.2**
Mean values ± standard deviations are shown.
*P<0.05 as compared to reference Plendil ER.

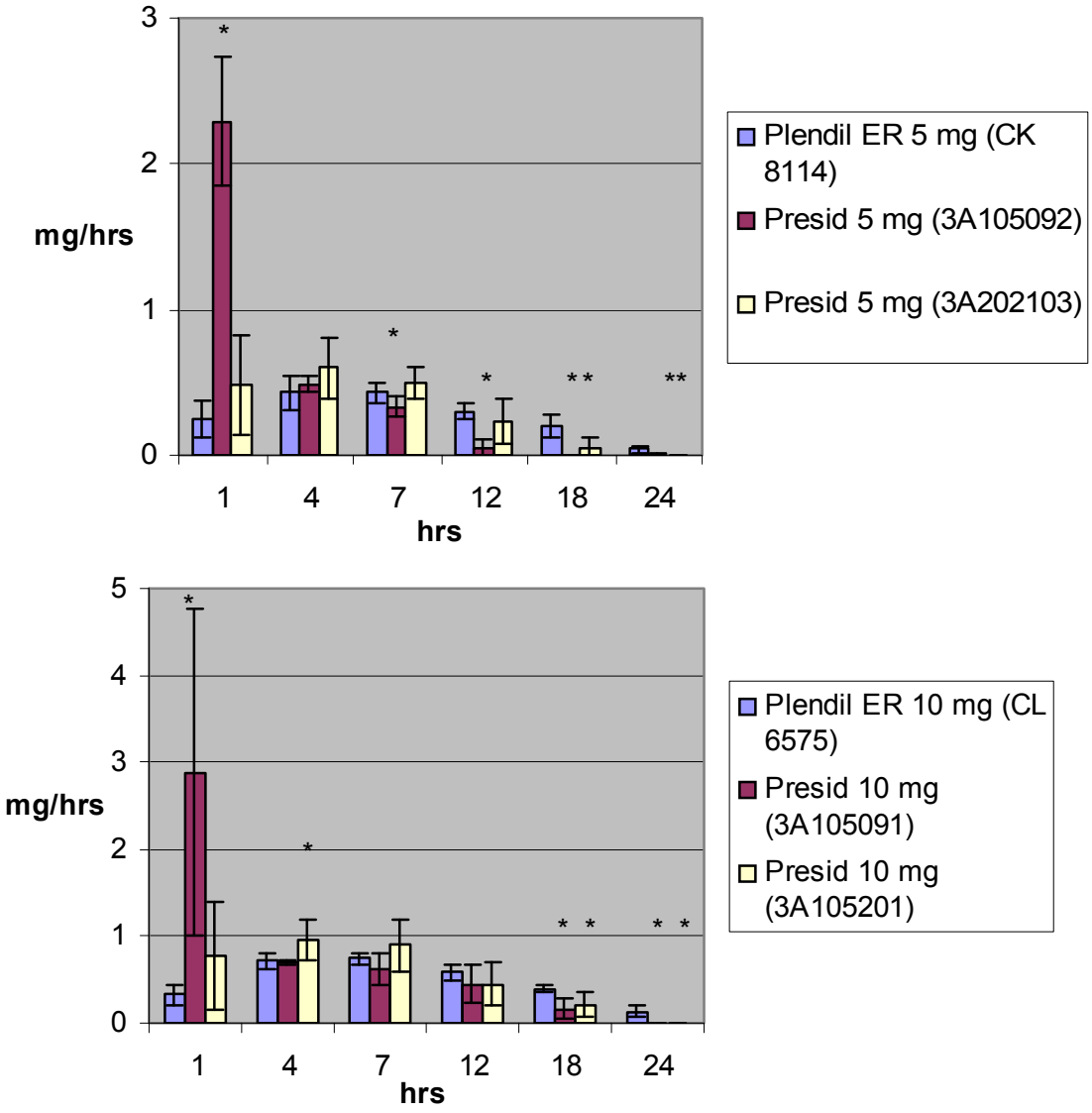

Fig. 2. **Release rate of felodipine in dissolution medium pH 4.5**
Mean values ± standard deviations are shown.
*P<0.05 as compared to reference Plendil ER.

There was no drug release in the period between 18 and 24 hours (Fig. 1–3). Differences compared with the standard (Plendil®) were significant for each batch of Presid® and for each medium (Fig. 1–3). The batches produced earlier (Presid 5 mg 3A105092 and Presid 10 mg 3A105091) controlled the drug release less than the following batches: Presid 5 mg 3A202103 and Presid 10 mg 3A105201. While Presid 5 mg (batch no. 3A105092) showed faster dissolution profile of the drug in all media and differences when compared with the standard (Plendil®) were significant almost for all data (Fig. 1–3), Presid 5 mg (batch no. 3A202103) showed better drug release characteristics during the period of 12 to 18 hours (Fig. 1–3).

Similar results were obtained for Presid 10 mg. Better dissolution profile of the drug appeared also in the latter batch (no. 3A105201). Nevertheless, both batches proved only partial control of the drug release, the period of release did not exceed 18 hours at the most (Fig. 1–3).

Clinical significance. Dissolution testing is considered convenient for prediction of the time-related absorption *in vivo* (10, 11). The results indicated no release of felodipine after 12 or 18 hours in generic product Presid 5 mg and Presid 10 mg; however, in some samples (Presid 5 mg 3A105092 (Fig. 1–3), Presid 10 mg 3A105091 (Fig. 2)), the release of the drug was even faster particularly during the first 4 hours.

As mentioned above, small or minimum drug release can cause insufficient plasma concentration of drug. High incidence of cardiovascular events together

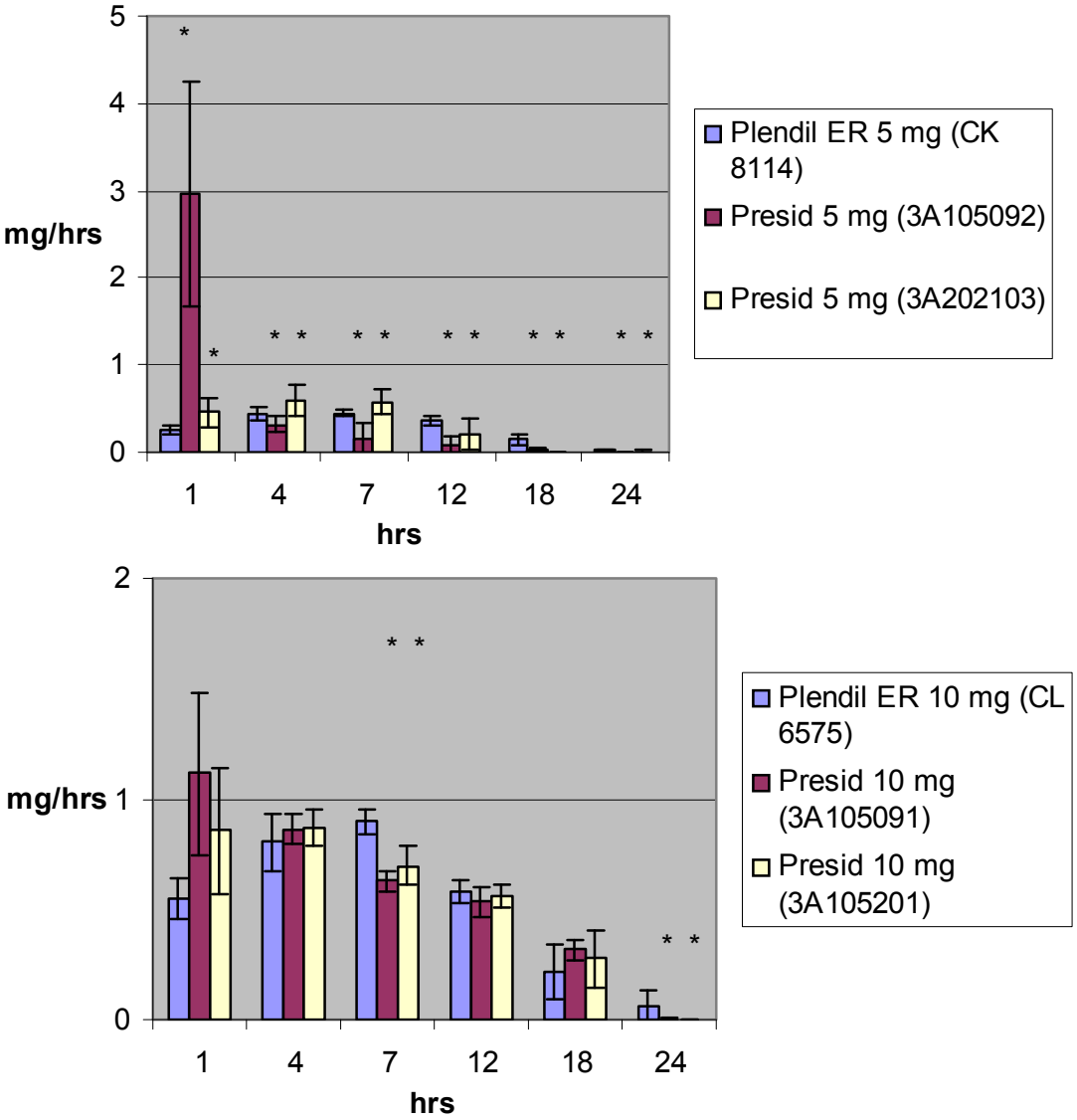

Fig. 3. **Release rate of felodipine in dissolution medium pH 6.5**
Mean values ± standard deviations are shown.
*P<0.05 as compared to reference Plendil ER.

with increasing blood pressure in morning hours can cause serious complications in hypertensive patients. The absence of blood pressure control after 12 hours can be very dangerous especially when the drug is applied in the morning.

In addition, fast release of felodipine after application followed high drug plasma concentration may cause other significant adverse effects. The most dangerous are the rapid drop in systemic blood pressure and tachycardia, as a result. Reflex tachycardia is dangerous especially in patients with angina pectoris (all forms) and heart failure. Other adverse effects, for example palpitation, dizziness, fatigue, flushing, peripheral edema (usually around the ankles), and headache are reported in patients treated with medicaments without a proper retardation (12). There is no doubt, it is not rational to use only 12- or 18-hour-acting form of drug. A 24-hour blood pressure control is necessary to prevent such serious events as stroke or myocardial infarction (13, 14).

Conclusions

The dissolution test confirmed controlled release of felodipine from original products, Plendil ER 5 mg and Plendil ER 10 mg. Experimentally obtained values proved that felodipine release from generic Presid 5 mg and Presid 10 mg was not controlled during the whole period of 24 hours. Insufficient control of the drug release (only 12 or 18 hours) can cause insufficient control of blood pressure particularly in the most critical morning hours, leading to a higher cardiovascular risk.

Felodipino išsiskyrimo iš originalaus ir generinio preparato su reguliuojamu veikimu palyginimas *in vitro*

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Raktažodžiai: felodipinas, disoliucijos testas, reguliuojamas veikimas, palyginimas.

Santrauka. Po to, kai nustoja galioti originalaus produkto patentas, farmacijos rinką papildo nemažai generinių preparatų. Tai vienas iš būdų, kaip sumažinti vaistų kainas, be to, laukiama, kad bus išlaikyta originalo kokybė, nes generiniai preparatai pagrįsti originalų farmakologiniais duomenimis. Šio eksperimento tikslas – remiantis tirpinimo testu *in vitro*, palyginti dviejų reguliuojamo veikimo felodipino preparatų pranašumą: generinio preparato *Presid*® ir originalaus preparato *Plendil*®. Minėti preparatai registruoti ir vartojami Čekijos Respublikoje. Tirpinimo testas, atliktas trijose terpėse (pH reikšmės 1,2, 4,5 ir 6,5), simuliuojančiose fiziologišką terpės pH reikšmę virškinamajame trakte, patvirtino aukštą originalių preparatų *Plendil ER* 5 mg ir *Plendil ER* 10 mg kokybę, kurią atitiko reguliuojamas felodipino išsiskyrimas iš modifikuotai vaistines medžiagas atpalaiduojančios tabletės 24 valandų laikotarpiu. Matuojant felodipino išsiskyrimą iš generinių preparatų **Presid** 5 mg ir **Presid** 10 mg, nustatyta, kad šis netruko 24 valandų, kaip buvo nurodyta pakuotės informacijoje. Panašūs rezultatai gauti tiriant generinius preparatus, platinamus Vokietijos rinkoje. Reguliuojamas felodipino išsiskyrimas, trukęs nuo 12 iki 18 valandų, gali būti nepakankamas norint užtikrinti tinkamą kraujospūdį, ypač kritinėmis paryčio valandomis, be to, sukelia didesnę širdies ir kraujagyslių sistemos sutrikimų riziką.

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