Abstract

Objective: The pharmacokinetics and pharmacodynamics of buffered sublingual captopril were assessed in patients with congestive heart failure (CHF).

Methods: The study was carried out in a randomised single-blind cross-over fashion (n = 6, 4 males and 2 females) and involved two study days, at least 7 days apart. Baseline measurements were carried out for plasma renin activity (PRA), blood pressure (B.P) and heart rate (H.R.). Captopril (12.5 mg) was administered sublingually with dibasic potassium phosphate which maintained salivary pH at 7, or perorally with 100 ml of water. Further B.P, H.R. measurements and venous blood samples were taken over a 3 hour period post-drug administration. Blood samples were analysed for captopril and PRA levels.

Results: t_{max} after buffered sublingual administration of captopril, which ranged from 40-60 min (median = 40 min), was significantly shorter than after peroral administration (range 60-120 min, median = 90 min). C_{max} was slightly greater after buffered sublingual than after peroral administration with mean values of 108.2 vs. 94.0 ng · ml^{-1}. AUC values were similar after both routes of administration. Systolic and diastolic B.P vs. time profiles for each administration method were significantly different i.e. sublingual administration produced an earlier reduction in B.P, however, HR did not differ significantly between the two routes.

Conclusion: The data indicate that this novel administration method of captopril leads to an increased rate, but an unchanged extent of captopril absorption, suggesting a modest therapeutic advantage with the use of buffered sublingual captopril if a rapid reduction in blood pressure is required.

Key words

Congestive heart failure, Captopril; sublingual, pharmacokinetic, pharmacodynamic

Introduction

Congestive heart failure (CHF) is a pathophysiologic state resulting from impaired cardiac function due to either a defect in myocardial contractility or an excessive haemodynamic burden [1]. Over the past decade, ACE inhibitors, such as captopril, have become a routine part of the treatment of CHF as they cause haemodynamic and neurohormonal changes that lead to a reduction of preload and afterload, thus decreasing symptoms of heart failure; they also significantly decrease CHF mortality [2].

Cody et al. [3] reported that, after peroral administration of captopril, pharmacokinetic parameters are similar, both for patients with CHF and those with hypertension, when compared to normal subjects. The only exception was that the time to peak plasma level (t_{max}) was slightly delayed in the patients with CHF. Many pathophysiological abnormalities are present in CHF, including oedema of the mucosal wall of the gastrointestinal tract, decreases in splanchic and renal blood flow and glomerular function. These changes may lead to variations in pharmacokinetic parameters of perorally administered captopril such as clearance, volume of distribution and elimination half-life [4, 5].

The sublingual route of administration has been investigated as a route of drug delivery for captopril. A number of authors have reported that sublingual captopril can be safely and effectively used in hypertensive crises [6-9]. Evidence of the therapeutic benefit of unbuffered sublingual captopril in CHF patients
was provided by the results of Haude et al. [10]. A significant improvement in haemodynamic values (cardiac index, stroke volume index and stroke work index) in patients with severe left heart failure was reported after sublingual administration of captopril in addition to a more prolonged effect, compared with sublingual nitroglycerin. The authors suggested that this route of administration may be of value to those patients who have been discharged from hospital and experience a worsening of heart failure symptoms; such administration would provide a fast and marked improvement in CHF symptoms.

Previous work in this laboratory has demonstrated that sublingual administration of captopril in healthy volunteers led to a more rapid attainment of plasma captopril concentrations and had a more rapid onset of pharmacological effect when compared with peroral administration [11]. Further studies demonstrated that buffered (pH 7) sublingual administration of this ACE inhibitor in healthy volunteers led to an increased rate of captopril absorption, the $t_{\text{max}}$ for captopril being approximately 11 minutes earlier after buffered versus unbuffered sublingual administration [12].

It would appear that buffered sublingual captopril could have a therapeutic advantage over conventional peroral administration and this may be of relevance in the treatment of severe CHF when rapid attainment of pharmacological effect may be desirable. To date, the pharmacokinetic and pharmacodynamic parameters after buffered sublingual administration of captopril in patients with CHF have not been studied. Thus the aims of the present study were as follows:

1. to assess the absorption pharmacokinetics of captopril (plasma concentrations) after buffered sublingual and peroral administration in patients with CHF;
2. to monitor the pharmacodynamics of captopril as indicated by blood pressure, plasma renin activity (PRA) and heart rate, after buffered sublingual and peroral administration;
3. to study the relationship between plasma captopril concentration and captopril pharmacodynamics after both routes of administration.

### Materials and methods

**Volunteer subjects**

Six patients (4 males and 2 females) with chronic cardiac failure aged 50–81 years participated in the study. The entry criteria for patients included:

1. New York Heart Association (NYHA) classes II–IV – heart failure, stable for at least 4 weeks.
2. Left ventricular impairment on radionuclide scan (EF < 45%) or echocardiogram.
3. Receiving treatment with diuretics and digoxin if in atrial fibrillation.
4. Required initiation of captopril therapy.
5. Willingness to participate in study.

**Study protocol**

The study was approved by the Ethical Committee, Faculty of Medicine, The Queen’s University of Belfast. The study was carried out in a randomised single-blind cross-over fashion and involved two study days at least seven days apart. An example of treatment schedule for one patient is given below:

### Treatment day one

The patient, already hospitalised, was fasted overnight and a light breakfast (400 kcal; 67 g carbohydrate, 12 g proteins and 9 g fat) was given at 08.30 h. An indwelling cannula was placed in a peripheral forearm vein. The patient was then rested for 30 min (lying on a bed) after which a blood sample for estimation of captopril and PRA was taken. Baseline B.P. and heart rate measurements were also carried out at that time. A captopril tablet (12.5 mg) was then administered sublingually together with 25 mg of dibasic potassium phosphate ($t = 0$). Previous experimentation has shown that this amount of buffer salt was sufficient to maintain salivary pH at approximately pH 7 after dissolution of the captopril tablet in the mouth and the same buffering technique had been used in a previous study [12]. Further B.P., heart rate measurements and venous blood samples were taken at 5, 10, 15, 20, 25, 30, 40, 60, 90, 120 and 180 min post-drug administration. Using the blood samples, plasma unchanged captopril concentrations were determined by HPLC, based on the method of Pereira et al. [13], as detailed by Al-Furah et al. [11]. This method differentiates between unchanged captopril and its breakdown products. The patient remained lying on a bed during the three-hour experimental period. Blood samples at 0, 10, 20, 30, 60, 120 and 180 min were assayed for PRA, measured by radioimmunoassay of generated angiotensin I, using Gammacoat® plasma renin activity radioimmunoassay kits (Baxter Healthcare Corporation, USA). The coefficient of variation ($\%\; n = 5$) of this assay method is 5.6% and 5.4% at concentrations of 4.3 and 7.6 ng ml$^{-1}$ h$^{-1}$ respectively.

The patient was asked to keep the captopril tablet in his/her mouth for 10 min without swallowing the saliva. After the 10 min period, the patient was asked to swallow the saliva and disintegrated tablet with 100 ml of water. The dissolution time of the captopril tablet under the tongue was determined by the patient raising his/her hand when they no longer felt solid material in the mouth. The patient was discharged on captopril therapy.

### Treatment day two

After a minimum period of 1 week the patient was re-admitted to hospital after 24 h without captopril and maintained captopril free for a further 24 h prior to an overnight fast. The same procedure as for treatment day one was repeated, but the captopril tablet was administered perorally with 100 ml of water, again 30 min after receiving the light breakfast.

Captopril plasma concentrations and PRA were estimated as described earlier. All medications taken by patients who took part in the study were recorded on the patient record sheet.

**Data analysis**

Captopril kinetic parameters (time to peak plasma level, $t_{\text{max}}$, maximum recorded plasma concentration, $C_{\text{max}}$, area under the concentration time curve, AUC 0, 40 min and AUC 0, 180 min) for both buffered sublingual and peroral administration of captopril were calculated for each patient. The AUC 0, 40 min was used in the present study as an additional means of quantifying the rate of absorption in the initial phase after drug administration. The AUC data were calculated using the trapezoidal rule. The relative