ORIGINAL ARTICLE

IN VITRO INTERACTIONS OF CAPTOPRIL WITH NSAID's

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ABSTRACT

Captopril is effective in the treatment of hypertension of all grades of severity. Present paper deals with the *in vitro* availability studies of captopril in presence and absence of commonly used NSAID's likes diclofenac sodium, flurbiprofen, mefenamic acid, meloxicam and tiaprofenic acid. Since it had been established that simultaneous administration of both drugs may alter the antihypertensive effect of captopril. In order to find out the kinetics and energitics of captopril in presence of NSAID's, these studies were carried out in buffers of pH 4, 7.4 and 9 at 37ºC and at elevated temperatures. These studies clearly indicate that most of the NSAID's bind to captopril, forming charge-transfer complexes revealing that the availability of captopril can be affected by the concurrent administration of NSAID's. Accordingly coadministration of both the drugs should be avoided.

Keywords: ACE-inhibitors; captopril-NSAID's interactions; diclofenac sodium; flurbiprofen; mefenamic acid; meloxicam; tiaprofenic acid; drug interaction

INTRODUCTION

Captopril is 1-[(2S)-3-mercapto-2-methyl-1-oxo-proptonyl]-L-proline (figure 1) (Jaime and William, 1991), the first orally active and specific inhibitor of angiotensin-converting enzyme. It blocks the conversion of angiotensin I to angiotensin II by inhibiting the angiotensin converting enzyme and inactivates bradykinin, a potent vasodilator. The hypotensive activity of captopril probably results both from inhibitory action on renin-angiotensin system and stimulating action on kallikerin-kinin system (Bertam 1998).

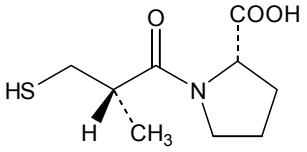

Fig. 1

A number of drug interactions of captopril with azathioprine (Robert *et al.*, 1985), antacids (Swartz and Williams, 1982), quinidine (Augenstein *et al.*, 1988), probencid [Joseph *et al.*, 1995], digoxin (USP NF, 1995 and Alfanso, 1995) and immunosuppressive agents (Colin, 1999) have been reported in the literature. It had been established that the antihypertensive effect of captopril could be reduced or abolished by use of various NSAID's like aspirin, ibuprofen and indomethacin, whereas sulindac only had a very small effect. Aspirin appeared to inhibit antihypertensive effects of captopril and other ACE-inhibitors and the favorable hemodynamic effects of ACE-inhibitors in patients with congestive heart failure. The inhibitory effect of aspirin on ACE-inhibitors was probably dose related (Seeling, 1990; Smith, 1993; Hall, 1992; Sloufi, 1994; Van, 1994 and Moore *et al.*, 1981). Simultaneous administration of these drugs may affect the bioavailability of captopril, which may result in the loss of therapeutic effects of drug. From above findings it was apparent that captopril interacted with NSAID's and hence in order to find out '*In vitro'* interactions of captopril with commonly used NSAID's, a study of the *in vitro* availability of captopril was carried out in presence of diclofenac sodium, flurbiprofen, mefenamic acid, meloxicam and tiaprofenic acid in simulated gastric and blood pH at 37 °C. The energetics of these interactions has also been studied.

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MATERIALS AND METHODS

Material

Captopril was a gift from Bristol-Mayers Squibb Pharmaceuticals (Pvt.) Ltd. Diclofenac sodium (Voren 25 mg), flurbiprofen (Froben 50 mg), meloxicam (Melfax 7.5 mg), mefenamic acid (Ponstan 250 mg) and tiaprofenic acid (Surgam 200 mg) were of Yung Shin Pharmaceuticals Ind. Co. Ltd., Abbott Laboratories (Pakistan) Ltd., Ali Gohar Pharmaceuticals (Pvt.) Ltd., Parke-Davis and Co. Ltd. and Aventis Limited respectively and were purchased from the market. Reference standards of all these NSAID's were supplied by Lab-9 of Department of Chemistry, University of Karachi. All reagents used were of analytical grade from E. Merck (Germany).

Methods

Primary solutions of 1mMole concentration of captopril were prepared individually in buffers of pH 4, 7.4 and 9. From these primary solutions stock solutions of 0.2mMole were prepared. Working standard solutions of concentration 0.05 to 0.14-mMole were prepared by diluting the appropriate amount of stock solution with the same buffer. Absorbance of all these solutions was measured at the absorbance maxima against blank. By scanning these solutions in the region of 700-190 nm, the maxima was found at 206 nm. Beer Lambert's law was obeyed at these concentrations and pH, where molar absorptivities were calculated for further calculations. Similarly, absorbances of all the working standard solutions of NSAID's were measured. The maxima of diclofenac sodium was observed at 271 nm in buffer of pH 4, 276 nm in buffers of pH 7.4 and 9, flurbiprofen at 247 nm, mefenamic acid at 285 nm, meloxicam at 362 nm and tiaprofenic acid at 311 nm in buffer of pH 4 while in buffers of pH 7.4 and 9, at 315 nm were observed which obeyed Beer Lambert's law.

In vitro availability studies of captopril and NSAID's were carried out in buffers of pH 4, 7.4 and 9, using dissolution equipment, which was manufactured according to the B. P 2002 Standards (BP, 2002) as mentioned in *table* 3.9-3.26 and plotted in *figure* 3.19-3.24. These studies were performed in absence and presence of NSAID's at 37 ºC and at elevated temperatures in buffers of pH 4, 7.4 and 9 and not in simulated gastric juice because the results of *in vitro* availability in simulated gastric juice indicated that very less amount of drug was available. In these sets of experiment, captopril 0.25 gm separately and along with NSAID's (diclofenac sodium 0.05 g, flurbiprofen 0.05 g, meloxicam 0.015 g, mefenamic acid 0.3 g, tiaprofenic acid 0.20 g) was added to the dissolution medium at zero time. Aliquots of 5 ml were withdrawn at every 15 minutes time interval for 180 minutes and assayed. The volume of dissolution fluid was maintained by adding an equivalent amount of dissolution fluid withdrawn, which had previously been maintained at same temperature in the same bath. The samples were scanned in the range of 190-700 nm against reagent blank and captopril and the interacting drugs were quantitated using a simultaneous equantion.

RESULTS AND DISCUSSION

The captopril molecule consists of a proline ring containing carboxylic, sulfhydryl and carbonyl group and propyl chain, which gives σ - σ*, σ - π*, n -σ*, π to π* and n to π* transitions. The strong absorption of captopril is due to the presence of carboxylic and carbonyl groups. Carboxylic group shows the most intense n to π* transition in the region of 205 nm, the carbonyl group shows π - π* in 180-190 nm region and the sulfhydryl group shows n to σ* transition at 210 nm region. Sulfhydryl group is readily ionizible due to which hypsochromic shift i.e. change in absorption maxima on dilution is shown. In 1mMolar solution it gives absorption at 212 nm region, which on dilution shifts to 206 nm.

The NSAID's are a heterogenous group of compounds often chemically unrelated, the prototype is aspirin hence these compounds are often referred to as aspirin like drugs (Borne and Verderame 1986). Rise in blood pressure was observed in patients with hypertension on captopril administration after being given indomethacin in doses ranging from 50 to 250 mg (Silberbauer *et al.*, 1982; Swartz and Williams, 1982; Dzau *et al.*, 1984; Witzgall *et al.*, 1982; Goldstone *et al.*, 1981; Ogihara *et al.*, 1981; Fujita *et al.*, 1981; Iniesta and Serna, 1991 and Sanchez *et al.*, 1992). Similarly rise in blood pressure was again observed in patients on enalepril administration one hour after being given 50 mg indomethacin (Walden *et al.*, 1991). Abolition of the hypotensive effects of captopril in an elderly man due to ibuprofen was also noted (Espino and Lancaster, 1992). Another study showed that captopril and ibuprofen had opposing effects on sodium and water handling by the kidney (Allon *et al.*, 1990).

i Simultaneous determination of captopril and NSAID's

During these interactions studies, the interacting drugs were estimated from the aliquots by measuring the absorbance of the solution at the λmax of both interacting drugs and with the help of following simultaneous equations.

$$C_a = \frac{A_y.b_2 - A_z.b_1}{a_1 b_2 - a_2 b_1} \quad (1)$$

$$C_b = \frac{A_y.a_2 - A_z\, a_1}{a_2 b_1 - a_1 b_2} \quad (2)$$

Where, C_a and C_b were concentrations captopril and NSAIDs, a_1 and a_2 were the absorptivities of captopril at y & z nm and b_1 and b_2 were absorptivities of NSAIDs at y & z nm, A_y & A_z were absorptions of the solution at λ_{max} of captopril and NSAIDs respectively.

ii Captopril interactions with NSAID's

The interaction studies of captopril with NSAID's were carried out in buffer of pH 4, 7.4 and 9 at 37, 48 and 60°C. The *in vitro* availability of captopril alone is shown in figure 2, while the results of the effects of NSAID's on the *in vitro* availability of captopril in buffers of pH 4, 7.4 and 9 are given in tables 1-3 respectively and are plotted in *figures* 3-5, wherein the difference in the extent of drug interaction can be observed.

Flurbiprofen interactions with captopril in buffer of pH 4 showed a significant rise in availability of captopril i.e. 627 % of captopril was available at the end of experiment. At accelerated temperature similar behavior was observed. On

Table 1: *In vitro* availability of captopril in absence and presence of NSAID's at pH 4

S. No.	Time	Captopril	Captopril concentration (Moles x 10^{-5}) in presence of			
			Flurbiprofen	Diclifenac sodium	Meloxicame	Tiaprofenac acid
1	0	0	0	0	0	0
2	15	77.29	254.17	90.94	105.61	318.71
3	30	77.73	540.4	60.26	106.49	218.73
4	45	77.75	547.37	36.73	106.66	189.96
5	60	77.79	529.13	56.61	107.4	172.46
6	75	80.33	529.07	25.57	109.02	172.8
7	90	80.91	550.36	31.73	109.48	171.91
8	105	81.29	600.33	43.47	111.13	156.32
9	120	81.43	584.18	3.67	113.67	131.38
10	135	84.97	594.41	9.5	125.38	69.84
11	150	91.12	625.67	33.69	126.65	152.47
12	165	92.3	624	8.82	135.35	70.93
13	180	100.83	627.77	1.94	145.58	43.87

Table 2: *In vitro* availability of captopril in absence and presence of NSAID's at pH 7.4

S. No.	Time	Captopril	Captopril concentration (Moles x 10^{-5}) in presence and absence of NSAID's				
			Flurbiprofen	Diclifenac sodium	Meloxicam	Mefanemic acid	Tiaprofenac acid
1	0	0	0	0	0	0	0
2	15	105.48	273.94	506.87	129.08	55.97	596.62
3	30	102.94	288.91	292.33	137.3	46.96	564.07
4	45	107.01	281.68	471.7	139.51	51.28	539.05
5	60	100.6	283.58	441.17	141.52	44.46	541.42
6	75	108.34	282.19	457.15	141.87	81.17	538.51
7	90	104.73	295.52	478.12	142.12	87.93	442.15
8	105	102.33	295.01	486.23	143.64	74.94	386.6
9	120	101.47	296.78	483.86	146.25	73.81	365.56
10	135	101.91	302.94	465.06	150.29	111.34	265.84
11	150	101.69	310.68	549.01	152.99	191.32	254.22
12	165	104.74	314.74	531.17	144.33	197.43	163.58
13	180	98.8	315.22	575.04	154.99	197.49	99.24

the other hand, interactions of captopril and flurbiprofen in pH 9 showed a fall in the availability of captopril, initially 315 % drug was available which reached to 249 % at the end of experiment. In both the cases formation of charge-transfer complex is evident from the higher availability of captopril.

When meloxicam interacted with captopril in buffers pH 4, 7.4 and 9, the interaction results showed that the availability of captopril was increased, at 37˚C, while maximum availability was 145, 154 and 149 % in buffers of pH 4, 7.4 and 9 respectively and same trend was shown at higher temperature.

There was also a rise in availabilities of captopril when interacted with mefanamic acid in buffers pH 9 and 7.4 at 37, 48 and 60^{o}C. In buffer of pH 9 mefanamic acid increased the availability of captopril up to 87 % at 37^{o}C and in buffers pH 7.4 maximum availability was 197 %. Diclofenac sodium also increased the availability of captopril in buffers pH 7.4 and 9 which was found to be 575% and 271% respectively, where as at pH 4, diclofenac sodium decreased the availability of captopril which was 1.94 % at 37^{o}C. The availability of captopril was also suppressed when interacted with tiaprofenic acid at all pH. At pH 4, initially 318% was available which decreased up to 43% at the end of reaction. In case of pH 7.4 and 9 availability of captopril was 99 and 7.50 % at 37^{o}C. It was also observed in these interaction studies that captopril caused a decline to NSAID's availability as well, which was more significant in case of mefanamic acid, tiaprofenic acid and meloxicam in all buffers (pH 4, 7.4 and 9). Only 30, 52 and 84% of meloxicam was available in pH 4, 7.4 and 9 respectively. Similarly 20 and 23 % of mefanamic acid was

Table 3: *In vitro* availability of captopril in absence and presence of NSAID's at pH 9

S. No.	Time	Captopril	Captopril concentration (Moles x 10^{-5}) in presence and absence of NSAID's				
			Flurbiprofen	Diclifenac sodium	Meloxicame	Mefanemic acid	Tiaprofenac acid
1	0	0	0	0	0	0	0
2	15	93.47	315.81	187.39	138.52	46.71	188.82
3	30	95.18	299.49	190.67	146.39	79.62	153.74
4	45	95.41	295.18	278.79	147.75	67.28	84.5
5	60	97.56	293.3	277.31	139.4	61.79	79.32
6	75	100.28	289.11	277.73	140.42	51.98	24.21
7	90	100.39	288.78	267.88	135.79	66.13	21.06
8	105	101.87	231.23	262.13	141.8	74.43	22.88
9	120	102.92	287.06	253.81	144.92	66.22	21.68
10	135	103.61	294.67	321.53	136.75	59.29	18.67
11	150	102.27	283.14	340.17	146.5	61.8	20.51
12	165	100.44	273.8	333.91	145.75	56.75	7.71
13	180	100.45	249.13	343.68	149.54	87.81	7.5

Table 4: Thermodynamic data of captopril on interaction with NSAID's

NSAID's	T	pH 4				pH 7.4				pH 9			
		K	ΔG°	ΔH°	ΔS°	K	ΔG°	ΔH°	ΔS°	K	ΔG°	ΔH°	ΔS°
Diclofenac	37ºC	668	-3993	-23939	-64.3	32452	-6377	504.8	22.2	9747	-5639	2077	24.9
	48ºC	314960	-8348	-28703	-63.4	25002	-6437	46.5	22.2	6349	-5566	2424	24.9
	60ºC	39.5	-2337	-23848	-64.6	34535	-6891	501.3	22.2	12434	-6218	2071	24.9
Flurbiprofen	37ºC	41789	-6532	-15613	-29.29	273.74	-3445	22827	84.75	3017	-4918	4702	31.04
	48ºC	72090	-7111	-16514	-29.29	724.17	-4186	23022	84.76	1810	-4769	5187	31.01
	60ºC	7045	-5843	-15596	-29.29	3594	-5399	22824	84.75	5189	-5641	4684	31.01
Maloxicam	37ºC	779423	-5501	16685	80.69	1216643	-8601	34616	139	313479	-7769	-4283	11.25
	48ºC	4323	-8248	17654	80.69	82543	-7196	5391	139	76923	-7151	-3541	11.25
	60ºC	52438	-10202	16666	80.69	64606996	-11859	34498	139	198019	-8042	-4295	11.25
Mefanamic	37ºC	----	----	----	----	8064	-5522	-12234	-21.65	884.96	-4165	-888	10.57
	48ºC	----	----	----	----	3035	-5097	-12047	-21.65	1366	-4589	-1197	10.57
	60ºC	----	----	----	----	2047	-5027	-12238	21.65	793	-4402	-883	10.57
Tiaprofenac	37ºC	36859	-6455	-21308	-47.91	729.	-4047	-3073	3.14	847	-4138	-10237	-19.67
	48ºC	19073	-6265	-21608	-47.80	1207	-4509	-3501	3.14	833	-4275	-10593	-19.68
	60ºC	3335	-5349.	-22929	-52.79	510	-4111	-3065	3.14	2710	-5211	-10211	-15.02

available in pH 7.4 and 9 respectively and 36, 18 % of tiaprofenic acid was available at the end of reaction in pH 4, 7.4 respectively. At accelerated temperatures same behavior was observed. Captopril has one chiral carbon center, a thiol linkage and carboxylic group which may act as reacting sites. The probability of carboxylic group reacting with any other drug is much more as compared to that of thiol group. But since NSAIDs themselves have a carboxylic group it is suggested that captopril interact with NSAIDs through its thiol group where it act as a base towards carboxylate ion of NSAIDs. However, in case of meloxicam the chances of attachment with OH group is more pronounced and in case of mefanamic acid the binding may be with secondary amine. These results indicated that captopril bonded significantly to NSAID's and formed charge transfer complexes moreover temperature also favored complex formation.

Thermodynamic studies further supported the results of interaction studies. Stability constant K and thermodynamic functions ΔG°, ΔH° and ΔS° for captopril and NSAID's complexation in buffer of pH 4, 7.4 and 9 were calculated and are shown in *table* 4.

From these results standard Gibb's free energy values showed that the reaction between the captopril and NSAID's was spontaneous. Furthermore, in buffer of pH 4, when captopril interacted with NSAID's, enthalpy (ΔH°) and entropy (ΔS°) values indicated that donor acceptor complex was formed due to chelation and hydrogen binding. Similarly, mefenamic acid in buffer of pH 7.4 and tiaprofenic acid in buffer of pH 9 formed complexes with captoril due to chelation and hydrogen binding. Where as in case of meloxicam in pH 4 and 7.4, thermodynamic functions ΔH° and ΔS° showed that hydrophobic interaction

would take place due to which availability of drug had increased. In the same way flurbiprofen and diclofenac sodium in pH 7.4 and 9 also showed positive signs of entropy and enthalpy, which indicated that complex, was formed due to hydrophobic interaction. Hydrophobic binding phenomenon was first studied in captopril in controlled release formulations Ikeda *et al.*, 2000), in which the tendency of hydrophobic part of molecules avoids water because they are not readily accommodated in the hydrogen-bonding structure of water. This interaction involves van der walls forces, hydrogen bonding of water molecules in a three-dimensional structure. In other interactions, when meloxicam and mefanamic acid interacted with captopril in pH 9, then resultant thermodynamic functions showed that chelation would take place which caused complex formation. Similarly, in buffer of pH 7.4 tiaprofenic acid formed complex with captopril due to chelation process. Enthalpy studies of captopril were first studied by Ortiz-Salmeron *et al.* (1998).

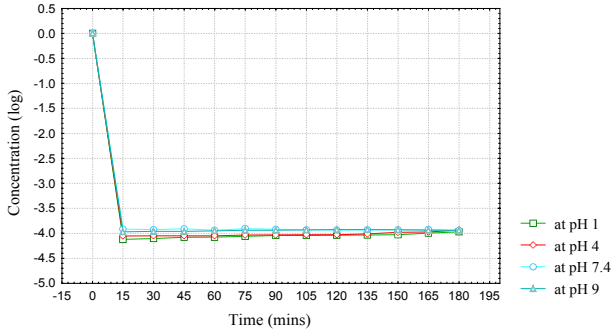

Fig. 2: Availability of captopril at various pH at 37°C.

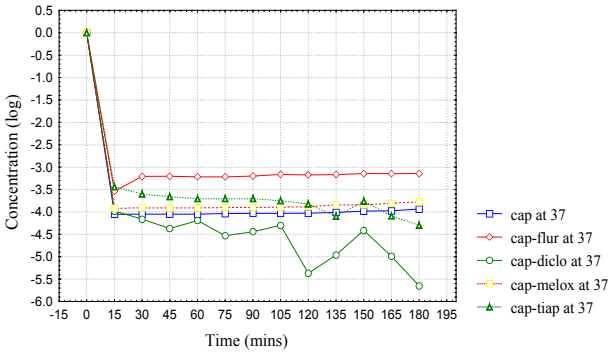

Fig. 3: Availability of captopril in presence of NSAIDs in pH 4 at 37°C.

The result of this paper also demonstrate a drastic change in availability of captopril in presence of NSAIDs. Hence, it is suggested from the above findings that combined use of NSAIDs with captopril is highly not recommended and should be avoided.

CONCLUSION

Results of the present study indicated that all NSAID's studied bind to captopril, and hence altered availability of captopril was noted thus proving that there was a strong drug-drug interaction between captopril and NSAID's. It bounds significantly to NSAID's and caused a prominent decline to its availability that was more significant in presence of mefanamic acid, tiaprofenic acid and meloxicam at all pH studied. Moreover, the results of thermodynamic data showed that a charge transfer complex formation took place. So captopril should not be given along with NSAIDs.

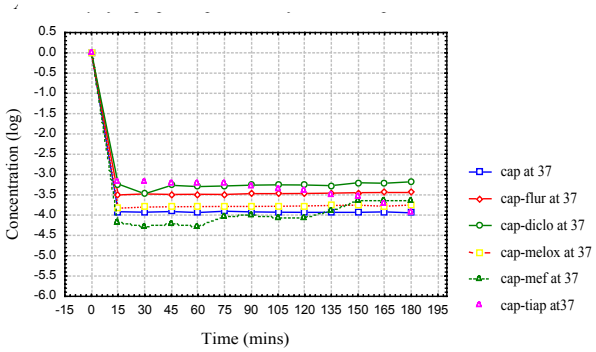

Fig. 4: Availability of captopril in presence of NSAIDs in pH 7.4 at 37°C.

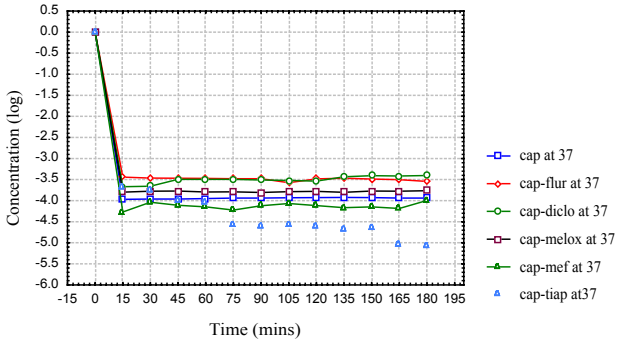

Fig. 5: Availability of captopril in presence of NSAIDs in pH 9 at 37°C.

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