

## CARBAMAZEPINE KINETICS IN CARDIAC PATIENTS BEFORE AND DURING AMIODARONE

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**SUMMARY** - Carbamazepine and amiodarone may often be used together, especially in countries where cardiomyopathies are common. In this study single doses of carbamazepine (400 mg) were given to patients with cardiac disease before and after one month of therapy with amiodarone, 400 mg daily. The kinetic profile of carbamazepine, its free fraction, and serum amiodarone, were measured at the two occasions. There was no statistically significant change in carbamazepine kinetics or free fraction, before and after the introduction of amiodarone. The concentrations of amiodarone after one month of therapy were low. It is suggested that the possible interaction in the hepatic metabolism was not demonstrated because amiodarone concentrations were not enough to inhibit carbamazepine metabolism.

**KEY WORDS:** amiodarone, carbamazepine, epilepsy, antiepileptic drugs, arrhythmia.

### Cinética da carbamazepina em pacientes cardíacos antes e durante amiodarona

Carbamazepina e amiodarona podem frequentemente ser usadas em conjunto, especialmente em países em que as cardiomiopatias são comuns. Neste estudo doses de carbamazepina (400 mg) foram administradas a pacientes com doenças cardíacas antes e depois de um mês de terapia com amiodarona, 400 mg ao dia. O perfil cinético da carbamazepina, sua fração livre e o nível sérico da amiodarona, foram avaliados nas duas ocasiões. Não foram observadas diferenças estatisticamente significantes na cinética da carbamazepina ou mesmo em sua fração livre, antes e depois da introdução da amiodarona. A concentração da amiodarona após um mês de terapia foi baixa. Conclui-se que a possível interação no metabolismo hepático não foi demonstrada devido as baixas concentrações de amiodarona, que provavelmente tenham sido insuficientes para inibir o metabolismo da carbamazepina.

**PALAVRAS CHAVE:** amiodarona, carbamazepina, drogas antiepilépticas, arritmias.

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Amiodarone is a widely used antiarrhythmic agent for the treatment of resistant supraventricular and ventricular arrhythmias. Carbamazepine is a widely used antiepileptic compound, which is metabolised by the cytochrome P450 system. Its metabolism may be impaired by drugs such as cimetidine<sup>8</sup>. Some patients have shown unexpected carbamazepine toxicity during amiodarone therapy, and the dosage necessary to produce clinical toxicity decreased with time after onset of therapy (Bittencourt, unpublished data personal experience). An interaction between the two drugs could be due to inhibition of liver metabolism, as predicted from other amiodarone interactions, such as with warfarin<sup>19</sup>. Between 0.5 and 2% of the Brazilian population have epilepsy and a possible indication for carbamazepine<sup>3</sup>. Central and South American trypanosomiasis, also called "Chagas' disease", is a common cause of ventricular and supraventricular arrhythmias which may be treated with amiodarone<sup>4</sup>. The concomitant utilization of amiodarone and carbamazepine may thus take place in these patients.

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The present study was designed to investigate this interaction and to exclude the possibility of other interactions at the levels of absorption, plasma protein-binding, and at the brain.

## MATERIAL AND METHODS

The study was prospective and controlled, each patient serving as its own control. The ethic principles of clinical investigation specified in the Helsinki declaration and its amendments were followed.

Five men and four women aged between 38 and 70 years ( $58.4 \pm 8.94$ , mean  $\pm$  standard deviation) were included on the study. Their weight varied between 58-79kg (mean=69.7kg). Two patients suffered of Chagas' disease, and the rest had ischaemic cardiomyopathy-related arrhythmias. In 6 cases this was premature ventricular contractions; in two cases it was high frequency supraventricular tachycardia and one patient has sinus arrhythmia. Patients were admitted to hospital before and one month after starting therapy with amiodarone (200 mg, orally). The dose of carbamazepine (400 mg, orally) was given 72 hours before amiodarone in the first admission and between 8 and 12 hours after amiodarone on the second. Patients did not change their therapeutic regimens while taking part in the study. Throughout the study they received amiodarone 200 mg orally every 12 hours. On the two occasions they received a single dose of carbamazepine (400 mg, orally), and blood samples were collected before and 1,2,4,6,8,12,24,48 and 72 hours after administration.

After centrifugation serum samples were kept at  $-20^{\circ}\text{C}$  until determination of serum concentration of carbamazepine and amiodarone by high performance liquid chromatography<sup>1</sup>. Area under the curve in the time X concentration graph of carbamazepine was measured using the linear trapezoidal rule. Statistical significance was tested using paired Student's t-test with  $p < 0.05$  being the minimum level of statistical significance. Plasma protein binding was determined by equilibrium dialysis at pH 7.4 and  $37^{\circ}\text{C}$  using trace amounts of  $14^{\circ}\text{C}$  carbamazepine on at least four of the plasma samples collected on each occasion. Serum concentrations of amiodarone/des-ethyl-amiodarone were determined by high performance liquid chromatography<sup>11</sup>.

Patients were fully examined and investigated during both admissions. Between 4 and 8 hours after the administration of carbamazepine patients were examined for signs and symptoms of toxicity such as dizziness, nausea, somnolence, diplopia, ataxia, tremor, vertical and horizontal nystagmus, smooth pursuit eye movements. These findings were quantified as absent, discrete, moderate or severe<sup>6</sup>.

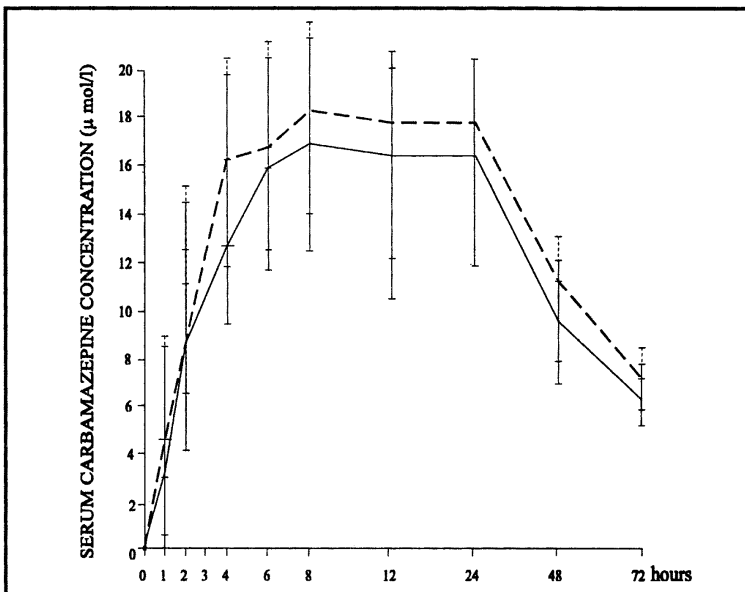


Fig 1. Time course of the serum concentrations of carbamazepine ( $\mu\text{mol/l}$ ) after a single oral dose of 400 mg, in 9 patients with cardiac disease, before (full line) and one month after (dotted line) therapy with amiodarone.

Table 1. Area under the curve (AUC) and constant of elimination (K) of carbamazepine before and after one month therapy with amiodarone in 9 subjects with cardiac disease.

Before Amiodarone			During Amiodarone		
Patient	AUC ( $\mu\text{mol/l.h}$ )	K ( $\text{H}^{-1}$ )	Patient	AUC ( $\mu\text{mol/l.h}$ )	K ( $\text{H}^{-1}$ )
1	1732.0	.0159	1	0263.0	.0159
2	1218.3	.0253	2	1015.5	.0253
3	2145.3	.0228	3	1274.1	.0228
4	2164.4	.0177	4	2383.4	.0144
5	1429.5	.0299	5	1704.7	.0197
6	1041.1	.0242	6	1221.3	.0164
7	1434.2	.0278	7	1819.2	.0155
8	1739.6	.0149	8	1366.3	.0179
9	21203.0	.0180	9	1390.6	.0310
Mean	1667.5	-	Mean	1615.3	-
Standard Deviation	415.2	-	Standard Deviation	492.8	-

## RESULTS

Figure 1 shows results of total carbamazepine concentrations in the 9 patients before and during amiodarone (200 mg, orally). The rate of absorption was relatively slow with a time to peak of  $9.0 \pm 6.6$  (mean  $\pm$  sd) h before and  $7.3 \pm 2.4$  h, during amiodarone therapy. Table 1 shows areas under the curve and k elimination constants of carbamazepine before and during amiodarone. Table 2 shows the free fractions of carbamazepine before and after one month of amiodarone therapy. Serum concentrations of amiodarone and its metabolite are shown on Table 3. There were no signs of toxicity before and until 8 hours after administration of carbamazepine in either admission. Clinical, laboratory and radiological investigations (chest X-ray, ECG, full blood count, ESR, creatinine, blood sugar) did not show significant changes except in arrhythmias between the two admissions. Area under the curve for carbamazepine given alone was  $1667.5 \pm 415.2$  (mean  $\pm$  standard deviation)  $\mu\text{mol/l.h}$ . Therapeutic concentrations were reached in patients 4, 5 and 9. Patient 9 had therapeutic serum concentrations for 24 hours. The plateau of serum concentrations between 12 and 24 hours ( $15.9 \pm 5.2$   $\mu\text{mol/l}$ , mean  $\pm$  standard deviation) was relatively low, and 72 hours after administration carbamazepine was still present in the blood. Terminal half-life elimination was  $34 \pm 8$  h before and  $37 \pm 9$  h during amiodarone therapy. The free fraction of carbamazepine was  $0.325 \pm 0.035$  before and  $0.323 \pm 0.040$  after treatment with amiodarone.

AUC during amiodarone was  $1615.3 \pm 492.8$  (mean  $\pm$  sd)  $\mu\text{mol/l.h}$ . There was no significant change compared to before amiodarone ( $p > 0.05$ ). Therapeutic serum concentrations were reached in the same 3 patients as before but also by Patient 3 during amiodarone therapy. The plateau of serum concentrations was approximately 18  $\mu\text{mol/l}$  (mean) between 12 and 24 hours after administration.

## COMMENTS

Although amiodarone has been used as an antiarrhythmic agent for over a decade knowledge about its kinetics is recent and incomplete<sup>14</sup>. It is slowly absorbed, with a peak serum concentration between 4 and 5 hours after oral administration. The bioavailability is low in view of the dissolution at the intestinal mucosa. In the circulation it is highly bound to proteins. Limits of "therapeutic" serum concentrations are difficult to determine. The lower limit has been estimated at the levels where there is recurrence of arrhythmia after amiodarone withdrawal, between 0.5 and 1.0  $\mu\text{g/ml}$ . Maximum therapeutic concentrations are unknown because months may elapse after the concentrations have reached a plateau and side-effects appear. Amiodarone leaves plasma rapidly and distributes throughout body tissues, mainly liver, lungs, heart and fat<sup>10</sup>. Only after equilibrium antiarrhythmic effect is seen, between 10 and 60 days after oral maintenance doses. When a quicker

Table 2. Free fractions of carbamazepine (CBZ) before and during amiodarone therapy in 9 patients with cardiac disease.

Patient	CBZ-free fraction CBZ alone			CBZ-free fraction CBZ+amiodarone		
	mean	sd	median	mean	sd	median
1	0.35	6.38	0.35	0.35	5.78	0.35
2	0.33	0.08	0.33	0.29	1.89	0.29
3	0.38	7.70	0.35	0.35	2.44	0.34
4	0.34	1.72	0.35	0.36	3.61	0.63
5	0.26	4.61	0.26	0.25	2.53	0.24
6	0.31	9.10	0.36	0.30	3.47	0.30
7	0.31	4.21	0.30	0.28	2.11	0.28
8	0.34	2.87	0.36	0.37	3.39	0.36
9	0.33	1.96	0.34	0.32	4.46	0.33

sd, standard deviation.

effect is needed it is important to start with loading doses. Plasma concentrations after oral administration are erratic until at least 4 or 6 weeks after maintenance or loading doses<sup>18</sup>. Elimination is biphasic and terminal elimination half-life exceptionally long, between 8 and 107 days<sup>2,9,12,17</sup>. Amiodarone is metabolized predominantly in the liver. There are two well-known metabolites, di-des-ethyl-amiodarone and des-ethyl-amiodarone, the latter found in man, although its clinical activity is unknown. During long-term therapy concentration of des-ethyl-amiodarone is one or two times greater than that of amiodarone. The relationship of the plasma concentration of des-ethyl-amiodarone/amiodarone is useful to evaluate compliance to short term therapy<sup>10</sup>. The side-effects of amiodarone appear mostly during chronic treatment and involve the cardiac, neurologic, and ocular systems, the skin and thyroid gland.

Carbamazepine is used for epileptic disorders, trigeminal and other neuralgias and for some psychiatric disturbances. Its absorption after oral administration is slow<sup>17</sup> and serum concentrations fluctuate widely during absorption, probably in relation to slow dissolution in the gastrointestinal fluid and in relation to its anticholinergic action during chronic treatment, which slows the time of gastrointestinal transit<sup>18</sup>. Peak plasma or serum concentrations are reached between 4 and 8 hours after ingestion, but later peaks between 24 and 32 hours have been reported. The relationship between oral dose and serum concentrations has been shown to be linear in some instances, and nonlinear in others<sup>16</sup>. Bittencourt and Richens<sup>6</sup>

Table 3. Serum levels of amiodarone (AM) / des-ethyl-amiodarone (DEA) (umol/l) in 9 patients with cardiac disease after one month therapy with amiodarone.

Patient	AM / DEA
1	0.55/0.98
2	0.64/0.72
3	0.26/0.69
4	0.21/0.52
5	0.42/0.76
6	0.48/0.58
7	0.51/1.37
8	0.90/1.55
9	0.36/0.36

demonstrated a linear relationship between serum concentration and effect on saccadic eye movements, but not between serum concentrations and the slower smooth pursuit eye movements, even though both were significantly impaired in healthy subjects after a single dose<sup>6</sup>. In the circulation 75% is bound to plasma proteins. Carbamazepine induces an increase in quantity of cytochrome p-450 during long-term therapy decreasing the plateau serum concentrations, the phenomenon known as auto-induction. In healthy subjects the half-life varies between 18 and 55 hours and total clearance between 0.0011 and 0.0210 l/kg/h after a single dose<sup>15</sup>. Side-effects are frequent

and usually not severe. They include somnolence, ataxia, dizziness, nystagmus, diplopia, slurred speech and headache<sup>5</sup>.

When the results of the present study are compared to those of comparable studies it may be noticed that absorption of carbamazepine is slower in middle aged cardiac patients than in healthy young individuals, aged  $25 \pm 4.2$  years<sup>7</sup>, who after an oral dose of 400mg developed serum concentrations respectively of 8.5, 15.3, 18.1, 21.5 and 19.6 umol/l at 1,2,4,6 and 8 hours. When these results, observed after doses of 400 mg, are compared to those observed after a single oral dose of 600 mg<sup>13</sup> given to neurological inpatients aged  $40 \pm 19.3$  years, it may be noticed that the greater oral dose produces therapeutic serum concentrations at 4 hours (22.3 umol/l), which continue rising at 6 hours (27.3 umol/l) and at 8 hours (31.5 umol/l, means). These findings are generally in disagreement with pharmacokinetic concepts that at the extremes of age the possibility of toxicity is greater. Few studies of carbamazepine kinetics in cardiac or elderly patients have been carried out<sup>15</sup>.

An absorption interaction between amiodarone and carbamazepine is difficult to be predicted since amiodarone undergoes desalkylation in the intestinal mucosa while carbamazepine undergoes a slow dissolution in gastrointestinal fluids. An interaction at plasma protein binding sites can be ruled out by the present results, but it might have been an alternative explanation for the initial clinical observation that led to the study.

Holt and colleagues<sup>10</sup> described the liver metabolism of amiodarone and Watt and colleagues<sup>19</sup> demonstrated its interaction with warfarin at the liver. Warfarin is also metabolized at the cytochrome oxidase p-450 enzymatic system. The interaction with warfarin was demonstrated with amiodarone concentrations of  $2.57 \pm 1.73$  umol/l and with des-ethyl amiodarone concentrations in the plasma of  $1.07 \pm 0.32$  umol/l. Levels found in the 9 patients of the present study were all below 0.65 umol/l for amiodarone and 7 of the 9 patients had des-ethyl amiodarone concentrations below 1.0 umol/l, while the other 2 had respectively 1.37 and 1.55 umol/l.

We would like to put forward the hypothesis that an interaction at the hepatic metabolism between amiodarone and carbamazepine was not demonstrated in this study because amiodarone serum concentrations were not sufficient to inhibit the metabolism of carbamazepine. In order for this interaction to be properly demonstrated we suggest that the dosage regimen of Siddoway and colleagues<sup>18</sup> be followed. In this scheme, 2000 mg amiodarone should be given to adults on the first day, 1400 mg daily over the second, third and fourth days, followed by 1000 mg daily for a week, 800 mg daily for 2 weeks, and 600 mg daily for 4 weeks. After this time, maintenance could be kept with 400 mg or 600 mg daily. The possibility that severe side-effects may occur at this dose should be kept in mind.

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