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SHORT COMMUNICATIONS

AMIODARONE AND DESETHYLAMIODARONE ELIMINATION KINETICS FOLLOWING WITHDRAWAL OF LONG-TERM AMIODARONE MAINTENANCE THERAPY

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INTRODUCTION

Amiodarone is an effective antianginal and antiarrhythmic agent introduced since 1967. However, there was no definite data on the relationship between clinical efficiency and plasma concentration of the parent drug. A preliminary kinetic study using ^{131}I(I)amiodarone[1] had shown a long elimination half-life of 28 ± 7 days for the compound and/or metabolite(s) (total radioactivity). These results were confirmed by the observation of a persistent amiodarone antiarrhythmic effect for up to 45 days after interruption of treatment.[2] A desethylated metabolite of the drug has been found in plasma samples of amiodarone treated patients at concentrations similar to those of the parent compound during long-term therapy.[3] Little information about pharmacokinetics of amiodarone and desethylamiodarone, particularly concerning the slower elimination phases, has been published. Terminal elimination half-life of amiodarone following withdrawal of long-term therapy has been found to range between 13 and 107 days.[4–9] However, except reference 8, all these studies have been conducted on a limited number of patients (1 to 6). Values ranging between 24 and 160 days have been reported for unidentified metabolite(s).[6,7] A recent study[9] reported similar values for desethylamiodarone (20 to 118 days). Finally, no data are available concerning the linearity of

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amiodarone and desethylamiodarone elimination kinetics except the apparent proportionate increase of steady-state mean concentrations with maintenance dose.[3–9]

MATERIALS AND METHODS

Patients and protocol

Twelve male patients, aged between 28 and 73 years and weighing between 54 and 94 kg, undergoing long-term oral amiodarone maintenance therapy, were withdrawn because of side-effects or inefficacy. All received the drug daily, 5 days a week. Three of them had 200 mg maintenance dose from 21 to 36 months and 9 had 400 mg maintenance dose for 4 to 50 months. Clinical characteristics of patients, dose, and duration of therapy are listed in Table 1.

All the patients received a last 400 mg dose and blood samples were drawn just before administration (C_0), then 3 h, 6 h, 1, 3, 10, 17, 24, 45, 73, and 87 days later.

Amiodarone and desethylamiodarone assays

Plasma levels of amiodarone and its N-monodesethylated metabolite were determined by high performance liquid chromatography.[10] One millilitre of plasma was spiked with the 2-ethyl-3-(3·5-dibromo-4-γ-di-*n*-propylaminopropoxybenzoyl) benzothiophene (L 8040, compound, Labaz laboratories, Brussels) used as internal standard and extracted by cyclohexane pestipur (pH 5·4). The organic layer was evaporated to dryness and reconstituted in chloroform. Fifty microlitres were injected into a Hewlett-Packard model 1084 B chromatograph equipped with fixed wavelength detector (254 nm). Separation was carried out on a Lichrosorb SI 100 7 μm column (Merck, Darmstadt, Germany) with a mobile phase consisting of a chloroform:ethanol:ammonium hydroxide (8N) mixture (99·71:0·25:0·04 v/v/v) at a flow rate of 2·0 ml min^{-1}.

Data analysis

The half-lives ($t_{1/2}$) of elimination phases were estimated by least-square regression of the appropriate log-linear data. The areas under the concentration-time curves (AUC) were calculated by the trapezoidal rule from time zero to the time t of the last sampling time, then extrapolated to time infinity after estimation of the terminal elimination half-life. Statistical examination of results has been performed by Student's t-test for difference between two means.

RESULTS

A representative plasma concentration-time profile of amiodarone and desethylamiodarone is shown in Figure 1. The kinetic data are listed in Table 2.

Table 1. Clinical characteristics. AP: Angina pectoris, AF: Atrial fibrillation, AFl: Atrial flutter, AR: Aortic regurgitation, AVJT: Atrioventricular junctional tachycardia, CM: Cardiomyopathy, MI: Myocardial infarction, MS: Mitral stenosis, VPB: Ventricular premature beats, VT: Ventricular tachycardia

Patients	Age (years)	Weight (kg)	Dose (mg)	Dose (mg kg^{-1})	Duration of therapy (months)	Indication for treatment	Cardiac disease
1	72	64	200	3·125	21	AP	MI
2	42	57	200	3·510	29	Paroxysmal AF	MS
3	72	70	200	2·857	36	AP	–
4	70	73	400	5·479	4	Paroxysmal AF	AR
5	73	54	400	7·407	4	AP	–
6	28	69	400	5·797	6	VT	–
7	61	90	400	4·444	7	VPB	CM
8	66	61	400	6·557	11	AP	MI
9	70	94	400	4·255	9	Paroxysmal AFl	AR
10	64	69	400	5·797	29	AP	–
11	62	90	400	4·444	40	Paroxysmal AF	–
12	60	70	400	5·714	50	AVJT	AR

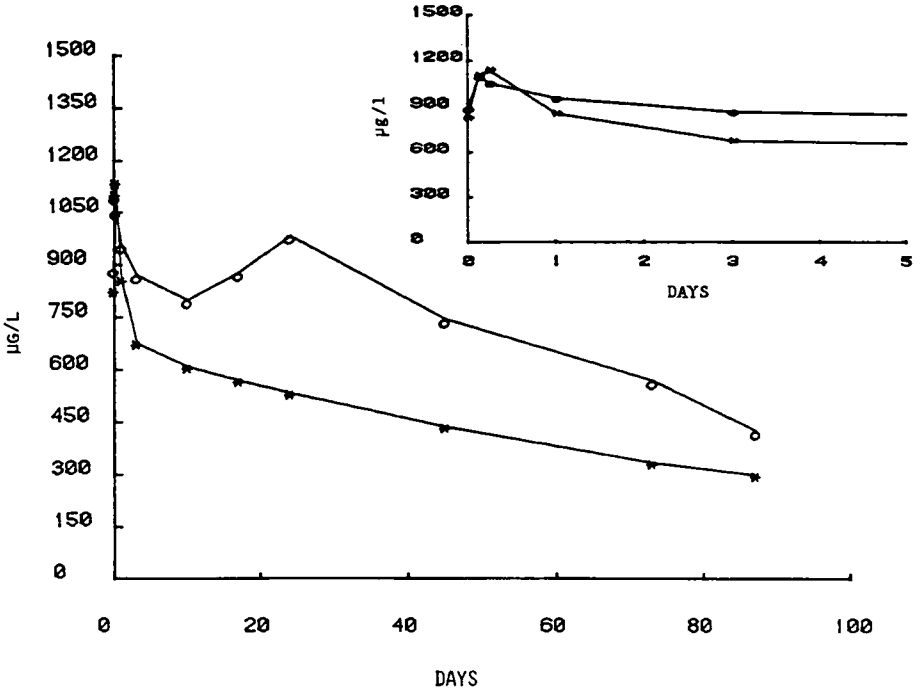

Figure 1. Amiodarone (⋆) and desethylamiodarone (○) plasma levels following withdrawal of 400 mg/day maintenance dose (patient no. 5)

In 3 patients with 200 mg maintenance dose, plasma levels before the last intake (C_0) averaged 0·75 ± 0·45 mg l^{-1} and 0·75 ± 0·32 mg l^{-1}, respectively, for amiodarone and its metabolite. The 9 patients receiving a two-fold maintenance dose were characterized by a proportional increase in mean plasma levels (1·34 ± 0·55 mg l^{-1} for amiodarone and 1·27 ± 0·45 mg l^{-1} for desethylamiodarone).

Amiodarone data showed a biphasic elimination. Mean values for half-lives were 16·8 ± 8·0 h ($n = 9$) for the first phase (α) and 46·8 ± 12·6 days ($n = 12$) for the second phase (β), the end of the α phase occurring generally at the third day. Metabolic kinetic profile was characterized by either a plateau or a sequence of rebounds depending on the subjects until the 24th day, then the concentrations decreased with an elimination half-life of 53·7 ± 22·2 days ($n = 12$).

However, terminal elimination half-lives for both compounds were significantly increased with the maintenance dose (32·7 ± 1·38 to 51·6 ± 10·9 days, $p < 0·05$ for amiodarone and 25·9 ± 0·75 to 63·0 ± 17·0 days, $p < 0·01$ for its metabolite).

Amiodarone and desethylamiodarone AUCs were 23·10 ± 11·81 and 30·27 ± 19·39 mg·day ml^{-1} for patients receiving the 200 mg maintenance dose and

Table 2. Kinetic data

Patients	Amiodarone				Desethylamiodarone			
	C_0 (mg l^{-1})	$t_{1/2}\alpha$ (h)	$t_{1/2}$ (days)	AUC (mg·day l^{-1})	C_0 (mg l^{-1})	$t_{1/2}$ (days)	AUC (mg·day l^{-1})	$\frac{\text{AUC(DEA)}}{\text{AUC(A)}}$
1	1·23	33·0	31·9	34·86	1·12	26·7	52·64	1·50
2	0·68	9·9	31·9	23·21	0·61	25.2	19·79	0·85
3	0·35	25.8	34.3	11·25	0·52	25·9	18·38	1·63
Mean	0·75	22·9	32·7	23·10	0·75	25·9	30·27	1·33
(± S.D.)	(0·45)	(11·8)	(1·38)	(11·8)	(0·32)	(0·75)	(19·39)	(0·42)
4	1·08	19·3	60·3	68·84	0·86	92·9	51·90	0·75
5	0·83	13.8	72·9	71·79	0·89	55·0	98·08	1·37
6	1·13	11·0	47·1	63·48	1·10	60·0	99·53	1·57
7	2·30	–	37·5	97·22	1·22	51·7	117·29	1·20
8	2·15	–	48·9	143·15	2·37	85·8	311·73	2·18
9	1·27	12·3	60·8	97·02	1·27	60·3	143·63	1·48
10	1·55	–	46·8	85·76	1·41	70·7	147·49	1·72
11	0·80	16.6	44·4	37·38	1·05	43·3	72·99	1·95
12	0·96	9·9	45·6	53·87	1·31	47·1	122·41	2·27
Mean	1·34	13·8	51·6	79·84	1·27	63·0	129·45	1·61
(± S.D.)	(0·55)	(3·56)	(10·9)	(30·76)	(0·45)	(17·0)	(75·02)	(0·48)

79·84 ± 30·76 and 129·45 ± 75·02 mg·day ml^{-1} after the 400 mg therapy. The ratio of amiodarone to desethylamiodarone AUCs averaged 1·54 ± 0·46.

DISCUSSION

Amiodarone and desethylamiodarone levels measured just prior to the last intake before withdrawal were very close in the same subject. Both mean values increased proportionately with maintenance dose suggesting linear pharmacokinetics, as described in previous studies.[3,7–9]

However, in the linear hypothesis one could expect less than a two-fold increase of mean AUCs in patients receiving the 400 mg maintenance dose (considering that, whatever the maintenance dose, all patients received a 400 mg last dose). On the contrary, the observed ratio of mean AUCs in patients with 400 mg and 200 mg maintenance doses was 3·5 and 4·3 for amiodarone and desethylamiodarone, respectively. These results suggest non-linear, rather than linear pharmacokinetics, for both compounds.

The desethylamiodarone to amiodarone AUCs ratio was independent of the maintenance dose; the mean value we found was higher than that reported by Holt *et al.*[9]

Our study confirmed the existence of a very slow elimination phase for amiodarone and desethylamiodarone. Mean half-lives were in the range of previous observations.[4–9] Nevertheless, a more detailed examination of the results have shown a significant dose-dependency of this parameter for both compounds. Such a result could explain the shorter half-lives reported by Holt *et al.*[9] after single dose amiodarone administration and is consistent with the disproportionate increase of mean AUCs with the maintenance dose.

A more rapid decrease phase occurred prior to the terminal elimination phase. Its half-life seemed independent of the maintenance dose but because of little data for this phase, half-life estimates must be regarded with caution.

The results indicate that a disproportionate increase of amiodarone and metabolite plasma levels occur when the 400 mg dose is administered following a 400 mg maintenance dose. However, the ratio DEA/A remains unchanged. A possible explanation of this phenomenon could be an influence of the maintenance dose upon the disposition of both compounds such as tissue accumulation,[11,12] biliary excretion[12] and/or other metabolic pathway(s).

If confirmed, the non-linear nature of amiodarone/desethylamiodarone kinetics should be taken into account in future pharmacokinetic modelling of both compounds.

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