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PHARMACOKINETIC INTERACTION BETWEEN DILTIAZEM AND AMIODARONE IN THE DOG

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ABSTRACT

The pharmacokinetic interaction between diltiazem and amiodarone was investigated in dogs. In the presence of amiodarone, diltiazem's AUC values were significantly increased and its total body clearance and volume of distribution at steady-state significantly decreased. This study indicates that cardiac patients on combined diltiazem-amiodarone therapy may indeed be in a high risk situation in regards to the unexpectedly high blood levels of diltiazem induced: with the ultimate introduction of such side-effects as (1) the lowering of blood pressure, (2) A/V block, and (3) sinus node depression. Such cases would require immediate dosage adjustment.

Assuming that the data obtained in this study can be extrapolated to humans, a patient's physiological parameters should be monitored at periodic intervals and, more importantly, the patient should report the first sign of any untoward effect.

KEY WORDS Diltiazem Amiodarone Pharmacokinetic interaction

INTRODUCTION

Diltiazem is a benzothiazepine derivative (calcium antagonist) which is used widely in the treatment of coronary heart disease, arterial hypertension, supraventricular tachyarrhythmias and obstructive hypertrophic cardiomyopathy.[1]

In humans, diltiazem is metabolized extensively: only 0·1 to 4 per cent of the dose is excreted unchanged in the urine.[2–5] Diltiazem has a mean half-life of 3·1 ± 1.0 h, a clearance of 1·3 ± 0·5 l h^{-1} kg^{-1}, a volume of distribution of 5·3 ± 1·7 l kg^{-1},[1,6] and it is highly bound to plasma protein, the unbound fraction (f_u) ranging from 0·196 to 0·226 and being independent of its plasma concentration.[2,7–9] Its primary metabolic pathway involves deacetylation.

In addition to treatment with calcium antagonists (such as diltiazem), cardiac patients often concurrently receive other cardiovascular drugs (e.g. amiodarone). Amiodarone is a type III antiarrhythmic agent which prolongs the action

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potential and the refractoriness of the purkinje fibers. As well, it increases the ventricle's fibrilation threshold.[10,11]

Amiodarone has a unique pharmacokinetic property in humans, having a half-life of up to and/or more than 60 days. It is metabolized extensively in the liver to desethyl amiodarone.[11,12]

As the concurrent administration of diltiazem and amiodarone is quite common in cardiovascular therapy, this study was undertaken in order to investigate any possible pharmacokinetic interaction between these two drugs. Attention was focused on the disposition of diltiazem and, therefore, it was administered intravenously to dogs, both alone and concurrently with amiodarone. Combined diltiazem–amiodarone therapy has thus the potential of altering the plasma levels of diltiazem and such an alteration may induce haemodynamic depression; expressable as a blood pressure fall, an A/V block or a sinus node depression.

MATERIALS AND METHODS

The experiments were carried out in five mongrel dogs, three males and two females, weighing between 16 and 25 kg. Using a cross-over design, each dog was injected intravenously (cephalic vein) with: (1) diltiazem (Dilatam® -20 mg, Abic, Israel) alone and (2) diltiazem (20 mg) and amiodarone (5 mg kg^{-1} - Cordarone®, Labaz, France). Due to amiodarone's relatively short half-life in the dog, a 3-week washout period was considered sufficient between any two consecutive studies. Although the drugs were injected slowly over a 5 min period, the data were treated pharmacokinetically as if the injection was given as an i.v. bolus. Venous blood samples (8 ml) were then collected at specified intervals via an indwelling catheter in the other cephalic vein (0, 2, 5, 10, 15, 20, 30, 40, 50 min; 1, 1·25, 1·5, 1·75, 2·, 2·5, 3·, 3·5, 4·, 5, 6, 7, 8 and 10 h). The plasma was separated immediately by centrifugation at 7000 rev min^{-1} for 15 min and stored at -20°. Before each assay, the plasma was allowed to reach room temperature. It was then vortexed, centrifuged, and the residual clot was removed. Diltiazem's plasma levels were assayed by HPLC.[13] Precision analyses of this assay, using eight replicate samples of diltiazem and its metabolite desacetyldiltiazem at plasma concentrations ranging from 10 to 1000 ng ml^{-1}, gave a coefficient of variation of 4 to 13 per cent.[13]

The linear terminal slope (ß) of log C (diltiazem plasma concentration) versus t (time) was calculated by the method of least squares. The terminal half-life of the drug was calculated from the quotient: (0·69)/terminal slope). The AUC (area under the C versus t curve) was calculated by using the trapezoidal rule with extrapolation to infinity — by dividing the last experimental plasma concentration by the terminal slope.[14]

Total body clearance of diltiazem (CL) was calculated using the quotient of dose and AUC. The volume of distribution (V_{β}) was calculated from the ratio of

the clearance and the linear terminal slope. The volume of distribution at steady-state (V_{ss}) and the mean residence time (MRT) were calculated by using equations (1) and (2).[15,16]

$$V_{ss} = \frac{D\ AUMC}{(AUC^2)} \quad (1)$$

$$MRT = \frac{AUMC}{AUC} \quad (2)$$

AUMC is the area under the product of time (t) and the plasma drug concentration (C) versus t from time zero to infinity. AUMC was calculated by the trapezoidal rule with extrapolation to infinity. All pharmacokinetic parameters were calculated in a non-compartmental manner, based on the statistical moment theory.[17]

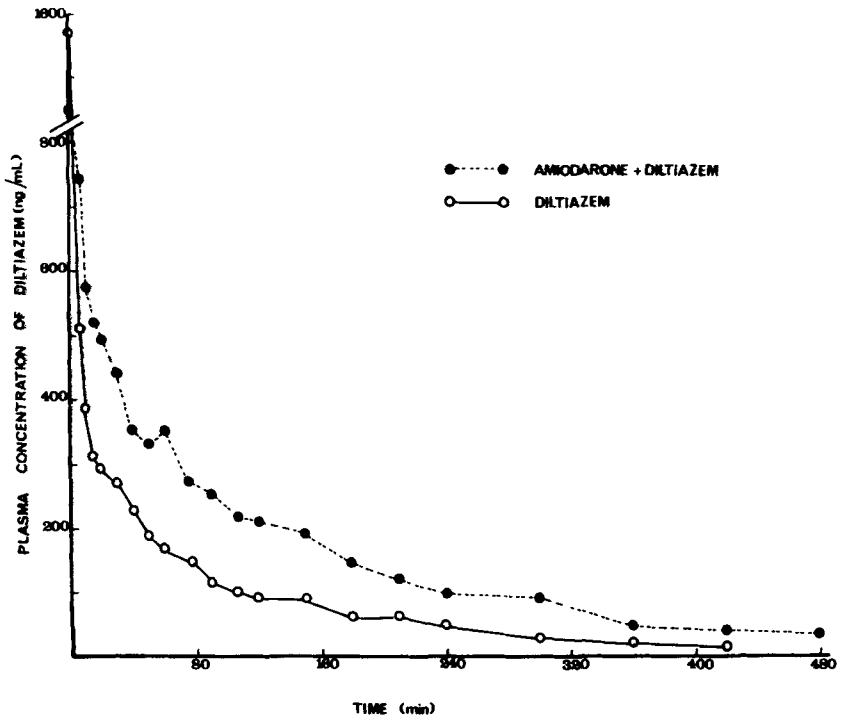

Figure 1. Mean plasma levels of diltiazem obtained after i.v. administration (20 mg) of the drug with and without amiodarone (100 mg) to five dogs

Table 1. Individual and mean pharmacokinetic parameters of diltiazem obtained after i.v. administration (20 mg) of the drug (DTZ, I) and after combined intravenous administration of diltiazem (20 mg) and amiodarone (100 mg) (DTZ+Amio, II) to five dogs

Pharmacokinetic parameter	Dog 3 DTZ I	Dog 3 DTZ+Amio II	Dog 6 DTZ I	Dog 6 DTZ+Amio II	Dog 10 DTZ I	Dog 10 DTZ+Amio II	Dog 11 DTZ I	Dog 11 DTZ+Amio II	Dog 12 DTZ I	Dog 12 DTZ+Amio II	Mean ± SD DTZ I	Mean ± SD DTZ+Amio II	
ß (min^{-1}) 10^{-3}	5·8	4·0	4·9	5·1	10·6	5·6	4·5	4·8	10·9	6·9	7·3±3·2	5·3±1·1	
$t_{1/2}$ß (min)	120	171	142	136	65	123	15	143	63	100	109±42	135±26	
AUC (mg $min\ l^{-1}$)	57	108	50	92	31	103	59	78	27	46	45±15	85±25	*$p<0·05$
CL (ml min^{-1})	353	186	404	218	637	193	340	257	730	434	493±179	258±103	*$p<0·05$
$V_ß$ (l)	61	46	83	43	60	34	75	53	67	63	69±10	48±11	*$p<0·05$
V_{ss} (l)	52	39	62	39	56	31	62	44	52	57	57±5	42±10	*$p<0·05$
MRT (min)	148	211	154	176	88	160	183	172	71	130	129±47	170±29	

*A significant statistical difference in the above marked parameters between treatment I and treatment II.
ß: linear terminal slope.
$t_{1/2ß}$: terminal half-life.
AUC: area under the plasma concentration versus time curves.
CL: total body clearance.
$V_ß$: volume of distribution.
V_{ss}: volume of distribution at steady state.
MRT: mean residence time.

RESULTS

The mean plasma levels of diltiazem in the five dogs studied are presented in Figure 1. Following i.v. administration, there were no detectable levels of diltiazem's major metabolite, desacetyldiltiazem. Table 1 summarizes the individual and mean pharmacokinetic parameters of diltiazem alone and in the presence of amiodarone. Figure 1 shows that in the presence of amiodarone, there is a significant increase in the plasma concentration of diltiazem. This is seen from the two-fold increase in diltiazem's mean AUC values.

Thus, following concurrent administration, there are significant statistical differences in diltiazem's CL, V_{β}, V_{ss}, and AUC values and no significant differences in its $t_{½\beta}$ and MRT values.

DISCUSSION

In this study, desacetyl diltiazem was not detected in the plasma. This is similar to data obtained in humans following the i.v. infusion of diltiazem.[6] As the deacetyl metabolite is formed by a first-pass effect, it is detected in plasma mainly following oral administration. The observed increase in diltiazem's plasma levels resulted from a decrease in its clearance (or metabolic clearance) and volume of distribution. However, as the decrease in both clearance and volume of distribution was of the same order of magnitude, there was no significant change in diltiazem's half-life.

The decrease in diltiazem's clearance could be due to its metabolic inhibition by amiodarone. This metabolic inhibition seems even more dramatic when it is considered that both compounds are metabolized, respectively, by the liver to desacetyl or desethyl metabolites. Smith *et al.* reported an unexpected accumulation of diltiazem during its chronic administration.[18] This may have been due to the saturation of the enzymes responsible for its metabolism. As diltiazem and amiodarone may share a concurrent metabolic pathway, a similar phenomenon may occur upon their co-administration.

In humans, amiodarone has an unusual half-life of 25 ± 12 days. Thus, drug levels following single dose administration are maintained usually for long periods of time. In dogs, however, amiodarone's half-life is only about 3 h.[19] Despite this short half-life, the interaction observed between the two drugs was quite dramatic.

Changes in protein binding do not affect the clearance of diltiazem. As diltiazem has a high extraction ratio (E), its metabolic clearance is not restricted. Thus, although it is largely independent of changes in plasma protein binding, it can be affected by changes in hepatic blood flow.

Relatively few reports have appeared which deal with amiodarone's interaction with other drugs.[10] Two reported interactions may be based upon such pharmacokinetic phenomena. The first is with warfarin and the second with digoxin.

The total plasma concentration of warfarin was reported to increase following the introduction of amiodarone therapy.[20,21] Inhibition of warfarin metabolism by amiodarone or a direct depression of the vitamin K dependent coagulation process were the possible suggested explanations for this interaction. A similar interaction was reported between digoxin and amiodarone;[22] a sharp increase in digoxin plasma levels also being observed following the administration of amiodarone.[23] This increase was accompanied by the appearance of cardiac digoxin side-effects. The myocardium has a high affinity for both of these drugs and since the onset of the interaction was rapid (within 1 day), the displacement of digoxin from cardiac muscle by amiodarone was suggested as the possible mechanism.[23] Thus, the potential mechanism of the interaction between diltiazem and amiodarone may be similar to those suggested for the interaction between amiodarone and warfarin, or digoxin.

The fact that the pharmacokinetic parameters of diltiazem are similar to both dogs and humans indicates the clinical relevance of this interaction study. Based upon the above findings and assuming that such data can be extrapolated to humans, it will then be imperative to monitor carefully all patients on combined diltiazem-amiodarone therapy.

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