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Review Article

The Role of CYP3A4 and CYP2C8 Polymorphism on Amiodarone Responses: Review Article

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ABSTRACT

Introduction: Amiodarone is one of drug with narrow therapeutics index. This medicine was metabolized by CYP3A4 and CYP2C8. The changes in the activity of this enzymes by CYP3A4 and CYP2C8 polymorphism will affect the effect. The study aimed to determine the impact of CYP3A4 and CYP2C8 polymorphism on amiodarone responses. **Method:** the study is review article with search article in PubMed with keywords: 'amiodarone' and 'polymorphism of CYP3A4' and 'polymorphism of CYP2C8'. **Results:** We collect 46 references to determine of impact polymorphism of CYP3A4 and CYP2C8 on amiodarone responses. **Conclusion:** Individual with CYP3A4*22 (rs35599367, 15389C>T); CYP2C8*2 (A805T), CYP2C8*3 (G416A, A1196G), and CYP2C8*4 (C792G) and CYP2C8*4 polymorphism have lower activity of CYP3A4 and CYP2C8 enzymes and potentially cause adverse effect.
Key words: Polymorphism, CYP3A4, CYP2C8, Amiodarone responses.

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INTRODUCTION

Amiodaron is class III antiarrhythmic.[1] This drug is indicated to protect from cardiac aritmia, among others ventricular fibrillation, ventricular tachycardia,[2] atrial fibrillation and supraventricular tachycardia.[3,4] Since this drug is narrow therapeutic index, amiodaron has high risk over effect. Some adverse effects of amiodarone are: hypotension, shock, bradycardia, AV block, and liver toxicity,[1] tremor, nausea, constipation and lung toxicity[2] and others.

Previous research has been done are: a) Research on frequency of CYP3A4 and CYP2C8 polymorphisms b) The effect of CYP3A4 and CYP2C8 polymorphisms on genetic expression. This research tries to find: a) The impact of CYP3A4 and CYP2C8 polymorphisms on kinetic and clinical responses b) The potential risk of adverse effects due to this polymorphism.

This medicine has molecular weight: 645.3116.[1]

Chemical Structure. [Figure 1]

Pharmacological properties

Amiodarone is slowly absorption with bioavailability varies 35 and 65%.[5] After per oral administration, Cmax in the plasma can achieved 3-7 hour. Steady-state concentrations (SSC) of amiodarone in the plasma is 0.4 to 11.99 µg/ml.[1,6] Volume of distribution (VD) varies range 9.26-17.17 L/kg in healthy people and 6.88-21.05 L/kg in the SVT patients,[5] with protein binding about 96%.[5,6] This drug is metabolized by the enzymes CYP3A4 and CYP2C8 to the main metabolite desethylamiodarone (DEA).[6]

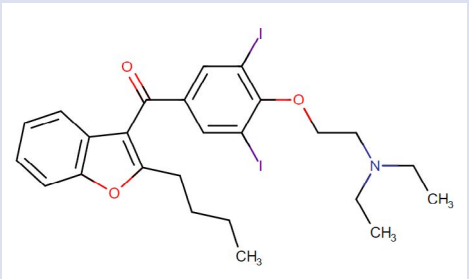

Figure 1: Chemical structure of amiodarone

Amiodarone elimination is mainly by hepatic metabolism and biliary excretion.[6] Only a small amount of the metabolite (desethylamiodarone (DEA)) is found in the urine.[5]

Amiodarone blocks the potassium current that causes cardiac muscle repolarization during the third phase of the cardiac action potential resulting in an increase in the duration of the action potential as well as the effective refractory period for cardiac cells. This causes a decrease in the excitability of cardiac muscle cells.[7,8]

The impact of CYP3A4 and CYP2C8 polymorphism on amiodarone responses

The CYP3A4 gene encodes CYP3A4 enzyme production. This enzyme metabolizes more than 50% of medicine.[9,10] CYP3A4 enzyme is presented in gastrointestinal tract, liver and renal dan prostate.[11,12] CYP3A4 gene has several polymophism in the form of SNPs such as CYP3A4*1B (rs2740574, –392A>G)[13] and CYP3A4*1G (rs2242480, 20230C>T) allele with increased CYP3A4 enzyme activity,[14-16] meanwhile CYP3A4*22 (rs35599367, 15389C>T) allele with reduced CYP3A4 enzyme activity.[17] The frequency of CYP3A4*1G mutations is relatively high in the Japanese population,[18] but Japanese individuals lack the CYP3A4*1B and CYP3A4*22 alleles.[17] The others polymorphism of CYP3A4 can be seen in table 1.

The CYP3A4 gene encodes the CYP3A4 enzyme. This gene is located on chromosome 10q24. CYP3A4 enzymes are located on the endoplasmic reticulum. This enzyme is a monooxygenase that catalyzes the metabolism of some drugs and the synthesis of

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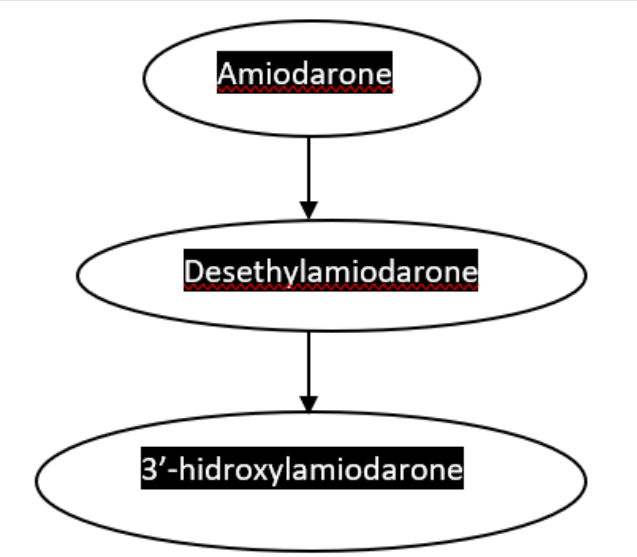

Figure 2: Metabolism amiodarone[6]

Table 1: **The polymorphism of CYP3A4.**

CYP3A4	Substitution of nitrogenous bases	Ref.
CYP3A4*1A	-392G>A	[23]
CYP3A4*1E	-392G>A, -369T>A	[24]
CYP3A4*1M	-392G>A, -156C>A	[25]
CYP3A4*1T	-392G>A, 26022T>C	[25]
CYP3A4*1G	-392G>A, 20239G>A	[25]
CYP3A4*2	-392G>A, 15722T>C	[26]
CYP3A4*3	-392G>A, 23181T>C	[26]
CYP3A4*4	-392G>A, 13880A>G	[27]
CYP3A4*5	-392G>A, 15711C>G	[27]
CYP3A4*6	-392G>A, 17670_17671insA	[27]
CYP3A4*7	6003G>A	[28]
CYP3A4*8	13917G>A (R130Q), 20239G>A	[28]
CYP3A4*9	14301G>A (V170I), 20239G>A	[28]
CYP3A4*10	-392G>A, 14313G>C	[28]
CYP3A4*11	21876C>T	[28,29]
CYP3A4*12	20239G>A, 21905C>T (	[28]
CYP3A4*13	22035C>T	[28,29]
CYP3A4*14	-392G>A, 44T>C	[30]
CYP3A4*15A,15B	14278G>A (R162Q), 20239G>A	[30,31]
CYP3A4*16A,16B	-392G>A, 15612C>G (T185S), 20239G>A	[25,29,30]
CYP3A4*17	15624T>C (F189S)	[32]
CYP3A4*18A,18B	-392G>A, 20079T>C (L293P), 20239G>A	[32]
CYP3A4*19	20239G>A, 23246C>T	[32]
CYP3A4*20	-392G>A, 25898_25899insA	[33]
CYP3A4*21	-392G>A, 20157A>G	[34]
CYP3A4*22	-392G>A, 15389C>T	[35,36]
CYP3A4*23	14277C>T (R162W), 20239G>A	[37]
CYP3A4*24	15658A>T (Q200H), 20239G>A	[37]
CYP3A4*26	-392G>A, 17642C>T (R268X)	[38]
CYP3A4*28	-392G>A, 64C>G (L22V), 20239G>A	[39]
CYP3A4*29	-392G>A, 13865T>A (F113I)	[39]
CYP3A4*30	-392G>A, 13916C>T (R130X)	[39]
CYP3A4*31	-392G>A, 20173C>A	[39]
CYP3A4*32	-392G>A, 20205T>C	[39]
CYP3A4*33	-392G>A, 21896G>T	[39]
CYP3A4*34	-392G>A, 23126A>G	[39]

Table 2: **The polymorphism of CYP2C8.**

CYP2C8	Substitution of nitrogenous bases	Ref.
CYP2C8*1A	NA	[40]
CYP2C8*1B	-271C>A	[41]
CYP2C8*1C	-370T>G	[41]
CYP2C8*2	11054A>T, 32299C.T	[41]
CYP2C8*3	2130G>A, 30411A>G, 32299C>T	[41]
CYP2C8*4	11041C>G	[41,42]
CYP2C8*5	-411C>T, 2189delA	[42-44]
CYP2C8*6	-271C>A, 4472G>A	[44,45]
CYP2C8*7	4517C>T	[45]
CYP2C8*8	-411C>T, 4517C>G.	[44,45]
CYP2C8*9	10989A>G	[45]
CYP2C8*10	26513G>T	[45]
CYP2C8*11	23452G>T	[46]
CYP2C8*12	32184delTTG	[44]
CYP2C8*13	10918T>G	[42]
CYP2C8*14	10961G>C	[42]
CYP2C8*15	4502G>A	[47]
CYP2C8*16	26356T>C	[47]
CYP2C8*17	10979A>G	[47]
CYP2C8*18	26445C>T	[47]

cholesterol.[19] CYP2C8 has a wild type CYP2C8*1[20] and three other allele variants namely CYP2C8*2 (A805T), CYP2C8*3 (G416A, A1196G), and CYP2C8*4 (C792G) are present among some ethnic populations. in the allele variant CYP2C8*2 there is substitution of Ile269Phe in exon 5 and is the most common variant of CYP2C8 in Africa; whereas the CYP2C8*3, G416A, and A1196G polymorphisms result in an Arg139Lys substitution in exon 3 and a Lys399Arg substitution in exon 8, respectively. CYP2C8*2 and CYP2C8*3 are associated with impaired metabolism of several drugs among others anticancer drug paclitaxel *in vitro*.[21] CYP2C8*4 polymorphism occurs with Ile264Met substitution in exon 5 which results in a decrease in CYP2C8 enzyme activity.[22] The others variant type of CYPC8 was presented in table 2.

Amiodaron is one of drug of narrow therapeutic index.[1] This drug was metabolized by CYP3A4 and CYP2C8 enzyme that code by CYP3A4 and CYP2C8 gene. Over or under expression of these gene will cause changes in CYP3A4 and CYP2C8 enzyme activity which in turn causes changes in drug kinetics of amiodarone. High activity of this enzyme was predicted to cause adverse effect and meanwhile low activity will cause failure of therapy.

CONCLUSION

Individual with CYP3A4*22 (rs35599367, 15389C>T); CYP2C8*2 (A805T), CYP2C8*3 (G416A, A1196G), and CYP2C8*4 (C792G) and CYP2C8*4 polymorphism occur with Ile264Met has higher risk adverse of amiodarone because this variant decrease enzyme activity of CYP3A4 and CYP2C8.

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