Austin Journal of Clinical Neurology

Open Access

Austin Publishing Group

Review Article

Antiarrhythmics and Anticoagulants in Clinical Practice

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Received: September 19, 2019; **Accepted:** November 01, 2019; **Published:** November 08, 2019

Abstract

Introduction: In addition to the individualization of therapy (genetic polymorphism) in the treatment of cardiac arrhythmias, an integrative and holistic approach to the patient is needed, as well as knowledge of the numerous interactions of medicaments used in their treatment.

Objective: A case study of a patient with cardiac arrhythmia following intense stress, after which the patient reacted poorly to the drug therapy applied in his case.

Case Report: Patient M. D., aged 70 years, was admitted to the Internal Department after stress of a higher intensity due to heart rhythm disorders by a type of tachyarrhythmia absolute with a heart rate of about 140/min. Instructional diagnosis: Extrasystole supraventricularis. Patient states that he have periodic pain in the chest, a feeling of lack of air several days before the reception. During hospitalization he is treated with: antiarrhythmic, anticoagulant therapy, diuretics, IPP. The patient did not respond adequately to therapy for 2 weeks; he was resistant to digoxin, verapamil, propafenone and amiodarone. After that, he is involved with metoprolol. He received enoxaparin 100 i.j./kg (sc) at 12 hours for the prevention of thromboembolism. The patient was converted to sinus rhythm only after 7 days. The cardiologist suspected of a poor complication. When asked if he regularly drunk the prescribed prescribed treatment, the patient replied that he had, and added that he had been drinking "tea from a haystack" for a month. Tea was bought in an unverified place. In the paper bag on which nothing was written, it was easy to spot the yellow flowers in the tea mix. The patient also added that, listening to the doctors' advice on television, he occasionally walked 40 minutes a day. Because of the expressed psychic component of the patient, the cardiologist had to moved patient to another room and turned off the monitor, because he constantly looked at him (eliminated the tension of the tension). Patient was relieved of his anxiety by steady telephony. A few weeks later, the general condition stabilized. The patient is discharged cardiopulmonary compensated. He is referred to the coronarography that was done and which showed a proper finding.

Conclusion: For the optimal outcome of therapy, a multidisciplinary approach and cooperation between all relevant professionals involved in the treatment of a patient (cardiologist, general practitioner, pharmacist, and other experts (dieticians, licensed walk instructor) is important.

Keywords: Stress, Cardiomyopathy, Apical ballooning, Arrhythmia

Introduction

In addition to the individualization of therapy (genetic polymorphism) in the treatment of cardiac arrhythmias, an integrative and holistic approach to the patient is required, as well as knowledge of the many drug interactions used in their treatment.

Due to sudden and severe stress, patients have arthritis that is difficult to stabilize in a short period of time, and such patients are often hospitalized to regulate the rhythm for a certain period of time.

Interactions of antiarrhythmic and anticoagulant drugs are common and numerous. Their wide range and frequency impedes the work of clinicians and the rapid healing of patients.

Cantarion (Hypericum perforatum) is a highly used medicinal plant whose active substance is hyperflorin. Cantarion extract increases the concentration of serotonin and noradrenaline neurotransmitters at synapses. Hypericum perforatum interacts with a large number of drugs when introduced into the body, usually in the form of teas. This interaction very often leads to an increase in the metabolism and the rate of excretion of these drugs, thus reducing their concentration in the blood, and therefore their effect and effectiveness. In some cases, the effect of the drug may be amplified, as well as possibly very dangerous side effects of the drug.

Objective

To present a case of a patient with cardiac arrhythmia who appeared after intense stress, after which he weakened his response to most of the medical therapy that was applied in his case.

Case Report

The patient M. D., 70 years old, was admitted to the Internal Department after a higher intensity stress due to heart rhythm disturbance by type of tachyarrhythmia absolute with a heart rate of

Citation: Lazarevic Marija Z, Zivkovic M and Petrovic Tesic G. Antiarrhythmics and Anticoagulants in Clinical Practice. Austin J Clin Neurol 2019; 6(1): 1135.

about 140/min. Directional diagnosis: Extrasystole supraventricularis. He has occasional chest pain, feeling short of air for several days before admission. Increased fatigue when going uphill. It has been treated for absolute arrhythmia a year ago. Prior therapy: verapamil 2 x 80 mg, quinapril + hydrochlorothiazide 20 mg + 12.5 mg 1 x ½, quinapril 10 mg 1 x 1, spironolactone 25 mg/day II, acetylsalicylic acid 100 mg 1 x 1, trimetazidine 2 x 35 mg, glyceryl trinitrate bromazepam 3 mg 1 x 1 as needed. TA is 120/70 mmHg. ECG on admission: fibrilatio atriorum, fr 155/min, normogram, ST and T b.o. EHO hearts: LP 55, LK 58/45, EF 45%, MR 1 - 2 +, TR1 - 2 +, Sp DK 45 mmHg, asc. Ao 42 (Tables 1 and 2). Uradene su labaratorijske analyze koje su pokazale da se vrednosti biomarkera ishemije miokarda nalaze u referentnim granicama (Table 3). During hospitalization he was treated with: antiarrhythmics, anticoagulant therapy, diuretics, IPP. The patient did not respond adequately to therapy for 2 weeks; was resistant to: digoxin, verapamil, propafenone and amiodarone. He was then switched on to metoprolol. He was receiving enoxaparin 100 i.j./kg (sc), for 12 hours to prevent thromboembolism. The patient was converted to sinus rhythm only after 7 days the frequency went down from 150/min to 100/min. The cardiologist suspected poor compliance. Asked if he regularly drank pre-prescribed therapy, the patient replied that he did and added that he had been drinking "tea from the walking grass" for a month. He bought the tea in an unverified place. In the paper bag that said nothing, it was easy to spot the yellow flowers in the tea mix). He drank tea for two days in the morning and in the evening, one cup before medication and sometimes at night when he would be awakened by chest pain and a lack of air. The patient also added that, while listening to the doctors 'advice on television, he occasionally walked for 40 minutes a day. Because of the pronounced psychic component of the patient, the cardiologist had to move the patient to another room and turn off the monitor because he was constantly staring at it (eliminating the influence of tension). The patient was relieved of his anxiety by telephone.

After a few weeks, the general condition stabilizes. The patient is released cardiopulmonary compensated.

The following therapy is suggested: amiodarone tbl. 200 mg 3 x 1, metoprolol tbl. With modified release 95 mg 1 x 1, furosemide tbl. 1 x 1/II day, potassium - pulvis chloride 1, 0 g 1 x1/II day, pantoprazole 40 mg 1 x 1, warfarin tbl. ½ + ¾ + ½ + ¾, up to INR control, bromazepam 3 mg 2 x 1. INR control, PV is scheduled for 7 days. He was referred to a coronarography that was done and showed a neat finding.

Discussion

The paper presents a case in which a patient after intense stress develops a cardiac arrhythmia which during hospitalization is converted to a sinus rhythm after seven days, and stabilization of the general state occurs only after a few weeks when the patient is released home cardiopulmonary compensated. Intense stress is involved in the onset of this arrhythmia and also contributes to its prolonged effect on the patient's condition due to his or her anxiety. The patient's psychic condition affects the somatic component in the form of cardiomyopathy and tachyarthmia of the absolute, which with reduced efficiency responded to the applied medicamentous therapy.

Antiarrhythmics have great potential for interactions due to small therapeutic breadth (warfarin, digoxin, amiodarone), long-term administration and even lifelong use of warfarin in patients with artificial valvular involvement, extensive metabolism at first passage through the liver (lidocaine, metoprolol), nonlinear pharmacokinetics [1-3]. These interactions occur after per os or parenteral administration, before or after administration, *in vivo* or *in vitro* [4]. These drugs should be carefully included and excluded from therapy (amiodarone, warfarin). They are unwanted, sometimes fatal, but may also be useful as a combination of digoxin and beta-blockers/Ca blockers in the treatment of atrial fibrillation [5, 6]. Sometimes interactions are difficult to recognize because they manifest after prolonged administration with nonspecific symptoms that overlap with disease, age, or side effects of antiarrhythmics (proarrhythmogenic potential), such as bradycardia due to a combination of amiodarone and metoprolol synergism [8-10].

Verapamil, sotalol with long-term use with herbal remedies (licorice, hay, aloe) increases the risk of hypokalaemia and arrhythmias, which is an indirect interaction, and it is therefore necessary to determine serum potassium levels and monitor symptoms of hypokalemia. The tendency for the interaction of digoxin with food rich in plant fibers (wheat, pectin) is also known. This interaction reduces the bioavailability of digoxin by 16 to 32%

Table 1: Echo cardiographic findings.

Structure	Reference Values	Results
Aortic root	do 37mm	36
Separation of cusps	>16mm	25
Left atrium	do 40mm	48
LPIA	<1,2	
Right ventricle	<25mm	29
Bulbus aorta		
Aortic arch		
Aorta ascendens		38

Table 2: Echo cardiographic findings.

Structure	Reference Values	Results
EDD	do 56mm	51
ESD	do 40mm	36
EF	>60%	56%
FS	28-44%	30%
Septum	<11mm	12
Zadnji zid	<11mm	9

Table 3: Results of laboratory analyzes.

Analysis	Value
AST(SGOT)	21,0
LDH	187,0
CK	127,0
CK-MB	22,0
CRP	0,1
Immunohemija	
Troponin	<0,200

due to the slowing of the passage through the gastrointestinal tract and the reduced release of the drug from the formulation. Therefore, the use of digoxin should be avoided with meals rich in vegetable fiber [11].

The uterus suppresses ischemia-associated ventricular arrhythmias (fibrillations). It has a mild protective effect compared to amiodarone based on muscarinic receptor stimulation. The prolongation of the refractory period has been demonstrated in rats, however, further studies of this effect are needed [12].

Due to the fact that our patient did not respond sufficiently effectively to the medicamentous therapy, the possibility of interaction of these drugs with the cantarion (Hypericum perforatum L) was considered. The patient regularly consumed before oral therapy prescribed by a cardiologist and a cup of St. John's wort, which he accompanied at night in the case of severe pain and tightness in the chest. The Cantarion is a strong inducer of CYP 3A4, CYP 2C9, CYP 2C8, CYP 2C19, a moderate inducer of CYP 1A2, CYP 2E1, CYP 2D6 and leads to strong P-gp expression. The mechanism of action in clinically relevant interactions with warfarin and phenprocoumon, respectively is the induction of CYP 3A4 and CYP 2C9, resulting in the effect of decreased efficacy of increased clearance and decreased levels of about 25%. The mechanism of action in clinically relevant interactions with warfarin is the induction of CYP 3A4, and in combination with digoxin, is P-gp expression and a decrease in plasma concentration.

Variable response to antiarrhythmic therapy may also result in polymorphisms of the VKORC1 gene and the CYP 2C9 gene (S - enantiomer), and genotyping (VKORC1 and CYP 2C9) would reduce the variation of the therapeutic response by one third. However, in addition to the individualization of therapy (genetic polymorphism), an integrative and holistic approach to the patient or psychosomatic medicine approach is required.

In the administration of low molecular weight heparin, numerous interactions with drugs that affect hemostasis are also possible: NSAIDs, acetylsalicylic acid, glucocorticoids, thrombolytics and oral anticoagulants, anti-aggregation drugs (ticlopidine, clopidogrel) including glycoprotein II receptor antagonists. Concomitant use should be avoided because of the risk of bleeding. When using drugs that cause hyperkalemia: NSAIDs (naproxen, ketorolac, indomethacin), ACE inhibitors should monitor serum potassium levels especially in at-risk patients (diabetes, chronic renal failure, metabolic acidosis) and for longer than seven days of therapy.

The high potential for warfarin interactions is due to: small therapeutic width, CYP 450 dependent metabolism, high plasma protein binding rate (97%) [13, 14]. The use of streptokinase and alteplase is contraindicated in the use of warfarin, and the drugs to be avoided are: clopidogrel, eptifibatide, tirofiban, LMWH, fondaparinux, NSAIDs (and salicylates and COX-2 inhibitors), antidepressants (SSRIs and SNRIs) [15, 16]. Warfarin enhancing drugs are: amiodarone, propafen, fibrates, statins, erythromycin, sulfamethoxazole, metronidazole, azole antifungals, paracetamo, tamoxifen, omeprazole, disulfiram, allopurinol. The action of warfarin is antagonized by: barbiturates, carbamazepine, oral contraceptives, rifampicin, azathioprine, with corticosteroids and ritonavir having variable effect [17, 18].

The Cantarion produces strong induction of CYP 3A4, CYP 2C9, CYP 2C8, CYP 2C19, moderate induction of CYP 1A2, CYP 2E1, CYP 2D6 and strong expression of P-gp. Therefore, drug interactions with warfarin induce CYP 3A4 and CYP 2C9, decrease levels by about 25%, and are contraindicated, CYP 3A4 inducing verapamil and digoxin leading to P-gp expression and decreased plasma concentrations [19-21].

The complexity of the interactions of anti-arthromics and anticoagulant drugs requires greater care when administering them precisely because of the very frequent concomitant use as is the case with the patient.

Conclusion

For the optimal outcome of therapy, a multidisciplinary approach and collaboration of all relevant professionals involved in patient treatment (cardiologist, general practitioner, pharmacist, and other professionals (dietitians, licensed walking instructor) may be important). Individual patient approach (personalized therapy), assessing the benefit/risk balance of medicines, managing drug interactions, monitoring drug side effects, caring for a patient's quality of life (diet, physical activity, psychosomatic aspects of the disease) and managing patients' self-medication needs (herbal remedies, dietary supplements, OTC preparations) contemporary practices that must be continuously monitored and refined.

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