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Case Report

Carbimazol and acenocoumarol, where is the problem?

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ABSTRACT

Acenocoumarol and carbimazole are two drugs widely prescribed, they can sometimes be used in the same time. There is no known drug interaction between the two drugs but we report a case of a serious hemorrhagic complication following the concomitant use of the acenocoumarol and carbimazole. A 70-year old man treated by acenocoumarol for an aortic and mitral valve replacement. For a clinical and biological hyperthyroidism, he began treatment with carbimazole, ten days before admission. Three days later, he developed a mucocutaneous icterus with major hemorrhagic syndrome. The outcome was favourable after stopping medication and the use of vitamin K.

Keywords: Acenocoumarol, Carbimazole, Drug interactions

INTRODUCTION

Acenocoumarol is a vitamin K antagonist, widely prescribed for prophylaxis and treatment of many thrombo-embolic disorders. The occurrence of hemorrhagic complications is the main side effect of these drugs and can sometimes be due to drug interactions. In most cases these interactions are known and predictable and they can be life threatening.[1]

Carbimazole is an effective antithyroid used for the treatment of hyperthyroidism. It is a pro-drug (3-carbethoxy methimazol) converted to the active form (methimazol) in the liver. Carbimazol is generally safe. Minor sensitivity reactions can be observed during the treatment. However serious adverse reactions, such as agranulocytosis and severe hepatitis can rarely occur.[2] We report a case of a serious hemorrhagic complication caused by acenocoumarol and carbimazole combination.

CASE REPORT

We report the case of a 70-year old man, with an aortic and mitral valve replacement since 1995, treated by acenocoumarol with regular and satisfactory monitoring of prothrombin ratio and international normalized ratio (INR) with a target INR of 2.5. No further treatment was reported. The patient presented ten days before admission, a clinical and biological hyperthyroidism (TSH<0,05mUI/l). Chest radiography showed a left deviation of the trachea and CT-scan confirmed the presence of a heterogeneous goiter. The patient then began treatment with carbimazole at a dose of 30mg/day. Three days later, he developed a mucocutaneous icterus without fever or itching associated with major hemorrhagic syndrome due to hematemesis, hematochezia, melena, hematuria, and bruises. On admission, the patient was asthenic, weighing 57Kg to a size of 1.63m (BMI=21Kg/m^2), afebrile (37.2°C), with mucocutaneous icterus and ecchymotic spots on the abdomen and limbs, there were no scratch marks or hepatomegaly or splenomegaly. Results of initial laboratory evaluation showed markedly elevated serum bilirubin levels, elevated liver enzymes, gamma glutamyl transferase and alkaline phosphatase. (The results are documented in the Table 1). Coagulation tests revealed an incogulable blood but the factor V, blood and platelets counts were in the normal ranges. Results of tests for

hepatitis viruses (hepatitis A, B, C virus, HIV, EBV, CMV, Echo, Coxsackie), autoimmune diseases (AMA, ANA, SMA, Anti-DNA, ANCA), metabolic diseases and hepatic toxins were unremarkable. The acenocoumarol medication was then, stopped and the patient was treated with vitamin K (one injection a day for 3 days). Bili-MRI, abdominal ultrasound and endoscopy that were performed after normalization of the INR, Were unremarkable. Evaluation of cardiac function by Doppler ultrasound showed a mechanical prosthesis in the aortic position and valvular and ischemic heart disease combined with left ventricle dysfunction (ejection fraction 45%). The outcome was favorable with disappearance of hemorrhagic syndrome, regression of jaundice and progressive correction of the biological parameters. Once liver function stabilized; the goiter was treated by surgery after a rapid lugol preparation and increasing doses of propranolol.

Table1: Laboratory tests results.

	Day 0 (admission)	Day 3	Day 4	Day 6	Reference range
Prothrombin ratio (%)	Incoagulable blood	64	79	100	
INR	-	1.54	1.16	1.0	
Factor V (%)	85	-	-	-	70-120
ALP (IU/L)	280	210	177	147	40-129
GGT (IU/L)	152	115	98	68	8-60
AST (IU/L)	78	70	63	55	10-38
ALT (IU/L)	56	51	44	55	10-40
Total bilirubin (mg/dl)	27.0	33.7	38.0	23.1	< 1
Direct bilirubin (mg/dl)	17.0	21.2	23.9	14.5	< 0.2

INR: International normalized ratio; ALP: Alkaline phosphatase; GGT: Gamma glutamyl transferase; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase.

DISCUSSION

Carbimazol is antithyroid synthesis (ATS) most commonly used in the treatment of hyperthyroidism. It inhibits the synthesis of thyroid hormones by interfering with iodine uptake of thyroglobulin. After intestinal absorption, carbimazol is rapidly hydrolysed to methimazol in the liver and excreted by the kidneys. The major side effects of ATS are hematologic and are represented mainly by leukoneutropenia whose major form is agranulocytosis, hepatotoxicity is a less common but well-known side effect.[3] Wang and all report that the use of carbimazole increases the incidence rate of hepatitis (0.32/1000 person-years), this risk is increased with the high doses.[4] The mechanism would be immuno-allergic. Reintroduction test, which is not recommended, is frequently positive. Liver biopsy shows cholestasis predominantly centrilobular. In addition to these sever liver side effects, less sever hepatic effects are known such as increased liver enzymes without increased bilirubin.[5] In our patient, the absence of other causes of hepatopathy, the timing of the symptoms' onset at baseline, and the improvement after stopping medication, suggests that this reaction is due to Carbimazol. Acenocoumarol is a widely-used drug with proven efficacy in the prevention of thrombotic and embolic events. It has a narrow therapeutic index; therefore, even small changes in plasma concentration could lead to marked alterations in therapeutic effect or toxicity with increasing the risk of bleeding. Many interactions between acenocoumarol and certain drugs or foods are known, and can cause overdose or conversely a lack of efficacy.[6] This observation is the first to our knowledge reporting the occurrence of bleeding triggered by the concomitant use of acenocoumarol and carbimazol. The pathophysiological mechanism of this interaction is unknown. Is it an interaction between acenocoumarol and carbimazol, or an additive hepatic effect, or an immunological mechanism?

Difficult to control variations of the INR are common in hyperthyroidism. Indeed, it has been hypothesized that in hyperthyroidism the catabolism of vitamin-K dependent clotting factors is increased; so the effect of oral anticoagulants is potentiated. Consequently, when an antithyroid drug is administered this hypercatabolism would diminish and the anticoagulant effect would similarly diminish.[7] In present case, the opposite effect occurred which could be secondary to the predominant and major impact of methimazole on the liver leading to plummeting concentrations of coagulation factors because of a marked reduction in their synthesis. In addition, acute hepatic failure, could contribute to the impaired clearance and thus over dosage of acenocoumarol. These are only hypotheses that must be verified by other prospective and experimental studies on the interaction between acenocoumarol and carbimazol.

CONCLUSION

The use of the acenocoumarol is not always easy, especially in specific medical situations and when

combined with other drugs. The practitioner must always take into account the numerous drug interactions of this drug class. Present case illustrates the potential risks associated with the concomitant use of acenocoumarol and carbimazol and may lead to a life-threatening.

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