Clinically important interaction between metoprolol and propafenone

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A combination of antiarrhythmic drugs with β_1 selective blocking agents has often been used. Both these types of drugs are metabolized via the cytochrome P450 (CYP) enzyme system, and therefore potential drug interactions are of considerable clinical significance. The antiarrhythmic agent propafenone undergoes CYP 2D6–dependent metabolism.[1] Propafenone is also an inhibitor of the enzyme; the inhibitory constant has been estimated at 50 nmol/L, similar to that of quinidine (60 nmol/L).[2] Metoprolol, a β_1 selective blocking agent, undergoes extensive presystemic elimination by CYP 2D6, and it has been shown that metabolites do not substantially contribute to the β_1-blockade.[3,4] Metoprolol has a dose-dependent effect; dose is commonly titrated to the highest dose tolerated in order to achieve the maximal effect in the absence of adverse effects.[5] A 2- to 5-fold increase in steady-state levels of metoprolol has been described after adding propafenone to metoprolol therapy.[6] The disposition of CYP 2D6 substrates also depends on the CYP 2D6 genotype. In general, 4 subgroups might be differentiated: poor metabolizers (PM), intermediate metabolizers (IM), extensive metabolizers (EM), and ultrarapid metabolizers (UM). Poor metabolizers lack any functional allele. Ultrarapid metabolizers have more than 2 functional alleles. Intermediate metabolizers are heterozygous for a specific variant allele or possess alleles with reduced activity.[7]

We present a case of an interaction between metoprolol and propafenone in which high metoprolol concentrations affect the patient's condition.

Case

A 66-year-old woman (weight 81 kg) was referred to our outpatient department because of decompensated hypertension (World Health Organization classification grade III). Blood pressure in a sitting position was 154/82 mm Hg, and heart rate was 60 beats/min. The patient had undergone kidney transplantation for polycystic kidney disease several years ago and was taking 175 mg/d of cyclosporine and 50 mg/d of azathioprine. Further comorbidities were ischemic heart disease without angina pectoris syndrome (New York Heart Association class III or IV) and chronic venous insufficiency. At the time of admission, the patient was being treated with the following cardiovascular medication: 200 mg/d of metoprolol, 100 mg/d of losartan, 1 mg/d of rilmenidine, 60 mg/d of furosemide, captopril as needed, 100 mg/d of acetylsalicylic acid, and 20 mg/d of isosorbide mononitrate. To prevent atrial fibrillation, 600 mg of propafenone daily was prescribed. During her follow-up, 5 mg/d of amlodipine was introduced to the therapy. After the medication adjustment, the patient's blood pressure was compensated (**Table 1**); however, she was repeatedly complaining about increased tiredness and dyspnea on exertion. Therefore, determination of metoprolol and α-hydroxymetoprolol serum concentrations was indicated.[8] Three hours after the patient's metoprolol-dose intake, her metoprolol–α-hydroxymetoprolol metabolic ratio (MR) was used for CYP 2D6 phenotyping.[9] Genotyping of CYP 2D6 was also performed. A DNA direct sequencing analysis of the whole coding sequence of the CYP 2D6 gene was performed using a genetic analyzer. Copy number variants of the gene were detected using the long-range polymerase chain reaction method and amplified products were visualized on 1% agarose gel electrophoresis.

The patient had an IM genotype with detected variant alleles CYP 2D6*4/*9. However, 3 hours after the dose intake, the metoprolol–α-hydroxymetoprolol MR was 104.3, indicative of a PM phenotype. **Table 1** shows metoprolol and α-hydroxymetoprolol serum concentrations. A survey

EDITOR'S KEY POINTS

- Propafenone might inhibit metoprolol metabolism, and high metoprolol serum concentrations might have clinical effects. Clinicians should be aware of this potential interaction and start with low metoprolol doses and follow up with patients carefully.
- Therapeutic drug monitoring could serve as a valuable tool in clarifying a patient's condition.

POINTS DE REPÈRE DU RÉDACTEUR

- La propafénone pourrait inhiber le métabolisme du métoprolol, et des concentrations sériques élevées de métoprolol pourraient avoir des effets cliniques. Les cliniciens devraient être au fait de cette interaction potentielle, commencer par de faibles doses de métoprolol et assurer un suivi rigoureux des patients.
- La surveillance thérapeutique du médicament pourrait s'avérer un outil précieux pour clarifier la condition du patient.

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of the patient's concomitant medication revealed her use of propafenone, an inhibitor of CYP 2D6 activity. The patient's metoprolol dose was reduced to 100 mg daily. Her condition improved, and her tiredness and dyspnea disappeared.

About half a year later the patient was admitted to the internal medicine department for chest pain on exertion and on rest lasting for about 14 days, with radiation to the right arm, dyspnea, orthopnea, and edema of the lower limbs. Blood pressure on admission was 160/80 mm Hg, and heart rate was 51 beats/min. She was diagnosed as having global cardiac failure with atrial fibrillation with slow ventricular response. Relevant therapy was initiated with an adjustment of her medication. Her metoprolol dosage was reduced to 12.5 mg daily, and propafenone was withdrawn. Two weeks later the patient was hemodynamically stable and was discharged from the hospital.

Several days after discharge, the patient herself increased her metoprolol intake to a previous dose of 100 mg daily. During the next outpatient's visit, her CYP 2D6 phenotype after propafenone discontinuation was determined (**Table 1**); a substantial decrease in metoprolol–α-hydroxymetoprolol MR was revealed, switching the patient's phenotype from PM (MR=104.3) to EM (MR=1.4).

Discussion

This case demonstrates an inhibitory effect of propafenone on metoprolol biotransformation resulting in the occurrence of adverse effects due to high metoprolol levels.

Propafenone has been shown to be metabolized by the same hepatic enzyme as the sparteine-debrisoquine polymorphism but with higher affinity for CYP 2D6, thereby being able to cause a shift of metabolizer phenotype.[1] Metoprolol undergoes extensive presystemic elimination, with this enzyme accounting for 70% to 80% of its metabolism. In our patient, a marked decrease in metoprolol–α-hydroxymetoprolol MR was observed after propafenone therapy had been stopped, and the patient's phenotype switched from PM to EM. Because the patient's other medications were retained, we attribute this phenotypic shift to vanished inhibitory effect.

Labbé et al found that the addition of propafenone to CYP 2D6 substrate mexiletine in people with EM phenotypes caused pharmacokinetic changes of mexiletine to such an extent that differences between those with EM phenotypes and PM phenotypes were almost absent.[10] Thus, results of phenotyping might be falsified by the presence of interfering medications, resulting in discrepancy between the phenotype and genotype. Wagner et al found that the addition of propafenone increased steady-state levels of metoprolol 2 to 5 times in 4 patients. Two patients even developed side effects while receiving the drug combination (severe nightmares and left ventricular failure), which disappeared after the metoprolol dose was reduced or discontinued.[6] Our patient suffered from tiredness and dyspnea on exertion likely owing to high metoprolol serum concentrations caused by the inhibitory effect of propafenone. Substantial increases in metoprolol concentrations have also been observed after the addition of the antiarrhythmic drug amiodarone and the antihistamine diphenhydramine.[11,12] The addition of selective serotonin reuptake inhibitors, fluoxetine and paroxetine, has also resulted in severe adverse effects, which subsided after discontinuation of the inhibitors.[13,14]

Table 1. Patient's metoprolol and α-hydroxymetoprolol serum concentrations; metoprolol–α-hydroxymetoprolol metabolic ratio; heart rate; and blood pressure before metoprolol intake and 1 or 3 hours after metoprolol intake, with and without propafenone

METOPROLOL DAILY DOSE	METOPROLOL SERUM LEVEL (µg/L)	α-HYDROXYMETOPROLOL SERUM LEVEL (µg/L)	METOPROLOL–α-HYDROXYMETOPROLOL METABOLIC RATIO	HEART RATE (BEATS/MIN)	BLOOD PRESSURE (mm Hg)
200 mg with propafenone					
• Before metoprolol intake	152.4	4.4	34.6	66	136/76
• 1 h after	333.2	3.8	87.7	59	134/72
• 3 h after	412.2	4.0	104.3	61	128/76
100 mg with propafenone					
• Before metoprolol intake	79.2	7.7	10.3	68	132/68
• 1 h after	168.6	4.0	42.2	67	138/74
100 mg without propafenone					
• Before metoprolol intake	10.3	32.0	0.3	55	124/62
• 1 h after	53.8	44.0	1.2	62	126/70
• 3 h after	134.9	97.7	1.4	53	NA

NA—not available.

In our case the patient's genotype was heterozygous for CYP 2D6*4/*9 alleles. Individuals who carry the CYP 2D6*9 allele have an altered ability to metabolize CYP 2D6 substrates and have IM phenotypes, whereas the CYP 2D6*4 allele results in a loss of enzyme activity.[15] The combination of IM phenotype and defective alleles is not associated with a PM phenotype; however, it shows a substantially higher MR than does the EM-PM genotype.[16] The S-enantiomer of propafenone has also been shown to display β-blocking action. The degree of β-blockade reflects genetically determined variations in propafenone metabolism, with subjects with the PM phenotype having considerably more β-blockade.[17] Unfortunately we were not able to determine the propafenone serum concentration and subsequently assess its contribution to the occurrence of adverse effects. However, after the metoprolol dose was reduced to half (100 mg/d), the side effects disappeared.

Interestingly, blood pressure and, in particular, heart rate did not change substantially after metoprolol dose reduction and after propafenone discontinuation. Pharmacodynamic modeling of the β_1-blocking effect of metoprolol shows a steep linear relationship to plasma concentration, with a maximum effect at 400 nmol/L (106.96 μg/L). However, only 30% of the maximum β_1-blocking effect is necessary for a clinically significant effect; this limit was observed at a metoprolol plasma concentration of 45 nmol/L (12.03 μg/L).[4] We speculate that the permanent metoprolol serum concentrations in our patient above this concentration limit preserved stable heart rate in spite of gradual decline in metoprolol concentrations.

Conclusion

Coadministration of propafenone and metoprolol might result in elevation of metoprolol serum concentration and affect a patient's clinical condition. Clinicians should be aware of the potential interaction when prescribing this combination and start with low metoprolol doses, as well as follow up with patients carefully. Therapeutic drug monitoring could serve as a valuable tool in clarifying a patient's condition.

Ms Duricova was a postgraduate student in the Department of Clinical Pharmacology, **Dr Perinova** was a specialist in analytics in the Department of Clinical Pharmacology, **Ms Jurckova** was a specialist in genetics in the Department of Medical Genetics, **Dr Kacirova** was a medical doctor and Head of the Department of Clinical Pharmacology, and **Dr Grundmann** was Associate Professor in the Department of Clinical Pharmacology, all at the University Hospital Ostrava in the Czech Republic.

Competing interests
None declared

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