

## Pharmacological Interaction Between Flecainide and Benziodarone

**To the Editor,**

Interactions between drugs are one of the most frequent causes of iatrogenic response—sometimes with extremely serious consequences—and account for up to 7% of all hospitalizations.<sup>1</sup> Although most of these interactions are predictable and therefore avoidable, unexpected cases may appear with new or infrequently used drugs.

We recently attended a 71-year-old woman with a history of kidney transplantation 7 years earlier, complicated by membranous nephropathy and severe nephrotic syndrome, with creatinine levels of 1.4 mg/dL and creatinine clearance of 71 mL/min. The patient was being monitored by the outpatient cardiology department for mild hypertensive heart disease and paroxysmal atrial fibrillation successfully controlled with oral flecainide. She was also receiving amlodipine, losartan, furosemide, chlorthalidone, calcitriol,

acetylsalicylic acid, prednisone, cyclosporine, cyclophosphamide and insulin for steroid diabetes. The last nephrology follow-up visit disclosed hyperuricemia of 11.20 mg/dL. Because of intolerance to allopurinol, the patient was started on benziodarone 100 mg/day. Atorvastatin 10 mg/day was resumed (it had been discontinued several months earlier) for hypercholesterolemia of 447 mg/dL. Three days later, the patient went to the emergency room for asthenia and poor overall condition. Physical examination indicated no abnormalities; blood biochemistry evidenced creatine phosphokinase 354 U/L, creatinine 1.44 mg/dL and urea 155 mg/dL. ECG at admission showed changes compared to baseline (with flecainide), QRS duration prolongation of 169 ms (21% increase) caused by the association of complete right bundle branch block with a previous anterior hemiblock, QTc interval prolongation of 482 ms (22% increase) and PR interval prolongation of 203 ms (18% increase). Flecainide and benziodarone were discontinued due to suspected drug interaction, as well as atorvastatin due to mild rhabdomyolysis. The symptoms disappeared within 48 hours and the repeat ECG indicated values very close to baseline. Flecainide therapy was gradually resumed without complications, until the usual dosage of 100 mg every 24 hours was reached.

Flecainide is a class IC antiarrhythmic agent used to treat ventricular and supraventricular arrhythmias in patients with no structural heart disease. Flecainide is mainly metabolized by cytochrome P450 2D6 in the liver, giving inactive or only slightly active metabolites.<sup>2</sup> It is also eliminated by renal excretion as parent drug, with up to 50% excreted unchanged in urine. Therefore, patients with impaired renal function may experience a slight delay in excretion.

Benziodarone is a benzofuran, a group of drugs that includes amiodarone. It has similar effects on the thyroid due to the iodine in the molecule. Although initially used as antianginal drug,<sup>3</sup> it is currently used as a uricosuric agent in severe hyperuricemia when the patient cannot tolerate allopurinol.<sup>4</sup> Mouloupoulos et al,<sup>5</sup>

found that the effects of benziodarone on the ECG are minimal, although no further studies have confirmed this conclusion. The product information recommends decreasing the warfarin dose because of potential enhancement of its effect, probably by the same mechanism (cytochrome P450 inhibition) causing amiodarone to interact with warfarin.

We suggest that benziodarone might interact with flecainide, increasing its mean half-life by inhibiting cytochrome P450 2D6, although there are no studies that demonstrate this effect. Mild renal insufficiency would act to enhance this phenomenon, as it reduces drug elimination slightly.

Until studies to clarify this question are conducted with benziodarone (and benzobromarone, another drug of the same group also marketed as a uricosuric), this combination of drugs should be avoided or used only with strict monitoring.

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## REFERENCES

1. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA* 1998;279:1200-5.
2. Conard GJ, Ober RE. Metabolism of flecainide. *Am J Cardiol* 1984;53:41B-51B.
3. Oter R, Vilalta C, Balaguer I, Domínguez J. Benziodarone in coronary insufficiency therapy, double blind test. *Rev Clin Esp* 1968; 108:384-8.
4. Marcén R, Gallego N, Gámez C, Orofino L, Ortuño J. Hyperuricemia after kidney transplantation in patients treated with cyclosporine. *Am J Med* 1992;93:354-5.
5. Mouloupoulos SD, Koutras DA, Stamatelopoulos S, Souvatzoglou A, Pipingos GD, Philippou G. Comparison of the effect of amiodarone and benziodarone on thyroxine metabolism and surface ECG. *Endocrinol Exp* 1989;23:269-78.