in patients with lone AF, and correction of BNP followed the return to sinus rhythm. The present findings agree with these studies, but unlike them, this study evaluated patients with AF who had underlying hypertension and coronary artery disease and compared subjects with persistent AF with patients who had paroxysmal AF. It did not seem that duration of AF significantly affected BNP levels. The mean plasma BNP level before conversion to sinus rhythm in the paroxysmal AF group was higher than in the persistent AF group, but was not statistically significant.

In conclusion, the present study demonstrates that AF affects BNP secretion in patients with persistent and paroxysmal types of arrhythmias and with normal left ventricular function and that restoration of sinus rhythm leads to a decrease in BNP concentrations. The presence of AF should be taken into consideration when interpreting plasma BNP levels in patients with heart disease.


Efficacy of Substituting Innovator Propafenone for Its Generic Formulation in Patients With Atrial Fibrillation

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The clinical outcomes of 114 patients with atrial fibrillation who had been treated with the innovator propafenone, and in whom the drug was then replaced with generic propafenone because of cost containment, were compared. The generic formulation was found to be at least as safe and effective as the innovator drug, with regard to atrial fibrillation recurrence, emergency room and hospital admissions, and necessity for concomitant therapy. ©2004 by Excerpta Medica, Inc.

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Generic drug use reduces health costs to health care suppliers and consumers. However, the process of approval of a generic formulation differs from that of an innovator drug, necessitating only the demonstration of chemical and bioequivalence between the two.1 Opponents of generic formulations have raised serious concerns about the efficacy and safety of the generic substitution of narrow therapeutic index medications (e.g., antiarrhythmics).2 An amendment to the Israeli “Pharmacists’ order” passed in the Israeli parliament during 1999 allowed the pharmacists to substitute a generic formulation for the innovator drug unless intentionally stated otherwise by the prescribing physician.3 After this, the major health maintenance organization in Israel (Clalit Health Services, insuring 60% of the Israeli population) made the decision to substitute the generic formulation Profex (Dragenopharm GnGH and Co KG, Tritmoming, Germany; distributed in Israel by Taro Pharmaceutical, Haifa, Israel) for the innovator propafenone Rythmex (Knoll, Delkenheim, Germany, distributed in Israel by Teva Pharma, Netanya, Israel). In this study, we assessed the impact of comprehensive substitution of propafenone for its new generic formulation in patients treated for paroxysmal or persistent atrial fibrillation (AF).

We retrospectively identified a cohort of 119 patients with paroxysmal AF treated with Rythmex for ≥18 consecutive months and in whom the drug was replaced with Profex. The cohort was then followed
for another 18-month period or until discontinuation of the drug. Three patients died during the generic formulation period and 2 discontinued therapy. Data were therefore compared for 114 patients during the full 2 time periods.

Demographic and clinical variables were abstracted from the patients’ hospital charts. Data included the rates and causes of emergency room (ER) visits and hospital admissions, as well as concomitant medications, rates of Holter monitoring, and the need for AF cardioversion. Information regarding drug substitution was abstracted from the Clalit Health Services district pharmacist records. Continuous and dichotomous variables were compared using Student’s t test for matched samples and McNemar’s tests, respectively. SPSS 10.0 software (SPSS Inc., Chicago, Illinois) was used for the statistical analysis. The study was approved by the Soroka University Center’s ethics committee.

Age (mean ± SD) was 65.3 ± 11 years, and 66% of the patients were women; 50% of patients were diagnosed with an additional chronic disease. Concomitant diseases were hypertension in 40%, coronary artery disease in 19%, and diabetes mellitus in 3% of patients. Six percent of patients had a history of cerebrovascular accident. No significant changes were made in drug therapy between the 2 study periods. Concomitant medications were antiplatelet and/or aspirin in 68% and 68%, amiodarone in 5% and 9%, β blockers in 42% and 44%, and calcium channel blockers in 35% and 40% of patients in the innovator and generic periods, respectively. The number of clinical events is listed in Table 1. No increase in the rates of ER discharges, hospital admissions, or in the number of cardiology clinic visits were detected. There were significantly more ER visits before the drug switch, mainly for an arrhythmia. There were also no significant differences in the rates of cardioversion of AF, supraventricular tachycardia ablations, or pacemaker implants. Yearly recurrence of clinical AF was 52% before and 34% after the drug change (p = 0.03). Three patients died during the generic drug (follow-up) period with a mean age of 84 years. Causes of death were sepsis (1 patient) and unknown in 2 patients. Two other patients discontinued therapy; 1 for AF recurrence and the other for frequent palpitations.

The US Food and Drug Administration’s testing for bioequivalence is carried out under a standard protocol. Each generic product is compared with the innovator drug in a crossover study in which blood levels of the drugs are measured over time and bioequivalence is assessed. However, as clinical trials directly comparing “head-to-head” innovator and generic formulations are scarce, physicians have to base decisions regarding generic drug use on minimal available data. Although pharmacologic comparison studies do exist for some medications, their relevance to daily practice is unknown. In a survey of 64 arrhythmia experts, 24 reported a definite recurrence of the arrhythmia when their patient was on a generic substitution. Although this rate is alarming, the possibility of a severe reporting bias limits the conclusions. Moreover, case reports and series of adverse and proarrhythmic effects of generic formulations may result in a reduced rate of prescribing generic drugs instead of further investigation.

In our cohort, the generic preparation prescription did not result in an increase in any variable related to arrhythmia recurrence. We even found ER visits to be fewer with the generic formulation. Although this may be incidental, another explanation could be that when prior ER admissions (during the innovator drug period) were not found to be serious, general practitioners reduced ER referrals during the generic drug period. It is also possible that some patients were diagnosed with AF or started on the innovator drug just before the beginning of our data collection. Patients who are recently diagnosed may tend to be more active in seeking medical care, such as ER visits, than those who are more “experienced” with their disease or medication.

No differences were found in the rate of use of other cardiovascular medications, especially antihypertensives and anticoagulation. Furthermore, as these might interact with propafenone, we did not find a higher rate of complications related to blood pressure or inappropriate anticoagulation levels.

The strength of this study is the opportunity to examine the 2 medications on the very same patients, making every patient their own control, thus avoiding mismatching for demographic and clinical variables. In a similar setup and design, the innovator drug Coumadin (Bristol-Myers Squibb, New York, New York) switched to the generic drug warfarin was studied. No changes were noted in international normalized ratio control or warfarin management. Another similar design study found that in heart-transplant patients converted from Imuran (Faro Pharmaceuticals) to generic azathioprine, no compromise in safety and efficacy was observed. Generic substitution of Imuran resulted in an annual cost savings of $318 per

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<th>TABLE 1 Clinical Events During Both Study Periods</th>
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<tr>
<td>Event</td>
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<tr>
<td>Innovator Propafenone Period</td>
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<td>Generic Propafenone Period</td>
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<td>Cardiology clinic visits</td>
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<td>Total events</td>
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<td>For an arrhythmia</td>
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<td>For chest pain</td>
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<td>Other</td>
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<td>Hospital admissions</td>
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<td>Total events</td>
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<td>For cerebrovascular accident</td>
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<td>Holter monitoring</td>
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<td>Pacemaker implantation</td>
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* p<0.01; † p = 0.05. Data shown are numbers of events.
We investigated whether a simple blood test of plasma N-brain natriuretic peptide (N-BNP), compared with echocardiographic left ventricular ejection fraction (LVEF), both measured at rest, correlated well with aerobic exercise capacity (peak oxygen consumption [VO\(_2\)]) in patients with chronic heart failure. Plasma N-BNP was found to significantly correlate with peak VO\(_2\) (p < 0.001) and exercise duration (p = 0.001), whereas LVEF showed very poor correlations with peak VO\(_2\) and exercise duration (both p > 0.3). The results suggest that N-BNP actually reflects functional cardiac impairment better than LVEF.

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It is axiomatic that symptoms of heart failure (HF) are manifested more during exertion than at rest. Conceptually, HF is primarily the failure of the cardiac pump to function adequately to support the more dynamic circulation required during exercise.1 Conversely, the extent of impairment in pump function is indirectly represented by a decrease in exercise capacity, best measured by peak exercise oxygen consumption (VO\(_2\)), but approximated by exercise duration.1 We tested whether plasma N-brain natriuretic peptide (N-BNP) from a blood sample taken at rest can be as good as left ventricular ejection fraction (LVEF) measured at rest in indicating cardiac dysfunction during peak exercise.

Consecutive patients with stable chronic HF in New York Heart Association functional classes I to IV who were capable of exercising (n = 86, age 55 ± 12 [mean ± SD] years, 84% men, LVEF 37 ± 15%) participated in this study. Most of the patients (64%) had an ischemic etiology, whereas the remainder had dilated cardiomyopathy (30%) and valve diseases. Ten age-matched volunteers without heart disease (mean age 52 ± 12 years; 9 men) also participated. A sample of venous blood was taken to determine N-BNP levels using a validated in-house noncompetitive assay.2 All subjects underwent cardiopulmonary exercise testing to measure standard parameters, including peak VO\(_2\) and exercise duration. Echocardiography was performed at rest in patients to measure LVEF.

The Mann-Whitney U statistic test for unpaired samples was performed to assess differences in N-BNP levels between patients with HF and in control subjects. Values of N-BNP were normalized by logarithmic transformation (log N-BNP) before correlation with exercise parameters using Pearson’s correlation methods. Nonparametric (echocardiographic) data were correlated with the logarithmic transformation of N-BNP using Spearman’s rank correlation methods.

Circulating N-BNP measured at rest was found to correlate well with peak VO\(_2\) in the entire cohort (R =

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Comparison of Plasma N-Brain Natriuretic Peptide, Peak Oxygen Consumption, and Left Ventricular Ejection Fraction for Severity of Chronic Heart Failure

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4. Pouwels M-JM, Hooymans PM, van der Aa GC, Grimbau FW. Comparison of