Long-Term Effects of Theophylline in Atrial Fibrillation with a Slow Ventricular Response

Paolo Alboni, MD, Nelly Paparella, MD, Riccardo Cappato, MD, Roberto Pirani, MD, Panayiu Yiannacopulu, MD, and Gian Enrico Antonioli, MD

In 17 patients (aged 78 ± 9 years) with symptomatic atrial fibrillation and a slow ventricular response not related to drugs, a resting electrocardiogram and 24-hour Holter recording were obtained before and to 6 days after administration of slow-release theophylline (700 mg/day), and successively every 3 months during the long-term phase. Fourteen patients had organic heart disease, and 13 complained of syncope or presyncope, and 4 of asthenia and easy fatigability. At the steady-state evaluation, theophylline significantly increased resting heart rate (HR) by 42%, mean 24-hour HR by 31% and minimal 24-hour HR by 34%. Cardiac pauses >2,500 ms disappeared or markedly decreased. The daily number of wide QRS complexes increased. Serum theophylline level was 13 ± 6 ng/ml. During the follow-up period (20 ± 18 months), the mean daily theophylline dosage was 450 mg and the mean serum theophylline level 9 ng/ml. Seven patients died: 1 because of heart failure, and 6 because of noncardiac death. One patient complained of a syncopal episode during 1 visit. The drug markedly reduced asthenia and easy fatigability. During the long-term phase, HR increased spontaneously in 3 patients, and the treatment was interrupted. In 2 patients, theophylline had to be discontinued because of gastric intolerance. During long-term therapy, HR was similar to that observed at the steady-state evaluation, despite the reduction in daily dosage. The data suggest that theophylline is an effective therapy in most patients with symptomatic atrial fibrillation and a slow ventricular response.

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Methods

Patients: We selected 17 consecutive patients (9 women and 8 men; mean age 78 ± 9 years, range 52 to 92) with chronic AF and a slow ventricular response not induced by drugs (the last 12 were reported previously, and the other 5 were observed subsequently). We included patients with a mean resting HR <60 beats/min, symptoms attributable to slow HR, and absence of bundle branch block of advanced degree (QRS ≥120 ms). Criteria for exclusion included the following: recent myocardial infarction, acute disease of any type, significant renal or hepatic disease, and congestive heart failure (New York Heart Association class IV). Fourteen patients had organic heart disease: 8 hypertensive cardiovascular disease, 4 ischemic heart disease and 2 mitral valve disease. Sixteen patients were in New York Heart Association class I–II and 1 in class III. Twelve patients complained of syncope or presyncope before hospitalization; 4 complained of marked asthenia and easy fatigability, and 1 of dyspnea after slight effort. Diuretics, converting enzyme inhibitors and nitrates could be administered if necessary.

Procedures: Each patient gave informed consent. Chest X-ray examination, echocardiography and standard laboratory tests were performed. Resting HR was measured from a 10-second standard electrocardiogram. Patients underwent 24-hour Holter monitoring for 2 consecutive days, using a 2-channel recorder. Oral theophylline therapy was then initiated at the dosage of 700 mg/day in 2 divided doses using a slow-release tablet. Five to 6 days later, standard electrocardiography and Holter recording were repeated with the same methodology. Both before and after theophylline treatment, the parameters were reported as the mean of the 2 consecutive 24-hour Holter recordings to reduce spontaneous variability and therefore better evaluate the effects of the drug. The serum theophylline level was determined 3 hours after the intake of the morning dose. Patients were then enrolled in a long-term phase, and were observed at the outpatient clinic 1 month later and every 3 months thereafter. Clinical history, physical examination, resting
theophylline level were obtained during each visit. Dosage modifications were made, as necessary, to eliminate symptoms and cardiac pauses, and limit drug-related side effects. If any episode of syncope recurred or if side effects persisting through dosage reduction occurred, theophylline therapy was discontinued. Statistical evaluations were performed using the Wilcoxon test. Results are presented as mean ± SD.

RESULTS

Steady state: The effects of theophylline on HR are reported in Table I and Figure 1. Mean resting HR, and mean, minimal and maximal 24-hour HR increased significantly after drug administration by 42, 31, 34 and 14%, respectively. The daily number of cardiac pauses >2,500 ms decreased after theophylline (p <0.01). The daily number of wide QRS complexes, couplets and triplets increased after the drug, but not significantly. No episode of ventricular tachycardia was observed before or after theophylline. The drug did not significantly change systolic and diastolic blood pressure. Serum theophylline level ranged from 5 to 21 μg/ml (mean 13 ± 4).

Follow-up: The mean follow-up period was 20 ± 18 months (range 1 to 55). Long-term therapy was initiated at a dosage of 400 to 600 mg/day (Diflumal, Malesci). During follow-up, 7 patients died after 15 ± 14 months of treatment. One patient died of heart failure, 2 of arterial embolism and 4 of noncardiovascular disease (pneumonia, pulmonary and rectal neoplasm, and pulmonary complications after prostatectomy). No patient died suddenly. One patient complained of syncope during 1 visit, he refused pacemaker implantation, continued theophylline treatment and remained asymptomatic in the subsequent 21 months. In the other patients, syncope or presyncope did not occur during follow-up. The drug markedly reduced asthenia and easy fatigability in patients complaining of these symptoms. Three patients complained of palpitations, despite the reduction in the daily dosage of the drug to 200 to 300 mg; resting HR was 90, 95 and 110 beats/min, respectively. The drug was discontinued after 20 ± 11 months of treatment, and in the subsequent visits, resting HR was between 80 and 100 beats/min for a mean period of 8 ± 3 months. In 2 patients, theophylline had to be discontinued at approximately 1 month, because of nausea, despite gradual reduction in the dosage. During follow-up, other patients complained of slight gastric disturbances that disappeared after a temporary or permanent reduction in dosage.

The values of the electrocardiographic parameters during follow-up are reported in Table I and Figure 2. Electrocardiographic parameters of the 7 patients followed for ≥24 months are shown in Figure 2. Resting HR, and mean and minimal 24-hour HR during follow-up were similar to those observed at the steady-state evaluation, although the mean dosage of theophylline had been reduced. Furthermore, the daily number of cardiac pauses during follow-up was similar to that observed at the steady-state evaluation. At 1 visit in 2 patients, the follow-up HR decreased to control values; in
both patients, the serum theophylline level was \(<5\) ng/ml, and it is possible that they were noncompliant with their medication schedule for a period of time.

DISCUSSION

Electrophysiologic investigations showed that theophylline enhances atrioventricular nodal conduction; it shortens both the interval and cycle length of the fastest 1:1 atrioventricular conduction.\(^1\)\(^5\) The most probable mechanism by which theophylline exerts positive chronotropic and dromotropic action appears to be an antagonism of the cardiac effects of adenosine, which has been shown to depress sinus node automaticity and atrioventricular nodal conduction in laboratory animals and humans. In the present study, we investigated the effects of slow-release theophylline in patients with symptomatic AF and a slow ventricular response. At the steady-state evaluation, the drug significantly increased resting HR, and mean and minimal 24-hour HR, and abolished or markedly decreased cardiac pauses. We previously reported an increase in exercise HR by 26%.\(^2\) The data show that theophylline enhances conduction through the atrioventricular node, resulting in a faster ventricular response rate. During long-term therapy, HR was similar to that observed at the steady-state evaluation, despite the reduction in daily dosage; it is possible that this is partly related to a spontaneous increase in HR in some patients. During long-term therapy, only 1 patient complained of syncope at 1 visit; the other patients have remained symptom-free. Therefore, the results suggest a reduction in bradycardia-related symptoms in patients treated with theophylline; this observation appears to be strengthened by the marked reduction in the frequency of cardiac pauses. However, the natural history of AF with a slow ventricular response is unknown, and to better assess this issue, a randomized study of long-term efficacy is needed. The marked reduction in asthenia and easy fatigability during long-term treatment is interesting; it can be related to both the increase in HR and a direct effect on the central nervous system.\(^1\)\(^4\)

In the present patients during follow-up, mortality has been very high, and this appears to be partly due to the high mean age (approximately 80 years). However,
death was not attributable to the atrioventricular conduction disturbance in any patient, because none died suddenly. Three patients (17%), after a mean period of treatment of 1.5 years, complained of severe palpitations; HR had increased spontaneously, and the drug was discontinued (i.e., we observed a spontaneous recovery of the atrioventricular conduction disturbance of uncertain origin, which was not described previously).

In 2 patients, theophylline had to be discontinued because of nausea; it was reported previously that in approximately 15% of subjects, theophylline should be withdrawn because of gastric intolerance.

The data suggest that the initial dosage of the drug should be 500 to 600 mg/day, and it can be slightly decreased or increased according to the clinical course. Serum theophylline level should be ≥5 ng/ml; for lower values, the effects of the drug on HR are inconstant; furthermore, to prevent side effects of the drug, the serum concentration should be ≤15 ng/ml.