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Clinical research

Report of erectile dysfunction after therapy with beta-blockers is related to patient knowledge of side effects and is reversed by placebo

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Aims Patients with cardiovascular diseases frequently complain of erectile dysfunction especially when treated with beta-blockers. In order to assess whether the effect of beta-blockers on erectile dysfunction is in part related to patient knowledge of the drug side effects, 96 patients (all males, age 52±7 years) with newly diagnosed cardiovascular disease and not suffering from erectile dysfunction entered a two phase, single cross over study.

Methods and results During the first phase of the study patients received atenolol 50 mg o.d. (A), 32 patients were blinded on the drug given (group A), 32 were informed on the drug given but not on its side effects (group B) and 32 took A after being informed on its side effects on erectile function (group C). After 3 months the incidence of erectile dysfunction was 3.1% in the group A, 15.6% in group B and 31.2% in group C ($P<0.01$). All patients reporting ED entered the second phase of the study and were randomised to receive Sildenafil 50 mg and placebo in a cross over study. Sildenafil citrate and placebo were equally effective in reversing erectile dysfunction in all but one patient reporting ED with Atenolol.

Conclusion Our results show that the knowledge and prejudice about side effects of beta-blockers can produce anxiety, that may cause erectile function.

Introduction

Erectile dysfunction (ED), the persistent inability to achieve and/or maintain an erection sufficient for satisfactory sexual activity,[1] is a higly prevalent medical problem affecting a significant proportion of men. Its prevalence increases with age reaching rates from 39% to 67% in the age range from 40 to 70 years. ED has important impact on quality of life and, is believed to be related to drug therapy, leads to non-compliance to therapy. Keene et al. reported drug-related erectile dysfunction in approximately 25% of cases, being mostly readily reversible when the drug is stopped, or a suitable alternative is given.[2] Cardio-active drugs are commonly associated with adverse side effects amongst which ED is a common one.[3] The complaint of erectile dysfunction is frequent in patients with cardiovascular disease especially when treated with beta-blockers. Issue of cause and effect are confused because cardiovascular disease 'per se' may cause erectile dysfunction, as there appears to be a higher rate of sexual dysfunction in untreated men with cardiovascular disease compared with men of similar age.

Animal studies have reported that beta-blockers such as propranolol may induce ED through central and

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Table 1 Clinical features of study patients

	Atenolol-do not know drug	Atenolol-do not know side effects	Atenolol—know side effects
Mean age	52±7	52±11	53±9
Cigarette smoking	24%	30%	26%
Hypertension	52%	50%	60%
Diabetes	20%	14%	24%
Angina	60%	60%	60%
Hyperlipidemia	60%	48%	58%

peripheral (genital) effects as it increases the latency to ex copula ejaculation, the latency to initial erection and reduces the number of erectile reflexes.[4] Similar findings have been reported with other beta-blockers although their effect on sexual behaviour is more evident with the lipophilic beta-blockers than with the hydrophilic. Early human studies have suggested a high incidence of ED in treated hypertensives and helped to re-enforce the idea that beta-blockers may induce ED. Despite the common belief of the induction of ED with beta-blocker use, clinical studies failed to confirm a relationship between use of such drugs and ED.[3] ED in patients with cardiovascular disease may be related to psychological factors involving the fear of the disease and of the effect of the drugs prescribed. The role of psychologic component and of anxiety in sexual dysfunction is well demonstrated and placebo may be very effective in the treatment of ED due to psychological problems. However, treatment of erectile dysfunction includes a wide range of locally acting substances and/or prostheses. Phosphodiesterase 5 inhibitors have been recently introduced as orally active treatment for erectile dysfunction and have also been proven effective in patients with a wide range of cardiovascular diseases.[5]

Aim of our study was to evaluate whether the effect of beta-blockers on erectile dysfunction is, in part, related to patient knowledge of the drug side effects and whether when occurring ED is reversed by the phosphodiesterase 5 inhibitor Sildenafil citrate or placebo.

Methods

The study population included 96 patients (all males, age 52±7 years) with newly diagnosed (<6 weeks) cardiovascular disease (40% hypertension, 60% angina) without contraindications to beta-blockers, never on previous cardiac medications and not suffering from erectile dysfunction (Table 1). The study design was a two-phase study. The first phase was a parallel study with a treatment period of 90 days. After the administration of a multidimensional quality of life questionnaire designed to assess the presence of erectile dysfunction (International Index of Erectile Function, IIEF), patients received atenolol 50 mg o.d. (A).[6] Thirty-two patients in the first group did not know the drug they were taking, 32 received A and were informed on the drug they were taking but not its side effects with regard to ED and 32 patients were given A knowing its side effects on the erectile function. The phrase used to inform patients regarding the possible occurrence of ED was '. . .it may cause erectile dysfunction but it is uncommon' for all patients of the latter group. The multidimensional IIEF Questionnaire was re-administered in all patients at the end of the 90-day trial. Patients reporting ED with A entered the second phase of the study that was double blind, placebo-controlled, with single cross-over. Patients were randomized to receive Sildenafil 50 mg or matching Placebo for at least three different attempts to be carried out in one week. The questionnaire on ED was administered again at the end of each treatment period of the placebo-controlled study (Fig. 1). End-point of the study was the occurrence of ED. Data are presented as mean±1 SD or percentages when appropriate. Student's paired *t* test or Wilcoxon Signed Rank test or chi square test were used to compare continous normally or not normally distributed and qualitative variables where appropriate at baseline and after each therapy. A P value <0.05 was considered statistically significant.

Results

Baseline clinical features of study patients are reported in Table 1. No difference in clinical characteristics or use of any cardio-active class of drugs during the study period was noted between groups (Table 2). The incidence of erectile dysfunction was 3.1% (only 1 patient) in the group not knowing which drug they were taking, 15.6% (5 patients) in the group knowing that they were receiving a beta-blocker and 31.2% (10 patients) in the group also knowing the side effects of the drug (P<0.01) (Fig. 2).

In patients reporting ED after Atenolol, Sildenafil citrate 50 mg and placebo were equally effective in reversing erectile dysfunction in all but one patient (Fig. 3). The latter patient, however, had a good response to Sildenafil citrate 100 mg given in an open fashion at the end of the study.

Discussion

The present study suggests that report of ED in patients receiving beta-blockers may be mostly psychological in origin as it is more frequent in patients knowing this side effect of the drug and it is reversed in the majority of cases by placebo. We found a striking difference in the self-report of ED according to patient knowledge of possible side effect on erectile dysfunction that can be explained only by a psychological effect. Cardiovascular disease 'per se' may cause ED that may be worsened by cardio-active drugs through various mechanisms. Amongst cardiovascular drugs sympatholytics (central alpha-agonists, beta-blockers), diuretics and ACE-Inhibitors are most commonly associated with report of sexual side effects. The majority of reports on sexual

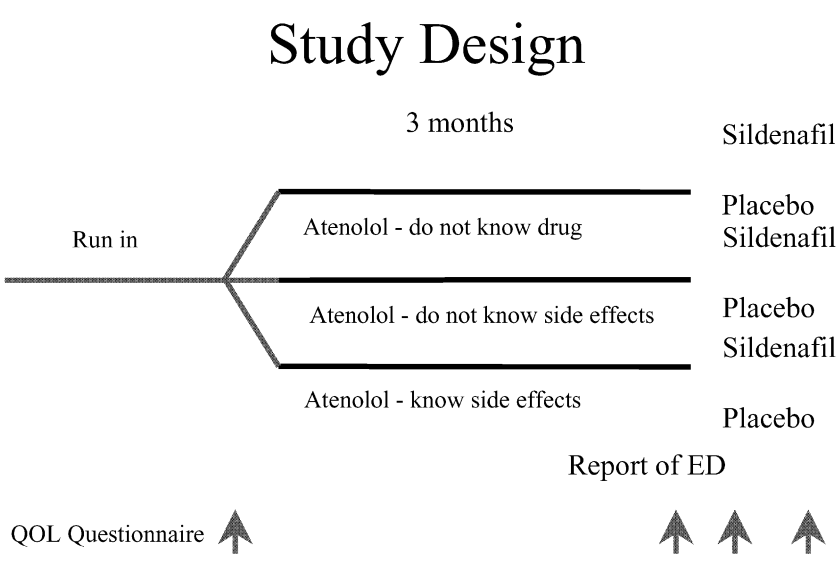

Fig. 1 Study design. Time of Questionnaire administration (grey arrows) and the three different arms of the study (90 days long each one). All patients received atenolol 50 mg o.d. The first group of patients did not know the drug they were taking, the second group was informed on the drug they were taking but not its side effects with report to ED and the third group took Atenolol knowing its side effects on the erectile function. After three months patients were randomized to receive a single administration of Sildenafil 50 mg or Placebo in a double blind single cross over study one week. The questionnaire on ED was administrated at the end of the Atenolol phase and at the end of each arm of the placebo controlled study.

Table 2 Concurrent medications in study patients

	Atenolol-do not know drug	Atenolol-do not know side effects	Atenolol—know side effects
Aspirin/antiplatelet agents	84%	81%	81%
Statins	59%	56%	53%
Calcium Channel Blockers	22%	25%	25%
ACE Inhibitors	31%	37.5%	37.5%
Diuretics	25%	25%	21.8%
Nitrates	9%	6%	9%
Trimetazidine	53%	56%	53%

dysfunction associated with these drugs have been based entirely on retrospective and self-reported data.[7]

Erectile dysfunction is the most common sexual problem in men, after premature ejaculation, affecting up to 30 million in the United States.[8] This disease may cause anger, depression, anxiety and bad feelings about their self-worth and self-confidence, impairing the quality of life.[9] Keene et al. suggested that drug therapy accounts for erectile dysfunction in approximately 25% of cases and is mostly readily reversible when the drug is stopped.[2] Early reports from the Medical Research Council Working Party on Mild to Moderate Hypertension showed that erectile dysfunction occurred more frequently in patients taking either bendrofluazide or propranolol than in those taking placebo.[10] Subsequently, Rosen et al. that investigated the sexual sequelae of several classes of anti-hypertensive drugs (beta-blockers, alpha-agonists, diuretics) in normal and hypertensive males in a comparative study with placebo, found a lack consistent drug effects on measures of sexual response. In accordance with the study of Rosen et al. we found that the incidence of ED in patients blinded on study drug was low. In our study the incidence of erectile dysfunction was as high as 31.2% in the patients knowing the possible side effects of the drug, while in the group of patients that did not know the drug they were taking the incidence was ten times less frequent. These findings demonstrate on one hand the importance of psychological mechanism inducing erectile dysfunction, and on the other hand the fact that the most of beta-blockers affect on erectile dysfunction is caused by psychological concerns. The mostly psychological nature of beta-blocker-induced ED is further suggested by the fact that in the majority of cases ED was completely reversed by placebo. Our data are in agreement with recent prospective randomized double blinded studies that found that sex life and erectile dysfunction are not affected by beta-blockers.[11] The anxiety and fear play an important role in causing sexual dysfunctions.[12] Several studies suggest that anxiety is common among people with sexual dysfunctions, with different levels and natures of anxiety and that anxiety reduction procedures improve some,

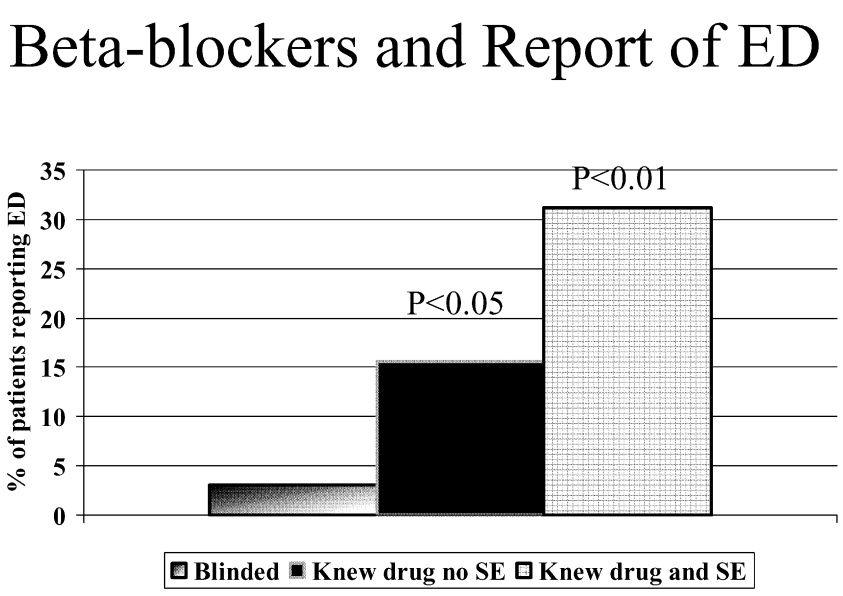

Fig. 2 Incidence of erectile dysfunction in the different group. Grey into white bar: patients not knowing the drug they were taking. Black bar: patients knowing the drug receiving but not its side effects. Grid bar: patients knowing the side effects of the drug they were receiving.

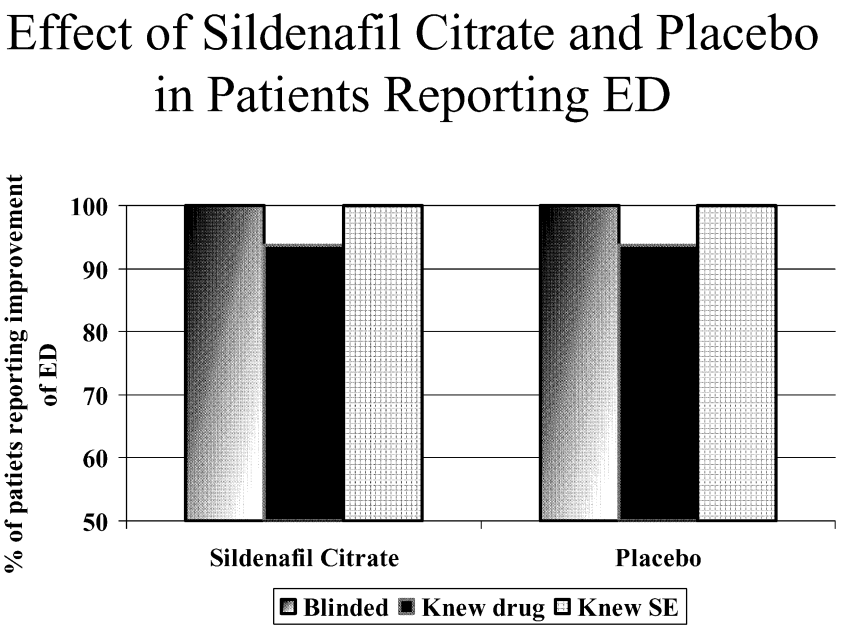

Fig. 3 Percentage of patients reporting improvement of ED after administration of Sildenafil or Placebo. Sildenafil citrate and placebo were equally effective in reversing erectile dysfunction in all but one patient. Grey into white bar: patients not knowing the drug they were taking. Black bar: patients knowing the drug receiving but not its side effects. Grid bar: patients knowing the side effects of the drug they were receiving. ED=erectile dysfunction; QOL=quality of life questionnaire; SE=side-effects.

also if probably not all, aspects of sexual dysfunctions.[12] The result of our study suggest that knowledge about side effects can produce anxiety, that may affect erectile function.

In conclusion the occurrence of erectile dysfunction on beta-blockers is low, much lower than commonly thought. The results of the present study suggest that both patient's and doctor's expectations on the risk of experiencing erectile dysfunction may influence the occurrence of this bothersome side-effect.

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