Cardiology

Prevention of Suboptimal β-Blocker Treatment in Patients with Myocardial Infarction

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OBJECTIVE: To review the published data and clinical guidelines on the use of β-blockers in myocardial infarctions (MIs) and contrast that with actual clinical practice.

DATA SOURCES: A MEDLINE search (January 1970–June 1999) was performed to identify all relevant articles. References from these articles were also evaluated for review if deemed important.

DATA SYNTHESIS: Intravenous and oral β-blockers have been proven to improve outcomes in patients with MIs in numerous clinical trials. In current clinical practice, only 15% of MI patients receive intravenous β-blockers and long-term β-blocker therapy is used in <40% of patients without contraindications. However, they could be safely administered to 40% and 70% of these patients, respectively. Furthermore, most of these patients are receiving doses far below those found beneficial in clinical trials. Many of the real and perceived contraindications to β-blockers are reviewed to allow the practitioner to identify patients who are incorrectly excluded from β-blocker therapy. Also discussed are special clinical situations in which the benefits observed during clinical trials may not apply.

CONCLUSIONS: β-blockers are valuable drugs in the treatment of peri- and post-MI. In clinical practice, most patients are not treated or are inadequately treated with β-blockers. Pharmacists should ensure that such patients actually have an absolute contraindication or unusual situation where therapy is not firmly indicated. Patients without absolute contraindications warrant titration to specific target doses or a target heart rate of 55–60 beats/min.

KEY WORDS: β-blocker, myocardial infarction, contraindication, mortality.

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β-blockers are important agents in the acute and chronic pharmacotherapy of myocardial infarction (MI). In the clinical situation, however, underutilization, underdosing, and, to a lesser extent, the use of β-blockers despite existing contraindications are common. This is most likely due to a misunderstanding of the clinical benefits, their time course, the heart rate and dosing goals used in clinical trials, and the actual contraindications of use. This article reviews (1) pharmacologic benefits, (2) results of randomized clinical trials, (3) use of β-blockers in current clinical practice, (4) actual and perceived contraindications to using β-blockers during acute and post-MI, and (5) the use of β-blockers in special situations (non-Q-wave MI, cocaine-induced MI).

Pharmacologic Benefits

REDUCING SUBSTRATES FOR VENTRICULAR TACHYARRHYTHMIAS

Acute myocardial ischemia and myocardial injury cause increased neural release of catecholamines as well as their discharge from storage depots in the left ventricle.[1] This occurs along with β-receptor up-regulation within 15–30 minutes of coronary occlusion and enhanced coupling of the β-receptor to adenylate cyclase. All of these factors increase the generation of the second messenger cyclic adenosine monophosphate (cAMP), which can make ventricular fibrillation more likely.[1] cAMP can increase the risk for reentry ventricular tachyarrhythmias by activating calcium-dependent slow channel responses in depolarized fibers.[2] Excess cAMP can also cause substantial increases in cytosolic calcium, which can initiate delayed afterdepolarizations.[2]

Ischemia alone can make ventricular arrhythmias more likely, but this risk is enhanced in the presence of high sympathetic tone.[3] The ventricular fibrillation threshold is an experimental indicator of overall ventricular vulnerability to fibrillation. In experimental studies, ischemia decreased the ventricular fibrillation threshold, which indicates that fibrillation is more likely.[4] Conversely, β-blockers raise the ventricular fibrillation threshold in ischemic and nonischemic myocardium.[4-6] The effect of β-blockers on raising the ventricular fibrillation threshold was greater than that of lidocaine in an experimental model.[6] Both lipophilic (metoprolol)[5] and hydrophilic (esmolol)[6] agents were evaluated in these models.

Hydrophilic agents work only at the myocardial level to prevent arrhythmias; lipophilic agents work at both the myocardium and the central nervous system.[3,7] Intracerebral injections of propranolol (a β-blocker with high lipophilicity), in doses too low to have direct myocardial effects, prevented ventricular fibrillation in two animal investigations.[8,9] Another animal study[10] comparing intravenous atenolol (a β-blocker with low lipophilicity) with metoprolol (an agent with moderate lipophilicity) demonstrated greater suppression of ventricular fibrillation in the metoprolol group. The reason for greater arrhythmia suppression with metoprolol was presumably an increase in cardiac vagal tone toward a normal level. Catecholamines in the central nervous system can inhibit the influence of the parasympathetic nervous system on the heart (through vagal suppression) via β_1 receptor stimulation.[3,7] In this study,[10] metoprolol had cerebrospinal concentrations that were similar to those in plasma, while the cerebrospinal concentrations of atenolol were only 10% of those in the plasma. A study[11] of experimental MI using electrical vagal stimulation verified that enhanced vagal tone reduces the incidence of ventricular fibrillation.

β-blockers may also prevent arrhythmias after MI by preventing increases in ischemia-induced QT dispersion. QT dispersion (determined by subtracting the longest QT interval in a 12-lead electrocardiogram [ECG] recording from the shortest QT interval) provides an index of the degree of heterogeneity of repolarization within the ventricles of the heart. Increased QT dispersion is associated with an increased risk of ventricular arrhythmias after MI.[12] When post-MI patients exercise, the QT dispersion significantly increases in those with residual myocardial ischemia. Rest does not immediately improve the clinical situation, as increases in QT dispersion are maintained for at least two hours after exercise.[13] β-blockers prevent increases in QT dispersion presumably by preventing the occurrence of ischemia in these patients. In one study,[14] patients with ischemic heart disease who were receiving β-blockers achieved a QT dispersion rate that was significantly lower than that in patients with ischemic heart disease not treated with β-blockers. A second study[15] in patients receiving β-blockers after MI demonstrated a decrease in QTc dispersion, while those without β-blockade had an increase in dispersion.

β-blockers can resolve ischemia or limit injury primarily by decreasing myocardial oxygen demand via a negative chronotropic effect and by decreasing blood pressure. β-blockers prolong the resting phase of the heart (diastole) through negative chronotropic effects as well. Prolongation of diastole augments myocardial perfusion and improves myocardial oxygen supply. In healthy individuals, β-adrenoceptor blockers reduce myocardial contractility.[16] In patients with chronic heart failure, however, β-blockers initially have a negative inotropic effect (minimized by initiating heart failure β-blocker therapy with exquisitely low doses and prudent titration), but increase inotropy over time as the diminished β-receptor density increases towards a more normal level.[17-19]

The negative chronotropic, inotropic, and antihypertensive effects of β-blockers can limit infarct size by decreasing myocardial oxygen demand in the periinfarction period.[16] This limits the amount of nonconductive scar tissue that forms and reduces the risk of unidirectional block of impulses that can set up reentry arrhythmias.[20] During an acute MI, there is a close correlation between infarct size and the reduction in heart rate from β-blockers ($r = 0.97$). A reduction in the heart rate of at least 15 beats/min during infarct evolution is associated with an infarct size reduction of >25%. A reduction of <8 beats/min is associated with no reduction in infarct size. A significant correlation was also found between reduction in heart rate and nonfatal reinfarctions, potentially due to the mechanisms specified below.[21]

REDUCING RISK OF REINFARCTION

β-blockers may reduce the risk of reinfarction through effects on the endothelium and atheroma. The endothelial layer (also known as the intima) is the layer of the vessel in physical contact with circulating blood components. The endothelium plays a central role in regulating arterial tone and caliber, while also preventing platelet adhesion and thrombosis. In response to increased shear stress, the endothelial layer of a normal coronary artery will secrete endothelial-derived relaxing factor to cause local vasodilation. Since this does not occur systemically, blood flow through that segment is enhanced without changing systemic blood pressure.[22] However, in segments with atherosclerosis, attenuation of the normal vasodilatory response or paradoxical vasoconstriction results.[23] This increases the shear stress on the atheroma, which may increase the risk of plaque rupture.[22,24] In addition, this endothelial dysfunction increases contact between the vessel wall and circulating platelets.[22-24] Hence, endothelial dysfunction can trigger a rupture and predispose the ruptured segment to enhanced platelet-thrombus formation.[22,24] β-blockers have been shown in an animal study[25] to improve acetylcholine-induced vascular dilatation, probably via increased release of endothelial-derived relaxing factor from the endothelium.

β-blockers may also prevent atheroma propagation in some situations. In one study,[26] stressed primates consuming atherogenic diets were randomly allocated to propranolol or no treatment. Stressed animals treated with propranolol developed over 60% less atherosclerotic plaque area

than untreated animals. However, propranolol did not have the same protective effects on nonstressed (presumably low catecholamine) primates with an atherogenic diet. Slowing the rate of plaque progression can allow for plaque stabilization, which could reduce the risk of plaque rupture and reinfarction.[27]

Landmark Trials

Numerous randomized, double-blind, placebo-controlled trials have determined that the use of β_1 selective and β-nonselective blockers after MI is associated with mortality benefit.[28-33] An overview[34] of 28 trials with β-blockers used during and after MI showed an average reduction in mortality of 28% at one week; most of the benefit was seen within the first 48 hours. Continuing mortality benefit has been noted for at least six years with β-blockade.[29,32] The mortality benefit is due, in large part, to a reduction in reinfarction and sudden cardiac death.[28-34] In the 16 trials that specifically reported the effect on sudden cardiac death, β-blockers reduced the risk by 34%.[35] The risk of reinfarction was reduced by 18%.[34]

β-blockers with marked intrinsic sympathomimetic activity (e.g., pindolol, oxprenolol) do not seem to have a role in the treatment of MI, since trials evaluating these drugs have shown negative trends.[35,36] However, acebutolol, an agent with mild intrinsic sympathomimetic activity, has shown marked mortality benefit (48% reduction in overall mortality) and the benefit was maintained at five years.[29,37]

The importance of intravenous dosing of β-blockers during acute MI was demonstrated by the first ISIS (International Study of Infarct Survival).[28] In this trial, patients were randomly allocated to intravenous atenolol or placebo if they were within 12 hours of symptom onset. Oral atenolol was given after intravenous therapy and then continued for an additional six days. Vascular mortality was significantly decreased by 15% in the first seven days.

β-blockers have four potentially important ancillary properties: intrinsic sympathomimetic activity, β_1 selectivity, membrane stabilizing activity, and lipophilicity. A meta-analysis of 73 trials was conducted[38] to determine if ancillary properties of β-blockers can help predict the degree of mortality benefit in the peri- and post-MI periods. The results were divided among drugs with and without each of the four ancillary properties. This meta-analysis demonstrated that, overall, the absence of intrinsic sympathomimetic activity and membrane stabilizing effect and the presence of β_1 selectivity and lipophilicity were most efficacious at reducing one-week mortality, long-term mortality, reinfarction, and sudden death.

The preceding studies were performed with patients not receiving thrombolytic therapy or primary angioplasty. This has led some clinicians to wonder if β-blockade would still be beneficial with concomitant thrombolytic therapy, percutaneous transluminal coronary angioplasty (PCTA), aspirin, heparin, coronary artery bypass surgery, and/or angiotensin converting enzyme inhibition.[16] Carvedilol, a nonselective, lipophilic β-blocker with α-blocking and antioxidant properties, was compared with placebo in a small study of 151 patients with acute MI.[39] Within 24 hours of chest pain, patients received intravenous carvedilol or placebo over 15 minutes followed by oral carvedilol or placebo for six months. In this study, 97% of the patients also received thrombolytics (median time to thrombolysis was ~3.8 h), all patients received aspirin, and 97% received heparin. The carvedilol group had significantly fewer cardiac events than the placebo group. Although it was not powered to detect significant differences between groups for the combined end point of mortality and reinfarction, the combined risk was reduced by about 45% ($p = 0.12$).

In the TIMI II (Thrombolysis in Myocardial Infarction) study,[40] patients with an acute MI were randomly allocated to receive immediate intravenous metoprolol therapy followed by oral therapy, or oral therapy starting on day 6 after MI. All patients also received thrombolytic therapy, aspirin and heparin. This study showed a significant ($p = 0.005$) reduction in recurrent ischemia when β-blockade was used early in therapy. Furthermore, patients receiving intravenous β-blocker therapy within two hours of symptom onset demonstrated a significant ($p = 0.01$) reduction in the combined risk of death or recurrent MI. Thus, early intravenous blockade provides additional benefit, more than that received with a thrombolytic agent. The effects of β-blockers were evaluated in a retrospective analysis of the SAVE (Survival and Ventricular Enlargement) study,[41] a trial that assessed the effect of captopril on overall mortality in patients with left-ventricular dysfunction after MI. Approximately 34% of the patients received thrombolytics, 77% received aspirin, 50% received captopril, and 24% were revascularized before randomization. The risk of cardiovascular death was significantly ($p < 0.001$) reduced by 30% and the risk of developing severe heart failure was significantly ($p < 0.001$) reduced by 21% in the patients who received β-blockers. Both studies[40,41] demonstrate that β-blockade can benefit patients receiving numerous other proven therapies. The dosing regimens for various β-blockers studied in MI are given in Table 1.[28-31,33,39,40]

Current Clinical Practice

Although the clinical trials with intravenous and oral β-blockers have shown impressive results, a large population of patients who would benefit from this therapy do not receive it in actual practice. Overall, 40% of all patients with acute MI could be safely treated in the short term with intravenous β-blockade, and at least 70% of patients could receive long-term therapy with β-blockers.[42] Surveys indicate that intravenous β-blockers are used in <15% of patients and oral β-blockers are used in <40% of patients without specific contraindications.[42,43] Furthermore, 52–89% of patients in clinical practice are receiving β-blocker doses that are <50% of those studied in clinical trials.[44]

As previously stated, the degree of heart rate reduction is strongly correlated with the infarct size and is associated

with the risk of nonfatal reinfarction.[21] Whether it also corresponds to a reduction in overall mortality is not known. A retrospective study[45] compared patients receiving <50% of the studied doses (from previous randomized trials) with those receiving ≥50% of the previously studied doses. Patients in the group receiving less β-blockade had a lower mortality rate than those receiving more β-blockade; however, some points need to be noted. First, this was a retrospective review of medical records, so it is not known whether the groups were actually similar. Second, only 14.5% of the total patient population were receiving <75% of the recommended dose, so this study actually compared patients who are underdosed (37.3% of patients receiving 50–75% of the recommended dose) with patients who are even more underdosed (39.7% of patients receiving 25–49% of the recommended dose). Third, the results are confounded by the comparison of β-blocker doses rather than a pharmacodynamic end point. Since the goals of therapy in clinical trials were to achieve a specific dose or a preselected heart rate, it is not known how dissimilar the groups' hemodynamics were in this trial. Since clinical trials determined that β-blockers given in certain doses or titrated to specific heart rate goals can improve mortality rates, the dosages should be adjusted to achieve these end points in all patients.

Another problem encountered in clinical practice is the use of β-blockers when they are actually contraindicated. In a retrospective study[46] using a large managed-care organization database, 11% of the patients treated with β-blockers after an MI had specific contraindications for such therapy.

Actual and Perceived Contraindications

HEART RATE AND ECG DOSING VARIABLES

β-blockers are contraindicated if the patient's heart rate is <45 beats/min due to the increased risk of hypoperfusion.[47] If a patient's heart rate is <60 beats/min at baseline, there may not be any added benefit, and β-blockers should probably not be given.[48] In some cases, β-blockers should be dosed to achieve target doses (Table 1) or achieve a target resting heart rate of 55–60 beats/min.[48]

β-blockers reduce atrioventricular (AV) nodal conduction and are contraindicated in patients with significant AV blockade (PR interval >0.24 sec, second- or third-degree

Table 1. Common β-Blocker Regimens from Randomized Trials[28-31,33,39,40]

Drug	Study	Main Exclusions	Intravenous	Oral
Atenolol	ISIS-1[28]	already on BB or verapamil, HR <50 beats/min, SBP <100 mm Hg, 2nd- or 3rd-degree heart block, severe heart failure, bronchospasm	5 mg over 5 min (drug stopped if HR <40 beats/min), at 10 min if HR >60 beats/min; 5 mg over 5 min (10 mg maximum)	100 mg po qd (or 50 mg bid) thereafter
Acebutolol	APSI[29]	age >75 y, malignancy, valvular disease, coma, asthma, chronic bronchopneumopathy, Raynaud's syndrome, HR <45 beats/min, complete AV block, acute heart failure treated with >1 drug	none given	200 mg bid
Metoprolol	Goteborg[30]	HR <45 beats/min, SBP <100 mm Hg, pulmonary rales >10 cm, poor peripheral circulation, AV block, bronchial asthma, currently on BB	5 mg bolus repeated q2min 3 times (2nd or 3rd bolus not given if HR <40 beats/min, SBP <90 mm Hg, PQ <0.26 sec, shortness of breath worsened, cold sweating, nausea)	50 mg 15 min after last iv bolus, then 50 mg qid for 48 h, then 100 mg bid (if full iv dose not given, 25 mg given q6h for 48 h, then 100 mg bid)
Timolol	Norwegian Multicenter[31]	HR <50 beats/min, 2nd- or 3rd-degree heart block, SBP <100 mm Hg, COPD, severe intermittent claudication, COPD, BB use, severe hepatic or renal disease, unstable diabetes mellitus	none given	5 mg bid for 48 h, then 10 mg bid (patients withdrawn if HR <40 beats/min)
Propranolol	B-HAT[33]	not specified (patients with contraindications excluded)	none given	40 mg tid for 1 mo, then 60 or 80 mg tid
Carvedilol	Basu et al.[39]	α- or BB use, CCB use, Killip class IV heart failure or cardiogenic shock, HR <45 beats/min, SBP <90 mm Hg, 2nd- or 3rd-degree heart block, left bundle-branch block, severe valvular disease, insulin-dependent diabetes, renal failure, malignancy, pregnancy	2.5 mg over 15 min	6.25 mg 4 h after iv infusion and 6.25 mg bid for 2 d; then 12.5–25 mg bid (pts. with HR >55 beats/min and BP >120/95 mm Hg on day 14 had a dosage increase)
Metoprolol	TIMI II[40]	HR <55 beats/min, SBP <90 mm Hg, rales above 1/3 of lung, 2nd- or 3rd-degree heart block, asthma, currently on BB, verapamil, or diltiazem	5 mg bolus repeated q2min 3 times (additional boluses not given if HR <55 beats/min or SBP <90 mm Hg)	50 mg bid for 2 d, then 100 mg bid

APSI = Acebutolol et Prevention Secondaire de L'Infarction; AV = atrioventricular; BB = β-blocker; B-HAT = Beta-Blocker Heart Attack Trial; COPD = chronic obstructive pulmonary disease (includes asthma); CCB = calcium-channel blocker; ISIS = International Study on Infarct Survival; PQ = the P-Q interval on the electrocardiogram (PQ >0.24 sec indicates significant 1st-degree heart block); TIMI = Thrombolysis in Myocardial Infarction.

heart block).[47-49] First-degree AV block means that there is an abnormal delay in the passage of impulses from the atria to the ventricles. Second-degree AV block is characterized by a variable blockage of atrial impulses resulting in intermittent block of atrial impulses to the ventricle. In third-degree AV block, there is no conduction of atrial impulses to the ventricles, which results in independent depolarizations of the atria and ventricles.[49] β-blockers are also contraindicated in sick sinus syndrome (a syndrome in which the patient wavers between atrial fibrillation or sinus tachycardia and severe bradycardia) unless a working pacemaker is in place because the drug could be harmful during the bradycardic phase.[47,48,50]

BLOOD PRESSURE AND CONTRACTILITY VARIABLES

Patients with a baseline systolic blood pressure of <90–100 mm Hg should not receive β-blockade due to the antihypertensive effects of these drugs.[16,28,49] Subsequent doses of β-blockers should be withheld if the systolic blood pressure is <90 mm Hg.[30] However, other agents that are commonly used in the treatment of MI, such as nitrates and calcium-channel blockers, can be discontinued or reduced in dosage to allow the use of β-blockers.[51] These agents are used to relieve chest pain, but β-blockers are also effective agents for chest pain.[52] In the MIAMI (Metoprolol in Acute Myocardial Infarction) trial,[52] there was a significant reduction in the need for calcium-channel blockers ($p < 0.001$) or narcotic analgesics ($p < 0.001$) for chest pain when β-blockers were given. There was a trend toward reducing the need for nitrate therapy in the β-blocker group as well ($p = 0.10$). The need for four or more doses of a narcotic was reduced by 22% in the β-blocker group.

The negative inotropic and chronotropic effects of β-blockers can acutely reduce cardiac output and are therefore contraindicated in patients with preexisting decompensated heart failure and acute pulmonary edema.[28,30] This does not mean that a large MI that may result in left-ventricular dysfunction is a contraindication for β-blockade. On the contrary, data suggest that patients with more severe MIs and reduced ejection fractions after MI have greater benefit with β-blockade than those with less severe MIs.[16,41,53] In a subgroup of the SAVE trial, which evaluated patients with left-ventricular dysfunction after MI, β-blockers significantly reduced the risk of cardiovascular death ($p < 0.001$) and the risk of developing severe heart failure ($p < 0.001$).[41]

Even patients with stable heart failure before receiving β-blockade (heart failure history before the MI or as a result of the MI) can benefit from post-infarction β-blocker therapy. In a subgroup analysis[54] of the BHAT (Beta-Blocker Heart Attack Trial), patients with stable heart failure before receiving propranolol therapy achieved a mortality reduction similar to that of propranolol-treated patients without heart failure. Propranolol also reduced the occurrence of sudden death more frequently in patients with heart failure. In this study, propranolol therapy did not increase the overall incidence of heart failure exacerbation, nor did it increase the incidence of heart failure exacerbation in the patients with a prior history of heart failure. However, during the first 30 days of this study, which had an average follow-up of 25 months, propranolol use was associated with a higher incidence of heart failure exacerbations in patients with a history of heart failure.

In general, it is not advisable to use β-blockers in mild to moderate acute heart failure during the periinfarction period. However, it may be safe to use the α- and β-blocking agent, carvedilol.[39] In a subgroup analysis of patients in mild to moderate acute heart failure (Killip classification I–III) during the periinfarction period, the use of intravenous carvedilol followed by slowly titrated oral therapy (Table 1) was shown to be safe. Carvedilol use in these patients was not associated with any adverse events, increased use of nitrates or diuretics, or an increase in cardiac events versus placebo. However, cardiac events were not decreased in patients who received carvedilol during short- or long-term follow-up versus those who received placebo. This is in contrast with the entire study population, where carvedilol use significantly ($p < 0.02$) reduced cardiac events versus placebo. The only benefits associated with carvedilol therapy in patients with acute heart failure were in surrogate parameters such as left-ventricular ejection fraction, degree of wall motion abnormality, and end-systolic volume.

In patients with New York Heart Association class II or III heart failure who are β-blocker naive, β-blocker (or α- and β-blocker) therapy is associated with mortality benefit as long as therapy is started with lower doses and is titrated prudently.[55] The specific agents and dosing regimens studied are outside the scope of this article.

PULMONARY PATIENTS

β-blocking agents have been shown to induce bronchoconstriction in some patients with chronic obstructive lung disease (COPD).[56] However, it is usually patients with reversible obstructive lung disease (bronchial asthma, asthmatic bronchitis) who are at risk of bronchospasm after using β-blockers. Even in nonreversible lung obstruction, such as chronic bronchitis, caution is required because there may be an asthmatic component in addition to the fixed obstructive symptomatology.[56] In patients with nonreversible obstruction, the β_1 selective agent esmolol did not alter pulmonary function.[57]

Nonselective β-blockers such as propranolol are contraindicated in patients with asthma or reversible lung obstruction. β_1 selective blockers are not contraindicated in these patients, but strong caution is required.[56] In a head-to-head comparison in asthmatic patients, metoprolol 8 mg caused significantly less suppression of the forced expiratory volume in one second (FEV_1) and forced vital capacity compared with propranolol 5 mg ($p < 0.05$ for both variables).[58] However, metoprolol caused significantly more suppression in these variables than placebo ($p < 0.05$ for both variables). Another placebo-controlled study[59] evaluated propranolol (100 mg), and the β_1 selective agents

atenolol (100 mg) and acebutolol (300 mg). Propranolol again had a greater suppressant effect on FEV_1 than the other agents, but all treatment groups suppressed FEV_1 versus placebo. Isoproterenol infusion increased the FEV_1 above baseline values in patients on atenolol and acebutolol, but not in those receiving propranolol.

Although β_1 selective agents may be safer in asthmatics, as the dose increases there is an increased risk of worsening pulmonary function. In a double-blind study[60] of eight patients given increasing doses of metoprolol (50, 100, 150, 200 mg), there was a trend toward a greater decrease in the peak expiratory flow with the 150- and 200-mg doses than with the lower doses.

Treating patients with fixed obstructive lung disease with a β_1 selective agent may be justified because the potential benefits are great. In one retrospective trial,[61] the use of β-blockers in patients with COPD was associated with a mortality risk reduction of 40%.

DIABETIC PATIENTS

Epinephrine promotes glycogenolysis and mobilizes glucose in response to hypoglycemia (counter-regulatory response).[47,62] β-blockers can inhibit this compensatory response to some extent, although cardioselective agents are less likely to inhibit the compensation. Because of this, patients with diabetes (especially type 1 diabetes mellitus) are somewhat more prone to hypoglycemia. β-blockers also decrease most symptoms of hypoglycemia, such as tachycardia and tremor, but not sweating, since sweating is a cholinergic rather than sympathetic response to hypoglycemia.[47,62]

Even though there is an increased risk of hypoglycemia and a reduction in hypoglycemic symptoms, the use of β-blockers in diabetics in the acute and post-MI period is associated with a 36% mortality risk reduction. This is important because diabetic patients historically have worse outcomes than those without diabetes after an MI.[61]

Given these effects, it is important to ensure that every patient with diabetes who is initiating β-blocker therapy has the ability to use a blood glucose monitor and to know that monitoring is required if sweating (not associated with warmth or physical activity) occurs. Urine glucose monitoring is not sufficient because it only detects hyperglycemia.[63] Therapy also should not be initiated in unstable diabetics, such as those recently initiating insulin therapy or in whom glucose control is very poor.[31]

REYNAUD'S PHENOMENON

β-adrenoceptors have been identified in arteriovenous anastamoses of the digits.[64] They are only stimulated via humoral catecholamines, but elicit vasodilation; β-blockade could interfere with this. Also, it has been theorized that unopposed α-adrenoceptor stimulation from β-blockade could cause vasoconstriction. Vasospastic phenomenon has been noted with both nonselective and β_1 selective blockers. However, in a study[64] of 16 patients with Raynaud's phenomenon given metoprolol 100 mg, propranolol 80 mg, and placebo in a crossover study, no increased incidence of vasospastic attacks were noted and no significant alterations in finger hemodynamics occurred. None of these patients had hypertension, which is common because the average blood pressure in patients with Raynaud's phenomenon is significantly lower than that in healthy subjects. This is important because studies[65] have shown that hypertensive patients with Reynaud's phenomenon are at higher risk for digital vasospasm and have higher digital arterial tone during cooling than normotensive patients. Hence, strong caution is warranted in all patients with Reynaud's phenomenon; in normotensive patients with an acute MI and Reynaud's phenomenon, the benefits may outweigh the risks.

Special Situations

Non-Q-wave MIs (NQWMIs) are similar to Q-wave MIs except that the electrocardiographic Q-waves do not deepen after myocardial injury.[66,67] Several coronary angiographic studies[66] performed during evolving NQWMIs usually demonstrated subtotal coronary occlusion and a high infarct-vessel patency rate, which suggests spontaneous early coronary reperfusion. These findings support the hypothesis that NQWMIs represent aborted Q-wave MIs. This leads to a larger mass of surviving but jeopardized myocardium within the perfusion zone of the infarct-related vessel segment. Patients with NQWMI are almost three times more likely to have reinfarction than those with Q-wave MIs.[66] Whether β-blockers are efficacious in this subgroup of patients is controversial.

In a subgroup analysis[68] of patients with NQWMIs in the MIAMI trial, the mortality rate was higher in the metoprolol group (5.0%) than the placebo group (3.2%); this finding was not significant. In a subgroup analysis[69] of patients with NQWMIs in the BHAT, the mortality rate was virtually the same in the propranolol (7.8%) and placebo (7.9%) groups. In a subgroup analysis[70,71] of patients with NQWMIs in the Norwegian Multicenter Study, the timolol group had significantly lower mortality (7.2%) than those in the placebo group (13.7%). One point to consider is that subgroup analysis has a potential for bias and, hence, all the results need verification in a clinical trial, with mortality in NQWMI patients being the primary outcome variable.[67]

Cocaine-induced MI is characteristically distinct from other types of MIs due to its severe coronary vasoconstrictory component.[72,73] Cocaine causes marked coronary arterial vasoconstriction by blocking presynaptic reuptake of norepinephrine and dopamine in central and peripheral sites. Peripheral norepinephrine causes α_1 adrenoceptor stimulation and is devoid of β_2 adrenoceptor stimulation. Hence, norepinephrine induces vasoconstriction in the coronary arteries. In patients undergoing cardiac catheterization, the administration of cocaine reduced coronary arterial diameter and coronary sinus blood flow while increasing the heart rate–systolic arterial pressure product (an

estimate of myocardial oxygen demand). Administration of propranolol to these patients did not reduce the heart rate–systolic arterial pressure product, but did increase the vasoconstriction. In this situation, β-blockers seem to diminish the chances of β_2 adrenoceptor stimulation by the endogenous catecholamine epinephrine and remove the β_2 adrenoceptor–induced vasodilatory effect in the coronary arteries. In animal models, propranolol increases cocaine-associated death. Therefore, propranolol should be avoided in cocaine-induced MI.[72,73]

POTENTIAL ROLE OF THE PHARMACIST IN IMPROVING β-BLOCKER UTILIZATION

In current clinical practice, β-blockers are severely underutilized and underdosed in the peri- and post-MI periods. This places many patients at increased risk of ventricular arrhythmias, reinfarction, and postinfarction heart failure. Pharmacists are in a unique position to ensure that patients receive β-blockade in the peri- and post-MI period and to protect patients with absolute contraindications from receiving therapy. Hospital pharmacists can alert other healthcare practitioners when: (1) β-blocker therapy is warranted but not started, (2) dosing needs to be increased to achieve the target heart rate or therapeutic doses, (3) concomitant therapy needs to be altered to allow use of a β-blocker or increased dosage of the β-blocker, (4) precautions are acceptable based on the potential benefit, and (5) when a drug should not be started due to contraindications. Such pharmacist interventions have already been shown to be successful in the cardiac intensive care unit.[51] This is important, as therapeutic benefit can occur within the first seven days. Community pharmacists can also play a vital role in ensuring optimal use of β-blockers as they collectively interact with all patients receiving pharmacotherapy after MI. The benefits of β-blockade continue for years after the MI, so optimizing chronic therapy is important. Such a service would simply be an extension of pharmacists' current role of protecting the patient from drug misadventures. Performing this function will also become easier as patient information becomes more accessible to the community practitioner, but such information is not required.

Patients without contraindications need to receive β-blockers if they have Q-wave MIs that were not precipitated by cocaine insufflation or inhalation. Patients with significant heart block, sick sinus syndrome (without a pacemaker), uncompensated heart failure, acute pulmonary edema, Killip class IV cardiogenic shock, systolic blood pressure <90 mm Hg, or a heart rate at or below the optimal range without β-blocker therapy should not receive β-blockade. However, this leaves many patients with only perceived contraindications who could potentially derive tremendous benefit from therapy. β-blockers should be strongly promoted for patients with large infarcts, infarcts resulting in left-ventricular dysfunction or stable heart failure, stable heart failure patients who have an MI, normotensive patients with Raynaud's phenomenon experiencing an infarction, and infarction patients with proven irreversible obstructive lung disease. Intravenous β_1 selective agents should be strongly considered for stable diabetics in the periinfarction period, along with close monitoring of their blood glucose concentrations. Oral β-blockers can also be strongly considered in the postinfarction period as long as the patients undergo extensive counseling on the nonadrenergic symptoms of hypoglycemia (especially sweating) and how to perform blood glucose monitoring. Therapy may be considered for patients with reversible lung obstruction, although only β_1 selective agents should be used, and in hypertensive patients with Raynaud's phenomenon. However, special caution is needed and the risks may outweigh the benefits in some patients with reversible lung disease and Reynaud's phenomenon. Special drug counseling should be provided if β-blockers are to be used in reversible lung disease (i.e., proper use of β-agonist inhalers and/or use of peak expiratory flow meters) to minimize the chance for adverse drug events.

Even patients with contraindications to therapy at one point may have resolution of the situation and can subsequently receive a β-blocker. When a patient has a contraindication, it should be specified. This allows for later monitoring to elicit whether the contraindication still exists. For example, a patient with an infarction that affects nodal tissues in the heart may have bradycardia or transient heart block that may resolve over a few days. It would be unfortunate to deny the patient β-blocker therapy thereafter because of a transient contraindication. Similarly, patients usually have a blood pressure–related exclusion to β-blocker use when receiving other agents that can precipitate hypotension. In the periinfarction period, many patients receive intravenous nitroglycerin. Intravenous nitroglycerin does not have proven mortality benefit. Reducing the dose

Table 2. Optimal β-Blocker Dosing in Patients with Myocardial Infarction

iv dose	metoprolol: 15 mg over 15 min (5 mg q5min for 3 doses) atenolol: 10 mg over 15 min (5 mg over 5 min, wait 5 min, 5 mg over 5 min) carvedilol: 2.5 mg over 15 min
When to stop iv infusion	total dose given or HR <40 beats/min, PR interval >0.24 sec, SBP <90 mm Hg, appreciable worsening of shortness of breath
Oral daily dose	metoprolol: 50 mg qid or 100 mg bid atenolol: 50 mg bid or 100 mg qd propranolol: 40 mg tid for 1 mo, then 80 mg tid timolol: 5 mg bid for 48 h, then 10 mg bid acebutolol: 200 mg bid carvedilol: 6.25 mg 4 h after iv infusion and 6.25 mg bid for 2 d; then 12.5–25 mg bid
When not to titrate oral dose upward	achieved optimal dose, HR 55–60 beats/min
When to withold oral dose or decrease dose	increased shortness of breath, HR <40 beats/min, SBP <90 mm Hg, PR >0.24 sec

of intravenous nitroglycerin can allow the blood pressure to recover to the point that β-blockade can be initiated. In the postinfarction period, β-blocker therapy should be optimized before adding other antianginal agents, such as oral nitrates and calcium-channel blockers. These latter agents can reduce blood pressure and prevent attainment of the target heart rate or optimal β-blocker dose, and they do not produce lower mortality rates. Healthcare practitioners must be willing to sacrifice these agents to optimize β-blockade.

β-blocker therapy should not only be initiated, but also dosed to achieve desired parameters. The desired parameters are summarized in Table 2.

Summary

β-blockers successfully reduce morbidity and mortality after an MI. Presently, this drug class is underutilized and all too often is also underdosed. Pharmacists are currently involved in decreasing the occurrence of adverse events, but we also need to focus on ensuring that patients receive optimal pharmacotherapy. This includes knowing which agents have proven mortality benefits, understanding actual contraindications to use, and knowing optimal dosing and counseling parameters, as well as techniques to increase utilization and optimize dosing.

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EXTRACTO

OBJETIVO: Revisar la información publicada en las literatura y las guías clínicas sobre el uso de los bloqueadores de receptores adrenérgicos beta en el infarto de miocardio y contrastar dicha información con la práctica clínica actual.

MÉTODOS: Investigación de MEDLINE (enero 1970–junio 1999) para identificar literatura relevante sobre el tópico en cuestión. También evaluación de las referencias incluídas en los artículos identificados si se considerasen importantes para esta resvisión.

DISCUSIÓN: En estudios clínicos relaizados, los bloqueadores de receptores adrenérgicos beta orales, e intravenosos han demostrado producir resultados favorables en pacientes con infarto de miocardio. Se estima que un 40% de todos los pacientes con infarto de miocardio agudo pudieran ser tratados a corto plazo con estos agentes administrados por vía intravenosa, y que al menos un 70% de los pacientes pudieran recibirlos a largo plazo por vía oral. Sin embargo, las encuestas indican que los bloqueadores de receptores adrenérgicos beta intravenosos son usados en menos del 15% de los pacientes y los orlaes en menos del 40% de los pacientes sin contraindicación específica. Además se sabe que la mayoría de estos pacientes reciben dosis mucho menores de las usadas en estudios clinícos. Por tal motivo, este artículo intenta esclarecer las contraindicaciones reales y las percibidas para permitir al practicalemente médico idenficar pacientes que han sido incorrectemente excluídos del tratamiento con estos agentes. Desafortunadamente, muchos pacientes con percibida contraindicaciones para el uso de estos agentes puedieran realmente beneficiarse de esta terapia, aún más que aquellos pacientes promedios

con infarto de miocardio. Este artículo también revisa situaciones clínicas especiales donde los beneficios derivados de los estudios clínicos puede que no se apliquen.

CONCLUSIONES: Los bloqueadores de receptores adrenérgicos beta son medicamentos valiosos en el tratamiento del infarto miocardio, no sólo durante su acontencimiento sino después de ocurrido. En la práctica clínica, la mayoría de los pacientes no reciben estos agentes o reciben dosis subóptimas. Los farmacéuticos deberías confirmar que los pacientes que no reciben estos agentes poseen una contraindicación absoluta para no utiliazarlos, o están dentro de una categoría en la cual su uso no está firmemente indicado. Los pacientes sin contraindicación absoluta deberían alcanzar las dosis efectivas o une frecuencia cardíaca de 55–60 latidos por minuto.

ENCARNACIÓN C SUÁREZ

RÉSUMÉ

OBJECTIF: Réviser les données et les lignes directrices publiées sur l'utilisation des bêta-bloquants dans l'infarctus du myocarde et les comparer avec la pratique clinique.

MÉTHODES: Une recherche MEDLINE, couvrant la période de janvier 1970–juin 1999, a été effectuée afin de retracer tous les articles pertinents à ce sujet. Les bibliographies de ces articles ont également été évaluées lorsque jugée utiles.

DISCUSSION: Plusieurs études cliniques ont démontré que l'administration de bêta-bloquants par voies intraveineuse et orale améliorait la mortalité et la morbidité chez les patients ayant souffert d'un infarctus du myocarde. En clinique, seulement 15% des patients reçoivent un bêta-bloquant et les bêta-bloquants oraux sont prescrits à moins de 40% des patients ne présentant pas de contre-indication. De plus, la majorité de ces patients se voient prescrire des doses qui sont inférieures à celles qui ont été utlisées dans les études cliniques. Les contre-indications absolues et relatives sont également passées en revue de façon à permettre au clinicien d'identifier les patients qui sont incorrectement exclus de ce type de traitement. Malheureusement, plusieurs patients présentant une contre-indication relative ne reçoivent pas de bêta-bloquants alors que ce sont eux qui en retireaient les plus grands bénéfices. Certains situations cliniques particulières pour lesquelles les bénéfices observés au cours des études cliniques ne sont pas applicables sont également passées en revue.

CONCLUSIONS: Les bêta-bloquants sont très utiles en péri et en post-infarctus du myocarde. En clinique, la plupart des patients ne reçiovent pas de bêta-bloquants ou en reçoivent à dose sous-optimale. Les pharmaciens devraient s'assurer que les patients qui ne reçoivent pas de bêta-bloquants présentent une contre-indication absolue à leur utilisation ou se retrouvent dans une situation particulière de patients pour laquelle ce traitement n'est pas clairement indiqué. Les patients qui ne présentent pas de contre-indications absolues devraient recevoir un bêta-bloquant à la dose démontrée efficace au cours des études ou viser une fréquence cardiaque de 55–60 pulsations par minute.

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