Part II Evidence from a clinical pharmacological standpoint

A BRECKENRIDGE

The current debate on the value of beta-adrenoceptor blocking drugs after myocardial infarction must be based on an assessment of the benefits which these drugs confer and be set against the adverse effects which they may produce. In this risk-versus-benefit analysis the greater the benefit conferred, the greater the risk which becomes acceptable. If the benefits from beta-blockers are perceived as trivial, the incidence of side effects becomes extremely important in any decision on their widespread use.

In this part of the main paper three aspects of the beta-blockade are discussed: (*a*) an analysis of adverse reactions occurring with beta-blockers after myocardial infarction; (*b*) an opinion on the patients who might be given beta-blockers after myocardial infarction; and (*c*) an assessment of the optimal duration of beta-blocker treatment in these patients.

Adverse reactions after beta-blockade

Beta-blockers were introduced into cardiovascular therapeutics in the 1960s for the treatment of angina and hypertension.[1] Compared with many of the previously available drugs—certainly in the field of hypertension—their acceptability, based on fewer adverse effects, was high. In the succeeding 15 years, however, the side effects of beta-blockers have merited serious consideration, as they are not necessarily trivial. This was illustrated several weeks ago by Stephen Smith,[2] who recounted his experiences when he took a beta-blocker for clinical research purposes. Not only did he become extremely lethargic, but his sleep was disturbed by bad dreams. Physical weariness and aching thigh muscles accompanied any exertion. He also became hypoglycaemic (subjectively and objectively), but eating larger meals to compensate provoked symptoms of "dumping," which he attributed to the drug's effect on gastrointestinal motility. (This sad series of events poses interesting questions about the subject's drug metabolism phenotype, so perhaps Professor Smith's experimental encounters with beta-blockers have yet another round to go.)

SECONDARY PREVENTION STUDIES

The adverse reactions to beta-blockers encountered during six recent secondary prevention studies have been analysed.[3-8] These studies include: (1) the propranolol multicentre trial[3]; (2) the Norwegian timolol study[4]; (3) the Swedish metoprolol study[5]; (4) the Norwegian propranolol study[6]; (5) the propranolol BHAT study[7]; and (6) the north of England sotalol study.[8] The reasons for including these six studies are (*a*) that all are recent studies and conform to acceptable design and analysis criteria including the use of adequate patient numbers (see part I); (*b*) all used currently available beta-blockers; and (*c*) all examined the incidence of adverse effects of beta-blockers.

The studies differed in several important respects. Firstly, the Swedish metoprolol study comes into the category of early intervention, since the mean time of starting metoprolol was 11·3 hours after the infarction. In the other five studies the beta-blocker was given between 4 and 13·8 days after the event and thus the studies come into the late intervention category (see part I). Secondly, while the Norwegian propranolol study[6] assessed patients in a high-risk category defined by the occurrence of severe arrhythmias during early stages of the illness, the other five included all patients after infarction subject only to rigorous exclusion criteria. Lastly, the pharmacology of the beta-blockers differed (table I). Which, if any, of these three factors contributed to the incidence of adverse reactions is not clear. Since an analysis of the time course of side effects in the Swedish metoprolol study has not yet been published, it is difficult to know whether early intervention is more likely to be associated with a higher incidence of adverse effects; according to the figures provided in the initial report this does not seem to be the case. Furthermore, high-risk patients[6] do not seem to suffer excessively from the adverse effects of beta-blockade. Also, no one ancillary pharmacological property of any beta-blocker appears to confer a greater degree of unacceptability with respect to side effects. The incidence and nature of those exclusion criteria in the six studies which are based on contraindications to beta-blockade are shown in table II. There was a high degree of uniformity among the criteria. Severe systemic disease included mental disease, alcoholism, and renal and liver disease.

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Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool

A BRECKENRIDGE, MD, FRCP, professor of clinical pharmacology

TABLE I—*Pharmacological properties of the beta-adrenoceptor-blocking drugs studied*

	Cardioselectivity	ISA	QLA
Metoprolol	+	−	−
Propranolol	−	−	+
Sotalol	−	−	−
Timolol	−	−	+

ISA = intrinsic sympathomimetic activity; QLA = quinidine-like activity; + = present; − = absent.

TABLE II—*Contraindications to beta-blockade*

Study No:	1	2	3	4	5	6
% Patients excluded		18	28	36·6	18	22
Due to:						
Heart failure	+	+	+	+	+	+
A-V block	+	+	+	+	+	+
Bradycardia	+	+	+	+	+	+
Systolic blood pressure < 100 mm Hg		+	+	+	+	+
Claudication		+			+	
Asthma	+	+	+	+	+	+
Systemic disease		+	+	+		+

+ = present.
Nos 1-6 correspond to studies described in text.

Severe adverse reactions and withdrawal

Even after the exclusion of between 18% and 36% of all patients because of contraindications to beta-blockers, there was still a high rate of withdrawal due to drug-induced adverse effects (table III). An appreciable incidence of severe adverse effects was also found in the placebo-treated patients. This was highest in the multicentre propranolol study,[3] in which 12% of all patients given placebo had to be withdrawn because of adverse effects. In the patients given beta-blockers in the six studies the incidence of withdrawal due to severe adverse drug reactions ranged from 5·7% to 20·7%. Cardiovascular problems, not

TABLE III—*Adverse reactions leading to withdrawal*

Study No:	1	2	3	4	5	6
% Incidence of adverse reactions:						
With active treatment	12·4	20·7	12·9	16·3	12·7	5·7
With placebo	12·0	8·7	8·4	10·0	9·3	1·5
Hypotension		+	+		+	+
Bradycardia	+	+	+	+		+
A-V block	+	+		+		
Heart failure				+		
Asthma						
Diarrhoea					+	
Reduced sexual activity					+	

+ = Incidence significantly greater in active group.
Nos 1-6 correspond to studies described in text.

surprisingly, accounted for the greatest number of these—especially hypotension (usually defined as a systolic blood pressure of < 100 mm Hg with or without giddiness) in four of the six studies, bradycardia (heart rate below 45/min) in five of the six studies, and atrioventricular block greater than first degree in three out of six. Surprisingly, heart failure was uncommon; in only the high-risk patients in the Norwegian propranolol study[6] did this prove to be a problem. In no instance did asthma lead to an excess of withdrawals in the drug-treated group compared with the placebo group. Thus, except for those patients known to be prone to develop asthma from administration of beta-blockers, this treatment appeared to be effective prevention. Diarrhoea was a notable problem in the BHAT study but in no other. Interestingly, reduced sexual activity in male patients was a limiting effect in the BHAT study also.[7] Beta-blockers have been reported to cause male impotence,[9 10] and the recent preliminary report of the MRC study on mild hypertension[11] also shows that men given beta-blockers are significantly more often impotent compared with those given placebo.

Less severe adverse reactions

There is a considerable variation in the incidence of less severe side effects, which did not lead to withdrawal from these six studies (table IV). This may be due to the different methods used to collect data (for example, direct questioning, spontaneous complaints, or use of questionnaires). The frequency of these less severe side effects is given in table IV as a ratio between those patients given active treatment and those given placebo, where these data can be extracted from the original reports. Hypotension (three out of four studies), bradycardia (two out of four), and cold extremities (two out of four) were most frequent. Asthma (but obviously mild) was found in two out of four; various forms of gastrointestinal upset occurred sporadically. Tiredness and depression were also reported; interestingly, two of the four studies found that dryness of the eyes was also a problem. In the wake of the practolol problem, investigators were obviously concerned lest other beta-blockers might cause similar effects when given over a long time. Overall, the incidence of the less severe side effects reported in these studies was appreciable.

TABLE IV—*Adverse reactions not leading to withdrawal*

Study No:	2	4	5	6
Incidence (ratio) of adverse reactions: Active *vs* placebo treatment	1·49:1	1·72:1	1·07:1	1·14:1
Hypotension	+	+		+
Bradycardia	+	+		
Cold extremities	+		+	
Asthma	+		+	
Nausea				+
Constipation		+		
Diarrhoea			+	
Tiredness	+			
Depression		+		+
Dry eyes		+		+

+ = Incidence significantly greater in active group.
Nos 2-6 correspond to studies described in text.

Other adverse reactions

On the "risk" side of the risk-versus-benefit equation for beta-blockade after myocardial infarction, other adverse effects have to be considered, although they were not commented on in the six studies analysed. Beta-blockers may cause alterations of plasma lipids—namely, a fall in high-density lipoproteins and a rise in low-density lipoproteins and triglycerides.[12] This is an undesirable feature in their long-term use, but the magnitude of the changes is not excessive. Another adverse effect which has received publicity is the cardiovascular dangers of sudden withdrawal of beta-blockers resulting in recrudescence of angina and even myocardial infarction.[13 14] Reassuringly, the overall incidence of this problem seems small and the number of cases reliably documented is not great. If withdrawal of treatment with beta-blockers at the end of a study of secondary prevention of myocardial infarction proved, however, to result in an excessive mortality, this rather sanguine view of withdrawal may have to be revised.

DRUG INTERACTIONS

Drug interactions with beta-blockers have been reviewed.[15] Those of greatest importance would appear to be with hypoglycaemic agents, parenteral or oral, where non-cardioselective beta-blockers can cause a delay in the rise of blood sugar after hypoglycaemia. Furthermore, the lack of tachycardia in beta-blocked patients if they become hypoglycaemic can prove detrimental. Interactions between beta-blockers and cardiodepressive anaesthetics (for example, cyclopropane) may lead to intraoperative cardiac embarrassment. A third type of interaction with beta-blockers which may prove of clinical importance has been suggested by Deacon and her colleagues,[16] who showed that in in-vitro animal studies lipid-soluble beta-blockers (for example, propranolol and oxprenolol) inhibited the metabolic degradation of lignocaine. If this finding occurs in man with drugs other than lignocaine, then this interaction may be of considerable importance.

Thus, adverse effects caused by these drugs are clearly considerable. One additional consideration is the effect that beta-blockers have on exercise capacity.[17] Their long-term use may result in severe limitation of the amount of physical activity which a normal subject may take let alone a patient after a myocardial infarction. Such adverse reactions can possibly be predicted in the case of the lipid-soluble, highly metabolised beta-blockers (for example, propranolol).[18] According to these workers, patients who metabolise beta-blockers slowly are more likely to develop serious adverse effects; furthermore, such patients can be defined by assessing their ability to metabolise a marker substance such as debrisoquine. A similar prediction could probably be made by measuring plasma beta-blocker concentrations, but most secondary prevention studies have used fixed doses of beta-blocker rather than doses adjusted according to plasma concentration.

Selection of patients after myocardial infarction

As Hampton has indicated in part I, analysis of recent well-conducted trials of beta-blockade in secondary prevention indicates an improvement in survival of about 25%. If one extrapolates from the results of these trials to clinical practice, all patients apart from those with the exclusion criteria previously defined should be treated. An alternative stratagem is to give beta-blockers only to those patients who require these drugs for other reasons (angina or hypertension). The prognosis for the young patient after a small myocardial infarction is good[19]; thus therapeutic intervention with any form of secondary prevention treatment may be unnecessary. Whether a subgroup of young patients with small infarcts exists who would benefit from beta-blockade after the infarct needs further clarification.

Several groups, in accordance with the early studies of Theroux and his colleagues,[20] exercise patients with myocardial infarction before discharge from hospital in an attempt to assess their prognosis. Whether electrocardiographic and haemodynamic data during these investigations might be used to predict those patients who might benefit from beta-blockade is an interesting consideration.

At present, I treat patients with beta-blockers after myocardial infarction when (*a*) they fall into a high-risk category because of the size of the infarct and the frequency of severe arrhythmias during the early phase of the infarct; and (*b*) they have other clinical indications for beta-blockade (for example, angina, hypertension, or arrhythmias), in which case they are given beta-blockers about a week after the infarct. I do not give beta-blockers to young (< 50 years) patients with small myocardial infarction at present.

Duration of treatment

In many respects, this is the most difficult decision to make. Drug treatment should be continued only for as long as it is seen to confer benefit; this may be hard to define. Analysis by life tables from the Norwegian timolol[4] and the BHAT studies[7] shows a divergence of survival between placebo and active treatment groups for the first 12 months. After that time the number of patients is smaller and the evidence of continuing divergence between treated and control groups is less convincing. It is doubtful if parallel survival curves for the two groups indicate continuing benefit. Any convergence of the curves would suggest harm from treatment, but this was not observed in either study. In retrospect, it would have been worthwhile in one of the large studies that at its defined end-point the group given active treatment had been randomised into two groups, one of which was continued on active treatment and the other given placebo. Ethical and other considerations may make this impractical, but until such a study is carried out accurate definition of the duration of treatment will be difficult.

Conclusions

The incidence of adverse reactions from beta-blockers in patients after myocardial infarction is not insignificant and constitutes an important aspect of the decision whether to treat all patients. While an improvement in mortality of 25% may sound impressive, in reality it represents a change in death rate from eight patients per 100 to six per 100. Since most general practitioners will see fewer than 10 patients with myocardial infarction a year, such statistics may seem unconvincing, especially in the face of a high incidence of adverse effects.

My present practice is to limit treatment with beta-blockers to those patients at high risk after myocardial infarction (for example, those with large infarcts or with pronounced cardiac arrhythmias during the acute phase of their illness) and to those requiring beta-blockers for other reasons, such as hypertension, angina, or arrhythmias after the acute event. Further data are needed on the efficacy of beta-blockers in those patients with small infarcts based on provocative tests such as exercise testing. The prediction of those patients who are more likely to develop severe adverse effects from beta-blockade may become clearer, and this will help define the group of patients in whom beta-blockade is acceptable after myocardial infarction. Present evidence would support the administration of beta-blockers for 12 months, but for longer periods the evidence is not convincing.

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Part III Some conclusions

GEOFFREY ROSE

In recent years advances in cardiology have been much more concerned with the investigation of heart disease than with our ability to treat it medically. Clinicians will therefore particularly welcome recent therapeutic advances in beta-blockade, because they improve the balance between investigation and treatment.

In part I Professor Hampton summarised the remarkably numerous clinical trials of beta-blockade after infarction, and in part II Professor Breckenridge reviewed some of the outstanding therapeutic issues. Some important conclusions are now firmly established; but it is equally important to recognise what remains uncertain and to avoid unreasonable extrapolations.

Firstly, treatment with beta-blockers started in the first weeks after myocardial infarction has been shown to reduce the mortality in the next 1-2 years by about 25%. This could amount annually in the UK to about 2500 extra survivors of this high-risk period. (This estimate is based on the treatment of patients under the age of 65; in the aged, side-effects are more troublesome and benefits have not been clearly shown.) The quality of life in these extra survivors is not known, but it is not necessarily worse than average.

Secondly, this reduction in mortality represents a major advance in controlling coronary heart disease. The long-term prognosis of the new survivors is, however, uncertain. Since atherosclerotic disease is generally progressive, most will presumably ultimately die of it. We should speak of lives prolonged, not of lives saved: a man's life has been saved from coronary heart disease only when he dies of something else! If the benefits of the treatment prove to be confined to the first two years after infarction, then the effect on national mortality may not be more than about a 2% reduction. Such a benefit is in no way to be decried; but we must avoid thinking that beta-blockers are the answer to the problem of coronary disease. Major control of this mass disease requires mass primary prevention.

Thirdly, few therapeutic advances in cardiology have been placed so clearly beyond argument. This implies that placebo-controlled trials will no longer be acceptable in the generality of survivors of myocardial infarction. The question for other kinds of treatment (platelet-acting drugs, sulphinpyrazone, surgery) is now simply whether they will confer useful benefit in addition to that proved by beta-blockers. This imposes alarming demands on the size and design of future trials, and there will be no easy answers (and perhaps, for some important questions, no answers at all).

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Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine, London
GEOFFREY ROSE, DM, FRCP, professor of epidemiology