Beta-blockade and surgery

See page 1353 for the article to which this Editorial refers

Since clinical confirmation of the original predicted uses of beta-adrenoceptor blocking drugs (beta-blockers) in arrhythmias, angina pectoris, and phaeochromocytoma, many unpredicted and unexpected applications, starting with hypertension have been reported[1-3]. Even one of the original major contraindications, heart failure, has recently become a major indication for beta-blockers[4]. Finally, a recent valuable survey of the use of beta-blockers in over 200 000 post myocardial infarction patients by Gottlieb et al[4] demonstrated that chronic obstructive airways disease should no longer be regarded as a contraindication. The 9228 patients with COPD who received beta-blockers had an absolute risk reduction of death of 11% over 2 years, which is a relative risk of 0.60 (CI 0·57–0·63), compared to the 32 586 patients with COPD who did not receive beta-blockers post-infarction.

Patients with ischaemic heart disease, or with risk factors for myocardial ischaemia, are at increased risk when undergoing even non-cardiac surgery. Patients who have episodes of ischaemia or who experience non-fatal myocardial infarction in the first week after surgery have a two to 20-fold risk of serious cardiovascular outcome in the 2 years after surgery[5]. Several studies have demonstrated a relationship between elevated heart rate in anaesthesia and the occurrence of myocardial ischaemia[5]; this is not surprising since an increase in heart rate is a well-established factor in increased myocardial oxygen consumption[6].

Warltier et al[7] recently discussed various approaches to the prevention of peri-operative myocardial ischaemia and concluded that the only well-established prophylactic therapy was beta-blockade. They also emphasized the value of dose titration based on the optimum reduction of heart rate. There are fewer data on other drugs. The alpha1 agonist mirazerol reduces both tachycardia and intra-operative ischaemia, but at present, evidence on morbidity and mortality is lacking. Evidence with diltiazem is limited, while dihydropyridines are not useful for prophylaxis of intra-operative myocardial ischaemia, although they are able to reverse coronary spasm. The evidence for nitrates as prophylactics is equivocal; they may be deleterious if perfusion pressure falls, especially in patients with relative hypovolaemia[7].

Early studies with propranolol and other beta-blockers, mainly employing intravenous administration, demonstrated elective and prophylactic control of supraventricular and ventricular tachyarrhythmias peri- and postoperatively[6]. There has been particular focus on esmolol, which is an ultrashort acting beta1 selective antagonist that is rapidly hydrolysed by red cell esterases with a half life of about 9 min. Its action is terminated 5–10 min after the end of an infusion[6]. Esmolol has been used to control blood pressure and heart rate increases associated with general anaesthesia, such as intubation. It also reduces the incidence of ventricular arrhythmias. It has been shown to reduce episodes of ischaemia in patients undergoing coronary angioplasty[6]. In a recent report of a randomized study in patients at risk for coronary artery disease, all undergoing a similar anaesthetic procedure for elective total knee arthroplasty, postoperative ECG ischaemia was reduced by esmolol (0 of 52 vs 4 of 55, P=0·04), there was also a non-significant trend towards reduced ischaemic outcomes in the patients who received an esmolol infusion[8]. A non-randomized study in patients undergoing emergency surgery after failed PTCA suggested that esmolol might improve peri-operative morbidity and mortality[9].

Yeager and his colleagues[10], discussing some early studies of beta-blockade in non-cardiac surgery employing retrospective controls, suggested that beta-blockade might reduce peri-operative myocardial infarction. They reported a case control study in which 53 peri-operative myocardial infarctions were identified in a series of 2088 patients undergoing major vascular surgery over a 4-year period. These patients were matched with 106 control patients without peri-operative myocardial infarction. Beta-blockers were used in 50% of the control group compared to 30% in those patients who experienced an infarct (P=0·01). There was no difference in the usage of nitroglycerin (35% and 40%), or calcium channel blockers (42% and 49%), respectively. The utilization of ACE inhibitors (24% and 15%) was also not significantly different[10]. Weightmann et al.[11] assessed 1593 consecutive patients undergoing coronary artery bypass surgery, where the overall in-hospital mortality was 3·3%. The relative mortality associated with various drugs was assessed. The relative risk of death was not significantly affected by the administration, in the period up to 5 days of the operation, of aspirin (1·0), calcium antagonists (1·1),...
ACE inhibitors (0·8), digoxin (0·7), or warfarin (0·3), where in all cases the confidence limits crossed unity. However, mortality was reduced in patients who received beta-blockers (0·4 (CI 0·2–0·8)), and increased in patients who had received nitrates within 5 days of operation (3·8 (CI 1·5–9·6)), although this might reflect an increase in risk in the patients who received nitrates.

Mangano et al.[3] performed a randomized double-blind trial of the beta₁ selective antagonist, atenolol. They administered 5 mg intravenous pre-operatively. A second 5 mg dose was given if the heart rate was over 55 beats.min⁻¹ and systolic blood pressure ≥100 mmHg in patients with ischaemic heart disease, or with at least two cardiac risk factors, and undergoing non-cardiac surgery. Thereafter, oral 50 mg or 100 mg was given daily, if the heart rate was above 65 and the systolic blood pressure ≥100 mmHg, for the remainder of the postoperative stay up to a maximum of 7 days. All but two of the 194 patients discharged from hospital were followed for 2 years. Mortality 6 months post-discharge was 0% in the atenolol group and 8% in the control group (P<0·001); at 1 year 3% vs 14% (P=0·005) at 2 years 10% vs 21% (P=0·019). At 2 years post surgery the atenolol-treated group showed a 48% reduction in cardiac events (P=0·008). In a further report of this study[12] atenolol was reported to reduce the incidence of peri-operative ischaemia. On postoperative days 0–2 ischaemia occurred in 17 of 99 atenolol-treated patients, and in 34 of 101 placebo-treated patients (P=0·008); on days 0–7: atenolol 24 of 99, placebo 39 of 101 patients (P=0·029). It was also noted that an episode of ischaemia 0–2 days postoperatively doubled the risk of death over 2 years (RR 2·06, CI 1·04–4·06).

Poldermans and colleagues[13], in their first report, described a randomized open trial of bisoprolol plus usual care vs standard care in patients undergoing major subdiaphragmatic vascular surgery who had cardiac risk factors, plus hypokinesis as measured by echocardiography, induced in response to an infusion of dobutamine. Bisoprolol 5 mg was started at least 1 week pre-operatively and it was increased to 10 mg if the heart rate remained above 60 beats.min⁻¹. Intravenous metoprolol was used postoperatively if it was not possible to give bisoprolol orally or by nasogastric tube. Patients were followed-up for 30 days after surgery. Of 1351 patients who were screened, 846 had cardiac risk factors and 173 of these had a positive dobutamine stress echocardiogram. One hundred and twelve patients were randomized, 59 to bisoprolol added to standard care, 53 to standard care alone. The majority of exclusions (n=53) were patients who were already receiving beta-blockers, while eight had extensive wall motion abnormalities in response to the dobutamine infusion. Patients were followed-up for 30 days post-operatively. The main results are summarized in Table 3 of the current report[14]. There were two (3·4%) cardiac deaths in the bisoprolol group and nine (17%) in the standard care group (P=0·02); non-fatal infarcts were zero and nine, (17%) respectively (P=0·001), and deaths and infarcts combined were 3·4% and 34%, respectively (P<0·001), a relative risk of 0·09 (CI 0·02–0·37).

The current report[14] concerns the follow-up, i.e., from 30 days post-operation to a median of 22 months, range 11–30 months post surgery, of the 101 surviving patients, i.e. 57 in the bisoprolol group and 44 in the standard care group. There was a facility in the design of the study to increase the dose of bisoprolol to 15 mg daily if the heart rate remained over 60, or to reduce it to 2·5 mg if the heart rate fell below 50 beats.min⁻¹. However, while it is most important to recognize the importance of dosage variability in optimum cardiac slowing, as a result of beta-blockade, and that in clinical practice dosage outside common usage will occasionally be required, in the event the dose actually employed was 5 mg in 32 patients and 10 mg in the remaining 25 patients. In this follow-up period there were six cardiac deaths (11%) in the bisoprolol group and nine (20%) in the standard care group (NS) four of whom had had a non-fatal peri-operative myocardial infarction. Incidence of non-fatal myocardial infarction was one (2%) and five (11%), respectively P=0·083, with combined end-points of seven (12%) and 14 (32%) (P=0·025). The combination of peri-operative events[13] and follow-up period events[16] reveals that cardiac death occurred in eight (13·6%) with bisoprolol, and in 18 (34%) with standard care (P=0·014), that there was one non-fatal infarct (1·7%) with bisoprolol, and 14 (26·4%) with standard care (P=0·003), with combined end-points of nine (15·3%) and 32 (60·4%) (P=0·001), respectively.

Based mainly on the reports of the peri-operative use of atenolol[5,11], Warltier[15] wrote a review entitled ‘β-adrenergic blocking drugs, incredibly useful, incredibly under-utilised’. This is probably still a fair comment, although beta-blockers are becoming more accepted peri-operatively. They are now recommended by the American College of Physicians in patients with coronary artery disease or with risk factors for coronary disease[15]. The reports of Poldermans and colleagues[12,13] provide important new information so that the total evidence for peri-operative use of beta-blockers is now more compelling. The mechanism for the value of beta-blockers is perhaps not absolutely clear[15]. It is well established,
as indicated above, that operative episodes of myocardial ischaemia are associated with a poor post-operative prognosis. Beta-blockers, since their earliest use, have been well established as antiischaemic agents. They improve the balance of oxygen demand and supply. Their most important action is to cut down oxygen use as a result of adrenergic inhibition; additionally they may improve coronary flow to ischaemic areas of the heart.

The major reason for the under-utilization of beta-blockers peri-operatively seems to lie in a misconceptions of the risk benefit ratio. There is indeed a risk of conduction disturbances, aggravating left ventricular insufficiency, or increasing airways obstruction in asthmatics. However, it should now be remembered that the long-term use of beta-blockers dramatically improves prognosis in patients with heart failure and in patients with high risk, i.e. post infarction, with co-existent chronic obstructive airways disease. The tolerability of beta-blockers, when they are indicated, can usefully be assessed pre-operatively in elective surgery in patients at risk, or in urgent cases, the ultra-short acting beta-blockers esmolol may be employed to test tolerability.

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References