CLINICAL INVESTIGATIONS

Effect of chronic intercurrent medication with β-adrenoceptor blockade or calcium channel entry blockade on postoperative silent myocardial ischaemia†

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We have examined observational data from four published studies investigating the incidence of postoperative silent myocardial ischaemia (post-SMI) for the effects of chronic intercurrent therapy with β-adrenoceptor blockade or chronic calcium channel entry blockade. A total of 453 patients underwent ambulatory ECG monitoring before and for 2 days after non-cardiac surgery; 79 patients were receiving chronic intercurrent β-adrenoceptor blockade and 70 calcium channel entry blockade for ischaemic heart disease or arterial hypertension. Using logistic regression analysis, we defined a model for post-SMI that included four significant terms: β-adrenoceptor blockade; calcium channel entry blockade; arterial hypertension; and vascular surgery. Using univariate regression, there was no effect of chronic β-adrenoceptor blocking therapy on post-SMI (odds ratio 0.94 (95% confidence intervals 0.54–1.65)), but there was a higher incidence of post-SMI in patients receiving chronic calcium channel entry blocking drugs (odds ratio 1.95 (1.15–3.32); \( P = 0.015 \)). There was no interaction between β-adrenoceptor blockade and calcium channel entry blockade for postoperative SMI (odds ratio 2.48 (0.71–8.73)), but there was an interaction between β-adrenoceptor blockade, calcium channel entry blockade, hypertension and vascular surgery (\( P = 0.0201 \)). These findings are at variance with those which have shown effects of preoperative β-adrenoceptor blockade on the incidence of post-SMI over the first 7 days after operation, and on mortality rates to 2 yr. There are no comparable data examining the effects of chronic intercurrent calcium channel entry blockade.

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The prevalence rates of pre- and postoperative silent myocardial ischaemia (SMI) detected by ambulatory monitoring in patients undergoing non-cardiac surgery vary with the population studied; higher rates are found in those with either clinical evidence of coronary artery disease (CAD) or those with two or more risk factors for CAD. Thus in our own studies, we found that the incidence of preoperative SMI was 7.6–21.0% in patients undergoing general abdominal or vascular surgery1–5 and 22.8–31.0% in the postoperative period.3–5 In a recent review article, Coriat reported a preoperative incidence in predominantly vascular surgery patients of 12–28% and a postoperative incidence of 23–47%.6

Previous data from this department7,8 and the recent studies of Mangano and colleagues9 and Wallace and colleagues10 have examined ways of reducing the incidence of myocardial ischaemia. Thus Stone and colleagues demonstrated the efficacy of a single dose of β-adrenoceptor blockade with premedication in reducing perioperative ECG changes of ischaemia (from 28% to 2%),7 while Wallace and colleagues found that 7 days of perioperative beta-blockade with atenolol

given either by slow i.v. infusion over 15 min or orally, reduced the incidence of SMI over the first 7 days after operation (17% vs 34% over the first 2 days after operation \(P=0.008\)) and 24% vs 39% over the first 7 days after operation \(P=0.03\)).

In this study, we have retrospectively examined data from four observational studies of perioperative ambulatory ECG recording (aECG) from Oxford\(^{3,15,11}\) to see if chronic intercurrent therapy with \(\beta\)-adrenoceptor blocking drugs or calcium channel entry blockade reduced the incidence of postoperative SMI.

**Patients and methods**

After obtaining approval from the Local Ethics Committee and informed consent, 455 patients undergoing urological \((n=93)\), orthopaedic \((n=144)\), vascular or general abdominal surgery \((n=218)\) underwent ambulatory ECG monitoring using Kontron Micro KI 5100 solid state digital recorders before operation and for the first 2 days after operation. All patients receiving chronic intercurrent medication \((\geq 1\) month duration) continued this up to and including the morning of surgery, and recommenced as soon as feasible after the end of operation. \(\beta\)-Adrenoceptor blocking drugs used were mainly atenolol, but some patients were receiving oxprenolol, bisoprolol, propranolol, metoprolol, labetalol and sotalol. Similarly, most patients on chronic calcium channel entry blockade were receiving nifedipine, although some were receiving amlodipine, diltiazem, verapamil or felodipine.

Data from the ECG recorder were analysed using a computer program designed for analysis of ST-segment changes (Medilog Prima ECG Analysis System). A significant episode of ST-segment change was defined as horizontal or downsloping ST-segment depression of 1 mm or more, or ST-segment elevation of 2 mm or more lasting for 60 s or longer and followed by return to baseline for at least 1 min. Baseline was measured at a point 60 ms before the maximum R wave and the ST-segment was measured at a point 100 ms after the maximum R wave. All recorded episodes of ST-segment change were verified visually by one of the investigators.

The choice of premedication, anaesthetic technique, postoperative analgesia, intensity of intraoperative monitoring and postoperative oxygen therapy were at the discretion of the anaesthetist and according to the surgery undertaken. All cardiovascular drugs were recommenced by the morning after surgery unless the patient had a heart rate \(<50\) beat \(\text{min}^{-1}\) or a systolic arterial pressure \(<100\) mm Hg.

Patients were excluded from the study if their preoperative ECG revealed: evidence of left ventricular hypertrophy and strain changes in the lateral chest leads; conduction defects; changes caused by digoxin medication; or if there was inadequate data recording \(<8\) h) on any day in the pre- or postoperative period.

**Statistical analysis**

The primary end-point of the study was the occurrence of postoperative SMI and its association with \(\beta\)-adrenoceptor blockade or calcium channel entry blockade. Odds ratios were derived for the association between postoperative SMI and treatment. The statistical significance of these univariate associations was examined using chi-square tests for categorical data. The association between postoperative SMI and other patient characteristics and cardiovascular variables (sex, age \(>70\) yr, history of smoking, vascular surgery, history of myocardial infarction or angina pectoris, history of arterial hypertension based on a general practitioner diagnosis and institution of appropriate medication, diabetes mellitus, preoperative SMI) was examined in the same way. A probability of less than 5% was accepted as statistically significant.

Data were analysed using logistic regression analysis (using Stata version 6.0 on a Viglen Pentium III 233 MHz microprocessor), where the terms for chronic intercurrent \(\beta\)-adrenoceptor blockade or calcium channel entry blockade were retained as the terms of interest. The influence of potential confounders was examined and retained in the final model if they had a clinically significant impact on the coefficients for \(\beta\)-adrenoceptor blockade and calcium channel entry blockade. Statistical significance was determined using a log-likelihood ratio test and the Wald test, and a probability of less than 5% was taken as significant.

The power of the study was calculated using the frequencies of postoperative SMI reported by Wallace and colleagues.\(^{10}\) We determined that groups of 79 patients receiving \(\beta\)-adrenoceptor blockade and 374 unexposed controls would allow us to detect a difference in postoperative SMI at the 5% level with a power of 85%. A similar calculation based on the post hoc numbers of patients with postoperative SMI in the exposed calcium channel entry blockade and unexposed control groups indicated that the study had 65% power to detect a difference at the 5% significance level.

**Results**

Anaesthesia and surgery were uneventful in 454 patients; there was one intraoperative death. Three patients died of acute myocardial infarction during the first 3 days after operation. In two of these there were postoperative aECG data, and therefore these patients were included in the analysis. In the third, aECG data were available for the preoperative but not for the postoperative period, and this patient and the intraoperative death were excluded from further analysis. Therefore, we analysed data from 453 patients, of whom 308 (68%) were male and 45% were aged more than 70 yr.

Two hundred and fifty-one of 453 patients had coronary artery disease (previous myocardial infarct, typical angina or atypical angina with a positive stress test) or two or more risk factors for coronary artery disease (age \(>70\) yr, hypertension, current smoker, hypercholesterolaemia, diabetes mellitus): 210 (46.4%) patients were receiving treatment for hypertension and 74 (16.3%) for ischaemic heart disease.

Seventy-nine (17.4%) patients were receiving chronic intercurrent \(\beta\)-adrenoceptor blockade for ischaemic heart disease or arterial hypertension on admission to hospital, and
70 (15.5%) were receiving calcium channel entry blocking drugs. Twenty patients were receiving both β-blockade and calcium channel entry blocking medications. Seventy-eight percent of patients were receiving β-adrenoceptor blocking drugs for hypertension, 5% for coronary artery disease and 12% for both; similarly, 63% of patients taking calcium channel entry blocking drugs were receiving treatment for hypertension, 13% for coronary artery disease and 24% for both. Fifty-nine of 79 patients receiving β-adrenoceptor blocking drugs were receiving atenolol; others were receiving oxprenolol (one), bisoprolol (three), propranolol (six), metoprolol (five), labetolol (one) and sotalol (four). Fifty-three of 70 patients receiving calcium channel entry blocking drugs were receiving nifedipine; others received amiodipine (six), diltiazem (six), verapamil (four) or felodipine (one). The age ranges included in the patient groups and indications for treatment, and other relevant cardiovascularly active therapies are shown in Table 1.

The association between the different variables and postoperative SMI, as examined by univariate analysis, is shown in Table 2. There was a significant association with four variables: preoperative SMI, vascular surgery, arterial hypertension and intercurrent treatment with calcium channel entry blocking drugs. There was no effect of β-adrenoceptor blockade on postoperative SMI ($P=0.892$). In 19 patients receiving both β-adrenoceptor and calcium channel entry blockers, 9 had no ECG changes associated with a perioperative SMI; four had postoperative SMI and six had both pre- and postoperative SMI.

The data were then submitted to logistic regression analysis. We examined for: the effects of confounding variables, as determined in Table 2; their effect on the coefficients of the odds ratio of the association for β-adrenoceptor blockade and calcium channel entry blockade; and postoperative SMI. We also examined for any potential interaction between β-adrenoceptor blockade and calcium channel entry blockade, and indications for the prescribing of these two drugs. However, there was no significant interaction between β-adrenoceptor blockade and calcium channel entry blockade for the occurrence of postoperative SMI (odds ratio 2.48 (95% confidence intervals 0.71–8.73)).

The final coefficients for the best fit model are shown in Table 3. There was no effect of diabetes mellitus, sex, history of smoking, angina or past myocardial infarction, or age greater than 70 yr. There were significant associations between calcium channel entry blockade and hypertension (odds ratio 9.32 (4.51–19.77)), calcium channel entry blockade and coronary artery disease (angina or a past history of myocardial infarction) (5.01 (2.71–9.02)), and β-adrenoceptor blockade and hypertension (21.05 (9.07–50.67)).

**Discussion**

In this re-analysis of observational data from four reported studies where the end-point was postoperative SMI, we found no effect of chronic intercurrent β-adrenoceptor blockade on the incidence of SMI, but noted an increased incidence of SMI in patients receiving chronic calcium channel entry blockade for either arterial hypertension or

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**Table 1** Age, indications for therapy and patients receiving other therapies in the different patient groups (number of patients in each subgroup). HT=Hypertension; Isch HD=Ischaemic heart disease; ACEI=Angiotensin converting enzyme inhibitors

<table>
<thead>
<tr>
<th>Indications for therapy</th>
<th>Age (yr)</th>
<th>Pre-SMI</th>
<th>Post-SMI</th>
<th>Pre-SMI</th>
<th>Post-SMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Adrenoceptor blockers</td>
<td>45–88</td>
<td>50</td>
<td>3</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Calcium channel entry blockers</td>
<td>49–84</td>
<td>30</td>
<td>8</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Combined blockade</td>
<td>55–78</td>
<td>12</td>
<td>1</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Neither</td>
<td>40–97</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

**Table 2** Cross-tabulation for univariate analysis of categorical risk factors and postoperative silent myocardial infarction (SMI) in 453 patients. 1=Yes, 0=No, except in the case of sex, where 1=male and 0=female. β-Block=β-Adrenoceptor blockade; CEB=Calcium channel entry blockade. Pre-SMI and post-SMI=pre- and postoperative silent myocardial ischaemia

<table>
<thead>
<tr>
<th>Patients coded 1</th>
<th>Patients coded 0</th>
<th>Odds ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. with post-SMI</td>
<td>No. with no post-SMI</td>
<td>No. with post-SMI</td>
<td>No. with no post-SMI</td>
</tr>
<tr>
<td>Pre-SMI</td>
<td>53</td>
<td>13</td>
<td>78</td>
</tr>
<tr>
<td>β-Block</td>
<td>22</td>
<td>57</td>
<td>109</td>
</tr>
<tr>
<td>CEB</td>
<td>29</td>
<td>41</td>
<td>102</td>
</tr>
<tr>
<td>Hypertension</td>
<td>71</td>
<td>139</td>
<td>60</td>
</tr>
<tr>
<td>Vascular surgery</td>
<td>54</td>
<td>86</td>
<td>77</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>20</td>
<td>38</td>
<td>111</td>
</tr>
<tr>
<td>Male sex</td>
<td>87</td>
<td>221</td>
<td>44</td>
</tr>
<tr>
<td>Smoking</td>
<td>23</td>
<td>64</td>
<td>108</td>
</tr>
<tr>
<td>Angina</td>
<td>12</td>
<td>22</td>
<td>119</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6</td>
<td>28</td>
<td>125</td>
</tr>
<tr>
<td>Age &gt;70 yr</td>
<td>66</td>
<td>138</td>
<td>65</td>
</tr>
</tbody>
</table>
coronary artery disease. We chose to analyse our data in the same manner as Mangano and colleagues, that is by comparing exposed patients (those receiving a particular drug therapy) against unexposed patients (those not receiving that particular drug). Interactions between drugs and their effects on postoperative SMI were determined by logistic regression analysis.

We have reported previously the effects of both a single oral premedicant dose of a β-adrenoceptor blocking drug in mild untreated hypertensive patients and chronic intercurrent β-adrenoceptor blockade with atenolol in treated hypertensive patients undergoing non-cardiac surgery under general anaesthesia.7 8 There was a reduction in the incidence of observed ECG changes associated with myocardial ischaemia from 28% to 2%. Furthermore, the studies of Mangano and colleagues and Wallace and colleagues also showed a reduction in perioperative SMI and mortality over the first 2 yr after surgery.9 10

In our patients undergoing non-cardiac surgical procedures under general anaesthesia, those maintained on chronic intercurrent β-adrenoceptor blocking therapy did not show a reduction in the incidence of postoperative SMI. Why should our results be at variance with those of Stone and colleagues7 8 and Wallace and colleagues?10

Compared with Stone and colleagues,7 where untreated patients with mild hypertension (diastolic pressure <100 mm Hg) received a single dose of a β-adrenoceptor blocking drug with their premedication, patients in this meta-analysis continued to receive their normal β-adrenoceptor antagonist medication. Thus patients in our earlier study were different from the present group of patients, being mild-to-moderate untreated hypertensive patients (diastolic arterial pressure <100 mm Hg, with no ECG evidence of either left ventricular hypertrophy or myocardial ischaemia) compared with patients with arterial hypertension or ischaemic heart disease, or both. Chronic β-adrenoceptor treatment has been coupled with an increase in plasma high-density lipoproteins, which may itself increase the incidence of latent ischaemic heart disease.

In the second study by Stone and colleagues,8 we compared patients maintained on β-adrenoceptor blocking drugs with untreated controls, and showed a peroperative incidence of ECG changes compatible with myocardial ischaemia of 0% (none of 14) vs 28% (11 of 39). However, this was a small study, and no patient had symptoms or clinical evidence of ischaemic heart disease.

There were also differences between our patients and those reported by Wallace and colleagues.10 We did not confine our study to patients with ischaemic heart disease or to those with two or more risk factors, but chose to examine a general non-cardiac surgical population. Thus the incidence of patients with either coronary arterial disease or ‘at-risk’ of coronary disease was 55.4% in our study compared with 100% in the studies of Mangano and colleagues9 and Wallace and colleagues.10 There was also a significantly higher incidence of hypertension in association with diabetes mellitus in the American series. There may be differences in the incidence and types of other preoperative drug therapies and in compliance with their administration, in addition to differences in the duration and conduct of anaesthesia and surgery. Of additional concern is the fact that some patients in the Wallace study were receiving chronic β-adrenoceptor blockade which was stopped abruptly at the time of randomization—this may lead to the development of withdrawal features.12 However, subsequent correspondence would suggest there were equal numbers of patients where β-adrenoceptor blockade was withdrawn before operation in both treatment arms.

Diabetes mellitus is a powerful risk factor for atherosclerosis, especially if associated with arterial hypertension and abnormalities of lipid metabolism (the so-called syndrome X).13 Mangano and colleagues found three univariate predictors that influenced cardiac death: atenolol, diabetes mellitus and early postoperative SMI on days 0–2.9 Atenolol improved 2-yr survival in diabetic patients by approximately 75%; in the absence of β-adrenoceptor blockade, the relative odds ratio for adverse outcome from diabetes mellitus were increased four-fold. Moreover, with multivariate analysis, diabetes mellitus alone and not atenolol treatment was a predictor of cardiac outcome.

In a separate study, using multivariate logistic regression to define risk factors, Hollenberg and colleagues found diabetes mellitus to be a predictor of postoperative SMI.14 Thus diabetes may be a more important contributor towards

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**Table 3** Logistic regression models for interaction of risk factors for occurrence of postoperative SMI after anaesthesia and surgery. *Comparison of likelihoods; 1df

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds ratio (95% CI)</th>
<th>P</th>
<th>Log likelihood ratio test vs preceding model</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Adrenoceptor blockade</td>
<td>0.76 (0.44–1.35)</td>
<td>0.341</td>
<td></td>
</tr>
<tr>
<td>Calcium channel entry blockade</td>
<td>2.24 (1.31–3.83)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>β-Adrenoceptor blockade</td>
<td>0.64 (0.35–1.15)</td>
<td>0.137</td>
<td>2.94 0.0866</td>
</tr>
<tr>
<td>Calcium channel entry blockade</td>
<td>1.90 (1.08–3.35)</td>
<td>0.026</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.50 (0.94–2.40)</td>
<td>0.086</td>
<td></td>
</tr>
<tr>
<td>β-Adrenoceptor blockade</td>
<td>0.67 (0.37–1.21)</td>
<td>0.180</td>
<td>5.41 0.0201</td>
</tr>
<tr>
<td>Calcium channel entry blockade</td>
<td>1.77 (1.00–3.13)</td>
<td>0.050</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.38 (0.86–2.22)</td>
<td>0.177</td>
<td></td>
</tr>
<tr>
<td>Vascular surgery</td>
<td>1.69 (1.09–2.63)</td>
<td>0.019</td>
<td></td>
</tr>
</tbody>
</table>

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cardiac complications than atenolol is in preventing it. The incidence of diabetes mellitus in our patients was low (7.5%) compared with 31% in the study of Wallace and colleagues.\(^{10}\) Hence any effect of \(\beta\)-adrenoeceptor blockade in improving outcome by reducing the influence of diabetes mellitus might be expected to be small or insignificant.

However, our results are in keeping with those of Hollenberg and colleagues\(^{14}\) who were unable to find any difference in the incidence of postoperative SMI between patients maintained on \(\beta\)-adrenoeceptor blocking drugs and those not receiving them. Similarly, both Mangano and colleagues and Browner and colleagues failed to find any effect of \(\beta\)-adrenoeceptor blocking drugs on postoperative complications and mortality in patients undergoing non-cardiac surgery.\(^{15\ 16}\) As further support for a possible difference between the populations studied by us and Mangano and colleagues, there are mortality data from the two study populations. While Mangano found cardiac mortality at 2 yr to be reduced in the atenolol-treated population from 12.5% to 4.2%,\(^{9}\) Howell and colleagues, using a case-control design interrogation of the Oxford Record Linkage Study, found no association between preoperative \(\beta\)-adrenoeceptor antagonist therapy and cardiovascular death within 30 days of surgery.\(^{17}\)

The increased association of ischaemia and treatment with chronic calcium channel entry blockade (although only having a power of 65% to detect a significant difference at the 5% level) has been paralleled in other studies. Psaty and colleagues found an association between short-acting calcium channel entry blocking drugs and an increased risk of myocardial infarction in hypertensive patients,\(^{18}\) and Mangano and colleagues found a univariate association between calcium entry blocking drugs and adverse long-term outcome in non-cardiac surgical patients.\(^{15}\) In the latter study, other significant correlates included presence of cardiac disease, peripheral vascular disease, postoperative SMI and preoperative medication with nitrates. However, multivariate regression analysis failed to support the significance of calcium entry blockade, although significant correlates included a history of typical angina and postoperative SMI. Similarly, no association was found in the studies of Braun and colleagues or Jick and colleagues.\(^{19\ 20}\)

Thus although Mangano and colleagues showed a positive effect of atenolol on both mortality and morbidity in a selected male population with a high incidence of hypertension and diabetes mellitus, we cannot confirm their findings. Furthermore, we found a significant association between postoperative SMI and calcium channel entry blockade. The clinical significance of these findings clearly establishes the need for prospective studies of cardiovascular outcome in patients receiving long-term intermittent therapy for hypertension or coronary artery disease, and the possible benefits of perioperative prophylactic administration of \(\beta\)-adrenoeceptor blocking drugs.

**Acknowledgement**

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**References**