ACE inhibitor premedication attenuates sympathetic responses during surgery

M. Böttcher, J. K. Behrens, E. A. Møller, J. H. Christensen and F. Andreasen

SUMMARY

We studied cardiovascular and catecholamine responses for 3 days in three groups of patients undergoing abdominal hysterectomy. The night before surgery and again 2 h before induction of anaesthesia, patients received the ACE inhibitor, ramipril, the beta, blocker, metoprolol, or placebo. In the actively treated groups, mean diastolic pressure was reduced during surgery and increases in heart rate and arterial pressure after surgical incision were attenuated. During operation, stroke volume (SV) and cardiac output (CO) were significantly higher in the ramipril group. In contrast, beta, adrenergic block caused no significant changes in SV or CO. The concentration of noradrenaline in plasma and urine indicated that ACE inhibition caused attenuated release of noradrenaline. The results support the concept that angiotensin II facilitates release of noradrenaline from sympathetic nerves and that ACE inhibition inhibits this release. (Br. J. Anaesth. 1994; 72: 633-637)

KEY WORDS


Surgery causes stimulation of the sympathetic nervous system, as reflected by increases in plasma concentrations of catecholamines and in haemodynamic variables [1]. This response is modified by administration of blockers (alpha and beta adrenoceptors) before anaesthesia [2, 3].

Several reports from animal and in vitro studies have indicated that therapy with angiotensin converting enzyme (ACE) inhibitors attenuates the sympathetic response to different stressful stimuli [4-9]. The mode of action has not been clarified and it is not known if this effect is present in humans and maintained during surgery.

The aim of this study was to evaluate the haemodynamic effects of and catecholamine responses to surgery in patients receiving a normal antihypertensive dose of an ACE inhibitor or a beta, adrenoceptor blocker.

PATIENTS AND METHODS

The study was approved by the local Ethics Committee and the Danish health authorities.

We studied consecutive patients admitted for elective hysterectomy, after obtaining written informed consent, according to the Helsinki II declaration. Patients with diabetes or cardiopulmonary, renal or malignant diseases (evaluated by physical examination, ECG and serum creatinine) and those receiving diuretics, beta blockers, ACE inhibitors or digoxin were excluded.

Thirty-five patients were enrolled but eight were excluded from the study: three patients were unwilling to participate and five patients met one of the exclusion criteria. Twenty-seven patients, mean age 44.1 (range 37-50) yr, completed the study. The study was a double-blind, double-dummy design. Patients were allocated randomly to receive one of the study medications at 22:00 on the night before operation and again 2 h before operation, together with routine premedication (diazepam 15 mg). Study medications were either metoprolol-CR 100 mg tablet (Selo-zok, Astra) and placebo capsule (group M), ramipril 5 mg capsule (Ramace, Astra) and placebo tablet (group R) or placebo capsule and placebo tablet (group P). Placebo medications were indistinguishable from active drugs and the code was not broken until all study results were obtained.

Anaesthesia was induced with pethidine 1 mg kg⁻¹ i.v. followed by thiopentone 5 mg kg⁻¹ i.v. supplemented with doses of 50 mg until the ciliary reflex was abolished. Vecuronium 6 mg was given to facilitate tracheal intubation (supplementation if necessary). Intubation (oral) was performed by the anaesthetist according to standard procedures. Anaesthesia was maintained with 0-1.5% halothane and 66% nitrous oxide in oxygen and pethidine 0.2 mg kg⁻¹ every 15 min. Atropine 0.5 mg was given if heart rate decreased to less than 45 beat min⁻¹. At the end of surgery, neostigmine 2.5 mg was given to antagonize neuromuscular block, together with atropine 1 mg. During surgery, all patients received 0.9%, NaCl 15 ml kg⁻¹ h⁻¹ and, in addition, approximately 3 ml per millilitre of blood loss. After operation, all patients received 0.9%, NaCl 1000 ml and 5.5% glucose 1000 ml until 09:00 the following morning and were allowed to drink at will.

MORTEN BÖTTCHER, M.D., FREDERIK ANDREASEN, M.D., D.M.SC., Institute of Pharmacology, University of Aarhus, DK-8000 Aarhus C, Denmark. JENS K. BEHRENS, M.D., ERLING A. MÖLLER, M.D., JØRGEN H. CHRISTENSEN, M.D., D.M.SC., Department of Anaesthesiology, Aarhus Municipal Hospital, DK-8000 Aarhus C, Denmark. Accepted for Publication: November 30, 1993.

Correspondence to F.A.
All patients were anaesthetized by one of two anaesthetists. Ten different surgeons performed the operations and no surgeon performed more than three operations. All operations were abdominal hysterectomies and standard procedures were followed. No complications were encountered during or after operation.

Arterial pressure and heart rate were measured by a non-invasive oscillometric method (Dinamap). Preoperative systolic and diastolic arterial pressures were recorded as the average of five consecutive contractions. CO was measured on six occasions: (1) 1 h after premedication (approximately 1 h before surgery) (Pre.); (2) 1 min after tracheal intubation (Intub.); (3) 1 min after skin incision (Inc.); (4) 1 min after removal of the uterus from the abdominal cavity (Hys.); (5) 1 min after skin closure (End); and (6) at 09:00 the morning after operation (day 3).

For measurement of plasma concentrations of noradrenaline, blood was collected from a large antecubital vein, into pre-cooled tubes kept on ice. The samples were obtained at the same times as determinations of CO specified above, centrifuged at 3000 rpm for 15 min at 4 °C and plasma was stored at −80 °C until analysis. Noradrenaline was measured using high pressure liquid chromatography and electrochemical detection [12]. Blood (12 ml) was obtained for each sample and the first 2 ml was discarded. For measurement of excretion of noradrenaline, urine was collected from 09:00 the day before operation (day 1) until 48 h after operation. Urine was collected in special collectors containing 100 ml of HCl 1 mol litre⁻¹ and stored at 4 °C during collection. After collection, urine was mixed and samples were taken and stored at −80 °C until analysis.

Statistical analysis

For comparison of baseline values, urinary volume and excretion of noradrenaline, the Mann–Whitney non-parametric test was used. For comparison of arterial pressures and heart rates during and after operation, repeated measures ANOVA was used. For comparison of noradrenaline, CO and SV data, the Mann–Whitney non-parametric test was used. As only four predefined events were evaluated, no Bonferroni correction was necessary [13]. Statistical significance was accepted at the 5 % level. All tests were performed using the computer package SOLO version 4.0 by BMDP Statistical Software, CA, U.S.A., on a standard PC.

RESULTS

There were no differences between the groups in preoperative or surgical data (tables I and II). Fischer’s exact test failed to show any difference between the number of doses of atropine given.

Heart rate (HR), systolic (SAP) and diastolic arterial pressures (DAP) were recorded every 5 min during operation (fig. 1). None of the operations was completed in less than 50 min and during this period, DAP was significantly lower in the treated groups compared with the placebo group (P < 0.05). There was no difference between groups M and R. The apparent difference in SAP between the groups was not statistically significant. HR did not differ significantly between groups. There were significant increases in HR, DAP and SAP in the placebo group (P < 0.05) but no significant increases in the treated groups (fig. 2). The magnitude of the increase did not differ between these two groups. Both SV and
CO were increased significantly in group R at Pre. and Inc. compared with groups P and M (fig. 3). At Intub., CO was also significantly higher than in groups P and M. After operation, heart rate was significantly lower in group M than in groups P and R (fig. 4). There were no significant differences in SAP after operation, while DAP was reduced significantly in group R compared with placebo.

Significant increases in plasma concentrations of noradrenaline were found in groups P and M during operation when values at surgical incision (Inc.) and mid-operative values (Hys.) were compared (fig. 5) (516 (365–854) vs 1008 (324–2332) pg ml⁻¹ (P < 0.05) in the placebo group and 344 (106–934) vs 774 (398–1713) pg ml⁻¹ (P < 0.05) in group M). In group R, only marginal increases occurred (431 (69–899) vs 114 (398–1713) pg ml⁻¹) and values were significantly lower than in group P at Hys. and End. Plasma concentrations of noradrenaline were higher in groups P and M 24 h after operation (day 3), but these were not significantly different from the values in group R. There were no differences in urinary output between groups, except for day 2 when group R had a significantly lower urinary volume than
FIG. 4. Heart rate (HR) and systolic (SAP) and diastolic (DAP) arterial pressures after operation in the ramipril (■), placebo (○) and metoprolol (□) groups (mean, SEM). Significant differences (P < 0.05): * ramipril vs placebo; † metoprolol vs ramipril; ‡ metoprolol vs placebo.

FIG. 5. Plasma concentrations of noradrenaline (NA) during operation in the ramipril (▼), placebo (○) and metoprolol (□) groups (mean, SEM). * P < 0.05, ramipril vs placebo. (See text for abbreviations.)

FIG. 6. Urinary volume and total urinary noradrenaline (NA) excretion over 24 h in the metoprolol (M), placebo (P) and ramipril (R) groups (mean, SEM). Day 2 is the day of operation. Significant differences (P < 0.05): * vs placebo; † vs metoprolol.

Previous studies have demonstrated that beta adrenergic block [2] and ACE inhibition [14] attenuate the cardiovascular responses to anaesthesia and surgery. However, so far there have been no studies comparing the efficacy of these two different pharmacological regimens. The present study was designed to undertake such a comparison using average antihypertensive doses of the two different classes of drug.

We found that in both of the actively treated groups, DAP was reduced by approximately 10 mm Hg during surgery and that increases in HR, DAP and SAP caused by skin incision were attenuated. The effect of metoprolol on the circulation may be explained by the well known negative chronotropic and inotropic effects of beta adrenoceptor block. The effect of ACE inhibition may be mediated by a combination of a reduction in the concentration of angiotensin II in circulating blood and a decrease in sympathomimetic activity, as reflected by low concentrations of noradrenaline in plasma and urine. Angiotensin II may have a presynaptic facilitating effect on release of noradrenaline (see below) [4, 7, 8, 15, 16].

The anticipated increase in plasma concentration of noradrenaline in response to skin incision [1] did not occur in the group given ACE inhibitors and there were persistently lower urinary concentrations...
of noradrenaline throughout the study. In the metoprolol group, plasma concentrations of noradrenaline in response to skin incision did not differ from those in the placebo group and urinary excretion of noradrenaline was depressed only on day 1. Although noradrenaline responses did not differ significantly between the actively treated groups, these findings support the view that ACE inhibition attenuates release of noradrenaline [4, 7, 8, 15, 16].

SV increased at Pre. and Inc. and CO increased at Pre., Int. and Inc. during ACE inhibition in comparison with the findings in the placebo and metoprolol groups. During the corresponding 24-h period, urinary volumes were significantly lower during ACE inhibition than during beta block. As the postoperative values for DAP were also lower during ACE inhibition, the lower urinary volumes may be explained by lower glomerular filtration rate. The mechanism for increased SV may be greater intravascular volume and this would correlate with the lower urinary volumes produced on day 2.

There has been some concern about the accuracy of the bioimpedance method for measurement of CO. However, these concerns have related to seriously ill patients (especially those with pulmonary oedema) and to very obese patients (more than 10% overweight), where absolute values were less reliable. In our study, CO did not differ between groups (after exclusion of two patients from the placebo group and one patient from the metoprolol group who had body weights of more than 10% above ideal weight). We used CO data for comparing group values and it has been suggested [11, 17, 18] that the bioimpedance technique used in this situation is appropriate.

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REFERENCES