Br. J. Anaesth. (1983), 55, 405

METOPROLOL, FENTANYL AND STRESS RESPONSES TO MICROLARYNGOSCOPY

Effects on arterial pressure, heart rate and plasma concentrations of catecholamines, ACTH and cortisol

J. MAGNUSSON, O. WERNER, C. CARLSSON, N. NORDÉN AND K.-I. PETTERSSON

SUMMARY

Forty patients undergoing microlaryngoscopy were anaesthetized with thiopentone and nitrous oxide. Twenty patients received metoprolol 200 mg in a slow-release tablet once daily for 4 days up to, and including, the morning of operation, and 10 mg i.v. shortly before induction of anaesthesia. The other patients received placebo tablets and physiological saline i.v., instead. Both groups of 20 patients were further subdivided, half of the patients receiving fentanyl 1.0–1.5 mg during anaesthesia, the effect of which was antagonized by naloxone at the end of the procedure. The other patients received saline i.v. instead of fentanyl or naloxone. Metopropolol decreased heart rate and the general level of arterial pressure during anaesthesia, but did not affect the fluctuations in pressure. Arterial plasma noradrenaline concentrations during microlaryngoscopy were enhanced by metoprolol, in comparison with placebo, the reverse being the case for cortisol concentrations. Fentanyl decreased arterial pressure and plasma ACTH and cortisol concentrations regardless of whether the patient had received metoprolol. Plasma adrenaline and noradrenaline concentrations were decreased by fentanyl in the patients receiving metoprolol.

Although β-adrenoceptor antagonists decrease the occurrence of arrhythmia and tachycardia caused by stressful stimuli during anaesthesia (Rollason and Russell, 1980), their effect on acute alterations in arterial pressure is less clear. For instance, the hypertensive response to laryngoscopy and intubation was not decreased appreciably by practolol i.v. shortly before the induction of anaesthesia with thiopentone (Siedlecki, 1975; Werner et al., 1980).

In a previous study Werner and colleagues (1980) noted that practolol i.v. did not decrease significantly the hypertensive response to microlaryngoscopy, a response that may be pronounced even in subjects who are normotensive before anaesthesia (Weigand, 1970). The full antihypertensive effect of β-blockers is seen only after hours, or days, of treatment (Conway and Amery, 1975) and this suggests that the effects on arterial pressure during anaesthesia, after several days of pretreatment with β-blockers by mouth, may be different from those seen after acute administration i.v. The present paper describes a randomized investigation of the effects of 4 days pretreatment with a β-blocking drug before anaesthesia for microlaryngoscopy. The cardioselective β-blocker metoprolol was used and, in order to study the interactions between metoprolol, opiate analgesia and stress, half of the patients received fentanyl also.

J. MAGNUSSON, M.D., O. WERNER, M.D., C. CARLSSON, M.D. (Department of Anaesthesia); N. NORDÉN (Department of Clinical Chemistry); K.-I. PETTERSSON (Department of Ear, Nose and Throat Surgery); University of Lund, S-221 85 Lund, Sweden.

PATIENTS AND METHODS

The investigation was approved by the local Human Study Committee. Forty patients, aged 39–79 yr, undergoing microlaryngoscopy were studied. None had received antihypertensive or antiarrhythmic drugs (diuretics, β-blocking drugs or digitalis) previously. Each patient was examined by one of the authors 3 days before anaesthesia, at which time informed consent was obtained and arterial pressure measured by upper arm sphygmomanometry. Patients were then divided in four groups ($n = 10$) by stratified randomization according to the value of their systolic arterial pressure (150 mm Hg or less, or greater than 150 mm Hg). Stratification was abandoned in the last few patients to achieve equal numbers in the groups. The groups were:

(I) Controls. These patients received thiopentone and nitrous oxide only.

(II) Patients in this group received thiopentone and nitrous oxide as in group I. In addition, they re-

ceived fentanyl i.v. shortly before microlaryngoscopy and naloxone following surgery.
(III) Patients in this group received metoprolol 200 mg, in a slow release form, once daily for 4 days. The first tablet was given in the afternoon shortly after the patient had been examined and the last tablet at 6 a.m. on the day of operation. An additional 10 mg was given i.v. 1–3 min before anaesthesia. The techniques of anaesthesia was as in group I.
(IV) Patients in this group received metoprolol (as group III). However, the technique of anaesthesia was the same as in group II (thiopentone, nitrous oxide and fentanyl followed by naloxone).

Assignment to the different groups was double-blind. Thus, patients not given metoprolol (groups I and II) received placebo tablets and received physiological saline i.v. instead of metoprolol before anaesthesia. Patients not given fentanyl and naloxone received equivalent volumes of physiological saline i.v. However, the nature of the treatment could often be deduced from the response of the patient during anaesthesia.

Microlaryngoscopy was performed usually between 1 and 3 p.m. Patients were premedicated with morphine and hyoscine according to age (table I). A cannula was inserted in the radial artery 10–30 min before the induction of anaesthesia and arterial pressure was measured continuously (HP 1280 C transducer (Hewlett Packard)) and displayed with the ECG on a Mingograph 81 recorder (Siemens-Elema). The transducer was calibrated each day against a water column corresponding to 100 mm Hg. Since the day-to-day variations were small, calibration over the full range (0–300 mm Hg) was performed only once.

Atropine 1.0 mg was administered 4 min before the induction of anaesthesia, and then followed by metoprolol 10 mg, or saline. Anaesthesia was induced with thiopentone. Suxamethonium was administered and the lungs ventilated, using a face-mask, with 5–10 breaths of 100% oxygen, after which tracheal intubation was accomplished with the aid of a Macintosh laryngoscope. This was held in place so that the vocal cords were visualized for 30 s. A Portex 6.5-mm endotracheal tube was lubricated with amethocaine gel, otherwise no topical anaesthesia was given. Subsequently, the lungs were ventilated manually with 70% nitrous oxide in oxygen. Fentanyl 1.0 mg, or saline, was injected in divided doses starting about 5 min after the intubation of the trachea, that is, about 8 min before microlaryngoscopy with the Kleinsasser instrument. Additional fentanyl 0.5 mg, or saline, was given after 20 min of microlaryngoscopy if required. An infusion of suxamethonium ensured adequate muscle relaxation during microlaryngoscopy. Naloxone hydrochloride 0.4 mg i.v. and 0.4 mg s.c., or saline, was injected some 2–4 min after the end of the microlaryngoscopy. The tracheal tube was removed about 5 min later, when adequate spontaneous breathing was established.

Mean arterial pressure (MAP), at rest, 3 days before anaesthesia was calculated as: systolic

TABLE I. *Comparisons between the groups. Values are mean ± 1SD, when applicable, except time intervals which are given as median and (range). ML = Microlaryngoscopy. *One patient received diazepam 10 mg i.m. instead*

	Group			
	I	II	III	IV
Males/females	9/1	8/2	8/2	6/4
Age (yr)	65 ± 11	61 ± 13	56 ± 10	56 ± 11
Weight (kg)	80 ± 21	71 ± 12	75 ± 17	74 ± 13
Premedication (mg)				
Morphine	6.5 ± 3.2	6.3 ± 2.9	7.2 ± 2.9*	8.0 ± 3.5
Hyoscine	0.26 ± 0.12	0.25 ± 0.12	0.29 ± 0.12	0.32 ± 0.12
Anaesthetic drugs (mg kg^{-1})				
Thiopentone	4.3 ± 0.7	4.4 ± 0.8	4.4 ± 0.4	4.2 ± 0.5
Suxamethonium, initial	1.0 ± 0.2	1.0 ± 0.1	1.1 ± 0.1	1.1 ± 0.1
Suxamethonium, maintenance	5.3 ± 3.1	2.9 ± 2.1	4.8 ± 1.8	1.8 ± 1.1
Time intervals (min)				
Premedication–anaesthesia	86 (40–280)	94 (55–120)	88 (60–127)	90 (35–110)
Induction–intubation	3.0 (2.5–3.3)	3.0 (1.8–4.5)	2.5 (2.5–4.3)	2.5 (2.3–4.0)
Start–end of ML	7 (6–12)	8 (5–25)	8 (3–26)	12 (8–19)

pressure × 1/3 + diastolic pressure × 2/3. On all other occasions MAP was obtained from the arterial pressure tracing. Values for systolic arterial pressure (SAP) were also noted. However, it was realized that, on occasions, the pressure tracing from the radial artery was distorted. Heart rate was assessed from the ECG. The observer was not informed of the nature of the treatment.

Blood samples were withdrawn from the arterial cannula into prechilled test tubes and immediately immersed in ice-cold water. Plasma was separated within 20 min by 3 min of centrifugation, and stored at −70 °C until assay. Samples for noradrenaline and adrenaline assay were withdrawn in tubes containing EGTA and glutathione. A radioenzymatic assay was used (Peuler and Johnson, 1977), slightly modified according to Eriksson (1981). The within-sample coefficient of variation for the assay was 5–7% for adrenaline, and 4–6% for noradrenaline, depending on concentration. The corresponding figure, between samples, was about 10% for both substances. The detection limit was 0.1 nmol litre^{-1} for adrenaline and 0.2 nmol litre^{-1} for noradrenaline. The normal range for arterial plasma concentrations in resting subjects was 0–0.4 nmol litre^{-1} for adrenaline and 0.8–2 nmol litre^{-1} for noradrenaline (P. Hjemdahl, personal communication). Recovery of catacholamines with the assay used has been stated to be 65–85% (Peuler and Johnson, 1977). Samples for assay of adrenocorticotropin (ACTH), and cortisol were collected in tubes containing EDTA. A radioimmunoassay (CIS-Sorin, France) was used for the measurement of ACTH concentration. The coefficient of variation between-samples was 17% for concentrations < 50 ng litre^{-1} and 10% for concentrations > 50 ng litre^{-1} with a lower limit of detection at 10 ng litre^{-1}. The upper normal limit at 8 a.m. was 90 ng litre^{-1} (Hedner, Nordén and Valdemarsson, 1981). A solid phase radioimmunoassay was used to measure the plasma cortisol concentration (Clinical Assay, Mass., USA). The between-sample coefficient of variation was 11%. The normal values at 8 a.m. were 280–830 nmol litre^{-1}. Samples for metoprolol assay were collected in test tubes containing sodium heparin and analysed as described by Ervik (1975).

Samples were obtained on four occasions: (a) 5–15 min before the induction of anaesthesia; (b) during undisturbed anaesthesia—just before microlaryngoscopy; (c) after 15 min of microlaryngoscopy or, if the investigation had been completed by that time, at the end of microlaryngoscopy, and (d) 2–4 min after extubation of the trachea.

Statistics. The Mann–Whitney (two-sided) rank sum test for unpaired data was used for between-group comparisons. Changes in heart rate and arterial pressure in relation to resting values in the untreated patient were compared rather than the directly recorded values. This was in order to decrease the effects of interindividual variation. In contrast, absolute values for plasma concentrations were compared, since no control value was available in the untreated patient. Groups I and II (both receiving placebo) were treated as a single group until fentanyl was given. This group was compared with groups III and IV (both receiving metoprolol), similarly combined. The following between-group comparisons were made after fentanyl: I–II, I–III, II–IV, III–IV. The significance of changes within groups was analysed with the Wilcoxon (two-sided) rank sum test for paired data.

Probability values less than 0.05 (indicated * in tables) were considered to indicate statistical significance. Values less than 0.01 are indicated **.

RESULTS

The groups were similar in respect of age, sex, weight, drugs given and the duration of the procedure, except that patients given fentanyl (groups II and IV) required less suxamethonium during the microlaryngoscopy (table I).

Mean arterial pressure (MAP). Group means were similar in the resting patient before metoprolol or placebo (table II). Before anaesthesia, average MAP was 14 mm Hg less among those given metoprolol, than among the others (n.s.). The difference in mean values for minimum MAP during induction was 16 mm Hg ($P < 0.05$). The average value for maximum MAP at laryngoscopy and intubation was 29 mm Hg less in patients given metoprolol (groups III and IV) than among the others ($P < 0.01$).

Immediately before the microlaryngoscopy, with the patient still undisturbed, MAP was 37 mm Hg less ($P < 0.01$) among patients receiving metoprolol, but not fentanyl (group III), than among the controls (group I). The difference between these groups during microlaryngoscopy, was 21 mm Hg (n.s., table II). Group means for MAP after extubation of the trachea were 10–23 mm Hg less among patients given metoprolol, than among the others (table II).

TABLE II. *Mean arterial pressure (mm Hg) (group means ± 1SD). Values in the third column are minimum values observed after thiopentone injection, but before intubation, while the fourth column shows maximum values within 3 min after intubation. Values in the sixth column were obtained after 10 min of microlaryngoscopy (ML), or 2 min before the end of microlaryngoscopy, whichever came first. Statistical differences between groups are indicated. *P < 0.05; **P < 0.01. Thus, there was a significant difference between groups I and II immediately before and during microlaryngoscopy (P < 0.01), but no significant difference on the other occasions. The significance of changes within groups was not assessed*

Group		Rest, untreated	5 min before anaesth.	Min. at induction	Max. at intubation	Immediately before ML	ML	5 min after extubation
I	Placebo tablets and saline	106 ± 10	101 ± 27	95 ± 23	167 ± 37	126 ± 32 **	159 ± 38 **	114 ± 29
II	Placebo and fentanyl	107 ± 10	106 ± 16	90 ± 15 *	172 ± 17 **	78 ± 16 **	105 ± 31	127 ± 11 *
				(groups I + II v. III + IV)		(group I v. III)		(group II v. IV)
III	Metoprolol and saline	104 ± 14	91 ± 19	76 ± 19	142 ± 25	89 ± 26 *	138 ± 27 **	104 ± 21
IV	Metoprolol, fentanyl and naloxone	105 ± 12	89 ± 14	76 ± 12	138 ± 31	65 ± 20	84 ± 27	104 ± 12
		↑ Metoprolol 0.2 g, or placebo for 4 days				↑ Fentanyl 1.0 mg, or saline		↑ Naloxone 0.8 mg, or saline

Fentanyl markedly decreased MAP during undisturbed anaesthesia (third column, table II). The effect of fentanyl on MAP during microlaryngoscopy was pronounced. The effect of fentanyl was abolished after naloxone had been given and the trachea extubated.

Systolic arterial pressure (SAP). Mean values in the four groups were similar in the resting patient before metoprolol or placebo (table III). Before anaesthesia, mean SAP was 22 mm Hg less among subjects receiving metoprolol, than among the others (n.s.). The corresponding figure for the difference in mean values during induction was exactly the same (22 mm Hg, n.s.). The mean SAP at intubation was 33 mm Hg less among patients given metoprolol, than among the others ($P < 0.01$).

Metoprolol decreased SAP measured immediately before microlaryngoscopy, in the undisturbed patient. The difference in SAP during microlaryngoscopy, between patients receiving metoprolol but no fentanyl (group III), and the controls (group I) was 32 mm Hg (n.s.).

Fentanyl markedly decreased SAP both during undisturbed anaesthesia and during microlaryngoscopy. There was no significant difference between groups after endotracheal extubation.

Heart rate. Mean values of the four groups were similar before metoprolol or placebo (table IV).

TABLE III. *Systolic arterial pressure (mm Hg) (group means ± 1SD). For explanation, see table II*

Group		Rest, untreated	5 min before anaesth.	Min. at induction	Max. at intubation	Immediately before ML	ML	5 min after extubation
I	Placebo tablets and saline	149 ± 18	147 ± 32	124 ± 29	225 ± 65	169 ± 46 **	214 ± 51 **	156 ± 45
II	Placebo, fentanyl and naloxone	147 ± 17	149 ± 27	119 ± 26	219 ± 27 **	100 ± 18 *	137 ± 40	167 ± 21
					(groups I + II v. III + IV)	(group I v. III)		
III	Metoprolol and saline	142 + 24	130 + 29	101 + 29	184 + 33	120 + 36 **	182 + 31 **	144 + 33
IV	Metoprolol, fentanyl and naloxone	141 ± 20	124 ± 22	98 ± 18	177 ± 39	86 ± 26	107 ± 33	142 ± 17
		↑ Metoprolol 0.2 g, or placebo for 4 days				↑ Fentanyl 1.0 mg, or saline		↑ Naloxone 0.8 mg, or saline

TABLE IV. *Heart rate (beat min^{-1}) (mean ± 1SD). SD in all columns except the resting is SD of the change in relation to resting values. For explanation see table II*

Group		Rest, untreated	5 min before anaesth.	Induction	Intubation	Immediately before ML	During ML	5 min after extubation
I	Placebo tablets and saline	79±7	63±17	94±16	106±13	90±13	93±12	89±10
II	Placebo, fentanyl and naloxone	73±13	65±12	93±12	108±13	80±8	83±9	91±13
			** (groups I + II v. III + IV)	**	**	** (I v. III) * (II v. IV)	** (I v. III) ** (II v. IV)	* (I v. III) ** (II v. IV)
III	Metoprolol and saline	76±5	49±7	72±9	74±9	68±10	67±11	74±12
IV	Metoprolol, fentanyl and naloxone	76±12	50±7	77±11	82±10	68±10	69±10	71±11
			↑ Metoprolol 0.2 g for 4 days, or placebo	↑ Atropine 1.0 mg to all	↑ Fentanyl 1.0 mg, or saline		↑ Naloxone 0.8 mg, or saline	

Metoprolol decreased heart rate significantly before, during and after anaesthesia. The heart rates of patients given fentanyl and naloxone were not significantly different from values obtained from patients given saline instead.

Plasma adrenaline concentrations. Mean values were above the normal range in resting relaxed subjects (see Methods). Mean values decreased during anaesthesia, significantly so in most groups (table V), and increased again during microlaryngoscopy. The increase was less pronounced in patients given fentanyl (groups II and IV) than in the others. There was a significant increase in adrenaline concentration in group IV after naloxone had been given and the trachea extubated. There were no significant differences between patients given metoprolol, and those given placebo.

Plasma noradrenaline concentrations. Mean values were slightly greater than the normal range for resting relaxed subjects (see Methods). There was an initial slight decrease during anaesthesia in group IV (table VI). Mean values increased in all groups during microlaryngoscopy, with significantly greater values in patients receiving metoprolol but not fentanyl (group III) than in any of the other three groups ($P<0.05$ or 0.01; table V). Mean values decreased after extubation, but significantly so only in group III.

Plasma ACTH concentrations (table VII). Mean values increased greatly during microlaryngoscopy among patients given saline instead of fentanyl (groups I and III), and tended to decrease afterwards. Concentrations during microlaryngoscopy, among patients given fentanyl, were several times lower than in the other groups. There was a significant increase in group IV ($P<0.01$) after naloxone

TABLE V. *Plasma adrenaline concentrations (nmol litre^{-1}) (mean ± 1SD). Significant changes between successive stages, within each group, and differences, between groups, at a certain stage are indicated. *$P<0.05$, **$P<0.01$. As an example, mean concentrations in group II decreased from 0.41 to 0.12 between the first and second blood samples ($P<0.01$). There was a significant difference in concentration between groups III and IV immediately before and during ML ($P<0.05$). Otherwise, there were no significant differences between groups*

Group		5–15 min before anaesthesia		Immediately before ML		During ML		2 min after extubation
I	Placebo and saline	0.57±0.53		0.31±0.27	*	0.91±1.25		0.59±0.32
II	Placebo, fentanyl and naloxone	0.41±0.29	**	0.12±0.05		0.38±0.51		0.43±0.25
III	Metoprolol and saline	0.83±0.48	**	0.25±0.13	**	0.84±0.61		0.59±0.42
				*		*		
IV	Metoprolol, fentanyl and naloxone	0.67±0.45	**	0.14±0.12	**	0.32±0.24	**	1.01±0.78

TABLE VI. *Plasma noradrenaline concentrations, nmol litre^{-1} (mean ± 1SD). See table V for explanation*

Group		5–15 min before anaesthesia		Immediately before ML		During ML		2 min after extubation
I	Placebo and saline	2.0±0.9		2.3±0.8	*	4.0±1.8		3.2±1.8
II	Placebo, fentanyl and naloxone	2.0±0.7		2.2±0.9	**	3.5±1.8 * (group I *v.* III)		3.2±1.2
III	Metoprolol and saline	2.4±1.2		2.9±1.4	**	7.4±3.3 **	**	4.2±2.5
IV	Metoprolol, fentanyl and naloxone	2.5±1.2	*	2.1±1.0	**	3.1±2.1		2.7±1.3

TABLE VII. *Plasma ACTH concentrations (ng litre^{-1}) (mean ± 1SD). See table V for explanation*

Group		5–15 min before anaesthesia		Immediately before ML		During ML		2 min after extubation
I	Placebo tablets and saline	49±107		48±66	*	217±167 *		185±180
II	Placebo, fentanyl and naloxone	13±24	*	31±54		24±27		58±83
III	Metoprolol and saline	33±38		41±45	**	174±114 **	**	113±97
IV	Metoprolol, fentanyl and naloxone	14±41		18±40		23±46	**	74±81

and extubation of the trachea.

Plasma cortisol concentrations (table VIII). Mean values increased significantly during microlaryngoscopy, in the patients given saline instead of fentanyl (groups I and III). The increase was still evident after anaesthesia in group III. Concentrations during microlaryngoscopy were smaller in the patients given fentanyl. Also, plasma concentrations at this stage were lower in group III (metoprolol) than in group I (control) — a reverse relationship compared with the plasma noradrenaline concentrations.

Plasma metoprolol concentrations. Measurements in groups I and II showed that no patient received metoprolol by mistake. Mean values in groups III and IV were similar during all stages, so the results were pooled. The concentrations were 472±315 (mean±1SD; range 76–1100) nmol litre^{-1} before anaesthesia and 541±300, 551±331 and 574±349 nmol litre^{-1} in the three later samples, the smallest recorded value being 150 nmol litre^{-1}. As mentioned earlier, metoprolol 10 mg was given i.v. after the first sample. The second sample was taken some 10–15 min later.

DISCUSSION

The mean values and inter-individual variation for plasma metoprolol concentrations, obtained by us, agree with the findings of Johnsson and colleagues (1980) on the pharmacokinetics of metoprolol when administered in a slow-release form. Metoprolol 10 mg i.v. increased the plasma concentration only slightly. Rollason and Russell (1980), gave 0.06–0.17 mg kg^{-1} i.v. and Coleman and Jordan (1980) only 2–4 mg i.v. Presumably, these doses resulted in lower plasma concentrations. Nevertheless, these authors also found that metoprolol was effective in limiting tachycardia during anaesthesia.

Our results in regard to arterial pressure before anaesthesia are consistent with those of Haglund and Collste (1980) who found that metoprolol had decreased systolic/diastolic arterial pressures by 13/11 mm Hg by the 2nd day of treatment, with no further decrease in pressures during the next few months. Nevertheless, the finding by Trimarco and associates (1982), that peripheral vascular resistance continued to decrease for the first 2 years during the

TABLE VIII. *Plasma cortisol concentrations, nmol litre^{-1} (mean ± 1SD). See table V for explanation*

Group		5–15 min before anaesthesia	Immediately before ML		During ML		2 min after extubation
I	Placebo tablets and saline	246 ± 154	358 ± 231	**	702 ± 269 **		747 ± 279
II	Placebo, fentanyl and naloxone	148 ± 71	248 ± 158		284 ± 242 * (group I *v.* III)		324 ± 227
III	Metoprolol and saline	166 ± 51	227 ± 138	**	453 ± 190 *	*	744 ± 336 **
IV	Metoprolol, fentanyl and naloxone	148 ± 60	155 ± 72		220 ± 150		223 ± 155

treatment of hypertension with metoprolol, implies that the changes in arterial pressure during anaesthesia and microlaryngoscopy might have been different, had we pretreated the patients for longer.

Although the pretreatment with metoprolol decreased arterial pressure during intubation and during, and after, anaesthesia and microlaryngoscopy, the fluctuations in mean values of arterial pressure, during anaesthesia, were not greatly affected (fig. 1). In the latter respect, the present findings agree with those obtained after the injection i.v. of the β_1-selective adrenoceptor blocker practolol (Siedlecki, 1975; Werner et al., 1980). Similarly, Pontén and colleagues (1980) found that variations in arterial pressure, during anaesthesia and surgery, were not decreased by continuing, instead of withdrawing, β-blocking therapy.

In contrast, Prys-Roberts and colleagues (1973), studying hypertensive patients under halothane–nitrous oxide anaesthesia, found that both decreases and increases in arterial pressure were attenuated by practolol, whether acutely after injection i.v. or after 2 days of oral pretreatment. However, interpretation of that study is difficult because other antihypertensive drugs were given besides practolol and control patients were obtained retrospectively.

Arterial pressure increased markedly during intubation of the trachea and the increases observed were somewhat greater than those noted by Stoelting (1977). Possibly, this was because our patients were somewhat older and, in addition, the arterial pressures before anaesthesia were slightly greater. During the microlaryngoscopy arterial pressures were high in the patients anaesthetized with thiopentone and nitrous oxide only. Although metoprolol did decrease arterial pressure during the various phases of anaesthesia, fentanyl was more

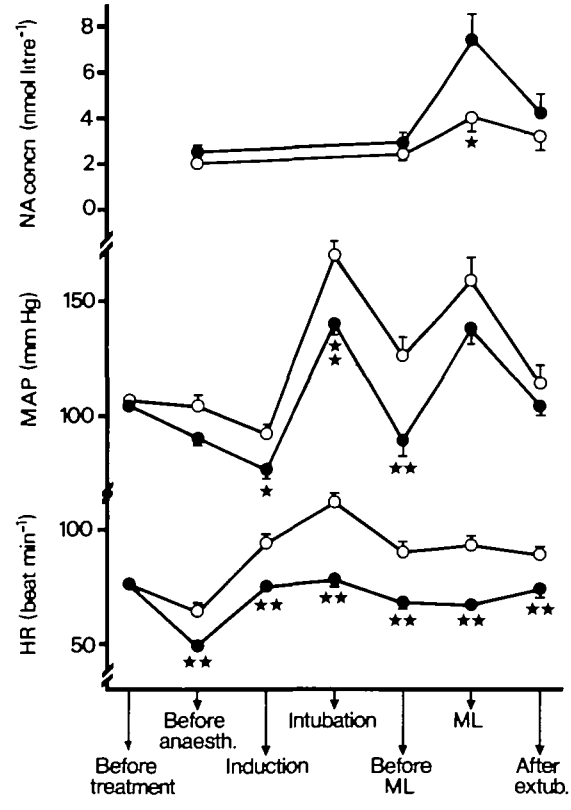

FIG. 1. Comparison of plasma noradrenaline (NA) concentrations, mean arterial pressures (MAP) and heart rates among patients receiving metoprolol (●) or placebo (○). Group mean and 1 SEM. (○) Represents pooled values for groups I and II during the first four stages, during which both groups were treated alike. Mean values of groups I and II were, in fact, similar on these occasions as is shown in tables II, III and V, which give a more detailed account of these results. Group II received fentanyl after intubation. Therefore, (○) represents only group I during the last three stages. Similarly, (●) represents groups III and IV during the first four stages, and group III only in the last three. Significant differences between patients given metoprolol, and those given placebo: $*P < 0.05$; and $**P < 0.01$.

effective. Therefore, we usually prefer to give fentanyl 0.5–0.8 mg for microlaryngoscopy, fentanyl 0.2–0.4 mg being given before the thiopentone to counteract any hypertension during intubation laryngoscopy. This does not provoke nausea or a circulatory "overshoot reaction" (Magnusson et al., 1982).

Although 20–35% of noradrenaline injected i.v. is removed in a single passage through the lungs (Fishman and Pietra, 1974), we preferred arterial sampling, to sampling from an arm vein, to avoid local factors which could have affected catecholamine concentrations. In view of the very marked arterial pressure response to microlaryngoscopy, in the patients not given fentanyl, it was only to be expected that plasma catecholamine concentrations would be high at this stage. What was remarkable was that the mean plasma noradrenaline concentrations, among patients given metoprolol but not fentanyl (group III), were almost twice those of the control patients (group I). Our findings in this respect are similar of those of Hansson and colleagues (1977). They found that increases in plasma noradrenaline concentration, in response to dynamic exercise, were greater during metoprolol medication than with placebo treatment. One possible explanation for these results is suggested by Esler and associates (1981), who reported that the removal of noradrenaline from plasma was slowed by β-blockade. Therefore, the difference in noradrenaline concentrations, between groups I and III, does not necessarily reflect a difference in overall sympathetic activity. Whatever the reasons for our findings, it is noteworthy that the plasma concentrations of noradrenaline during microlaryngoscopy were high and that direct circulatory effects can be expected (Hjemdahl et al., 1980). Measurements of peripheral vascular resistance in the different groups would have been of great interest in this context.

The pattern of ACTH concentrations was different from that of the catecholamines. The low mean ACTH concentrations, among patients given fentanyl, and the increase after naloxone may be explained by a direct inhibition of ACTH release by opiates (Volavka et al., 1979).

The cortisol concentrations are consistent with the ACTH concentrations, considering the fact that the cortisol response is more sluggish (Krieger, 1979). While cortisol concentrations during micro- (Dahlgren and Messeter, 1981). The effect of fentanyl is antagonized by naloxone after microlaryngoscopy were significantly greater in group I (placebo tablets, no fentanyl), than in group III (metoprolol, but no fentanyl), the reverse was true regarding noradrenaline. We cannot fully explain the discrepancy, but it certainly illustrates that changes in plasma concentrations of so called "stress hormones" must be interpreted with caution.

Our conclusion from the present study, and a previous one (Werner et al., 1980), is that it is preferable to use opiate analgesia to limit the stress response to microlaryngoscopy. We now seldom use β-blockade in patients not previously receiving such treatment.

ACKNOWLEDGEMENTS

Financial support was received from the Åke Wiberg foundation, Stockholm, and the Medical Faculty, University of Lund. Thanks are due to several members of the scientific staff at Hässle/Astra AB, Gothenburg, for valuable support and criticism. Mrs Britt-Marie Eriksson at the laboratory of Hässle/Astra deserves appreciation for performing the adrenaline and noradrenaline assays. Mrs Gunvor Ekdahl and Anders Beckman, R.N., provided excellent technical assistance.

REFERENCES

Coleman, A. J., and Jordan, C. (1980). Cardiovascular responses to anaesthesia. Influence of beta-adrenoreceptor blockade with metoprolol. *Anaesthesia*, 35, 972.

Conway, J., and Amery, A. (1975). The antihypertensive effect of propranolol and other β-adrenoceptor antagonists; in *Central Action of Drugs in the Regulation of Blood Pressure* (eds D. Davies and J. Reid), p. 277. London: Pitman Medical Publishing Co. Ltd.

Dahlgren, N., and Messeter, K. (1981). Treatment of stress response to laryngoscopy and intubation with fentanyl. *Anaesthesia*, 36, 1022.

Eriksson, B.M. (1981). Aluminium foil instead of glass plates for thin-layer chromatography in radioenzymic assay. *Clin. Chem.*, 27, 341.

Ervik, M. (1975). Quantitative determination of metoprolol in plasma and urine by gas chromatography. *Acta pharmacol. Toxicol. (Cph)*, 36 (Suppl. V), 136.

Esler, M., Jackman, G., Leonard, P., Skews, H., Bobik, A., and Jennings, G. (1981). Effect of propranolol on noradrenaline kinetics in patients with essential hypertension. *Br. J. Clin. Pharmacol.*, 12, 375.

Fishman, A., and Pietra, G. (1974). Handling of bioactive materials by the lung (second of two parts). *N. Engl. J. Med.*, 291, 953.

Haglund, K., and Collste, C. (1980). Time course of blood pressure, pulse rate, plasma renin and metoprolol during treatment of hypertensive patients. *Eur. J. Clin. Pharmacol.*, 17, 321.

Hansson, B.-G., Dymling, J.-F., Manhem, P., and Hökfelt, B. (1977). Long term treatment of moderate hypertension with the beta[1]-receptor blocking agent metoprolol. *Eur. J. Clin. Pharmacol.*, 11, 247.

Hedner, P., Nordén, N. E., and Valdermarsson, S. (1981). Falsely high values for corticotropin by the CIS-Sorin RIA method. *Clin. Chem.*, 27, 1146.

Hjemdahl, P., Pollare, T., Gillberg, M., and Åkerstedt, T. (1980). Concentration-effect relationships for infused catecholamines in man: Influence of propranolol and metoprolol. *Naunyn-Schmiedeberg's Arch. Pharmacol.*, 313, R60.

Johnsson, G., Jordö, L., Lundborg, P., Regårdh, C.-G., and Rönn, O. (1980). Plasma levels and pharmacological effects of metoprolol administered as controlled release (Durules) and ordinary tablets in healthy volunteers. *Int. J. Clin. Pharmacol., Ther. Toxicol.*, 18, 292.

Krieger, D. (1979). Plasma ACTH and corticosteroids; in *Endocrinology (volume 2)* (eds L. DeGroot, G. Cahill, L. Martini, D. Nelson, W. Odell, J. Potts and E. Steinberger), p. 1139. New York: Grune & Stratton.

Magnusson, J., Werner, O., Carlsson, C., and Pettersson, K. I. (1982). Narcotic antagonism by naloxone. Few side effects after a short procedure. *Anaesthesia*, (in press).

Peuler, J., and Johnson, G. (1977). Simultaneous single isotope radioenzymatic assay of plasma norepinephrine, epinephrine and dopamine. *Life Sci.*, 21, 625.

Pontén, J., Biber, B., Henriksson, B. Å., Hjalmarsson, Å., and Lundberg, D. (1980). β-receptor blockers and neuroleptanaesthesia; in *β-Blockade and Anaesthesia* (eds P. Poppers, B. van Dijk and A. van Elzakker), p. 172. Rijswijk, the Netherlands: Astra Pharmaceutika BV.

Prys-Roberts, C., Föex, P., Biro, G. P., and Roberts, J. G. (1973). Studies of anaesthesia in relation to hypertension. V: Adrenergic beta-receptor blockade. *Br. J. Anaesth.*, 45, 671.

Rollason, W. N., and Russell, J. G. (1980). Intravenous metoprolol and cardiac dysrythmias. An evaluation in the management of dysrythmias in outpatient dental anaesthesia. *Anaesthesia*, 35, 783.

Siedlecki, J. (1975). Disturbanoes in the function of cardiovascular system in patients following endotracheal intubation and attempts of their prevention by pharmacological blockade of sympathetic system. *Anesth. Resusc. Intens. Ther.*, 3, 107.

Stoelting, R. K. (1977). Circulatory changes during direct laryngoscopy and tracheal intubation. Influence of duration of laryngoscopy with or without prior lidocaine. *Anesthesiology*, 47, 381.

Trimarco, B., Wikstrand, J., Buzzetti, G., Ricciardelli, B., DeLuca, N., Volpe, M., and Condorelli, M. (1982). Regression of left ventricular hypertrophy and improvement of left ventricular function after long-term antihypertensive treatment with metoprolol. *Abstract, 9th Scientific Meeting of the International Society of Hypertension, Mexico City.*

Weigand, H. (1970). Über die Narkose bei der Mikrolaryngoskopie und endolaryngealen Mikrochirurgie. II. Das reflektorische Kreislaufverhalten und seine Beeinflussung durch Oberflächenanaesthetica. *Anaesthetist*, 19, 131.

Werner, O., Magnusson, J., Fletcher, R., Nilsson-Ehle, P., and Pahlm, O. (1980). I.v. practolol during microlaryngoscopy. Effect on arterial pressure, heart rate, blood glucose and lipolysis. *Br. J. Anaesth.*, 52, 91.

Volavka, J., Cho, D., Mallya, A., and Bauman, J. (1979). Naloxone increases ACTH and cortisol levels in man. *N. Engl. J. Med.*, 300, 1056.

REPONSES DU METOPROLOL, DU FENTANYL ET DU "STRESS" A LA MICROLARYNGOSCOPIE

Effets sur la tension artérielle, le rythme cardiaque et les concentrations de catécholamines, d'ACTH et de cortisol

RESUME

Quarante patients soumis à une microlaryngoscopie ont été anesthésiés au moyen de thiopentone et d'oxyde nitreux. Vingt d'entre eux ont pris 200 mg de métoprolol sous forme de comprimé retard une fois par jour pendant 4 jours jusqu'au matin de l'opération inclus, ainsi que 10 mg i.v. peu de temps avant l'induction de l'anesthésie. Aux autres patients, il a été administré des comprimés de placébo ainsi que des solutions physiologiques salines i.v. On a ensuite divisé par moitié ces deux groupes auxquels on a administré en cours d'anesthésie 1.0–1,5 mg de fentanyl dont l'effet a été antagonisé par de la naxolone en fin d'anesthésie. Les autres patients ont reçu une solution saline i.v. aux lieu et place du fentanyl ou de la naxolone. Le métoprolol a eu pour effet de faire baisser le rythme cardiaque et le niveau général de la tension artérielle pendant l'anesthésie, bien qu'il n'ait pas affecté les fluctuations de tension. Comparé au placébo, le métoprolol a eu pour effet d'accroître les concentrations dans le plasma de noradrénaline artérielle et inversement de faire baisser les concentrations de cortisol. Le fentanyl a fait descendre la tension artérielle et les concentrations d'ACTH et de cortisol dans le plasma, que le patient ait reçu ou non du métoprolol. Les concentrations de noradrénaline et d'adrénaline dans le plasma ont diminué sous l'effet du fentanyl chez les patients auxquels on avait administré du métoprolol.

METOPROLOL, FENTANYL UND STRESSREAKTIONEN AUF MIKROLARYNGOSKOPIE

Wirkung auf Blutdruck, Herzfrequenz und Plasmaspiegel von Katecholaminen, ACTH und Cortisol

ZUSAMMENFASSUNG

Vierzig Patienten wurden zur Mikrolaryngoskopie mit Thiopenton und Lachgas anästhetisiert. Zwanzig Patienten erhielten 200 mg Metoprolol in einer retard-Tablette vier präoperative Tage einmal täglich und am Morgen vor der Operation, außerdem 10 mg i.v. kurz vor der Narkoseeinleitung. Die anderen Patienten erhielten Placebo-Tabletten und physiologisches Kochsalz i.v. Beide Gruppen von je zwanzig Patienten wurden weiter unterteilt, wobei jeweils die Hälfte von ihnen während der Narkose 1,0–1,5 mg Fentanyl erhielt, dessen Wirkung bei Narkoseende durch Naloxon antagonisiert wurde. Die andere Hälfte erhielt Kochsalz i.v. anstelle von Fentanyl oder Naloxon. Metoprolol reduzierte während der Narkose die Herzfrequenz und die allgemeine Höhe des Blutdrucks, beeinflußte jedoch nicht die blutdruckschwankungen. Der arterielle Noradrenalin-Spiegel während der Mikrolaryngoskopie wurde durch Metoprolol verglichen mit dem Placebo erhöht, der Cortisol-Spiegel dagegen erniedrigt. Fentanyl verringerte den Plasma-ACTH-Spiegel, den Cortisol-Spiegel und den arteriellen Blutdruck, wobei vorhergehende Metoprololgabe keine Rolle spielte. Bei Patienten mit Metoprolol führte Fentanyl zu einer niedrigeren Plasma-Adrenalin- und Noradrenalinkonzentration.

RESPUESTAS DEL METOPROLOL, DEL FENTANILO Y DE DEPRESIÓN A LA MICROLARINGOSCOPIA

Efectos sobre la presión arterial, el ritmo cárdiaco y las concentraciones de catecolaminas, de ACTH y de cortisol

SUMARIO

Se administró una anestesia con tiopentona y óxido nitroso a cuarenta pacientes sometidos a microlaringoscopia. Se administró 200 mg de metoprolol a veinte pacientes en forma de pastilla a efecto remanente una vez al día durante 4 días hasta la mañana incluida de la operación y 10 mg i.v. poco antes la inducción de la anestesia. A los otros pacientes, se les administró pastillas de plácebo y solución salina fisiológica i.v. Ambos grupos de 20 pacientes fueron subdivididos una vez más, la mitad de los pacientes recibiendo 1,0–1,5 mg de fentanilo durante la anestesia, cuyo efecto fue antagonizado con naxolona al fin de la operación. Los demás pacientes recibieron solución salina i.v. en vez del fentanilo o de la naxolona. El metoprolol hizo bajar el ritmo cárdiaco y el nivel general de la presión arterial durante la anestesia, pero no afectó las fluctuaciones en la presión. Las concentraciones de noradrenalina en el plasma arterial durante la microlaringoscopia fueron realizadas por el metoprolol, en comparación con el plácebo, pero ocurrió el contrario para las concentraciones de cortisol. El fentanilo hizo bajar la presión arterial, el ACTH del plasma y las concentraciones de cortisol, independientemente del hecho que el paciente había recibido o no metoprolol. Las concentraciones de noradrenalina y de adrenalina en el plasma bajaron bajo el efecto del fentanilo en los pacientes que habían recibido metoprolol.