β -ADRENOCEPTOR BLOCKADE IN STRESS DUE TO ORAL SURGERY

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- 1 The effects of a single oral dose of 5 mg pindolol (P) and 100 mg metoprolol (M) were assessed in a double-blind study in 30 patients undergoing oral surgery.
- 2 Systolic and diastolic blood pressures and heart rate were reduced 90 min after oral medication and did not exceed initial values at rest during the procedure.
- 3 Noradrenaline, adrenaline and c-AMP concentrations did not differ at any time from the control values at rest after P, but were increased after local anaesthesia and during oral surgery after M as were the metabolic responses reflected by plasma concentrations of glucose and free-fatty acids.
- 4 Plasma levels of ACTH and cortisol showed the typical increase during the procedure, being independent of β -adrenoceptor blockade. In contrast to the cardioselective antagonist M, prophylactic administration of the non-selective drug P prevented the sympathetic and metabolic responses to the stress of oral surgery.
- 5 Hypothalamic and adrenal stimulation were not reduced by either selective or non-selective β -adrenoceptor blockade.

Introduction

During surgery sympathetic stimulation appears to play an important rôle in the aetiology of cardiovascular complications and particularly in sudden death in patients with coronary heart disease (Lown *et al.*, 1977). Numerous studies have revealed that the increases in systolic and diastolic blood pressures as well as increases in normal and arrhythmic heart rate are potentially dangerous in patients with cardiovascular risk factors. Even patients with no history of cardiac disease occasionally suffer severe complications when undergoing relatively minor surgery under local anaesthesia and presumably this reflects the presence of unsuspected heart disease. Not only the direct haemodynamic effects but also the secondary changes in myocardial metabolism resulting from sympathetic stimulation can lead to a deterioration of myocardial performance and are believed to be important in the initiation of cardiac complications (Opie, 1980). It may be of value therefore to pretreat patients with β -adrenoceptor antagonists in order to antagonize the harmful haemodynamic and metabolic responses to stress due to surgery under local anaesthesia (Machtens & Opitz, 1967).

In this study we have compared the effects of the β_1 -selective antagonist metoprolol and the non-selective β -adrenoceptor blocker pindolol on the sympathetically mediated haemodynamic and metabolic responses to stress due to oral surgery.

Methods

A controlled double-blind study was carried out in thirty patients undergoing oral surgery under local anaesthesia, all of whom had given their informed consent. Before surgery, after resting for a period of 30 min they received their oral medication (5 mg pindolol or 100 mg metoprolol) and remained in the sitting position for another 90 min. Plasma samples were taken and measurements of blood pressure and heart rate were performed at the end of the resting period (0), 90 min after oral medication (1), 5 min after local anaesthesia (2), 10 min after the beginning of surgery (3) and 30 min after the end of the procedure (4).

In all patients complicated dental extractions were performed. Blood loss was minimal and circulatory effects of adrenergic components given with local anaesthetics did not affect the results (Brisse, unpublished observations).

Fifteen patients were in each group; those who received pindolol (P) had an average age of 29.4 years (s.d. 11.9), seven were male, eight female and the duration of the oral surgery ranged from 15–50 min with a mean value of 30.3 min (s.d. 9.9). In the metoprolol (M) group the average age was 27.1 years (s.d. 10.0) seven were male, eight female and the duration of oral surgery lasted from

Table 1 Changes in systolic blood pressure during oral surgery after β -adrenoceptor blockade

Test period		Systolic blood pressure (mm Hg)			
		Pindolol (n = 15)		Metoprolol (n = 15)	
		mm Hg	Change from 0	mm Hg	Change from 0
0	Mean	126.7		124.9	
	s.d.	14.4		13.1	
1	Mean	112.3	-14.4	111.9	-13.0
	s.d.	12.2	13.5	13.3	17.1
			***		***
2	Mean	123.7	-3.1	119.0	-5.9
	s.d.	14.6	14.3	15.4	17.8
			NS		NS
3	Mean	130.2	+3.5	125.5	+0.7
	s.d.	12.4	12.7	11.7	13.7
			NS		NS
4	Mean	117.5	-9.2	110.2	-14.7
	s.d.	12.8	10.6	12.9	16.5
			*		***

Test period 0 at rest

1 90 min after 5 mg pindolol or 100 mg metoprolol

2 5 min after local anaesthesia

3 10 min after the beginning of oral surgery

4 30 min after the end of surgery

* $P < 0.05$; *** $P < 0.001$.

12–50 min with a mean value of 25.7 min (s.d. 11.5).

Noradrenaline and adrenaline plasma levels were determined by the radioenzymatic method of Passon & Peuler (1973), cortisol and ACTH by RIA (Beckman Instr./Frankfurt and IDW/Frankfurt), c-AMP by a radiochemical method (IDW/Frankfurt), glucose by the GOD-Perid-method (Boehringer/Mannheim) and free fatty acids by a photometric method (Dieterle *et al.*, 1968). Statistical evaluations were by the Mann-Whitney-test and the Wilcoxon-test for paired data (Sandoz/Nuernberg).

Results

The statistical evaluation showed, that both groups were comparable concerning age, sex distribution and the duration of the procedure. In all patients systolic and diastolic blood pressures were reduced 90 min after medication. After local anaesthesia only a slight increase was noted and 30 min after the end of the procedure both groups had systolic and diastolic blood pressure values similar to the resting values after medication (Tables 1 and 2).

Table 2 Changes of diastolic blood pressure during oral surgery after β -adrenoceptor blockade

Test period	Diastolic blood pressure (mm Hg)			
	Pindolol (n = 15)		Metoprolol (n = 15)	
	mm Hg	Change from 0	mm Hg	Change from 0
0	Mean	77.2	79.7	
	s.d.	8.2	6.7	
1	Mean	71.0	75.3	-4.4
	s.d.	8.5	9.4	8.5
		**		*
2	Mean	78.0	78.3	-1.3
	s.d.	8.6	7.9	8.1
		NS		NS
3	Mean	83.0	82.6	+2.9
	s.d.	10.5	8.5	8.0
		**		NS
4	Mean	75.2	74.9	-4.8
	s.d.	5.6	6.7	7.4
		NS		*

For details of test periods see Table 1.

* $P < 0.05$; ** $P < 0.01$.

Table 3 Changes of heart rate during oral surgery after β -adrenoceptor blockade

Test period	Heart rate (beats/min)				
	Pindolol (n = 15)		Metoprolol (n = 15)		
	beats/min	Change from 0	beats/min	Change from 0	
0	Mean	79.2	82.3		
	s.d.	10.1	10.3		
1	Mean	66.4	62.9	-19.3	
	s.d.	5.6	5.3	9.7	***
2	Mean	70.0	67.1	-15.2	
	s.d.	7.4	5.4	11.1	***
3	Mean	75.6	72.3	-9.9	
	s.d.	7.5	7.1	10.1	***
4	Mean	69.1	61.9	-20.4	
	s.d.	5.1	4.5	11.8	***

For details of test periods see Table 1.

*** $P < 0.001$.

Heart rate was within the normal range in all patients at rest. A significant decrease was noted at (1) 90 min after medication in both groups, but during the surgical procedure, heart rate was not significantly different from control values (0) after P, but after M during surgery (3) heart rate remained significantly lower than at time 0 (Table 3).

Noradrenaline concentration in plasma was not significantly changed during surgery after P, but after M it was increased after medication and during surgery (Table 4).

Adrenaline concentration in plasma remained constant after P. In contrast, there was a significant increase at (2) and (3) after M (Table 5).

c-AMP levels did not increase significantly during

surgery after P, but were diminished at test period 3 compared to test period 0; M did not prevent the stress-induced increase at (2) and (3), where a significant difference existed between the two groups (Table 6).

Glucose and free fatty acid concentrations in plasma remained constant during surgery after P. M only slightly inhibited the sympathetic glycolysis and lipolysis (Tables 7 and 8).

ACTH-levels in plasma were determined to assess hypothalamic and pituitary function. There was a large interindividual variation in the concentrations at any time, but during surgery (3) ACTH-levels significantly increased in both groups (Table 9).

Cortisol concentration in plasma can be regarded

Table 4 Changes in noradrenaline concentration in plasma during oral surgery after β -adrenoceptor blockade

Test period	Noradrenaline concentration in plasma (ng/l)				
	Pindolol (n = 15)		Metoprolol (n = 15)		
	ng/l	Change from 0	ng/l	Change from 0	
0	Mean	317.5	301.9		
	s.d.	114.8	121.5		
1	Mean	365.6	377.6	75.7	
	s.d.	129.3	310.9	254.6	*
2	Mean	342.1	401.4	99.5	
	s.d.	112.7	131.1	77.1	*
3	Mean	346.4	348.8	82.9	
	s.d.	127.8	181.5	178.6	*
4	Mean	334.9	309.9	8.0	
	s.d.	129.1	91.7	137.2	NS

For details of test periods see Table 1.

* $P < 0.05$.

Table 5 Changes in adrenaline concentration in plasma during oral surgery after β -adrenoceptor blockade

Test period		Adrenaline concentration in plasma (ng/l)			
		Pindolol (n=15)		Metoprolol (n=15)	
		ng/l	Change from 0	ng/l	Change from 0
0	Mean	135.2		101.1	
	s.d.	109.2		56.0	
1	Mean	121.2	-14.0	138.8	37.7
	s.d.	62.5	127.1	78.7	78.9
2	Mean	173.5	NS	223.1	NS
	s.d.	73.6	38.3	125.4	122.0
3	Mean	131.1	113.5	178.5	132.3
	s.d.	70.4	NS	100.2	***
4	Mean	143.7	-4.1	140.7	77.5
	s.d.	99.0	115.1	74.3	131.6
			NS		*
			8.5		39.7
			143.5		102.8
			NS		NS

For details of test periods see Table 1.

* $P < 0.05$; *** $P < 0.001$.

as a reference value of the adrenal response to pituitary stimulation. It was not inhibited by P or M. Significantly higher levels were measured at (2) to (4) in both groups, with a more rapid normalization after P and a significant difference between the 2 groups at (4) (Table 10).

Discussion

It is generally accepted that in patients with coronary heart disease stress can induce potentially dangerous haemodynamic and metabolic changes and that it should be possible to antagonize these responses by pretreatment with a β -adrenoceptor antagonist

(Bolte, 1979). The experimental model used in the present investigation, i.e. oral surgery under local anaesthesia, can be considered to represent a typical situation of psychic stress. The two antagonists tested differ in their pharmacological properties, metoprolol having a relative selectivity for β_1 -adrenoceptors and lacking intrinsic sympathomimetic activity while pindolol is a non-selective antagonist with pronounced intrinsic sympathomimetic activity (Prichard & Owen, 1980). The results reveal that although some common properties are apparent, in other respects the drugs differ markedly in terms of their influence on the haemodynamic and metabolic responses to psychic stress.

As reported by other authors, both metoprolol and

Table 6 c-AMP levels in plasma after β -adrenoceptor blockade; changes during oral surgery

Test period		Plasma c-AMP (pmol/ml)			
		Pindolol (n=15)		Metoprolol (n=15)	
		pmol/ml	Change from 0	pmol/ml	Change from 0
0	Mean	18.7		14.1	
	s.d.	10.2		9.8	
1	Mean	15.3	-3.5	14.5	0.3
	s.d.	8.6	6.8	6.5	9.8
2	Mean	16.1	NS	20.0	NS
	s.d.	9.3	-2.7	9.2	5.9
3	Mean	13.6	6.3	18.5	7.4
	s.d.	4.7	NS	6.6	**
4	Mean	15.1	-5.1	13.0	4.3
	s.d.	5.4	9.6	8.6	7.1
			*		*
			-3.7		-1.1
			10.0		4.9
			NS		NS

For details of test periods see Table 1.

* $P < 0.05$.

Table 7 Changes in glucose concentration in plasma during oral surgery after β -adrenoceptor blockade

Test period		Plasma glucose (mg%)			
		Pindolol (n = 15)		Metoprolol (n = 15)	
		mg%	Change from 0	mg%	Change from 0
0	Mean	128.1		122.1	
	s.d.	37.4		36.3	
1	Mean	134.4	6.3	132.3	10.1
	s.d.	31.5	24.7	45.2	44.5
2	Mean	130.9	NS		NS
	s.d.	27.2	2.8	137.5	15.3
3	Mean	129.7	27.2	44.7	48.8
	s.d.	32.6	NS		NS
4	Mean	134.3	1.6	165.7	43.5
	s.d.	48.9	21.3	39.8	43.7
			NS		NS
			6.2	123.0	0.9
			37.3	40.6	46.1
			NS		NS

For details of test periods see Table 1.

pindolol produced a reduction of 10–20% in resting systolic blood pressure and inhibited the increase in pressure in response to surgery (Stumpe, 1979).

Metoprolol produced a fall in resting heart rate and throughout the experimental period heart rate remained significantly below pretreatment levels. Pindolol treatment produced a less marked fall in heart rate and during the surgical intervention (3) this was not significantly different from the pretreatment values. The absence of marked reductions in heart rate following pindolol administration is a reflection of the pronounced ISA of the drug. Although the potential benefits conferred on a β -adrenoceptor blocker by ISA have been frequently discussed it is only relatively recently that the practical clinical benefits

of this property have become recognized (Frishman, 1980). The results suggest that in patients with low heart rates such as are often encountered in coronary artery disease, prophylactic treatment with a β -adrenoceptor blocker endowed with a clinically relevant degree of ISA may be preferable before exposure to stressful interventions.

In contrast to metoprolol, which did not abolish the stress-induced increases in plasma catecholamines, after pindolol treatment plasma levels of adrenaline and noradrenaline did not exceed the pretreatment values at any time during the procedure. The precise mechanism of this effect remains unclear. It is possible that pindolol reduces the release of catecholamines from the sympathetic nerve ending.

Table 8 Free fatty acids in plasma; changes during oral surgery after β -adrenoceptor blockade

Test period		Plasma free fatty acids (nmol/ml)			
		Pindolol (n = 15)		Metoprolol (n = 15)	
		nmol/ml	Change from 0	nmol/ml	Change from 0
0	Mean	377.4		296.1	
	s.d.	161.0		107.2	
1	Mean	353.6	–23.8	311.6	15.5
	s.d.	167.4	79.7	120.8	63.9
2	Mean	360.4	NS		NS
	s.d.	187.6	–17.0	380.1	84.0
3	Mean	358.6	128.5	160.1	138.7
	s.d.	157.4	NS		**
4	Mean	356.4	–18.8	436.8	140.7
	s.d.	153.4	118.2	151.9	100.9
			NS		***
			–21.0	392.0	95.9
			107.0	124.5	110.0
			NS		***

For details of test periods see Table 1.

** $P < 0.01$; *** $P < 0.001$.

Table 9 ACTH-level in plasma during oral surgery after β -adrenoceptor blockade

Test period		Plasma ACTH-level (pg/ml)			
		Pindolol (n = 15)		Metoprolol (n = 15)	
		pg/ml	Change from 0	pg/ml	Change from 0
0	Mean	45.5		28.3	
	s.d.	34.0		27.5	
1	Mean	60.0	14.5	41.3	12.9
	s.d.	53.7	46.6	42.0	48.7
2			NS		NS
	Mean	70.9	25.3	61.7	33.4
	s.d.	40.2	34.4	49.8	53.0
			NS		*
3	Mean	76.5	30.9	88.5	60.1
	s.d.	35.5	32.2	80.6	90.3
4			*		***
	Mean	68.7	23.2	57.1	28.8
	s.d.	44.5	31.6	63.7	71.9
			NS		*

For details of test periods see Table 1.

* $P < 0.05$; *** $P < 0.001$.

Alternatively, recent studies (Clutter *et al.*, 1980) suggest that the mild receptor stimulation produced by a β -adrenoceptor blocker such as pindolol with a pronounced ISA may lead to an increase in catecholamine clearance and this could be the underlying mechanism involved in the reduction in catecholamine levels after the drug. Whatever the mechanism, the results presented here are in agreement with those of other authors (Brecht *et al.*, 1976) who reported a reduction in plasma catecholamine levels during long term antihypertensive therapy with pindolol.

c-AMP is known to be a mediator of the cellular responses to β -adrenoceptor stimulation and changes in the plasma concentrations of c-AMP may be taken

as a reflection of peripheral β_2 -adrenoceptor stimulation (Brisse *et al.*, 1979; Wagner *et al.*, 1979).

Following administration of the non-selective blocker pindolol no stress-induced increases in plasma c-AMP levels occurred and this was paralleled by the absence of increases in plasma concentrations of glucose and free fatty acids. Pindolol exerted no effect on resting plasma glucose concentrations but inhibited the increase in response to stress. In contrast, after treatment with metoprolol which exerts a selective action on β_1 -adrenoceptors, the metabolic responses to stress were largely uninhibited and plasma levels of glucose, free fatty acids and c-AMP were increased. These findings correlate with the observed changes in plasma catecholamine concentrations and

Table 10 Cortisol concentration in plasma during oral surgery after β -adrenoceptor blockade

Test period		Plasma cortisol ($\mu\text{g}\%$)			
		Pindolol (n = 15)		Metoprolol (n = 15)	
		$\mu\text{g}\%$	Change from 0	$\mu\text{g}\%$	Change from 0
0	Mean	21.5		27.3	
	s.d.	9.6		9.8	
1	Mean	23.1	1.6	31.3	4.0
	s.d.	10.5	7.6	10.7	9.2
2			NS		NS
	Mean	32.9	11.5	35.9	8.7
	s.d.	21.3	15.7	13.4	9.8
			***		**
3	Mean	37.3	15.9	45.9	18.6
	s.d.	19.7	13.1	14.0	13.0
4			***		***
	Mean	28.1	6.6	45.3	18.1
	s.d.	12.7	10.1	17.8	17.2
			*		***

For details of test periods see Table 1.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

are in good agreement with the results reported by other investigators (Harms *et al.*, 1978). The results indicate that, when administered at selective doses, cardioselective antagonists are ineffective in inhibiting the metabolic responses to stress. This difference between the two drugs may be of particular clinical relevance in patients suffering from coronary artery disease since it is known that changes in myocardial metabolism resulting from peripheral β_2 -

adrenoceptor stimulation may have an unfavourable influence on myocardial oxygen consumption (Opie, 1980).

The hypothalamic and adrenocortical responses to stress as reflected by changes in plasma levels of ACTH and cortisol (Brisse *et al.*, 1980) were uninfluenced by pretreatment with either of the β -adrenoceptor antagonists investigated.

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