Effects of nifedipine on the peri-operative ECG, as determined by continuous Holter monitoring

A double-blind study

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Summary

A double-blind study was performed on 50 elderly patients undergoing hip-replacement surgery under general anaesthesia; 26 were given nifedipine and the remaining 24 placebo to determine effects on the continuously monitored (Holter) ECG during the 4 peri-operative days. Drugs were only administered during the latter 3 days of the observation period. Surgery was performed on the morning of the 3rd day.

A striking feature was the high incidence of arrhythmias in both groups of patients, a finding previously documented in both 'normal' and elderly people. A decrease in ST-segment changes was expected in the nifedipine-treated patients. An unexpected finding, therefore, was the lack of protection against cardiac ischaemic changes in the nifedipine-treated patients compared with the placebo patients.

Interpretation of the ST segment as seen in the Holter-monitored ECG remains controversial. We have no clear explanation for the lack of protection against ischaemic changes. The effects of profound vasodilatation produced by nifedipine in elderly patients subjected to major surgery, general anaesthesia including administration of enflurane, and a variable amount of blood loss in the postoperative period may be important factors. In conclusion, one should perhaps be cautious of nifedipine administration under these circumstances.

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Over the last 2 decades ambulatory electrocardiography has become an important tool in clinical cardiology. Continuous ECG monitoring of active subjects has evolved from early work by Holter.[1] Despite initial enthusiasm for the use of ambulatory cardiography in the diagnosis of ischaemia, practical and theoretical limitations of early recording and analysis equipment were stressed by Hinkle *et al.*[2] The advantage of 24-hour continuous ECG monitoring was demonstrated by Lopes *et al.*;[3] improved apparatus can record for 48 hours,[4] but for practical purposes 24-hour monitoring of ambulatory patients is that most widely used.

In the present study it was decided to evaluate the electrophysiological effects of nifedipine on the heart in a double-blind trial on elderly patients scheduled for total hip replacement under general anaesthesia. The patients were continuously monitored by Holter ECG for the 4 peri-operative days, including during the operation. The 1st day served as a control period and from the 2nd day onwards either nifedipine or placebo was administered sublingually.

Patients and methods

A double-blind study was performed on 50 patients, 37 females and 13 males with a mean age of 72 years (range 63 - 84 years). All these patients were comparable from a cardiovascular point of view (Table I). One patient in each group was receiving digoxin, although there was no clinical evidence of cardiac failure at the pre-operative visit. Twenty-six patients received oral nifedipine 10 mg 8-hourly for the latter 3 péri-operative days (surgery was performed on the morning of the 3rd day); 24 patients received a placebo and served as controls. The observation period was divided into four time intervals with subdivisions as follows: time interval I = the first 24 hours — no drug administration; time interval II = the second 24 hours — placebo or nifedipine commenced and administered until end of trial; time interval III = the third 24 hours (a — operation, b — 6 hours postoperatively, c — remainder of 24 hours); and time interval IV = the fourth 24 hours.

TABLE I. INCIDENCE OF CARDIOVASCULAR DISEASE IN EACH GROUP

	Placebo ($N = 24$)	Nifedipine ($N = 26$)
Hypertension	**11**	**13**
Antihypertensives	**0**	**4**
Diuretics	**3**	**2**
Both	**6**	**6**
Digitalis	**1**	**1**
No treatment	**1**	**0**
Angina	**1**	**1**
Vasodilators	**1**	**0**
Combined treatment	**0**	**1**
Atrial fibrillation	**0**	**1**
Heart blocks	**5**	**6**
Aortic stenosis	**0**	**0**

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Anaesthetic management

Patients were given premedication with pethidine hydrochloride and promethazine hydrochloride, the former alone being favoured for older patients. All patients were pre-oxygenated. Anaesthesia was induced with etomidate 0,15 - 0,2 mg/kg followed by pancuronium 0,1 mg/kg. The patients were ventilated with a fractional inspired oxygen concentration (Fio_2) of 0,4 in nitrous oxide. The trachea was intubated with a No. 8 or 9 cuffed endotracheal tube. Appropriate doses of fentanyl (0,1 - 0,2 mg) and a low concentration of enflurane (< 1,0%) were used for maintenance of anaesthesia. A Bird MK II-Ventviva combination in a closed circuit, incorporating a warm-water humidifier, was used for ventilation. At the end of the operation curarization was reversed with atropine and prostigmine.

The mean anaesthetic and operative times for the nifedipine group were 163 ± 6 minutes and 112 ± 4 minutes respectively. For the control group the times were 160 ± 5 minutes and 111 ± 5 minutes respectively. Postoperatively the patients were exposed to an Fio_2 of 0,4 for 24 hours using a face mask. The blood pressure and pulse rate were meticulously observed. All anaesthetics were administered by one of us (H. J. du T).

During the operation arterial pressure, central venous pressure (CVP), expiratory carbon dioxide concentration, ECG, inspired oxygen concentration, oesophageal temperature, blood gases and electrolytes were monitored; all were within the normal range. The mean intra-operative blood loss in the nifedipine- and placebo-treated patients was comparable (852 ± 52 ml and 819 ± 57 ml respectively).

Because of the vasodilatation produced by nifedipine and the methylmethacrylate (bone cement)[5] used, CVP monitoring was mandatory to prevent a fall in blood volume. CVP readings were kept at about 15 cm H_2O throughout the operation by the infusion of crystalloid solutions or blood.

Holter recordings

After careful skin preparation, five disposable electrodes were used to attach the leads to the chest. Two bipolar monitoring leads were used, i.e. V5 and aVF. With these two leads both anterolateral and inferior ST-segment changes could be observed.[6] Oxford Medilog 4-24 AM recorders were used. These recorders were updated to MR-14 models with a frequency response of 0,08 - 70 Hz in order to register more reliable ST-segment changes than obtainable with the standard recorders. The Oxford Replay Unit was used for playing back the tapes. The final analysis was carried out by H.F.H.W., H.W. and J.Z.P.

Results

Table II shows the overall incidence of ECG changes on Holter recordings in each of the patient groups. Results for different types of abnormalities will be analysed. Table III represents the incidence of the various types of heart block occurring during the pre-operative, operative and postoperative periods for both groups. Nifedipine did not alter the incidence of heartblock. In Table IV the spectrum of ventricular arrhythmias in both the nifedipine- and placebo-treated patients is shown. Nifedipine had neither beneficial nor deleterious effects on the spectrum of ventricular arrhythmias. The incidence of ST-segment changes in both groups of patients is shown in Table V. The expected beneficial effect of nifedipine on ST-segment elevation or depression was not encountered.

TABLE III. INCIDENCE OF HEART BLOCKS IN EACH GROUP

	Placebo ($N = 24$)		Nifedipine ($N = 26$)	
	Pre-op.	Op. and postop.	Pre-op.	Op. and postop.
LBBB	0	0	2	2
LBBB and 1° AV	0	0	2	2
RBBB	0	0	1	1
RBBB and 1° AV	0	0	1	1
1° AV	5	5	0	0
1° AV and Int. 2:1	0	0	0	0
Int. 2:1	0	1	0	0
Total	5	6	6	6

LBBB = left bundle-branch block; 1° AV = first degree atrioventricular block; RBBB = right bundle-branch block; Int. 2:1 = intermittent 2:1 atrioventricular block; Pre-op. = pre-operatively; Op. and Postop. = intra-operatively and postoperatively.

Discussion

Cardiovascular effects of nifedipine

Nifedipine causes dilatation of virtually all arterial beds with the coronary, cerebral and skeletal systems being the most sensitive.[7] Effects on veins are less well characterized.[8-10] In *in vitro* studies nifedipine exerts negative inotropic and chronotropic effects on the heart.[11-13] In *in vivo* experiments in animal and man the effects of nifedipine on the heart are those of positive chronotropism and inotropism. This disparity between the *in vitro* and *in vivo* results has led to the idea that the cardiac actions of nifedipine observed in animal and man are baroreceptor reflex-mediated in response to the decrease in total peripheral resistance.[11,12,14,15] However, despite the increase

TABLE II. INCIDENCE OF ECG CHANGES ON HOLTER RECORDINGS IN EACH GROUP

Time intervals	Group	Sinus tachy. > 120/min	Sinus brady. < 50/min	PAT > 120/min	PVC	ST↓ 2 - 5 mm	ST↓ > 5 mm	ST↑ 2 - 5 mm	ST↑ > 5 mm
I	P	2	6	5	12	1	0	1	0
	N	5	3	7	16	3	0	2	1
II	P	3	2	4	12	0	0	0	1
	N	1	2	7	13	2	0	2	1
IIIa	P	2	4	1	9	1	0	2	0
	N	2	3	3	11	5	0	2	1
IIIb	P	2	3	3	6	0	0	1	0
	N	1	2	2	12	3	0	1	0
IIIc	P	2	0	3	3	1	0	1	0
	N	0	0	5	5	4	0	2	0
IV	P	4	0	5	10	2	0	1	0
	N	2	1	9	13	2	1	1	0

Tachy. = tachycardia; brady. = bradycardia; PAT = paroxysmal atrial tachycardia; PVC = premature ventricular contractions; ST↓ = ST-segment depression; ST↑ = ST-segment elevation; P = placebo; N = nifedipine.

TABLE IV. SPECTRUM OF VENTRICULAR ARRHYTHMIAS IN EACH GROUP*

Time intervals	Group	< 30 PVC/h (Lown I)	> 30 PVC/h (Lown II)	Multiform (Lown III)	Coupling (Lown IVa)	VT (Lown IVb)	R on T (Lown V)	Bigeminy	Trigeminy	Total episodes
I	P	8	1	0	2	1	0	4	0	16
	N	6	2	3	2	2	1	3	4	23
II	P	8	0	0	3	1	0	1	1	14
	N	8	0	0	3	2	0	2	3	18
IIIa	P	5	1	0	2	1	0	1	2	12
	N	6	1	0	3	1	0	1	1	13
IIIb	P	2	1	2	1	0	0	0	0	6
	N	4	1	4	3	0	0	5	0	17
IIIc	P	1	0	0	2	0	0	1	1	5
	N	1	2	0	1	1	1	0	1	7
IV	P	6	0	0	3	1	0	1	3	14
	N	6	2	1	1	3	1	2	1	17
Total	P	30	3	2	13	4	0	8	7	67
	N	31	8	8	13	9	3	13	10	95

*Thirty-nine patients were involved, 20 in the placebo (P) group and 19 in the nifedipine (N) group.
PVC = premature ventricular contractions; VT = ventricular tachycardia.

TABLE V. INCIDENCE OF ST-SEGMENT CHANGES IN BOTH GROUPS

Time intervals	Group	ST↓ 2-3 mm	ST↓ 4-5 mm	ST↓ > 5 mm	ST↓ Total	ST↑ 2-3 mm	ST↑ 4-5 mm	ST↑ > 5 mm	ST↑ Total
I	P	1	0	0	1	0	1	0	1
	N	3	0	0	3	2	0	1	3
II	P	0	0	0	0	0	0	1	1
	N	2	0	0	2	2	0	1	3
IIIa	P	1	0	0	1	0	2	0	2
	N	2	3	0	5	1	1	1	3
IIIb	P	0	0	0	0	0	1	0	1
	N	3	0	0	3	1	0	0	1
IIIc	P	0	1	0	1	0	1	0	1
	N	4	0	0	4	1	1	0	2
IV	P	2	0	0	2	0	1	0	1
	N	2	0	1	3	0	1	0	1
Total	P	4	1	0	5	0	6	1	7
	N	16	3	1	20	7	3	3	13

ST↓ = ST-segment depression (12 patients were involved, 4 in the placebo (P) group and 8 in the nifedipine (N) group);
ST↑ = ST-segment elevation (6 patients were involved, 2 in the P group and 4 in the N group).

in cardiac function demonstrated in animal and man, the reduction in afterload, with a possible direct drug effect, causes a net reduction in myocardial oxygen demand.[11,15–17]

The ECG of the elderly person

Table VI lists some of the arrhythmias observed in elderly patients by Glasser *et al.*,[18] Camm *et al.*[19] and Gomes *et al.*[20] Our figures were derived from all patients during the 24-hour control period (no drugs were administered). The high incidence of arrhythmias in 'normal' elderly patients indicates that care should be taken when analysing results, especially when trial drugs are involved.

Ventricular arrhythmias

Ventricular arrhythmias are common in young healthy persons with no heart disease;[21] the prevalence increases with age and also in persons with heart disease.[22] Cohen *et al.*[23] have demonstrated in *in vitro* experiments that nifedipine has a minor effect on cardiac conductive tissue, hence the finding that nifedipine did not influence the incidence of conduction disturbances in our patients (Table III) was not unexpected.

Holter monitoring for the detection of myocardial ischaemia

Bragg-Remschel *et al.*[24] examined the reproducibility of a standard ST-segment shift using equipment from eight manufacturers, and concluded that although some manufacturers' equipment faithfully reproduced simulated ST-segment depression, others did not. More recently, improvements in tape-replay techniques have greatly increased the reliability of ST-segment analysis.[25–27] Using Avionics (Model 350 E and 400) tape-recorders Stern *et al.*[28] found good correlation between ambulatory ECG monitoring and coronary arteriograms and concluded that Holter monitoring was a reliable tool for

TABLE VI. COMPARATIVE INCIDENCES OF ARRHYTHMIAS IN ELDERLY SUBJECTS

	Age of patients (yrs)	No. of patients	% PAT	% VPC > 30/h	% Multi.	% Coupling	% VT	% Bigem.
Glasser *et al.*[18]	**60-84**	**13**	**54**	**15**	**77 (no distinction made in these arrhythmias)**			
Camm *et al.*[19]	**± 75**	**106**	**3**	**26**	**22**	**6**	**4**	**5**
Gomes *et al.*[20]	**60 ± 10**	**73**	**—**	**—**	**8,2**	**4,1**	**50,7**	**—**
Present study	**63-84**	**50**	**24**	**10**	**16**	**14**	**4**	**8**

PAT = paroxysmal atrial tachycardia; VPC = ventricular premature contractions; Multi. = multiform; VT = ventricular tachycardia; Bigem. = bigeminy.

diagnosing ischaemic heart disease provided the correct equipment was used.

Review of the current literature suggests that asymptomatic ST-segment deviation (elevation and depression) must be accepted as due to myocardial ischaemia until proved to the contrary.[29,30] Cohn[31,32] attributes this finding to a 'defective anginal warning system' that might reflect 'silent myocardial ischaemia', and this is more likely to be present with increasing age.

Analysis of ST-segment deviation in our study highlighted some interesting facts. The anticipated decrease in ST-segment depression or elevation was not achieved by the administration of nifedipine (Table V). Although the data in Table V cannot be subjected to rigid statistical analysis, certain trends do become apparent. It will be noticed that there is a 3:1 ratio in the incidence of ST-segment shifts in the patients allocated to the nifedipine and placebo groups respectively during the first 24 hours of no drug administration (time interval I). Summation of the incidence of ST-segment depression at the completion of the trial demonstrated a ratio of 20:5 in the nifedipine and placebo groups respectively, while the incidence of ST-segment elevation occurred in a ratio of 13:7. When the individual time intervals are analysed it becomes quite clear that the nifedipine group experienced a higher incidence of ST-segment deviation than the placebo group. An exception in this trend was observed with 4 - 5 mm ST-segment elevation, where this ratio was 3:6. Furthermore, nifedipine did not decrease the degree of ST-segment depression or elevation. In fact, during the operative period (time interval IIIa in Table V) the incidence of ST-segment depression was in a ratio of 5:1 in the nifedipine and placebo groups respectively. If it is accepted that both ST-segment depression and elevation may reflect 'silent myocardial ischaemia', it becomes justifiable to pool the patients. In that case it is possible to pool the data and conclude as follows: total number of ST deviations — 45; number of ST deviations with placebo — 12; and number of ST deviations with nifedipine — 33.

Utilizing a chi-square test gives a highly significant result ($P < 0{,}005$), indicating that under conditions of total hip replacement with general anaesthesia including enflurane, patients who receive nifedipine have a much higher incidence of ST-segment deviation than the placebo group.

Conclusion

The results of the trial are enlightening. Nifedipine did not afford the protection, with reference to ST-segment changes, that was expected; on the contrary, patients given nifedipine had a statistically significant increase in ST-segment deviation over the placebo group. As there is no previous reference to the use of nifedipine with extensive ECG monitoring during enflurane anaesthesia, the possibility exists that this inhalational anaesthetic agent with its cardiodepressant effects[33] combined with nifedipine therapy may be responsible for our results.

The summary of Kates and Kaplan[34] on the haemodynamic interactions of calcium blockers and inhalational anaesthetic agents is very apt: 'Like the channel blocking drugs, the net hemodynamic effects of the anesthetic agents in the intact animal and humans are a complex interaction of the direct tissue effects and the consequences of drug-induced changes in preload, afterload, cardiac rhythm and the autonomic tone on the cardiovascular system.'

Our results indicate that enflurane and nifedipine are not incompatible when major surgery is performed, but there is an indication for caution in the handling of patients receiving these agents.

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A new povidone-iodine cream for the treatment of burns

Comparison with a standard topical regimen

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Summary

A remarkable improvement in the rate of burn healing has been achieved with a mixture of povidone-iodine ointment (Betadine) and malic, benzoic and salicylic acids (MBS) (Aserbine). A study was undertaken to compare the effects of a new povidone-iodine formulation (Betadine cream) with and without MBS with povidone-iodine ointment plus MBS. All preparations were easy to apply and were readily removed, causing only mild discomfort on application in the majority of cases.

A significant difference in healing times was observed between povidone-iodine cream and povidone-iodine cream plus MBS. There was also a significant difference in the decrease in the number of positive bacterial cultures between these two treatments. This applied to both superficial and deep burns. No skin sensitivity reactions were reported with any of the preparations.

The addition of MBS to povidone-iodine cream did not produce as significant an improvement in results as its addition to povidone-iodine ointment.

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Much progress has been made in the last 15 years in the management of patients with burns, especially in the treatment of shock. Infection caused by the proliferation of pathogenic organisms, chiefly bacteria and fungi, is the foremost problem in treatment. It is important, therefore, to search for locally applicable preparations capable of effectively disinfecting the surface of the burnt area. The principal requirements of such a preparation are that it is non-irritant, easily applied (i.e. spreads well) and is without effect on acid-base balance.