A comparison of the efficacy of sotalol and nadolol in the suppression of ventricular ectopic beats

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Summary

The anti-arrhythmic efficacy of sotalol, a ß-blocking agent which possesses class III anti-arrhythmic properties, was compared with that of nadolol. Nadolol, like sotalol, is non-cardioselective, is water-soluble, has no first-pass effect, is excreted unchanged in the urine, has a comparatively long half-life requiring only once-daily dosage, and has no intrinsic sympathomimetic activity and no membrane-stabilizing action. Twenty-two patients with stable chronic ventricular arrhythmias after myocardial infarction were studied; to qualify for entry they had to exhibit a minimum frequency of 30 ventricular ectopic beats per hour over a 24-hour Holter monitoring period. The study was of single-blind, cross-over format with placebo periods before active drug administration and during the cross-over periods. Nadolol 80 and 160 mg and sotalol 160 and 320 mg were administered for 7-day periods. Routine laboratory tests were performed and serum drug concentrations measured at regular intervals. Both drugs at all dosages suppressed ventricular ectopic beats significantly ($P < 0{,}001$). No statistically significant prolongation of the QTc interval could be demonstrated with either drug. Side-effects were negligible.

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Administration of various ß-adrenergic receptor blocking agents will suppress ventricular ectopic activity in many patients.[1-5] Propranolol effectively controlled ventricular arrhythmias (i.e. 70 - 100% reduction in ectopic beat frequency) in 24 of 32 patients with high-frequency ventricular arrhythmias in a placebo-controlled trial.[1] The finding that the anti-arrhythmic effect in many patients required plasma concentrations greater than those producing substantial ß-adrenergic blockade raised the question whether blockade of cardiac ß-receptors can directly account for all the anti-arrhythmic actions of propranolol.[1] Winkle *et al.*[2] compared the anti-arrhythmic efficacy of propranolol, procainamide and quinidine in a group of patients with frequent ventricular ectopic complexes. In this group 48% of ventricular ectopic beats (VEBs) were suppressed by propranolol 240 mg daily. On an average dose of 160 mg propranolol daily, Koppes *et al.*[3] demonstrated a 61% decrease in VEB frequency in 32 patients 2 months after acute myocardial infarction. In a short-term study, acebutolol, a relatively cardioselective ß-adrenergic blocking agent, also demonstrated ventricular anti-arrhythmic properties.[4]

The anti-arrhythmic efficacy of sotalol, a ß-blocking agent which supposedly also possesses class III anti-arrhythmic properties,[5] was evaluated in 20 patients with frequent VEBs.[6] On a double-blind cross-over regimen, an overall reduction in VEB frequency of 67% was noted. During the open-phase titration period the overall reduction in VEB frequency varied between 50% and 82%.[6] These results are superior to those obtained with other ß-blocking agents. Confirmation of these additional beneficial properties of sotalol, over and above ß-blockade, needed to be established. The purpose of our study was to compare the anti-arrhythmic efficacy of sotalol with that of a ß-blocking agent with similar pharmacokinetic and pharmacological properties. Nadolol, like sotalol, is non-cardioselective, is water-soluble, has no first-pass effect, is excreted unchanged in the urine, has a comparatively long half-life necessitating only once-daily dosage, and has no intrinsic sympathomimetic activity and no membrane-stabilizing action.[7]

Patients and methods

Twenty-two patients participated in the study; all had given informed, signed consent. All had suffered one or more acute myocardial infarctions at least 3 months prior to the study, and all exhibited stable chronic ventricular arrhythmias. The frequency of VEBs had been 30 or more per hour during a 24-hour monitoring period (Table I). The following criteria were used to exclude patients: age more than 70 years, unstable concurrent illness, current therapy with digitalis, other ß-blocking agents and anti-arrhythmic agents, electrolyte disturbance, sick sinus syndrome, atrial fibrillation or flutter, second-degree atrioventricular block, unstable angina, chronic obstructive airways disease, and a history of asthma.

On the first day a clinical history was obtained and a physical examination was carried out on each patient. The patient then entered a single-blind, cross-over study, with placebo periods before active drug administration and during the cross-over periods. All patients received a placebo for 7 days, and were then started on either sotalol 160 mg or nadolol 80 mg once daily in a predetermined randomized order. After 7 days on the active drug the patients were again evaluated. When there was less than 90% reduction in VEB frequency the dosage of the drug was doubled for another 7 days, after which the patients were again evaluated. This was followed by another placebo period of 7 days. The whole sequence of events was then repeated in exactly the same way but with the other drug. Placebo tablets and active drugs were identical in appearance.

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A 24-hour Holter recording was done at each visit. Assessment of side-effects, a clinical examination, a resting and a stress ECG 6 hours after the oral dose, a full blood count, and serum urea, creatinine, urate, electrolyte and liver and cardiac enzyme determinations were done after the first placebo period and at the end of each drug administration period.

In addition, blood samples for measurement of drug concentrations were obtained 1,7 and 25 hours after the last daily dose. Sotalol was measured in the plasma by a liquid chromatographic method[8] and nadolol by a spectrofluorometric method.[9]

QT intervals were measured individually by different investigations without knowledge of the administered drug. The average QTc value was then calculated in individual cases.

All results were analysed statistically by applying the Wilcoxon matched-pairs, signed-ranks test. Probabilities were all calculated as $P = 2\alpha$ (i.e. no assumption was made that the drugs would either increase or decrease the parameters measured).

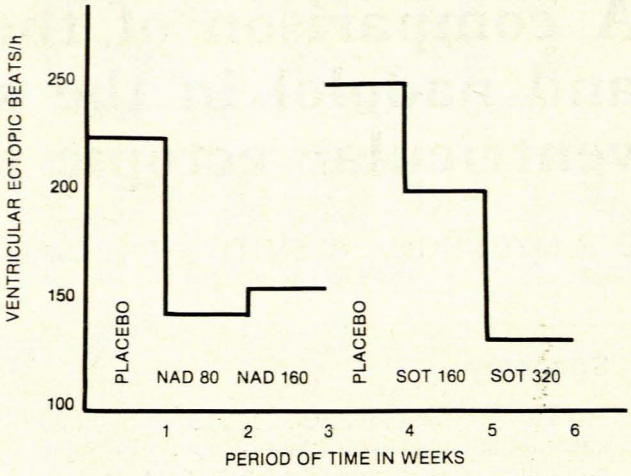

Fig. 1. Number of VEBs per hour during placebo and drug administration periods.

Results

The patient's ages ranged from 35 to 68 years (mean 55 years). Side-effects were noted in 4 patients on placebo: 2 complained of palpitations and 2 of dizziness. On nadolol 2 patients complained of dizziness, 1 complained of decreased effort tolerance and 1 experienced worsening of intermittent claudication. On sotalol 1 patient complained of dizziness and 1 complained of decreased effort tolerance.

On nadolol 80 and 160 mg/d the average pulse rate over 24 hours dropped from 85 to 64 and 63/min respectively ($P < 0{,}00006$ and $P < 0{,}0004$), whereas on sotalol 160 and 320 mg the corresponding values were 67 and 65/min respectively ($P < 0{,}00006$ and $P < 0{,}0003$).

The suppression of VEB frequency by the drugs is shown in Table I and Fig. 1. There was no significant difference between nadolol and sotalol in either dosage. With nadolol, the higher dosage was less effective than the lower ($P < 0{,}05$), but with sotalol the higher dosage was more effective than the lower ($P < 0{,}02$). No correlation could be found between the blood drug concentration (Table II) and VEB suppression with either drug.

No significant changes in the QTc interval could be demonstrated with either drug, nor were there significant differences in serum urate levels with placebo, nadolol or sotalol. There was no significant difference in the number of VEBs on stress testing during the placebo, nadolol or sotalol periods.

Discussion

Part of the anti-arrhythmic potential of ß-blockers is due to their ability to antagonize the effects of catecholamines on automacity and conductivity.[10] Sotalol is a ß-blocker which, in addition to the abovementioned class II activity, also delays repolarization of the ventricular action potential and is therefore also classified as a class III anti-arrhythmic agent.[5] The anti-arrhythmic efficacy of sotalol has been extensively

TABLE I. NUMBER OF VEBs PER HOUR DURING PLACEBO AND DRUG ADMINISTRATION PERIODS

		Nadolol			Sotalol	
Patient	Placebo	80 mg	160 mg	Placebo	160 mg	320 mg
1	309	466	448	531	519	490
2	437	17		153	99	4
3	51	18	2	43	26	37
4	35	0,5		36	7	1
5	162	25	75	103	57	41
6	129	25	19	29	16	17
7	118	88	73	137	31	10
8	115	166	94	249	272	142
9	202	112	76	60	43	16
10	44	13	13	26	21	10
11	286	153	124	241	53	18
12	770	413	295	670	239	288
13	376	57	65	253	224	228
14	177	1		738	925	159
15	21	5	7	30	11	7
16	71	113	62	68	141	94
17	92	0,9		50	3	
18	55	18	0,05	54	0,1	
19	328	225	200	701	165	259
20	30	0		6	0	
21	788	650	801	1 082	1 221	444
22	634	647	327	385	317	152

TABLE II. PLASMA DRUG CONCENTRATIONS (NADOLOL IN ng/ml AND SOTALOL IN μg/ml) AT INTERVALS AFTER ORAL DOSE

	Nadolol 80 mg			Nadolol 160 mg			Sotalol 160 mg			Sotalol 320 mg		
Patient	01h00	07h00	25h00	01h00	07h00	25h00	01h00	07h00	25h00	01h00	07h00	25h00
1		46	519	352	209	90	1 060	750	340	1 510	1 480	1 550
2	63		180				920	1 850	810	4 410	3 970	3 010
3	46		196		384	175	770	2 790	400	550	1 770	590
4	66		64				1 880	1 130	820	3 180	3 300	560
5	25			69	108		290		1 110	1 730	1 230	620
6	102	212	177	232	35	52	1 420	2 220	2 470	1 360	2 070	1 270
7	15		25	47	36	20	1 240		650	1 830	1 400	720
8	97	638	2 775	363	388	105	580		500	1 630	2 850	890
9	286	245	617	917	652	202	2 520	2 310	280	3 760	1 460	930
10	248	159	31	115	35	72	1 350	1 940	1 320	2 210	2 050	1 470
11	66		128	242	258	185	470	1 760	1 880	2 080		810
12	105	21	85	81	119	142	2 360	1 610	2 220	2 320	2 100	850
13	20		235	21	305	126	610	580	2 010	580	2 510	610
14	1 002	61	58				1 240	2 210	490	2 070	2 240	1 920
15	161	104	62	478	243	336	2 840	1 260	1 040	3 790	1 420	1 460
16	40	82	30	89	162	53	940		640	1 390		
17	315		40				440	1 550	450			
18	168	87	21	138	143	62	440	930	400			
19			40	50	104		1 410	1 800	450	2 050	2 910	1 190
20	62		60				870	1 250	620			
21	109	77	39	151	106	60		520	260	2 060	1 510	2 410
22	42	101	35	295	240	113	2 040	1 220	850	2 450	2 900	1 450

documented.[6,11-15] It would thus seem reasonable to use sotalol as a standard for comparison when assessing the anti-arrhythmic efficacy of other ß-blockers.

In this study a 25% fall in pulse rate during drug administration indicated adequate ß-blockade on both sotalol and nadolol.[16] Significant VEB suppression was obtained with both drugs in all dosages (Table I and Fig. 1). Patients responding with more than 90% VEB suppression were not included in the doubled dosage regimen; with nadolol, however, it seems as if the higher dosage was less effective than the lower ($P < 0,05$), whereas with sotalol the higher dosage was more effective than the lower ($P < 0,02$). This probably indicated that had the dosage of sotalol been further increased, suppression of VEBs would have been even more marked. On the other hand, more marked suppression of VEBs with higher plasma drug levels could not be demonstrated; in fact, no correlation between plasma drug level and VEB suppression was found. It is of note, however, that only a weak correlation could be found between the plasma level of nadolol and its antihypertensive effect.[17]

Even though a prolongation of the QTc interval could not be demonstrated with sotalol in this study, class III anti-arrhythmic activity may still contribute to the anti-arrhythmic action. The mechanism of anti-arrhythmic action of nadolol and other ß-blockers remains speculative, but in spite of this these agents may be used as first-line anti-arrhythmic agents because of their wide margin of safety.

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