723 Novel Receptor or Channel Modulating Agents

Monday, March 20, 1995, 4:00 p.m.–5:30 p.m.
Ernest N. Morial Convention Center, Room 26

04:00

723-1 Selective Reduction of Heart Rate with the Sinus Node Inhibitor Zatebradine (ULFS 49) Does not Lead to the Expected Improvements in Exercise Duration in Patients with Angina Pectoris

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Zatebradine is a novel compound blocking selectively the i_F-channel in the sinus node, which is believed to be the pacemaker current. Its effect on heart rate is believed to be very selective, without any other effects on the myocardium. Since it is widely believed that the beneficial effects of beta-blockers are due to their heart rate reducing properties, selective reduction of heart rate without negative inotropy should result in prolongation of exercise duration and reduction in myocardial ischemia in patients with angina pectoris. To investigate this hypothesis we performed a multicenter, randomized, double-blind, placebo-controlled, dose ranging study with zatebradine. Patients (n-237) with reproducible exercise induced angina pectoris with evidence of myocardial ischemia (≥1 mm ST-segment depression) received either placebo, 2.5, 5.0 or 7.5 mg zatebradine for 4 weeks. Symptom limited exercise tests were repeated at 3 and 12 hours post dose after 4 weeks of treatment.

Change from Baseline	Placebo		Zatebradine					
	3 h pa	12 h pa	2.5 mg		5.0 mg		7.5 mg	
			3 h	12 h	3 h pa	12 h pa	3 h pa	12 h pa
Total ETD (s)	30	30	33	25	42	28	50	38
Time 1 Min (s)	24	34	27	33	57*	34	57 *	48
HR Rest (bpm)	1.8	0.5	−6.4***	−6.2***	−12.1***	−8.0***	−20.5***	−13.7***
HR Ex (bpm)	3.8	3.8	−5.9***	−5.5***	−10.9***	−9.6***	−19.2***	−14.4***
EX SBP (mmHg)	−2.3	−0.4	6.4**	3.2	5.4*	4.1	3.4	6.0

h = hours, p.a. = post administration, s = seconds, *p< 0.05, **p< 0.01, ***p< 0.001, ETD = exercise test duration, HR = heart rate, EX = Exercise, SBP = Systolic Blood Pressure

Conclusion: Zatebradine is a powerful agent that reduces heart rate dose-dependently over at least 12 hours. The observed heart rate reduction did not translate into the expected improvements of exercise performance or reduction of myocardial ischemia suggesting that the anti-ischemic effect of heart rate limitation should be reconsidered.

04:15

723-2 Selective Antagonism of Adenosine A_1 Receptor Mediated Effects in Humans with N-0861, (N^6-Endonorboran-2-yl-9-Methyladenine)

Barry D. Bertolet, Elizabeth A. Franco, Richard A. Kerensky, Wilmer W. Nichols, Luiz Belardinelli, James A. Hill. *University of Florida, Gainesville, FL*

To determine the receptor subtype selectivity of the novel A_1-adenosine (ADO) receptor (R) antagonist, N-0861, the A_1 and A_2 R-mediated cardiac effects were investigated in 13 patients during continuous i.v. infusion and boluses of ADO before and after i.v. infusion of N-0861. Also, we sought to determine the effects of N-0861 on ADO-induced chest pain.

Methods: Measurements of A-H interval (A_1 effect), and coronary blood flow velocity (CBFV) (A_2 effect) were made before and after low dose (70 μg/kg) i.v. infusion and bolus (3 mg) ADO. N-0861 (0.25 mg/kg) was infused and the protocol repeated. At each stage, patients rated any chest discomfort from 0 (no pain) to 10 (very severe pain) using a Borg Pain Scale.

Results: No adverse effects of N-0861 were noted. No evidence of myocardial ischemia occurred during any part of the protocol. Chest discomfort occurred in 11 patients and was transient, ending shortly after the ADO infusion was terminated.

	ADO	N-0861 + ADO
A-H°	96 ± 21%	3 ± 5*
CBFV°	237 ± 147%	408 ± 374%
Borg Rating (infusion)	4 ± 2	0*
Borg Rating (bolus)	6.5 ± 4	4.5 ± 3

°expressed as percent increase over baseline;
*p < 0.05 compared to ADO alone

N-0861 abolishes the negative dromotropic effect and chest discomfort experienced during infusion of ADO, and attenuated discomfort observed during the boluses of ADO.

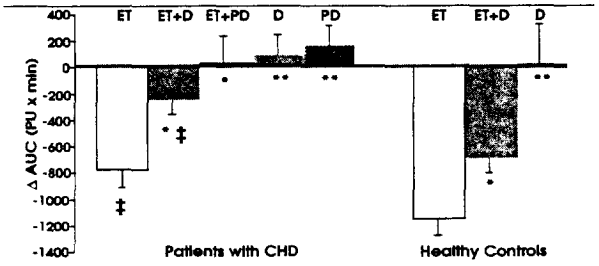
Conclusions: 1) These actions of N-0861 support the concept that the negative dromotropic effect and angina-like pain caused by ADO are A_1-ADO R mediated; whereas, the increase in CBFV is due to activation of A_2-ADO R's. 2) N-0861 appears to be an effective and selective A_1-ADO R antagonist in man. 3) In the presence of N-0861, ADO is a selective short-acting A_2 subtype R agonist.

04:30

723-3 Endothelin in the Skin Microcirculation of Patients with Coronary Heart Disease: Effect of Endothelin Antagonist and Calcium Antagonist

René R. Wenzel, Georg Noll, Nadine Duthiers, Thomas F. Lüscher. *Cardiology, University Hospital, Bern, Switzerland*

Endothelin, a potent vasoconstrictor peptide released from endothelial cells, is elevated in different cardiovascular diseases, i.e. atherosclerosis, acute myocardial infarction, diabetes mellitus and pulmonary hypertension. The effects of the ET_A-endothelin receptor antagonist PD 147953 (PD; 10^{-8} mol) and the calcium-antagonist diltiazem (D; 10^{-7} mol) on endothelin-1 (ET; 10^{-12} mol) induced changes in blood flow of skin microcirculation were studied in 10 patients (7 male, 3 female) with angiographically documented coronary heart disease (CHD) and in 10 healthy controls with a newly developed double injection model. Changes in blood flow were assessed with laser-Doppler-flowmetry. Data are shown as mean difference from saline ± SEM.



(AUC: area under curve of changes in arbitrary perfusion units (PU) over 30 min; */**p<0.05/0.001 vs ET, ‡p<0.05 vs controls)

Conclusions: In patients with CHD, the vasoconstriction to endothelin-1 is reduced compared to healthy young controls.

The calcium-antagonist diltiazem inhibits endothelin induced vasoconstriction in healthy volunteers and in patients with CHD. The endothelin-antagonist PD 147953 fully prevents endothelin-induced vasoconstriction in the skin microcirculation of patients with CHD in a 10 times lower concentration than the calcium antagonist.

04:45

723-4 Cardiovascular and Neurohormonal Effects of SDZ WAG 994, a Selective Adenosine A_1 Receptor Agonist, in Man

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Adenosine is the treatment choice for paroxysmal supraventricular tachycardia (PSVT). However, short half life and lack of an oral preparation limits its use. SDZ WAG 994 is a new orally active selective adenosine A_1 receptor agonist. Its rapid action and sustained effect (6 – 8 hr) might be advantageous in the treatment of PSVT. It also produces presynaptic inhibition of norepinephrine release but its effects in man have never been tested. We investigated the effects of oral administration of 2 & 5 mg SDZ WAG 994 on exercise parameters — (heart rate — HR, blood pressure, Anaerobic Threshold, Peak VO_2 & Ventilatory indices) & Neurohormones in 12 normal subjects in a single blind, placebo baseline-controlled, dose escalating design. SDZ WAG 994 did not affect resting HR but the 2 mg dose caused a decrease in peak exercise HR (by 11 beats/min, $p < 0.01$). The 5 mg dose had no fur-

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