effect shown in highly selected subgroups of patients cannot, however, be extrapolated to other groups of patients, although other studies, including those with a wider, less selected population,⁹⁻¹² indicate that even low-risk patients may profit from long-term beta-adrenoceptor blockade.

There has been much debate about analysis, presentation, and interpretation of beta-blocker post-infarction trials.²⁸⁻³⁰ We have presented our data so that end-point differences based on both the "intention-to-treat" and "in-trial" differences can be calculated, but we have chosen to analyse the results according to intention to treat. We hope that our results will make a small contribution to an important debate.

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References

- Pell S, d'Allonzo CA. Immediate and five-year survival of employed men with a first myocardial infarction. *N Engl J Med* 1964;**270**:915-22.
- Norris RM, Mercer CI. Long term prognosis following treatment in a coronary care unit. *Aust NZ J Med* 1973;**i**:31-3.
- Denborough MA, Lowell RR, Nestel PJ, Goble AJ. Arrhythmias and late sudden death after myocardial infarction. *Lancet* 1968;**ii**:386-88.
- The Coronary Drug Project Group. The importance of the electrocardiogram after myocardial infarction. *Ann Intern Med* 1972;**77**:677-89.
- Vedin JA, Wilhelmson CE, Elmfeldt D, Tibblin G, Wilhelmson L, Werkø L. Sudden death: identification of high risk groups. *Am Heart J* 1973;**68**:124-32.
- Kuller L, Lilienfeld A, Fisher R. Epidemiological study of sudden and unexpected deaths due to arteriosclerotic heart disease. *Circulation* 1966;**34**:1056-63.
- Wilhelmsson C, Vedin JA, Wilhelmson L, Tibblin G, Werkø L. Reduction of sudden deaths after myocardial infarction by treatment with alprenolol; preliminary results. *Lancet* 1974;**ii**:1157-60.
- Ahlmark G, Saetre H. Long-term treatment with beta-blockers after myocardial infarction. *Europ J Clin Pharmacol* 1976;**10**:77-83.
- Green KG, Chamberlain DA, Fulton RM, et al. Multicentre International Study: Improvement in prognosis of myocardial infarction by long-term beta-adrenoceptor blockade using practolol. *Br Med J* 1975;**iii**:735-40.
- Green KG, Chamberlain DA, Fulton RM, et al. Reduction in mortality after myocardial infarction with long-term beta-adrenoceptor blockade: Multicentre International Study: Supplementary Report. *Br Med J* 1977;**iii**:419-21.
- Andersen MP, Frederiksen J, Jørgensen HJ, et al. Effect of alprenolol on

- mortality among patients with definite or suspected acute myocardial infarction: Preliminary results. *Lancet* 1979;**iii**:865-7.
- The Norwegian Multicenter Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *N Engl J Med* 1981;**304**:801-7.
- Reynolds JL, Whitlock AML. Effects of beta-adrenergic receptor blocker in myocardial infarction for one year from outset. *Br Heart J* 1972;**34**:252-9.
- Barber JM, Boyle DM, Chaturverdi NC, Singh N, Walsh MJ. Practolol in acute myocardial infarction. *Acta Med Scand* 1975;suppl 587:213-9.
- Baber NS, Wainwright Evans D, Howitt G, et al. Multicentre post-infarction trial of propranolol in 49 in the United Kingdom, Italy and Yugoslavia. *Br Heart J* 1980;**44**:96-100.
- Wilox RG, Roland JM, Banks DC, Hampton JR, Mitchell JRA. Randomised trial comparing propranolol with atenolol and placebo in immediate treatment of suspected myocardial infarction. *Br Med J* 1980;**281**:885-8.
- WHO. *Ischaemic heart disease registers. Report of the fifth working group.* Copenhagen: WHO, 1971.
- Skjæggstad Ø, Hansteen V, Sivertsen E. Acute myocardial infarction in a medical intensive care unit during a 3-year period 1977-9. The correlation in 744 patients between prognosis and a grading of infarct size. *Journal of Oslo City Hospital*, in press.
- Lown B, Fakhro AM, Hood WB, Jr, Thorn GW. The coronary care unit, new perspectives and directions. *JAMA* 1967;**199**:188-93.
- Fellowship of Postgraduate Medicine: Ten years of propranolol. *Postgrad Med J* 1976;**52**,suppl 4:1-192.
- Coltart DJ, Meldrum SJ, Hamer J. The effect of propranolol on the human and canine transmembrane action potential. *Br J Pharmacol* 1970;**40**:148-62.
- Peto R, Pike MC, Armitage P, et al. Design and analysis of randomised clinical trials requiring prolonged observation of each patient. Introduction and design. *Br J Cancer* 1976;**34**:585-611.
- Frieman JA, Chalmers TC, Smith HJ, Kubler RR. The importance of beta, the type II error and sample size in the design and interpretation of the randomized controlled study. Survey of 71 "negative trials". *N Engl J Med* 1978;**299**:690-4.
- Woosley RK, Kornhauser D, Smith R, et al. Suppression of chronic ventricular arrhythmias with propranolol. *Circulation* 1979;**60**:819-27.
- Shand DG. Individualization of propranolol therapy. *Med Clin North Am* 1974;**58**:1063-9.
- Alderman EL, Coltart J, Wettach GE, Harrison DC. Coronary artery syndromes after sudden propranolol withdrawal. *Ann Intern Med* 1974;**81**:625-7.
- Julian DG. The significance and management of ventricular arrhythmias. *J R Coll Physicians London* 1980;**14**:17-21.
- Baber NS. Clinical experience with beta adrenergic blocking agents in myocardial ischaemia: A dilemma and a challenge. *Pharmacol Ther* 1981;**13**:285-320.
- Hampton JR. Presentation and analyses of the results of clinical trials in cardiovascular disease. *Br Med J* 1981;**282**:1371-3.
- Mitchell JRA. Timolol after myocardial infarction: an answer or a new set of questions? *Br Med J* 1981;**282**:1965-70.

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SHORT REPORTS

Sinus arrest during treatment with amiodarone

Amiodarone (Cordarone X) is widely used for treating resistant cardiac tachyarrhythmias and is generally assumed to have few limiting side effects.¹ We report two cases of sinus arrest, with depressed automaticity of escape foci, that required pacing after administration of amiodarone.

Case reports

Case 1—A 61-year-old man with a remote antero-septal myocardial infarction presented with recurrent sustained ventricular tachycardia. A week before admission a permanent ventricular pacemaker had been inserted for transitory complete heart block. Electrocardiography showed right bundle-branch block, left posterior hemiblock, and evidence of an old antero-septal infarction. When not paced his rhythm was sinus with first-degree atrio-ventricular block. Comprehensive intracardiac electrophysiological study disclosed a corrected sinus node recovery time of 220 ms (normal <525 ms), A-H interval 120 ms (normal 60-140 ms), and H-V interval 85 ms (normal 30-55 ms). Two morphologically distinct types of ventricular tachycardia

could be induced. Quinidine, procainamide, propranolol, digoxin, disopyramide, mexiletine, and several combinations of these failed to suppress the tachycardia. Amiodarone 600 mg daily was started. Six weeks later ventricular extrastimulation induced poorly tolerated ventricular tachycardia. In the meantime no spontaneous ventricular tachycardia had occurred and ambulatory electrocardiography showed complete suppression of ventricular ectopic activity. At that time no sinus node activity was present and the patient was pacemaker-dependent without an escape focus. Apart from amiodarone the only known cardioactive agents that he was taking were metoprolol and digoxin, both in conventional dosage and for several months before these studies. Electrolyte concentrations were normal. The patient was discharged taking these agents as no non-pharmacological treatment was indicated.

Case 2—A 67-year-old man with a history of myocardial infarctions in 1968 and 1977 presented with recurrent drug-resistant ventricular tachycardia that required numerous cardioversions. He was in congestive cardiac failure and had severe peripheral vascular disease and mild chronic renal failure. Electrocardiography showed normal sinus rhythm with an intraventricular conduction defect and evidence of old antero-septal and inferior infarctions. Electrophysiological study showed a corrected sinus node recovery time of 270 ms, A-H interval 125 ms, and H-V interval 80 ms. Sustained ventricular tachycardia (160/min) was induced by ventricular extrastimulation. Serial drug testing with many agents failed to suppress his arrhythmia. Treatment was initiated with amiodarone 1 g daily. Ventricular ectopy was suppressed, and nine days later repeat ventricular stimulation disclosed inducible ventricular tachycardia (125/min). Amiodarone was continued, and two days

later the patient was in slow junctional rhythm (35 beats/min), hypotensive, and poorly perfused. He responded promptly to ventricular pacing. At the time his other treatment included digoxin, frusemide, and isosorbide dinitrate. There was no electrolyte abnormality. No rise in enzyme activity occurred, and his serum digoxin concentration was 2.2 mg/l. Amiodarone was withdrawn and intermittent sinus node activity returned next day; within two days periods of normal sinus rhythm were noted. Spontaneous ventricular tachycardia requiring cardioversion recurred, however, so an atrioventricular sequential pacer was inserted and amiodarone reinstituted. As no other treatment was suitable for this patient he was discharged with this regimen.

Comment

Sinus bradycardia and sinoatrial block have been described as side effects of amiodarone,^{2,3} but to our knowledge sinus arrest has not been reported and no such case has been notified either to Sanofi Inc, the US agent for the manufacturers of the drug, or to the Food and Drug Administration. Both patients had normal sinus node automaticity as shown by corrected sinus node recovery times within the normal range, this being considered the best available test of sinus node automaticity and possibly of overall node function.⁴

Amiodarone depressed automaticity by inhibiting phase 4 depolarisation in the sinus node of rabbits *in vitro*,⁵ and these observations suggest that such a mechanism may account for this potentially lethal complication in susceptible patients.

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¹ Nademanee K, Hendrickson JA, Cannom DS, Goldreyer BN, Singh BN. Control of refractory life-threatening ventricular tachyarrhythmias by amiodarone. *Am Heart J* 1981;**101**:759-68.

² Modica G, DiFazio S, Timpanaro V, Centamore G. Impiego dell'amiodarone in tachiaritmie atriali associate a bradicardia sinusale. *Boll Soc Ital Cardiol* 1977;**22**:1985-91.

³ Alboni P, Fischer DM. Blocco seno-atriale in corso di terapia con amiodarone. *G Ital Cardiol* 1973;**3**:288-90.

⁴ Josephson ME, Seides SF. *Clinical cardiac electrophysiology*. Philadelphia: Lea and Febiger, 1979.

⁵ Goupil N, Lenfant J. The effects of amiodarone on the sinus node activity of the rabbit heart. *Eur J Pharmacol* 1976;**39**:23.

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Alveolitis after treatment with amiodarone

Amiodarone has been widely used in Europe and the United States for its antiarrhythmic and antianginal properties. It has recently become available in Britain. We report a case of severe pulmonary reaction in a patient given this drug.

Case report

A 69-year-old man presented in November 1980 with a six-month history of palpitations at rest. He denied exertional dyspnoea but had a chronic productive cough related to cigarette smoking and a mild seronegative arthritis controlled by indomethacin. Clinical examination showed no other abnormality and chest radiographs were clear apart from an old small calcified focus at the right apex. A 24-hour electrocardiogram suggested sick-sinus syndrome and treatment was started with amiodarone (Cordarone X) 100 mg twice daily for one week, increasing to 200 mg twice daily. He rapidly became asymptomatic. Six weeks later he developed exertional dyspnoea, which gradually increased over the next two months and prompted referral to a respiratory physician. Four days before he had discontinued amiodarone himself, believing it to be responsible. He was dyspnoeic on

minimal exertion, and examination showed widespread bilateral late inspiratory crepitations but no evidence of finger clubbing.

There was extensive bilateral fluffy opacification in the chest x-ray film (fig: top). Pressure of oxygen was 7.7 kPa (57.9 mm Hg) breathing air. Lung volumes showed a mild restrictive pattern with a total lung capacity of 5.6 l (76% predicted), and carbon monoxide transfer factor was reduced to 2.3 mmol/min/kPa (6.7 ml/min/mm Hg; 28% predicted). Erythrocyte sedimentation rate was 60 mm in first hour, liver function values and immunoglobulin concentrations normal, and antinuclear factor not detectable. The

Radiographs of chest showing (top) bilateral fluffy opacification and (bottom) improvement after prednisolone 60 mg daily.

patient was too ill for lung biopsy. His known cardiac disease plus the mild negative inotropic action of amiodarone suggested pulmonary oedema. Diuretics, however, failed to produce an improvement. Two weeks after stopping amiodarone he was less dyspnoeic but the chest radiograph and transfer factor were unchanged. He began prednisolone 60 mg daily with rapid improvement in exercise tolerance and progressive clearing of his lung fields (fig: bottom). Serial estimations of transfer factor showed a rise to 3.8 mmol/min/kPa (11.3 ml/min/mm Hg; 38% predicted) after six days and to 3.9 mmol/min/kPa (11.6 ml/min/mm Hg; 48% predicted) after 24 days.

He remained well and continued to take indomethacin and a reducing dose of prednisolone. His palpitations did not recur.