Acute coronary syndromes following abrupt cessation of oral propranolol therapy

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Abrupt cessation of oral propranolol therapy was followed by 15 acute coronary events in 14 patients with severe angina who had been receiving propranolol in daily doses of 80 to 400 mg for periods of 7 days to 6 years. Propranolol had been stopped 1 to 14 days before each acute event because of angiographic study (seven patients), increasing symptoms (three), acute coronary insufficiency (one), asymptomatic bradycardia (one), elective surgery (one) and unknown reasons (two). Before abrupt cessation of propranolol treatment anginal symptoms had been stable in six instances but had increased in the other nine. Cessation was followed by rapid progression of symptoms prior to 11 of the 15 acute events. There were six acute transmural myocardial infarctions with three deaths, three intramural myocardial infarctions, one with ventricular fibrillation, and six episodes of acute coronary insufficiency. Unstable angina followed nine of the events and responded to propranolol therapy (160 to 320 mg/d) in eight instances. Three other patients underwent aortocoronary bypass surgery; perioperative acute myocardial infarction occurred in two. These data suggest that in a minority of patients abrupt cessation of propranolol may be hazardous, particularly in severe or unstable disease. Cessation of propranolol therapy in such patients should be gradual and closely observed. Recurrent symptoms respond to reinstitution of propranolol therapy.

L'arrêt brusque du propranolol fut suivi de 15 événements coronariens aigus chez 14 patients souffrant d'angine sévère qui recevaient le propranolol à des doses quotidiennes de 80 à 400 mg pendant des intervalles de 7 jours à 6 ans. Le propranolol avait été discontinué soudainement 1 à 14 jours précédant chacun des événements aigus en raison de coronarographie (sept patients), progression des symptômes angineux (trois), insuffisance coronarienne aiguë (un), bradycardie asymptomatique (un), chirurgie élective (un) et pour des raisons inconnues (deux). Précédant l'arrêt brusque du propranolol les symptômes angineux avaient été stables dans six des cas mais avaient augmenté chez les neuf autres. L'arrêt de ce médicament fut suivi d'une progression rapide des symptômes angineux précédent l'événement aigu dans 11 des 15 cas. Les événements aigus furent les suivants: six infarctus transmuraux avec trois décès, trois infarctus sousendocardiques dont l'un fut accompagné de fibrillation ventriculaire, et six cas d'insuffisance coronarienne aiguë. Un syndrome d'angine instable suivit neuf de ces événements aigus, cédant chez huit à l'administration du propranolol à des doses de 160 à 320 mg par jour. Trois autres furent traités par pontage aortocoronariens; un infarctus peropératoire survint chez deux. Ces données suggèrent que chez une minorité de patients l'arrêt brusque du propranolol peut être dangereux, surtout chez le patient porteur d'angine sévère ou instable. L'arrêt du propranolol chez de tels patients devrait être graduel et surveillé de près. Une récidive de symptômes cède à la réadministration immédiate du propranolol.

Of the several β-adrenergic blocking agents that have been investigated clinically, propranolol is the only one currently available for general clinical use in North America. In adequate dosage it is of proven efficacy in reducing the frequency and severity of anginal attacks and increasing exercise tolerance.[1,2] Its use in patients with stable angina is increasing and it has been recommended for use in patients with the various syndromes of unstable angina.[3,4] While the drug is generally well tolerated, adverse reactions, including bradycardia, hypotension, bronchospasm, abdominal cramps and coldness of the extremities, may occur. In patients with borderline left ventricular function its negative inotropic properties and tendency to cause sodium retention may lead to clinical manifestations of congestive cardiac failure.

When therapy is given for relief of a specific symptom and proves effective, its sudden withdrawal may lead to recurrence of previous symptoms; this has been noted when propranolol is discontinued in patients with chronic angina. In January 1972, in a preliminary report on the use of propranolol in unstable coronary artery disease, it was noted that 2 of 57 patients had had an acute myocardial infarction shortly after abrupt cessation of propranolol therapy. The infarctions were thought to be chance occurrences that might have been expected in patients with severe coronary artery disease.[5] However, in a later controlled trial of propranolol in patients with unstable coronary artery disease, we noted three acute myocardial infarctions, with two deaths, and one episode of acute coronary insufficiency when propranolol was discontinued abruptly in eight patients.[6] In addition, during the past year, approximately 30 other cases have been reported suggesting that in patients with chronic angina, abrupt cessation of this drug may be followed not only by recurrence of symptoms but also by acute coronary events ranging in severity from clinical instability and acute coronary insufficiency to fatal myocardial infarction.[7-11]

Alerted by these observations, we have detected 15 acute coronary episodes following abrupt withdrawal of propranolol in 14 patients. In this paper we present a retrospective analysis of these 15 events, outlining the clinical characteristics of the patients and emphasizing the circumstances of the events, in order to identify patients in whom this phenomenon is apt to occur, and detail one case.

Clinical features of acute coronary episodes

The acute events detected in our patients fell into three categories:

1. Acute transmural myocardial infarction: prolonged chest pain, new Q waves on the electrocardiogram (ECG), and appropriate increases in serum concentrations of creatine phosphokinase (CPK), glutamic oxaloacetic transaminase (SGOT) and lactic dehydrogenase (LDH).

2. Intramural myocardial infarction: prolonged chest pain, ST-segment and T-wave (ST-T) abnormalities but no new Q waves on the ECG, and increases in serum concentrations of CPK, SGOT and LDH of more than 50% of normal.

3. Acute coronary insufficiency: pro-

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longed chest pain, ST-T abnormalities but no new Q waves on the ECG, and increases in serum concentrations of CPK, SGOT and LDH of less than 50% of normal.

Patient data and status before cessation of propranolol therapy

Clinical data on the 14 patients in this series, 10 men and 4 women, and pertinent details of the 15 acute events are summarized in Table I. Mean age was 58.2 years (range, 35 to 72 years). Propranolol had been administered in a mean daily dose of 220 mg (range, 80 to 400 mg) for a mean of 11.3 months (range, 7 days to 3 years). All but three patients had had severe angina pectoris (New York Heart Association [NYHA] class III or IV*) and nine had had a documented acute myocardial infarction. Before nine of the events an increase in anginal symptoms had been noted prior to abrupt cessation of propranolol, while symptoms had apparently remained stable in the other six.

Reasons for abrupt cessation

The reasons for abrupt withdrawal of propranolol are also listed in Table I. In two patients no reason for discontinuation could be identified. No other medications had been abruptly discontinued and no other known precipitating factors were apparent.

*Class III: activity greatly limited; comfortable only at rest. Class IV: confined to bed or chair; any physical activity produces discomfort.

Status after cessation

In the period following abrupt cessation of medication and preceding 11 of the 15 acute events, a clearly recognizable progressive increase in the frequency, severity and duration of anginal attacks was noted, beginning 24 to 48 hours after the last dose of propranolol and culminating in the acute coronary syndrome 1 to 14 days later, with a mean interval of 4.3 days. The 15 acute events included 6 acute transmural myocardial infarctions with 3 deaths, 3 intramural myocardial infarctions with 1 episode of ventricular fibrillation, and 6 episodes of acute coronary insufficiency requiring admission to hospital.

Following 9 of the 15 acute events there was continued clinical instability, defined as persistence of anginal pain, occurring unpredictably in spite of complete bed rest and administration of opiates, nitrates and anticoagulants. In eight instances reinstitution of propranolol at similar or slightly higher dosages (160 to 320 mg/d) was successful in controlling symptoms and in abolishing anginal attacks at rest, and no further myocardial infarctions or other acute events occurred in these patients during a mean observation period of 8 months (4 to 12 months). One patient, no. 14, was treated with nitrates alone; continued pain at rest persisted after discharge and reinfarction occurred within 6 weeks.

Three other patients underwent aortocoronary bypass grafting. In one, no. 5, the procedure was done as an emergency within 4 hours of onset of symptoms because of electrocardiographic evidence of inferior-wall injury. Although the patient survived the procedure, acute infarction evolved during the postoperative period. In the other two patients aortocoronary bypass grafting was carried out within 8 days. In one, no. 7, an intraoperative anteroseptal myocardial infarction occurred, and in the other, no. 13, the procedure was performed uneventfully in spite of enzymatic evidence of a small intramural infarction. This patient became asymptomatic after the procedure.

Case report

Patient 3

A 59-year-old man with a 2-year history of angina was admitted to hospital with a 2-week history of chest pain of increasing frequency (unstable angina). Pain at rest persisted in hospital and transient ST-T abnormalities appeared on the ECG. Concentrations of serum enzymes remained normal in serial studies. He agreed to enter a controlled randomized study of propranolol therapy for unstable angina and received medication in a dose of 40 mg *qid*. Symptoms regressed within 48 hours and he was discharged on the 12th hospital day. For 16 months he continued taking the study drug in a dosage of 40 mg *qid* and his condition remained stable with class II angina.† Following a 10-day period of more frequent angina he was readmitted to hospital and became asymptomatic. The study drug was abruptly withdrawn on the 5th hospital day prior to coronary angiography. Chest pain recurred at rest on

†Class II: activity slightly limited; comfortable at rest or with mild exertion.

Table I—Acute coronary syndromes after abrupt cessation of propranolol therapy

						Status before cessation				Status after cessation					
						Prop. therapy									
Patient no.	Age (yr)	Sex	Duration of disease	NYHA class* during therapy	Previous AMI	Dose (mg/d)	Duration (mo)	Symptoms	Reason for cessation	Increased symptoms in interval	Interval to event (d)	Event	Cont'd instability	Treatment	Result
1	72	F	3 yr	III	1	80	24	Increased	?	Yes	5	IMMI, VF	Yes	Prop.	Stable
2	71	M	13 yr	IV	2	160	36	Increased	↑ angina	Yes	14	ACI	Yes	Prop.	Stable
3	59	M	2 yr	III	2	160	16	Increased	Angio.	Yes	7	AMI	Yes	Prop.	Stable
4	61	F	3 yr	IV	0	240	30	Stable	Elective surgery	Yes	6	IMMI	Yes	Prop.	Stable
5	35	M	1½ yr	II	2	240	12	Increased	Angio.	No	7	AMI	—	Emerg. ACB	AMI
6	48	M	9 yr	IV	3	320	1	Stable	?	Yes	5	ACI	Yes	Prop.	Stable
				IV		400	5	Stable	Angio.	Yes	2	ACI	Yes	Prop.	Stable
7	52	M	7 mo	II	1	160	2	Stable	Angio.	No	4	ACI	No	ACB	AMI
8	61	M		IV	1	320	3	Increased	ACI	Yes	1	Fatal AMI	—	—	—
9	57	F	4 yr	III	1	240	21	Increased	↑ angina	Yes	4	Fatal AMI	—	—	—
10	63	F	5 yr	III	1	320	6	Increased	↑ angina	Yes	5	ACI	Yes	Prop.	Stable
11	70	M	2 wk	—	0	160	¼	Increased	AB	Yes	1	ACI	Yes	Prop.	Stable
12	64	M	5 yr	III	0	80	6	Stable	Angio.	Yes	2	Fatal AMI	—	—	—
13	52	M	3 yr	IV	0	160	4	Stable	Angio.	No	1	IMMI	No	ACB	Stable
14	51	M	3 mo	II	0	160	3	Increased	Angio.	No	1	AMI	Yes	NG, ISD	AMI

AMI = acute myocardial infarction; Prop. = propranolol; IMMI = intramural myocardial infarction; VF = ventricular fibrillation; ACI = acute coronary insufficiency; Angio. = preparation for elective coronary angiography; ACB = aortocoronary bypass; AB = asymptomatic bradycardia, 48 beats/min; NG = nitroglycerin; ISD = isosorbide dinitrate.

*New York Heart Association classification. Class II: activity slightly limited; comfortable at rest or with mild exertion. Class III: activity greatly limited; comfortable only at rest. Class IV: confined to bed or chair; any physical activity produces discomfort.

the 8th day and increased progressively in frequency and severity during the next 3 days. On the 12th day two prolonged bouts of chest pain occurred. Evolution of inferior-wall myocardial infarction was confirmed by serial electrocardiographic tracings and enzyme changes. The study drug proved to have been propranolol. Within 48 hours of the acute infarction clinical instability recurred; frequent anginal attacks at rest persisted for the next 3 days. Treatment with propranolol was reinstituted at a daily dose of 240 mg and the chest pain subsequently disappeared. Grade III angina persisted after discharge and coronary angiography was rescheduled for a date 3 months later. Two days before the procedure propranolol was again abruptly discontinued. Symptoms did not change until 48 hours later when, during the 1st day in hospital, chest pain at rest occurred several times. That evening he had severe prolonged chest pain with weakness and diaphoresis. Transient ST-T abnormalities were noted in leads 2, 3 and AVF but serial enzyme values remained normal. Coronary angiography was done on the 10th hospital day in spite of occasional chest pain at rest and disclosed a slightly dilated left ventricle with inferior-wall hypokinesis and triple-vessel disease not amenable to surgical treatment. He was discharged taking propranolol, 240 mg/d. Grade III angina persisted but there were no further periods of instability.

Comment: This patient had had severe angina with advanced coronary artery disease. A recent increase in anginal symptoms had preceded abrupt withdrawal of propranolol, which had been prescribed for unstable angina. Three days after abrupt withdrawal of the drug, symptoms increased clearly and rapidly, culminating in acute inferior-wall infarction. Continued instability reappeared 48 hours after the acute event and was controlled by reinstitution of propranolol therapy. Clinical instability without an acute event was noted a second time in this patient when again propranolol was abruptly stopped for coronary angiography.

Discussion

Exacerbation of symptoms may follow discontinuation of any effective therapy and this has been noted following withdrawal of propranolol in patients with chronic angina. Indeed, such a phenomenon has been cited as evidence of efficacy in the assessment of antianginal agents.[2] The events recorded in our 14 patients, however, represent not only recurrence of symptoms but true and potentially hazardous exacerbations of the underlying disease, ranging in severity from a state of progressive clinical instability to prolonged pain syndromes (acute coronary insufficiency), intramural myocardial infarction, transmural infarction and death. Such events are not uncommon in patients with long-standing coronary artery disease with severe angina and we cannot exclude with certainty the possibility that such events might not have occurred had propranolol therapy been continued. However, a causal relation is strongly suggested because of the following observations. Before 11 of the 15 acute events an exacerbation of anginal symptoms was noted within 24 to 48 hours after abrupt cessation of propranolol therapy and symptoms then progressively increased in frequency, severity and duration until the acute event, thus giving ample warning of the possible impending catastrophe. Such a progression has also been reported by others. Nellen[8] observed progressive and increasing angina for 14 days prior to infarction in a patient in whom propranolol had been abruptly stopped. Similarly, four of the six patients reported by Alderman and colleagues[10] had progressive symptoms for 2 to 21 days preceding the acute event. In a controlled trial of long-term propranolol therapy for unstable coronary artery disease, four acute events with two deaths were noted when propranolol was discontinued abruptly in eight patients, while no acute events followed abrupt cessation of placebo.[6] In addition, in 9 of the 14 patients clinical instability persisted after the acute event; 1 had a subsequent acute myocardial infarction and in the 8 others, reinstitution of propranolol therapy resulted in a favourable response and return to a clinically stable status. The acute syndromes did not appear to be related to dosage or duration of treatment. No other drug had been abruptly withdrawn and no other known precipitating factors were identified.

The true incidence of these acute syndromes in populations receiving propranolol is unknown and no controlled studies have been conducted. Though we have noted an increased incidence of anginal attacks after discontinuing propranolol therapy, the occurrence of clinical instability and of acute catastrophic events appears to be infrequent. Analysis of the events reported in this study suggests that such acute events are more likely to occur in patients with evidence of advanced coronary artery disease with severe angina, particularly if there has been a recent increase in symptoms. Thus, all but two of our patients had had severe, NYHA class III or IV angina before the acute event occurred and nine had had a myocardial infarction. Furthermore, 9 of the 14 patients reported increasing symptoms of angina prior to abrupt cessation of propranolol. Acute coronary events have not been reported after abrupt cessation of propranolol in patients receiving the drug for reasons other than ischemic heart disease.

The mechanisms of the occurrence of such acute syndromes are unknown. Coronary artery disease is known to be progressive; on the other hand, propranolol can greatly reduce myocardial oxygen demand. Recent work by Maroko and colleagues[12] suggests that in acute myocardial infarction induced experimentally propranolol seems to protect the ischemic myocardium and thus reduce the extent of ischemic injury and necrosis. It is therefore possible that, in spite of progression of the underlying coronary artery disease, propranolol may permit a critical balance to exist between myocardial oxygen supply and demand. The sudden upset of this critical balance by withdrawal of propranolol's oxygen-sparing effect on the myocardium may then enhance the induction of various degrees of myocardial ischemia and necrosis, with emergence of the associated acute coronary syndromes. Such a sequence of events has been proposed but remains speculative.[13]

Such events are not frequent. In most cases no untoward effects other than the usual and expected increase in the frequency of anginal attacks follow abrupt cessation of propranolol. However, since catastrophic events may sometimes occur, it would appear more prudent to avoid, when possible, rapid withdrawal, particularly in patients with severe angina. Such patients should be advised to have a ready supply of propranolol at all times. Should medication need to be stopped for reasons such as elective coronary angiography, the dosage should be tapered over a period of 6 to 10 days under careful supervision. The more severe the angina, particularly if there has been a recent increase in symptoms, the more careful one should be in discontinuing propranolol. Since progressive symptoms usually precede the acute events, are easily recognized clinically and respond to the reinstitution of propranolol therapy, patients must be urged to resume taking the usual dose of propranolol if symptoms of increasing angina appear.

It has also been suggested that propranolol be discontinued prior to elective aortocoronary bypass grafting,[14] and most cardiac surgical centres do so. Recently, however, this practice has been questioned and aortocoronary bypass procedures have been performed in patients receiving propranolol, with no apparent increase in the incidence of untoward effects attributed to the drug.[15] In view of the possible hazards of abrupt withdrawal of propranolol in patients with severe angina, and because increasing symptoms and acute events are apt to begin within 24 to 48 hours after abrupt discontinuation, this policy should be reassessed.

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CORRESPONDENCE

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simply taken over from another country at a more advanced stage of development or from a more favoured region within the same country, it is not clear how its adequacy can be established. It must also be borne in mind that, because of the dramatic technological changes that are taking place, the validity of any particular ratio is of limited duration".

The reply then stated: "This implies that any WHO recommendation on the physician/population ratio, especially applying to the whole world, would not make sense. The multiplicity of citations concerning this *spurious recommendation* [my italics] is probably just another example of the readiness of many authors to reproduce what they have read somewhere without bothering to check the correctness of their citation. Your scruples in this matter will allow you to break the chain."

I would ask *CMAJ* to help me break the chain by bringing to the attention of health care planners and medical educators in Canada the fact that the much-quoted WHO standard is a myth. Please accept my apologies for referring to it in my own paper.

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Requests for medical records

To the editor: I agree with Dr. Scrimgeour (*Can Med Assoc J* 114: 593, 1976) that little courtesy is demonstrated by confrères seeking medical information about a patient by means of a printed release form requesting the "complete medical history".

Not only the request but also the reply surely warrants more than a thoughtless resort to modern techniques of communication. Have others shared my experience as a recipient of information forwarded in response to a doctor-to-doctor letter requesting information about a previous illness? What is more thoughtless, senseless and wasteful than sending about 1.3 kg of photocopied material, containing in some instances the list of clothing and valuables recorded on admission to hospital? One more illness and the total accumulated data would have justified delivery by express rather than mail.

In the interest of economy, compassion for the mailman and effective exchange of information, could I not have a couple of well digested paragraphs rather than a catalogue assembled by an assiduous secretary?

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Journal perspectives

To the editor: The role of advertisements in defraying the cost of publications is well known and no one should disagree with you for including them in *CMAJ* (see *Can Med Assoc J* 114: 489, 1976). In some journals the cost to the advertiser depends, among other factors, on where the product appears in the issue. Thus, the advertisements are interspersed throughout the text, giving emphasis where it is deserved.

CMAJ has kept this format for as long as I have known it, but this format has the disadvantage of dividing the reader's attention. It is hard to concentrate on a serious text while one is being distracted by a photograph of a surrealist cube on the facing page.

I would like to suggest to the editors to consider seriously grouping the advertisements to precede and to follow the main text. This format is without doubt more clinical, will give more emphasis to the text and will make the latter easier to bind.

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