receiving phenylpropanolamine orally in the treatment of anorexia or nasal congestion.[20]

Clearly, α-adrenoceptor agonists may increase the blood pressure if sufficient amounts reach the systemic circulation. There is little evidence that the doses of phenylephrine recommended for topical intranasal use alter the systemic blood pressure with or without concurrent β-blocker therapy. However, since larger amounts of phenylephrine have been used in clinical practice for mydriasis, the "safe" dose should be established in controlled clinical trials with subjects whose blood pressure is normal and in patients receiving β-blocker therapy for hypertension.

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Torsades de pointes, a common arrhythmia, induced by medication

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Between May 1980 and April 1981 four patients were referred to one hospital with syncope or recurrent ventricular fibrillation while taking antiarrhythmic or phenothiazine drugs. In all the patients ventricular tachyarrhythmias with the characteristics of torsades de pointes were documented in association with prolonged QT intervals. With removal of the offending agent (in all the patients) supplemented by temporary overdrive pacing (in two patients) the tachyarrhythmias subsided. This study suggests that drug-induced torsades de pointes is an important clinical entity that occurs more frequently than has been suspected.

Entre mai 1980 et avril 1981 quatre patients ont été reçus en consultation à un hôpital souffrant de syncope ou de fibrillation ventriculaire récidivante alors qu'ils prenaient des médicaments antiarythmiques ou des phénothiazines. Chez tous ces patients on a vérifié des tachyarythmies ayant les caractéristiques de torsades de pointes en association avec une prolongation de l'intervalle QT. Le retrait de la médication responsable (chez tous les patients) et l'addition temporaire d'une stimulation électrosystolique rapide (chez deux patients) ont amené la résolution des tachyarythmies. Cette étude indique que les torsades de pointes provoquées par les médicaments représentent une entité clinique importante qui survient plus souvent qu'on ne l'avait soupçonné.

Ignorance is not so damnable as humbug, but when it prescribes pills it may happen to do more harm.

—George Eliot[1]

In 1967 Dessertene[2] used the term "torsades de pointes" (twisting of the points) to describe a bizarre form of ventricular tachycardia with unique morphologic features. The tachycardia was characterized by alternating cycles of electrical polarity with progressive sinusoidal changes in the amplitude of successive ventricular

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complexes (Fig. 1). Unlike ventricular fibrillation this arrhythmia frequently ended spontaneously.

More recently other investigators have verified the occurrence of this arrhythmia in both congenital and acquired syndromes in which the QT interval is prolonged.[3-11] The recognition of a drug-induced QT syndrome is critical since the potentially lethal rhythm disturbance can be treated by simply withdrawing the offending agent.

Because torsades de pointes is frequently mistaken for ventricular fibrillation secondary to organic heart disease[3] its incidence may be grossly underestimated. Between May 1980 and April 1981 four patients with syncope or recurrent ventricular fibrillation were referred to the arrhythmia service of University Hospital in London, Ont. All the patients had features characteristic of torsades de pointes associated with prolonged QT intervals. The arrhythmia ended in all the patients when the suspected agent was withdrawn. We present our experience with these patients, which suggests that drug-induced QT syndromes occur more frequently than has been suspected.

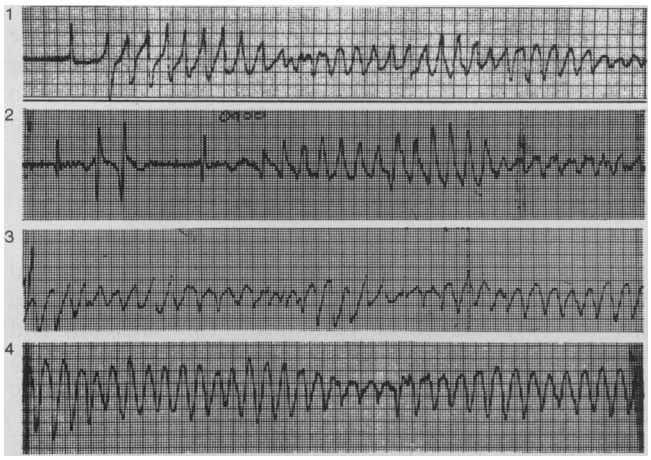

FIG. 1—Cases 1 to 4: Spontaneous torsades de pointes.

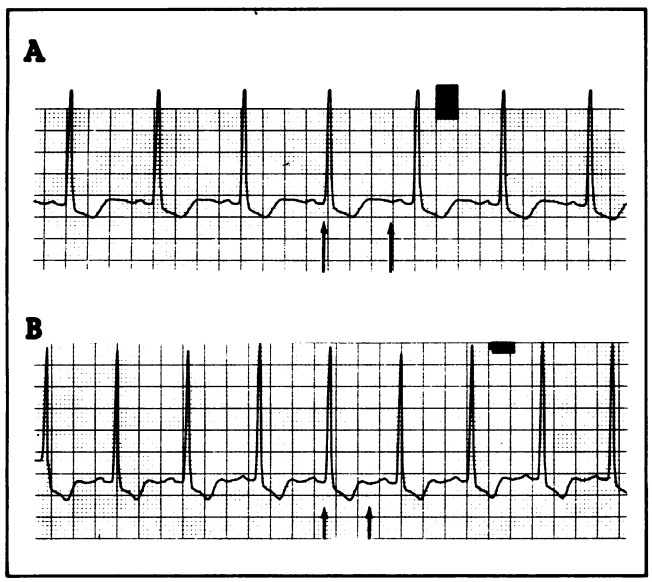

FIG. 2—Case 1: QT interval (arrows) before (A) and after (B) withdrawal of disopyramide, 0.64 and 0.38 seconds respectively.

Case reports

Case 1

A 57-year-old labourer with a history of hypertension and mild dyspnea on exertion was admitted to another hospital with progressive dyspnea. Pulmonary edema was diagnosed and he was treated with furosemide. Frequent premature ventricular depolarizations were successfully suppressed with intravenously administered lidocaine and then orally administered quinidine sulfate, 200 mg every 6 hours. Ventricular ectopic activity increased over the next 48 hours, so the quinidine was replaced with procainamide hydrochloride, 500 mg every 6 hours; however, the procainamide had no effect, so intravenous lidocaine therapy was again started, followed by intravenous disopyramide therapy when there was no response. Within 12 hours two episodes of unstable ventricular tachycardia occurred that required defibrillation. The patient was therefore transferred to our hospital.

The patient was slightly apprehensive but in no acute distress. No jugular venous distension was noted and his chest was clear; the first heart sound was normal, the second was single and faint, and a prominent fourth heart sound was present. There was a harsh grade 3/6 systolic ejection murmur, maximal at the aortic area and radiating to both carotid arteries. A chest roentgenogram showed cardiomegaly, and an electrocardiogram showed sinus rhythm, left ventricular hypertrophy and prolonged QT interval (0.64 seconds) (Fig. 2). The serum potassium level was 2.9 mmol/l.

Disopyramide therapy was stopped and lidocaine therapy continued. Over the next several hours the patient experienced several episodes of torsades de pointes (Fig. 3); although most ended spontaneously (Fig. 4), at least five required cardioversion. A pacing

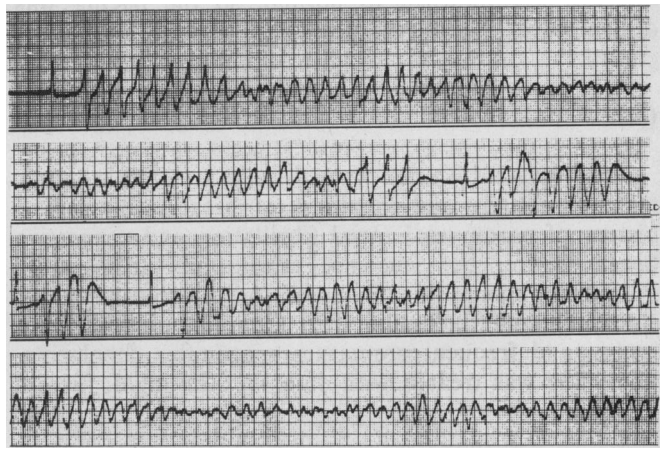

FIG. 3—Case 1: Paroxysms of torsades de pointes just before withdrawal of disopyramide.

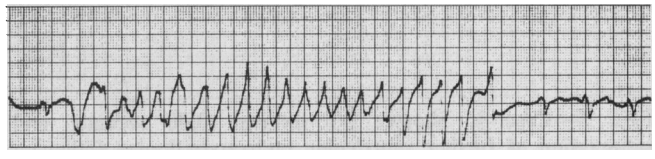

FIG. 4—Case 1: Episode of torsades de pointes that ended spontaneously.

catheter was introduced into the right ventricular apex and the rate of pacing empirically increased until the ventricular ectopic activity was suppressed (Fig. 5). Twelve hours later the pacing was stopped; the QT interval was within normal limits (Fig. 2). Frequent single ventricular depolarizations were subsequently treated with tocainide hydrochloride, 400 mg every 8 hours. The patient was discharged from hospital, and the syncope had not recurred at the time of the 6-month follow-up examination.

Case 2

A 71-year-old man was referred to our hospital from a nursing home after he had experienced, in 1 week, two episodes of syncope characterized by sudden loss of consciousness followed by prompt and uneventful recovery. At the time of admission he was taking doxepin hydrochloride, 10 mg four times a day, trifluoperazine, 2 mg twice a day, thioridazine hydrochloride, 25 mg four times a day, diphenylhydantoin, 200 mg three times a day, furosemide, 40 mg a day, digoxin, 0.25 mg a day and potassium chloride, 600 mg three times a day. The phenothiazines had been added 2 months earlier for depression. The patient had no history of cardiac disease. An electrocardiogram showed diffuse nonspecific ST-segment changes and a prolonged QT interval (0.62 seconds).

Shortly after admission three episodes of syncope occurred, and torsades de pointes was documented each time (Fig. 1). In two instances the sinus rhythm returned to normal spontaneously, and in one cardioversion was required. All medications were discontinued and intravenous lidocaine therapy was started. The resting heart rate was 50 beats/min. A temporary pacing catheter was placed in the right ventricular apex and a rate of 90 beats/min used. After 72 hours the QT interval had returned to normal, so the pacing was discontinued. No further episodes of tachycardia occurred.

Case 3

A 74-year-old woman was admitted to another hospital with fatigue and shortness of breath. She had a history of paroxysmal atrial fibrillation and congestive heart failure, but was not taking any medication. Pulmonary edema was diagnosed. An electrocardiogram showed atrial fibrillation with a rapid ventricular response and frequent premature ventricular depolarizations. She was treated with digoxin, 0.25 mg/d, furosemide, 40 mg/d, and disopyramide, 100 mg every 6 hours. Sinus rhythm was restored, but ventricular ectopic activity persisted, so the dose of disopyramide was increased to 150 mg every 6 hours. One week later two episodes of syncope occurred. She was transferred to the coronary care unit, where a third episode occurred in which torsades de pointes was documented (Fig. 1). At this time an electrocardiogram showed a sinus rhythm of 70 beats/min, diffuse ST-segment depression and a prolonged QT interval (0.59 seconds). Disopyramide was discontinued; however, a short time later at least 12 more episodes of torsades de pointes occurred, 4 of which required defibrillation. Therapy with lidocaine, procainamide and phenytoin failed to prevent the arrhythmia, so the patient was transferred to our hospital.

At the time of transfer the patient was experiencing atrial fibrillation with a rapid ventricular response, averaging 140 beats/min. The QT interval was 0.42 seconds. After reviewing the patient's records we suspected that she had a drug-induced QT syndrome. All the antiarrhythmic medications were discontinued and she was given digoxin, furosemide and a potassium supplement. Overdrive pacing was not done because we felt that spontaneous atrial fibrillation had achieved the required effect. Propranolol was subsequently added to her regimen to control the ventricular response, and ventricular tachycardia did not recur.

Case 4

A 71-year-old woman with a history of hypertension and paroxysmal atrial fibrillation was admitted to another hospital. Three years previously she had had two episodes of syncope for which she was given digoxin and quinidine. However, she had stopped taking these drugs because of nausea, vomiting and diarrhea.

At the time of admission the patient was experiencing spontaneous atrial fibrillation, with a mean ventricular response of 120 beats/min. There was no evidence of

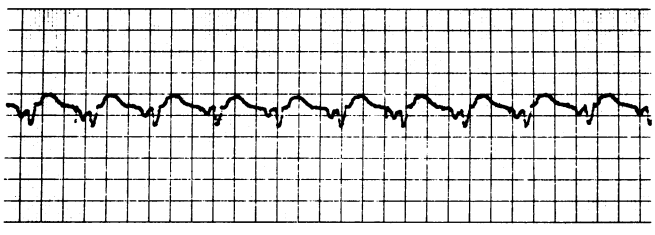

FIG. 5—Case 1: Shorter QT interval (0.40 seconds) and suppression of further ventricular tachyarrhythmias following treatment with overdrive right ventricular pacing at a rate of 110 beats/min.

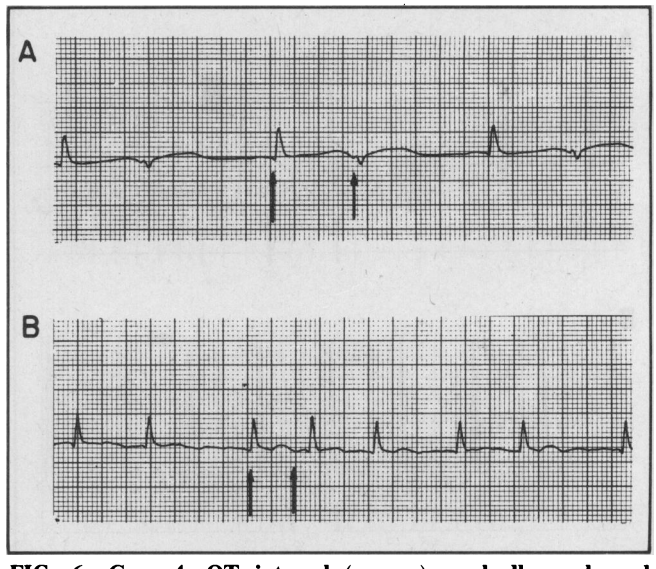

FIG. 6—Case 4: QT interval (arrows) markedly prolonged during disopyramide therapy (A) but shortened by spontaneous atrial fibrillation with more rapid ventricular response when patient not taking disopyramide (B).

heart failure or organic heart disease. Therapy with digoxin and quinidine was started, but because diarrhea developed, the quinidine was replaced by disopyramide, 150 mg every 6 hours. One week later an episode of syncope occurred and torsades de pointes was observed on the monitor (Fig. 1). Her serum potassium level was 3.2 mmol/l. The QT interval was prolonged, measuring 0.72 seconds (Fig. 6). Therapy with disopyramide was discontinued and a potassium supplement given. No further episodes of syncope occurred.

Discussion

The recognition of torsades de pointes associated with acquired prolongation of the QT interval is extremely important since removal of the offending agent is generally simple and therapeutic. The essential diagnostic features include the characteristic arrhythmia, a prolonged QT interval and disappearance of tachycardia when the offending agent has been removed and the QT interval restored to normal.[2] Our experience suggests that ventricular tachycardia associated with acquired QT syndromes is not rare.

Clinical features

The clinical features of our four patients are described in Table I. They ranged in age from 57 to 74 years. Syncope was the presenting problem in two patients and occurred subsequent to admission to hospital in the other two; most of the episodes of syncope were not accompanied by palpitation. Only one of our patients was known to have organic heart disease.

Electrocardiographic features

A prolonged QT interval during sinus rhythm was present in all four patients, and the corrected QT interval (according to Bazett's formula[12]) ranged from 0.5 to 0.72 seconds. Ventricular irritability presenting as frequent ventricular extrasystoles or bigeminy was present in all the patients before the onset of torsades de pointes, a prodrome observed by others.[3,11] The morphologic characteristics of torsades de pointes were present in all our patients, although we also noted paroxysms of the usual type of ventricular tachycardia with uniform morphologic features. This rhythm is usually grossly irregular, the rate varying between 200 and 300 beats/min. There was a cyclic variation in amplitude of the QRS complexes such that the peak appeared to be twisting sinusoidally around the isoelectric line. The distinguishing feature of torsades de pointes is the frequent spontaneous return to sinus rhythm, which is probably rare in true ventricular fibrillation.

Causes (Table II)

Membrane-active antiarrhythmic drugs, including quinidine,[9,13] disopyramide[14,15] and procainamide,[3,10] are the most frequently reported causes of acquired torsades de pointes. In three of our patients one or more of these drugs were being administered when the arrhythmia was noted. Phenothiazines, two of which were being administered to one of our patients at the time of presentation, have also been reported to cause arrhythmia.[3,16,17] Hypokalemia is the electrolyte disturbance most frequently reported as causing or contributing to

Table I—Clinical electrocardiographic and biochemical features in four patients with drug-induced torsades de pointes

Variable	Patient no. 1	2	3	4
Age (yr)/sex	57, M	71, M	74, F	71, F
Presenting problems	Dyspnea, syncope	Syncope	Dyspnea, atrial fibrillation, syncope	Paroxysmal atrial fibrillation, syncope
Associated conditions	Aortic stenosis	Chronic depression	Syncope	Hypertension, syncope
Complications before onset of torsades de pointes	Premature ventricular contractions, ventricular bradycardia	Premature ventricular contractions, junctional bradycardia	Atrial fibrillation, premature ventricular contractions	Ventricular bradycardia
No. of episodes of torsades de pointes				
Ending spontaneously	7	2	8	1
Requiring cardioversion	5	1	4	–
Medication	Disopyramide	Trifluoperazine, doxepin hydrochloride, phenytoin, furosemide	Disopyramide	Disopyramide
Serum levels				
Potassium (mmol/l)	2.9	4.1	3.5	3.2
Creatinine (μmol/l)	168.0	141.4	70.7	229.8
Treatment	Temporary overdrive pacing	Temporary overdrive pacing	Discontinuation of antiarrhythmics	Discontinuation of antiarrhythmics
QT interval (s)				
Before therapy	0.64	0.62	0.59	0.72
After therapy	0.38	0.41	0.42	0.43

torsades de pointes[3,8] and was present in three of our patients. It may be that there are many factors associated with a prolonged QT interval that contribute to the electrophysiological milieu resulting in this arrhythmia. Acquired QT syndromes usually occur as an idiosyncratic response to a given agent rather than as a toxic reaction to an overdose.[13,17-19] None of our patients had received any drug in excess of the recommended dose.

The pathogenesis of acquired QT syndromes is not known. It is possible that in susceptible individuals the offending drugs prolong the recovery of myocardial excitability and increase the dispersion of refractoriness, a situation believed to predispose to the development of re-entrant ventricular arrhythmias.[3]

Treatment

The treatment of torsades de pointes includes discontinuing all medications that may be implicated in the disorder and correcting any metabolic or electrolyte abnormalities, particularly hypokalemia. Acceleration of the heart rate results in shortening of the QT interval and cessation of ventricular arrhythmias. Ideally the heart rate must be derived empirically and is generally between 80 and 130 beats/min. It can be increased with the use of isoproterenol,[4,5] although we do not recommend that this agent be used routinely. It is preferable and safer to use ventricular[4-6] or atrial pacing,[20-22] the latter being the method of choice.[3] The pacing can be discontinued when the metabolic abnormalities have been corrected and the offending drugs withdrawn. Both the patient and the referring physician should be made aware of the need to avoid other medications known to cause this form of arrhythmia. Antiarrhythmics that are not generally known to prolong the QT interval, such as propranolol, phenytoin and bretyllium, can be used to treat subsequent rhythm disturbances, but only when treatment is clearly indicated.

Table II—Causes of torsades de pointes*

Congenital
Congenital QT syndromes
Jervell–Lange-Nielsen syndrome (with congenital deafness)
Romano–Ward syndrome (without congenital deafness)
Acquired
Drugs
Antiarrhythmic agents: quinidine, disopyramide, procainamide
Coronary vasodilators: phenylamine, lidoflazine
Phenothiazines, especially thioridazine, and tricyclic antidepressants
Complete or high-grade atrioventricular block
Electrolyte disturbances
Hypokalemia
Hypomagnesemia
Intrinsic heart disease
Myocarditis
Ischemic heart disease (uncommon)
Variant angina (uncommon)
Disease of the central nervous system
Subarachnoid hemorrhage
Complicating air encephalographic studies
Liquid protein diets
R-on-T pacemaker depolarization (very rare)

*Adapted, with permission, from Smith and Gallagher.[2]

Clinical implications

The "epidemic" of torsades de pointes at our hospital and the experiences reported recently by others[23,24] suggest that this form of arrhythmia is not a rare curiosity but an important clinical entity. It is understandable that the practitioner is inclined to attribute this ventricular arrhythmia to primary cardiac disease and therefore will increase the amount of antiarrhythmic medication or switch to a similar medication. However, the correct diagnosis of an acquired QT syndrome can lead to immediate and effective therapy. This diagnosis should be considered in any patient in whom syncope or ventricular tachycardia is of recent onset, especially when one of the medications we have mentioned has recently been prescribed.

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