Effects of a long-acting antiarrhythmic agent—QX-572¹—on therapy resistant ventricular tachyarrhythmias

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N,N-bis (phenylcarbamoylmethyl) dimethylammonium chloride (QX-572) was given to 12 patients with ventricular tachyarrhythmias resistant to other antiarrhythmic drugs, especially lignocaine. Most patients had acute myocardial infarction. The drug was slowly infused intravenously (8 mg/kg during 30 minutes) and was found very potent with a fully developed effect after about 20 minutes. In 9 of the patients the antiarrhythmic effect of a single infusion of QX-572 lasted more than 15 hours. A mild degree of tachycardia occurred in all patients during the infusion period. Blood pressure response was more unpredictable. In one patient there was a substantial increase in blood pressure after completion of the QX-572 infusion. A slight blood pressure increase after completed QX-572 infusion was observed also in some of the other patients. Slight circumoral paraesthesia was felt by all patients. Only minor side effects were found and they were considered of little clinical importance. There was no clear correlation between tachycardia and blood pressure changes and the antiarrhythmic effect of the drug. Its effectiveness in therapy-resistant ventricular arrhythmias and its long duration of action with no important side effects at therapeutically effective dosage might make QX-572 a valuable antiarrhythmic drug.

The most commonly used drugs for the treatment of ventricular tachyarrhythmias are quinidine, procainamide, and lignocaine. The most effective of these drugs, lignocaine, fails, however, in terminating ventricular arrhythmias in up to 20 per cent of the affected patients (Bigger and Heissenbuttel, 1969; Harrison and Alderman, 1972). There are also other drawbacks with these antiarrhythmic drugs. Side effects such as depression of myocardial contractility, hypotension, and conduction abnormalities have especially been described with the use of quinidine and procainamide but can be seen with other drugs (Mason *et al.*, 1973). Lignocaine is short acting and repeated injections or continuous intravenous infusion are required (Harrison and Alderman, 1972).

N,N-bis (phenylcarbamoylmethyl) dimethylammonium chloride (QX-572) is a quaternary ammonium compound and a lignocaine derivative (Fig. 1). In previous studies this new antiarrhythmic

drug was found to be effective against ventricular arrhythmias in animals (Covino and Rachwall, 1964; Katz, 1964; Madan, Khanna, and Madan, 1967) as well as in man (Katz, 1965; Schwartz, Stapleton, and Covino, 1967). Interest in the drug faded at that time probably because it has to be administered intravenously. This is because of its nature as a quaternary ammonium compound (Goodman and Gilman, 1970). Despite this limitation, such an antiarrhythmic agent might still be of value within a coronary care unit. The present investigation was undertaken to study the effect of QX-572 in patients with ventricular tachyarrhythmia, caused mainly by acute myocardial infarction, and resistant to common antiarrhythmic drugs, especially lignocaine. It was felt that QX-572 could have specific advantages by being very potent and long acting. Another advantage might be that the drug as a quaternary ammonium compound does not penetrate the blood brain barrier (Goodman and Gilman, 1970).

Subjects and methods

The drug was studied in 12 patients treated in a coronary

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QX-572

N,N-bis (phenylcarbamoylmethyl) dimethylammoniumchloride

FIG. 1 Structural formula of QX-572.

care unit. All patients had ventricular tachyarrhythmias which were considered resistant to other antiarrhythmic drugs. A brief case report of each patient is given below. A continuous electrocardiogram was recorded at a paper speed of 10 mm/sec on a Mingograf 34 (Elema-Schönander, Sweden), from 30 minutes before until 60 minutes after the start of the infusion of QX-572. Subsequently a one-minute long electrocardiograph strip (paper speed 25 to 50 mm/sec) was taken every full hour after the start of QX-572. Besides this all patients were under continuous oscilloscopic electrocardiographic monitoring according to the routine of the ward (Henning and Holmberg, 1971). Electrocardiograms were also recorded when ventricular arrhythmias were observed from the routine monitors by the nurses. Heart rate and brachial artery pressure using a cuff were measured every 5 to 10 minutes during 30 minutes before and 60 minutes after the start of QX-572 infusion and then at least once every hour. On admittance to the coronary care unit all patients had a short polyethylene catheter introduced into an arm vein. QX-572 was infused intravenously at a dose 8 mg/kg body weight over a period of

30 minutes with a few exceptions specifically outlined in the case reports.

Results

The results are given as individual case reports and in Fig. 2 to 10.

Case 1

A 69-year-old man, with coronary heart disease and one earlier myocardial infarction, was admitted with an acute myocardial infarction complicated by left heart failure and persistent therapy-resistant ventricular arrhythmia often in bigeminy. Lignocaine (2 mg/min supplemented with bolus injections of 100 mg), quinidine (1.6 g daily; serum level 3.5–4.8 mg/l.), diphenylhydantoin (oral dose 0.3 g daily and 100 mg intramuscular), procainamide (oral dose 2.0 g daily) as well as practolol (30 mg intravenously) did not suppress the arrhythmia. Treatment with these drugs, including simultaneous administration of lignocaine and quinidine, was continued for several days. QX-572 was tried after the drugs had been stopped for at least 24 hours. The ventricular

FIG. 2 Antiarrhythmic effect and response of heart rate and blood pressure to QX-572 in Case 1. Abbreviations used in this and the following figures: VPC=ventricular premature contractions; HR=heart rate; BP=blood pressure.

FIG. 3 Antiarrhythmic effect and response of heart rate and blood pressure to QX-572 in Case 2.

arrhythmia vanished rapidly, and the effect persisted for about 16 hours as can be seen from Fig. 2. At the end of the QX-572 infusion the patient experienced moderately severe short lasting central chest pain similar to earlier angina pectoris. This was most likely caused by tachycardia (97 beats/min) and disappeared within a few minutes after completing the infusion.

Case 2

A 68-year-old man with moderate hypertension, coronary heart disease, and a myocardial infarction two months before admission to hospital had a new myocardial infarction which was complicated by repetitive multifocal ventricular ectopic beats often in bigeminy. The ectopic beats persisted also during lignocaine infusion (2–3 mg/min) as well as when diphenylhydantoin was given (oral dose 0.3 g daily). The patient did not tolerate procainamide (rash) or quinidine (diarrhoea). QX-572 8 mg/kg body weight was planned to be infused during 30 minutes, but the infusion was stopped after 25 minutes (=6.7 mg/kg) as right bundle-branch block appeared. This persisted for 6 hours. The patient had shown intermittent bundle-branch block on several earlier occasions. The effect of QX-572 on the ectopic beats is shown in Fig. 3. The ventricular arrhythmia reappeared 34 hours after the QX-572 administration.

Case 3

A 50-year-old woman, with obscure cardiomyopathy possibly caused by myocarditis, was brought to the coronary care unit because of moderate left ventricular failure and frequent multifocal ventricular premature beats. Lignocaine (2 mg/min) decreased the number of premature beats but did not stop the arrhythmia com-

pletely. Quinidine (1.2 g daily), procainamide (oral dose 2.0 g daily), and diphenylhydantoin (oral dose 0.6 g daily) did not affect the arrhythmia. After withdrawal of other drugs QX-572 was infused. The ventricular ectopics were abolished for 8 hours (Fig. 4) and returned thereafter with similar frequency.

Case 4

A 34-year-old man with subvalvar aortic stenosis caused by obstructive cardiomyopathy, had postextrasystolic pressure gradient across the aortic valve of 90 mmHg. He showed numerous multifocal ventricular premature beats mostly as bigeminy and had short bursts of ventricular tachycardia. Alprenolol (oral dose 0.4 g daily) and practolol (30 mg intravenously) did not influence the arrhythmias. Procainamide produced dizziness and paraesthesia, and quinidine could not be given because of diarrhoea. QX-572 was infused with good response (Fig. 5) lasting for 16 hours. Later the patient was given ajmaline with satisfactory reduction in frequency of the ventricular premature beats.

Case 5

A 66-year-old man was admitted with acute myocardial infarction and frequent ventricular premature beats. Lignocaine (300 mg intramuscular) had a short-lasting effect (20 minutes). The arrhythmia reappeared and a short run of ventricular tachycardia was also noted. Intravenous lignocaine (100 mg bolus followed by 2 mg/min) gave rise to cerebral confusion and aggressiveness though some effect on the arrhythmia was recorded. After QX-572 the ectopic beats were completely abolished. The antiarrhythmic effect persisted for about 16 hours (Fig. 6).

FIG. 4 Antiarrhythmic effect and response of heart rate and blood pressure to QX-572 in Case 3.

FIG. 5 Antiarrhythmic effect and response of heart rate and blood pressure to QX-572 in Case 4.

FIG. 6 Antiarrhythmic effect and response of heart rate and blood pressure to QX-572 in Case 5.

Case 6

A 59-year-old man developed ventricular tachycardia 12 days after an acute myocardial infarction. The onset was preceded by multiple ventricular premature beats which could not be suppressed with lignocaine (4 mg/min supplemented with bolus injections) though the patient had convulsions. Procainamide (0.5 g intravenously) produced hypotension but the ventricular tachycardia persisted. Twenty minutes after the start of an infusion of QX-572 the ventricular tachycardia was abolished. Sinus rhythm was maintained for about 4 hours when ventricular bigeminy appeared. However, further QX-572 (4 mg/kg) restored sinus rhythm for another 3 hours. When ventricular ectopic beats again reappeared, QX-572 (2 mg/kg) was effective for only one hour (Fig. 7). Ventricular tachycardia reappeared later. Different ways were subsequently tried to stop the tachycardia. Practolol (30 mg intravenously) did not affect the rhythm nor did ajmaline (50 mg intravenously), lignocaine (4 mg/min supplemented with bolus injections of 100 mg), or quinidine (1.2 g daily) which produced anorexia when used for two days. With DC cardioversion the patient responded only to 400 joules, and stable sinus rhythm was obtained for just a few minutes. Since other antiarrhythmic agents were ineffective, further injections of QX-572 were administered. Each time the antiarrhythmic effect was almost predictable as described above, with an initial response to 8 mg/kg. An additional dose of QX-572 was needed after 4 hours. The ventricular tachycardia subsided after 6 days. During that time the patient had received totally 2.962 g of QX-572 (three times 8 mg/kg, three times 4 mg/kg, and

once 2 mg/kg). The patient received digoxin (0.25 mg daily, serum level 2.3 ng/ml with the red cell ^{86}Rb technique) when developing the ventricular tachycardia. The arrhythmia was finally interpreted as induced by digitalis.

Case 7

A 52-year-old man with left ventricular aneurysm after an acute myocardial infarction was admitted to hospital because of left ventricular failure and ventricular fibrillation. After DC conversion there were frequent ventricular premature beats not responding to lignocaine (4 mg/min supplemented by several bolus injections). QX-572 was administered initially without effect. At that time serum potassium was found to be low (2.7 mEq/l.). Infusion of potassium was started and the ectopic beats disappeared. The patient was on digitalis therapy and the arrhythmia was thought to depend on increased digitalis sensitivity caused by low serum potassium. However, quite frequent ventricular ectopic beats remained during the following days despite normal serum potassium and withdrawal of digitalis. This arrhythmia was resistant to lignocaine (4 mg/min which gave a serum level of 7.2 $\mu\text{g/ml}$). Lignocaine was withdrawn and a new trial with QX-572 was performed. The response was favourable for five hours. At that time the ectopic beats reappeared. Lignocaine was now effective up to 18 hours after the start of QX-572 infusion (Fig. 8). No side effects from QX-572 were observed, except a substantial increase in blood pressure and heart rate after the second QX-572 injection. After the first injection

FIG. 7 Antiarrhythmic effect and response of heart rate and blood pressure to QX-572 in Case 6.

tion blood pressure increased from 150/80 to 180/95 mmHg and heart rate from 88 to 102.

Case 8

A 54-year-old woman was resuscitated from ventricular fibrillation 10 days after an acute myocardial infarction. Despite lignocaine (4 mg/min supplemented with bolus

injections), which was stopped after cerebral side effects developed, and procainamide (1.1 g intravenous), ventricular fibrillation occurred 14 times during the next 15 hours. Between the attacks of ventricular fibrillation there were numerous ventricular ectopic beats and runs of ventricular tachycardia. QX-572 was administered and at the same time lignocaine was stopped.

FIG. 8 Antiarrhythmic effect and response of heart rate and blood pressure to QX-572 in Case 7.

After QX-572 the ventricular ectopic beats disappeared almost completely. No further attacks of ventricular tachycardia or fibrillation occurred. The patient improved and was dismissed from hospital.

About three weeks later she was readmitted because of syncope. The electrocardiogram showed ventricular ectopic beats and short bursts of ventricular tachycardia. Lignocaine (4 mg/min supplemented with bolus injections) and procainamide (oral dose 1.0 g) did not affect the arrhythmia. QX-572 was infused (planned dose 8 mg/kg=600 mg) and lignocaine withdrawn. After 270 mg QX-572, the patient had nausea and vomited. Immediately afterwards the blood pressure fell to a systolic pressure of 65 mmHg and the heart rate was reduced from 87 to 70 beats/min. The injection of QX-572 was stopped and the legs were raised. Five minutes later the blood pressure returned to normal. No ectopic beats were seen during three and a half hours. At that time ventricular ectopic beats and tachycardia reappeared. A second injection of 330 mg QX-572 was given to complete the planned total dose. This time there was only a slight fall in blood pressure and the heart rate increased somewhat. After the second QX-572 infusion the arrhythmia totally disappeared for another 2 hours. Thereafter ventricular ectopic beats reappeared and one run of ventricular tachycardia was recorded. Lignocaine (2 to 4 mg/min), which had previously been ineffective, now abolished the arrhythmia during the remaining part of the observation period of 24 hours. A left ventricular aneurysm complicating the first myocardial infarction was suspected.

Case 9

A 69-year-old man with previous hypertension developed acute myocardial infarction. The first day ventricular arrhythmia appeared and responded to lignocaine. When the infusion rate exceeded 2 mg/min the patient showed cerebral side effects in the form of confusion, agitation, drowsiness, and seizures. On the twelfth day the patient

had attacks of ventricular tachycardia without frequent preceding ventricular ectopic beats. Lignocaine proved effective only in a dosage of 3 to 4 mg/min but was again followed by cerebral side effects. When infusion was reduced ventricular tachycardia reappeared. During the next 4 days lignocaine induced cerebral side effects when an amount sufficient to suppress the arrhythmia was used. Finally QX-572 was infused and lignocaine was withdrawn. No further ventricular arrhythmias were noted. Quinidine (1.2 g daily) was started 12 hours after QX-572 and proved effective.

Case 10

A 54-year-old man with one earlier myocardial infarction was admitted with an acute anterior infarction complicated by left ventricular failure. Digitalis and diuretics were administered. The patient improved, but on the fifth day after infarction he developed ventricular tachycardia. The only effect of various antiarrhythmic agents administered intravenously was a reduction of ventricular rate after ajmaline (Fig. 9). DC conversion was not used as digitalis was suspected to be the cause of the arrhythmia. Twenty minutes after the start of QX-572 infusion sinus rhythm was restored. The arrhythmias did not return.

Case 11

A 67-year-old man, without earlier signs of cardiac disease, developed ventricular ectopic beats which initially responded to quinidine (1.2 g daily). Five months later the patient deteriorated. At this time there were numerous multifocal ventricular ectopic beats and runs of ventricular tachycardia. Diphenylhydantoin (oral dose 0.6 g daily) was added with effect only for a few days. These drugs were then withdrawn and intravenous antiarrhythmic treatment was started. Lignocaine (4 mg/min supplemented with bolus injections) did not prevent the arrhythmias. Single injections of procainamide

FIG. 9 Antiarrhythmic effect and response of heart rate and blood pressure to QX-572 in Case 10. DPH = diphenylhydantoin; VT = ventricular tachycardia.

FIG. 10 Antiarrhythmic effect and response of heart rate and blood pressure to QX-572 in Case II.

TABLE Data in 12 patients treated with QX-572

Case No.	Age (yr) sex	Diagnosis	Ventricular arrhythmia	Previous therapy	QX-572 Effect
1	69 M	Acute myocardial infarction	Ventricular premature beats; bigeminy	Lig; quin; DPH; proc; pract	Excellent
2	68 M	Acute myocardial infarction	Ventricular premature beats; bigeminy	Lig; DPH; proc; quin	Excellent
3	50 F	Cardiomyopathy	Ventricular premature beats	Lig; quin; proc; DPH	Excellent
4	34 M	Obstructive cardio-myopathy	Ventricular premature beats; bigeminy; ventricular tachycardia	Alp; pract; proc; quin	Excellent
5	66 M	Acute myocardial infarction	Ventricular premature beats; ventricular tachycardia	Lig	Excellent
6 a	59 M	Acute myocardial infarction; digitalis toxicity	Ventricular tachycardia	Lig; proc; ajm; quin; pract	Excellent
7 a	52 M	Coronary heart disease; left ventricular aneurysm	Ventricular premature beats	Lig	None
b			Ventricular premature beats	Lig	Good
8 a	54 F	Acute myocardial infarction	Ventricular fibrillation	Lig; proc	Excellent
b		Coronary heart disease; left ventricular aneurysm	Ventricular premature beats; ventricular tachycardia	Lig; proc	Good
9	69 M	Acute myocardial infarction	Ventricular premature beats; ventricular tachycardia	Lig	Excellent
10	54 M	Acute myocardial infarction; digitalis toxicity	Ventricular tachycardia	Lig; ajm; DPH; pract	Excellent
11 a	67 M	Cardiomyopathy?	Ventricular tachycardia	Lig; proc; pract; ajm; DPH	Excellent
12 a	63 M	Acute myocardial infarction	Ventricular tachycardia; ventricular fibrillation	Lig; proc; DPH	Excellent
b					

Lig = lignocaine, Quin = quinidine, DPH = diphenylhydantoin, proc = procainamide, pract = practolol, ajm = ajmaline, alp = alprenolol, RBBB = right bundle-branch block. * = QX-572 effective with lignocaine.

(0.2 g), practolol (15 mg), ajmaline (50 mg), diphenylhydantoin (0.25 g), were added successively to the lignocaine infusion but had no effect. Finally the patient developed persistent ventricular tachycardia. QX-572 was then infused. Sinus rhythm was restored 20 minutes after the start of the infusion and remained for more than 20 hours though some ventricular ectopic beats occurred after 13 hours. When the patient again developed persistent ventricular tachycardia 48 hours after the first QX-572 infusion (Fig. 10), another infusion was given with similar good result.

Case 12

A 63-year-old man with hypertension had an acute myocardial infarction with ventricular tachyarrhythmia. Despite lignocaine (4 mg/min supplemented by bolus injections) and procainamide (0.5 g intravenously and infusion of 90 mg/hour) rapid ventricular tachycardia and ventricular fibrillation occurred 11 times during 8 hours. QX-572 was infused. No further attacks of ventricular tachycardia, fibrillation, or any ventricular

ectopic beats were seen during the following 28 hours. The ectopic beats and runs of ventricular tachycardia then reappeared. Lignocaine was reinstituted and combined with diphenylhydantoin (0.25 g intravenously). This did not prevent some further attacks of ventricular fibrillation. QX-572 was then once more administered. During the next 6 hours short runs of ventricular tachycardia occurred twice. There were also some ventricular premature beats. Ventricular fibrillation, however, did not recur. Later quinidine and diphenylhydantoin was administered orally in combination. This regimen kept the ventricular arrhythmia under control.

To summarize the results (Table), QX-572 was injected 22 times in 12 patients with ventricular arrhythmias resistant to conventional treatment. In 7 patients (Cases 1, 2, 5, 6, 9, 10, 12) the arrhythmias were caused by coronary heart disease complicated by acute myocardial infarction. In 2 of these cases (Cases 6 and 10) digitalis toxicity and in one (Case 7) digitalis toxicity due to hypokalaemia were considered the important arrhythmia-provoking factors. Two patients (Cases 7 and 8) had coronary heart disease and previous myocardial infarction complicated by left ventricular aneurysm. Three patients (Cases 3, 4 and 11) suffered from cardiomyopathy. The amount of QX-572 was, on 18 occasions, 8 mg/kg body weight infused over a period of 30 minutes. In one of the patients (Case 6) this was supplemented with infusion of 4 mg/kg three times and 2 mg/kg once. QX-572 effectively abolished the arrhythmia in almost every case. The full antiarrhythmic effect was usually seen about 20 minutes after the start of QX-572 infusion. The antiarrhythmic effect was noted for more than 15 hours in 9 of the patients. In 2 cases (Cases 7 and 8) it seemed that ventricular arrhythmias resistant to lignocaine and QX-572 alone were abolished by the combination of these drugs.

Side effects

Circumoral paraesthesia and numbness were reported by all patients from about 15 to 20 minutes after the start of QX-572 infusion and lasting until 5 to 10 minutes after the completion of the drug administration. Heart rate increased in all patients except those with ventricular tachycardia. The maximal increase of about 20 beats/minute was reached at the end of the QX-572 infusion. Usually heart rate returned to control levels within 30 minutes. The blood pressure reaction was more unpredictable. Clinically important changes were not observed except in two patients. In one (Case 8) the blood pressure dropped to a systolic level of 65 mmHg in conjunction with nausea and vomiting.

Duration of effect (hours)	Side effects	Remarks
16	Chest pain	
> 20	RBBB ?	
8		
16		
16		
4 (a)		Response to QX-572 similar every time
3 (b)		
1 (c)		
0 (a)		
5 (+ 12*) (b)	BP increase	Digitalis toxicity + hypokalaemia (a)
> 20 (a)	BP drop	
3.5 + 2 (+ 12*) (b)		
> 15		
> 20		
20 (a)		Response to QX-572 similar both times
18 (b)		
28 (a)		
6 (b)		

On other occasions this patient received QX-572 without important blood pressure changes and since heart rate decreased at the time of blood pressure drop it was felt that vagal mechanisms could be of importance. The second patient (Case 7) experienced a substantial increase in blood pressure after the QX-572 infusion had been completed. The blood pressure spontaneously fell to ordinary levels during the next hour. This patient had also received QX-572 on an earlier occasion and at that time no untoward blood pressure change was observed. One patient (Case 1) experienced chest pain interpreted as angina pectoris at the end of QX-572 infusion. A combination of a slight increase of blood pressure and heart rate was probably responsible. The chest pain disappeared within a few minutes after completing the infusion. One patient (Case 2) who had shown intermittent right bundle-branch block on several occasions developed such a block 20 minutes after the start of QX-572. Consequently the drug was stopped but the exact correlation with QX-572 was uncertain. The highest total amount of QX-572 given to a single patient was 2.962 g (Case 6). This was given over a period of 5 days. Neither in this case nor any of the other patients were there any changes in laboratory findings concerning blood and liver or renal function which could be related to QX-572.

Discussion

In earlier studies QX-572 was found to abolish acetylcholine-induced atrial fibrillation in dogs (D'Amato and Truant, 1962). The drug has also proved effective in the treatment of ventricular tachyarrhythmias in animals induced by various means (Covino, 1962; D'Amato and Truant, 1962; Katz, 1963, 1964; Madan *et al.*, 1967). It was also shown that intracoronary infusion of QX-572 in dogs produced a positive inotropic effect and increased cardiac output and coronary blood flow (Katz, 1963). Covino and Rachwall (1964) studied the influence of the drug on isolated papillary muscles as well as in intact animals. They stated that QX-572 increased the diastolic threshold potential and prolonged the refractory period. They also noted a decrease in myocardial conduction velocity. QX-572 prolonged the refractory period more than quinidine while the increase in diastolic threshold potential was more pronounced after quinidine. Conduction velocity was lower after quinidine than QX-572 but decreased after both drugs.

Earlier clinical studies in man demonstrated that QX-572 was ineffective in the termination of chronic atrial fibrillation (Schwartz *et al.*, 1967). In patients who developed ventricular tachyarrhythmias during general anaesthesia with various drugs, QX-572 in

dosages of 2 to 8 mg/kg effectively abolished the arrhythmias in all cases (Katz, 1965). When QX-572 was given to patients with ventricular tachyarrhythmia complicating varying cardiac diseases, successful results were obtained in 17 out of 20 cases (Schwartz *et al.*, 1967). The most common side effect noted in these studies referred to was circumoral paraesthesia. Tachycardia was noted in some patients as well as moderate hypotension. The development of hypotension was thought to be related to the vasodilating action of QX-572 demonstrated earlier in animal studies (Schwartz *et al.*, 1967).

The present study confirms earlier reports of QX-572 as a potent agent against ventricular tachyarrhythmias. The antiarrhythmic effect of QX-572 in these rather malignant arrhythmias was obvious. In cases where repeated infusions were given reproducible response was obtained. All the patients in this study were treated with other antiarrhythmic agents before QX-572 was tried. In this study QX-572 was often given against life-threatening ventricular tachyarrhythmias. It was, therefore, not possible to require that earlier drugs should be totally excreted before QX-572 was given. Actually QX-572 was considered life saving in some of the present cases. Furthermore, the antiarrhythmic effect of QX-572 was found to be of long duration. This makes it reasonable to believe that possible effects of previously given antiarrhythmic drugs could be excluded. The long duration of action of QX-572 has been noted earlier (Schwartz *et al.*, 1967). This has also been found for other quaternary ammonium compounds (D'Amato and Truant, 1962).

The side effects of QX-572 noted here are in accordance with earlier findings. In the present study it should be noticed that many patients were in a poor clinical condition when receiving QX-572. This makes it difficult to evaluate the background for and importance of the observed reactions in blood pressure and heart rate. In some patients the correlation between these haemodynamic side effects and QX-572 was uncertain. The observed side effects were furthermore not considered of great clinical importance. A more pronounced fall in blood pressure has been described earlier in some patients (Katz, 1965; Schwartz *et al.*, 1967). It was, therefore, considered important to inject the drug very slowly when the present study was planned. The slow rate of QX-572 infusion obviously reduced the risk of blood pressure drop. The mechanism behind the substantial increase in blood pressure observed once in one patient after completion of QX-572 infusion is unknown. A slight tendency to a blood pressure increase after a completed

QX-572 infusion has been observed also in some of the other patients, which might indicate a correlation between QX-572 and this blood pressure reaction.

Overdrive is a well-known technique in the treatment of ventricular tachyarrhythmia. Usually the heart rate increased when the drug was given. However, there does not seem to be any correlation between the tachycardia, blood pressure changes, and the antiarrhythmic effect of QX-572. That the antiarrhythmic effect remains after the heart rate returns to normal also indicates that the heart rate effect *per se* does not contribute to the antiarrhythmic effect of the drug.

Since QX-572 as a quaternary ammonium compound is not absorbed orally, the use of the substance has earlier been considered to be of limited value (Schwartz *et al.*, 1967). However, the potency of QX-572 in therapy resistant ventricular tachyarrhythmias, its long duration of action, and apparent lack of dangerous side effects at therapeutically effective dosage, even in patients with a severely damaged myocardium, may make this drug a useful addition in the treatment of ventricular arrhythmias especially in coronary care units or during cardiovascular surgery.

A final judgment of QX-572 should, however, not be based only upon studies such as the present. For more valid conclusions concerning its antiarrhythmic activity and possible drawbacks controlled studies have to be performed. Such studies are in progress as well as studies on the electrophysiological and haemodynamic properties of the drug. The metabolism of the compound and the pharmacokinetics of its action are also under investigation.

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