Quinidine overdose

Neurological and cardiovascular toxicity in a normal person

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A case is described in which the ingestion of 4 g quinidine produced toxic effects involving mainly the cardiovascular and central nervous systems identified by electrocardiographic conduction defects, hypotension, coma, and convulsions. Different modes of therapy are discussed as is the discrepancy between blood quinidine levels and the presence of symptoms.

Since 1926 when Lewis and Drury investigated the pharmacological aspects of quinidine, there have been many reports on its toxic manifestations. Scientific investigation of toxicity has, of necessity, been carried out on animals. Luchi, Helwig, and Conn (1963) studied the toxic effects on the hearts of dogs. Cardiac toxicity in humans is usually reported as a clinical side effect during quinidine therapy. We report a case of oral quinidine overdose as a suicide attempt in a patient with no previous history of cardiovascular or neurological disease.

Case report

The patient, a 57-year-old woman, ingested 200 mg quinidine tablets. When seen 1½ hours later at a Central Receiving Hospital, she was ataxic and lethargic. Vomiting was induced at that time, but no tablet residue was obtained. She was then transferred to the Los Angeles County-University of Southern California Medical Center. On arrival on the admitting ward, 3 hours after ingestion of the tablets, she had a grand mal convulsion which recurred three times in the following 3 hours.

Physical examination Her skin was cold, moist, and cyanotic. The pulse was 90 a minute, poor volume and regular, blood pressure 50/20 mmHg, respirations 24/minute, and temperature 37°C. There was no jugular venous distension in the supine position. Praecordial examination revealed no heaves or thrills. The heart sounds were distant with no murmur, rub, or gallop. The chest

examination was initially normal, but later revealed diffuse bilateral sibilant rhonchi. She was semiconscious, responding to mild painful stimuli but not to the spoken word. There were no localizing central nervous system signs. Retinoscopy was normal.

Admission laboratory data Haemoglobin 13.0 g/100 ml; packed cell volume 38 per cent; white blood cells 17,200 cells/mm³; segmented neutrophils 76 per cent; bands 3 per cent; monocytes 5 per cent; eosinophils 0 per cent; basophils 0 per cent; blood sugar 250 mg/100 ml; blood urea nitrogen 10 mg/100 ml; serum potassium 3.3 mEq/l; serum sodium 142 mEq/l; serum bicarbonate 10 mEq/l.

Urinalysis: specific gravity 1015; pH 5.0; albumin 1+; 4-10 white cells and 10-15 red cells per high power field.

The chest x-ray was normal.

Therapy and progress The patient was given a 900 ml infusion of 1/6 molar lactate which had no effect on the blood pressure or the electrocardiogram. The blood pressure began to rise with an intravenous infusion of metaraminol (100 mg in 1 litre 5% dextrose and water); 88 mEq sodium bicarbonate was administered intravenously and followed by 45 mEq potassium chloride as a slow infusion in 1 litre of 5 per cent dextrose and water.

After initiation of therapy, the central venous pressure was found to be 18 cm water. Urine output in the first 3 hours was negligible but improved after the intravenous administration of 20 mg frusemide.

Within 3 hours, the blood pH was 7.33, and the blood pressure had risen to a systolic of over 100 mmHg. Electrocardiographic manifestations of toxicity persisted.

Because of the possible development of an uncontrollable ventricular arrhythmia or of cardiac

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standstill, a unipolar pacemaker catheter was placed in the right ventricle via the right external jugular vein under electrocardiographic guidance. It was impossible initially to achieve consistent pacing even at a level of 22 mA.

Continuous electrocardiographic monitoring was performed. Her convulsions were not associated with either cardiac standstill or ventricular arrhythmias. After about 5 hours of therapy, her condition gradually started to improve. She regained consciousness within 12 hours and was stable by the next day. She was discharged from the hospital clinically well after 4 days.

The serum quinidine level 6 hours after ingestion was 9.7 mg/l., and 80 hours after ingestion it had fallen to 0.35 mg/l.

Electrocardiograms Tracings were recorded at frequent intervals over the first 12 hours and daily thereafter. A selection is shown in the Fig.

The admission tracing (A) revealed a broad, notched P wave (thought to be indicative of slow intra-atrial conduction), prolonged PR, QRS, and QT intervals with a broad base T wave.

Subsequent recordings (B) showed progressive broadening of the QRS to 240 msec and QT interval to 520 msec 4 hours after ingestion. This was associated with a regular tachycardia of 107 a minute which could have been sinus, junctional, or ventricular in origin. This tracing strongly resembled that seen in hyperkalaemia. Extrasystoles, probably ventricular in origin, were seen on admission and 6½ hours after ingestion. Notching of the T waves was seen 6 hours after ingestion. Fifteen hours after ingestion, there were readily identifiable P waves with normal PR and QRS durations. With slowing of the rate, the QT interval had lengthened to 560 msec.

Forty-eight hours after ingestion (C) the electrocardiogram had almost returned to normal. There was some residual notching of the P waves in the precordial leads. The RSR' of the right precordial leads was retained from the admission tracing and the QT interval was slightly prolonged.

Pacing thresholds At the onset, we were unable to obtain a pacing threshold with 22 mA, whereas some 36 hours after admission, pacing was achieved with 3.5 mA.

Discussion

An interesting spectrum of cardiovascular and neurological side effects from a large oral dose of quinidine was observed in a previously healthy patient.

The cardiac toxicity is specifically of interest since it occurred in a normal heart. The rapid development of conduction defects and hypotension have been previously observed but usually in association with a variety of arrhythmias (Finnegan and Trounce, 1954; Selzer and Wray, 1964; Seaton, 1966). In these cases, quinidine was being used therapeutically in already diseased hearts. It may

FIG. Electrocardiograms: (A) admission; (B) lead II serial tracings; and (C) 48 hours after ingestion of quinidine.

be that quinidine-induced arrhythmias occur more readily if the myocardium is diseased. Hypotension has been attributed to vascular sympathetic blockade and depressed myocardial contractility (Luchi *et al.*, 1963).

The use of a demand pacemaker, to our knowledge, has not been previously described in the therapy of quinidine toxicity. We have shown, because of the very high pacing threshold, that this therapeutic approach may be of least use when it is most required, i.e. at the point when intractable ventricular tachycardia or asystole is likely to occur.

In comparison to cardiac toxicity, there is little published information on central nervous system symptoms. Thomson (1956) reviewed those cases with central nervous system abnormalities and found a pattern of coma, apnoea, and convulsions. It was, nevertheless, pointed out that these changes could have been produced by poor cerebral perfusion as a result of hypotension or transient cardiac arrhythmias. We are able to discount arrhythmias as a

cause of the central nervous system depression and convulsions in our case. Furthermore, unconsciousness continued for a period of 9 hours after blood pH and blood pressure were restored to normal levels. There was, therefore, good circumstantial evidence that the manifestations of central nervous system toxicity were directly due to the quinidine.

The drug is known to be well absorbed within the first 2 hours when taken orally and, especially when given in large doses, is rapidly bound to the protein and lipid moieties of the cell membrane (Luchi *et al.*, 1963). The serum level is thus a poor indicator of toxic effects. Bellet (1963) has commented that the effect of a given dose of quinidine is better reflected in the electrocardiogram than the serum level since quinidine tolerance varies greatly from person to person. The most pronounced electrocardiographic changes in our case did not correspond with the time at which serum levels could have been expected. The same principles are applicable to central nervous system toxicity.

Sokolow (1955), in discussing quinidine therapy, felt that 10 mg/l. was a toxic dose. Rapid attainment of these levels because of the increased cell membrane binding (Luchi *et al.*, 1963) explains the central nervous system and cardiac toxicity in our case with a predicted peak level of 12.7 mg/l.

Quinidine, by its activity on the cell membrane, is thought to increase intracellular potassium content at the expense of extracellular potassium. Extracellular hypokalaemia was present in our case, and 4 hours after ingestion the electrocardiogram showed changes similar to that found in hyperkalaemia. Different modes of therapy for quinidine toxicity have been suggested. Infusion of sodium lactate decreases quinidine concentration by expansion of the extracellular fluid compartment lowering the serum and presumably intracellular potassium as described by Singer *et al.* (1955) and increasing the blood pH which has been shown by Conn and Luchi (1961) to increase binding of quinidine to serum albumin. Recent work by Gerhardt *et al.* (1969) has shown that increasing the urinary pH decreases urinary excretion of quinidine. Finnegan and Trounce (1954) advocated the

use of adrenalin and described one case of cardiac arrest from quinidine toxicity successfully treated with intracardiac adrenalin. External electrical defibrillation has been successfully used by Rainier-Pope *et al.* (1962).

We have described the prophylactic use of a temporary demand transvenous pacemaker and have pointed out the difficulty caused by increase in the pacing threshold.

The serum quinidine estimations were performed by Bioscience Laboratories, Van Nuys, California.

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