Cerebral and cardiac toxicity of a small dose of lignocaine

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A patient is reported in whom an intravenous bolus injection of 50 mg lignocaine produced extreme sinus bradycardia (rate 14 to 20/min). Only 2 patients with such a response to a similarly small dose have been previously reported, but these reports indicate clearly that careful electrocardiographic monitoring is advisable when lignocaine is administered.

Lignocaine enjoys wide recognition as the drug of choice for the acute treatment of ventricular arrhythmias. Recent reports have called for caution in its use in patients who are elderly, or in those who have severe congestive heart failure or hepatic disease, inferior wall myocardial infarction, and those with dysfunction of the sinus node (Cheng and Wadhwa, 1973; Zelis, 1972). We wish to report here the extreme sensitivity (both cerebral and cardiac) to a relatively small dose (50 mg) of lignocaine in a patient in whom none of the above pathological states were present.

Case report

A 62-year-old diabetic man was admitted to hospital on 9 August 1973, with ventricular tachycardia. Six years before admission, he had suffered an acute inferior myocardial infarction. A second myocardial infarct in 1970 had been complicated by transient ventricular tachycardia. He was subsequently maintained on quinine sulphate 200 mg 4 times a day. Two weeks before the present admission, he had been admitted because of similar tachycardia and chest pains; cardioversion was successfully performed, no myocardial infarction was detected, and he was discharged after a few days.

On the day of the present admission, the patient was brought to the emergency room with chest pains and palpitations. The heart rate was 150/min, and the blood pressure was 160/90 mmHg (21.2/12.0 kPa). The chest was clear on auscultation, there were no murmurs, and there was no hepatic enlargement or tenderness. Blood urea, electrolytes, calcium, phosphorus, and liver enzymes (SGOT, SGPT, alkaline phosphatase) were

normal. Blood glucose was 150 mg/100 ml (8.33 mmol/l). An electrocardiogram showed a tachycardia at a rate of 150 beats per minute and widened QRS complexes. The rhythm was erroneously interpreted by the housestaff as being supraventricular tachycardia with aberration. The only treatment given during the first day was three oral doses of 250 mg procainamide. His chest pains subsided without any specific treatment and the blood pressure and pulse remained unchanged.

An electrocardiogram (Fig. 1) recorded on the second day revealed fusion beats and a biphasic pattern of the QRS complex in V_1 , features that suggested that the tachycardia was ventricular in origin. The patient was therefore given an intravenous bolus of 50 mg lignocaine over 2 minutes. The tachycardia promptly abated and was replaced by normal sinus rhythm (at a rate of 75/min) as the last few milligrams of drug were given.

However, within three to four minutes, the patient had, in quick succession, three generalized *grand mal* convulsions which lasted a few seconds each. He then received 2.0 mg diazepam intravenously, after which he remained drowsy. The respiratory rate remained good. An electrocardiogram recorded after the last convulsion showed normal sinus rhythm at a rate of 75 per minute. A few seconds later, the sinus rate was noted to slow considerably and was then replaced by a slow AV junctional rhythm (Fig. 2A) with a rate of 43/min. As this AV junctional rhythm also slowed, an extremely slow and unstable sinus rhythm became re-established (Fig. 2B-E) with a rate as slow as 14/min (Fig. 2E). Because of the onset of extreme sinus bradycardia cardiac massage was performed although spontaneous respiration persisted, and isoprenaline was injected intravenously. As a result, AV junctional rhythm with a rate of 90/min, and then normal SA nodal rhythm were re-established. The patient recovered fully. Serial myocardial enzymes

FIG. 1 *A*) Tracing obtained during sinus rhythm with frequent ventricular premature beats. *B*) Tachycardia with a rate of 150/min. The QRS complexes are similar to the ventricular premature beats in *A*. This feature and the appearance of fusion beats (e.g. first beat in aVR, penultimate beat in aVL, 6th beat in V1, 4th beat in V4, 5th beat in V5) indicate that the tachycardia is most probably of ventricular origin.

FIG. 2 Effect of lignocaine on the electrocardiogram. *A*) Slow AV junctional rhythm. Appearance of deflections of the baseline (marked x) which may represent artefacts caused by laboured breathing. *B*) and *C*) Further slowing of AV junctional rhythm and reappearance of an extremely slow SA rhythm (marked 1). The 3rd, 6th, and 8th QRS in *C* represent escape AV junctional beats. *D*) and *E*) Further slowing of SA nodal rhythm. Baseline deflections are no longer visible (lead III: ECG speed – 25 mm/s).

remained normal. A careful investigation (including inspection of the vials and the quantity of drug withdrawn for the treatment of the patient) failed to reveal any error in dosage of the lignocaine solution. A 12-lead electrocardiogram obtained subsequently during normal sinus rhythm with frequent ventricular premature ectopic beats (Fig. 1A) showed that the configuration of these ventricular beats was clearly similar to that of the QRS complexes during the tachycardia (Fig. 1B). This feature further confirmed the correctness of the impression of ventricular tachycardia.

The patient is being further investigated with regard to the possibility of a ventricular aneurysm being present and related to the occurrence of the ventricular tachycardia.

Discussion

Lignocaine is probably the safest drug available for the acute treatment of ventricular arrhythmias. This is due to the relative absence of side effects, as well as to the short duration of these side effects when they do occur. Yet, two recent cases and one editorial have called attention to the possibility of severe sinus bradycardia or standstill with relatively small doses of lignocaine (Lippestad and Forfang, 1971; Wood, 1971; Zelis, 1972). As far as we are aware this is the third reported case in the English literature of unusual sensitivity to a relatively small dose of the drug. Another report has recently documented the occurrence of sinoatrial standstill after lignocaine (Cheng and Wadhwa, 1973); however, the dose used was at the upper limit of the recommended range, the patient was 88 years old, and he was recovering from severe acute pulmonary oedema. An additional patient reported by Flensted-Jensen and Sandøe (1969) developed asystole after the injection of 150 mg of lignocaine. He also had had a large acute anterior wall infarction and had received antazoline. One other patient developed a similar reaction while receiving lignocaine by continuous infusion and after having been treated with quinidine sulphate (Jeresaty, Khan, and Landry, 1972). The patient reported here is unique in that he developed two separate manifestations of exquisite sensitivity to lignocaine: central nervous system toxicity, and cardiac toxicity in the form of extreme sinus bradycardia with a rate of 14 to 20/minute. These events, furthermore, occurred in the absence of congestive heart failure, thus excluding the possibility of excessive blood levels. There has not been any evidence of 'sick sinus syndrome' or of AV block at any time during the subsequent follow-up period, either of which might have accounted for the effects of lignocaine on the cardiac electrical events. Finally, the possibility of inadvertent overdosage was also excluded. It is therefore not clear why this patient developed such a severe reaction to only 50 mg lignocaine. One

can only surmise, as mentioned earlier, an exceptional cerebral as well as cardiac sensitivity to lignocaine.

The question of possible potentiation of lignocaine by other drugs must be raised. The possibility that the oral dose of 750 mg of procainamide the day before could have potentiated the effect of lignocaine is slight because of the short half life of this drug and the lapse of time between the last dose and the injection. The patient also received 2 mg diazepam intravenously as anticonvulsant therapy. The time relation between the injection of diazepam and the onset of bradycardia could easily be construed as indicating a cause and effect relation. However, diazepam has not been reported, to the best of our knowledge, to produce sinus bradycardia, except in large doses in two dogs in one experimental study (Nevins, 1971). It should be noted, as mentioned previously by Zelis (1972), that three instances of severe sinus bradycardia so far noted after lignocaine have occurred in patients who were receiving other drugs as well (Jeresaty *et al.*, 1972; Lippestad and Forfang, 1971; Wood, 1971). The possible additive effect of lignocaine and other drugs remains an unresolved question.

Reactions to lignocaine such as described here should not, however, be entirely unexpected in clinical situations for it is clear that some patients do exist who are extremely sensitive to lignocaine though it is admittedly difficult to produce sinus bradycardia with small doses of lignocaine in experimental animals (Lieberman *et al.*, 1968) or man (Rydén, Cullhed, and Wasir, 1972). Lignocaine also exerts little electrophysiological effect on atrial fibres in tissue bath preparations (Mandel and Biggar, 1971).

The necessity for careful observation after lignocaine administration, already indicated by Cheng and Wadhwa (1973), can only be again emphasized. The need to administer lignocaine with extreme caution has become well recognized in patients of advanced age, or in those with sinus node dysfunction or inferior wall myocardial infarction. Continuous infusion of lignocaine in the presence of hepatic dysfunction or severe congestive heart failure is especially hazardous, since they predispose to excessive blood levels of lignocaine. This report, and others, of sensitivity to small doses of lignocaine suggests in addition that it may not be advisable to administer the drug prophylactically to *all* patients with suspected acute myocardial infarction as has been recently advocated.

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Addendum

Since submission of our paper, another article (Parameswaran *et al.*, 1974) has demonstrated the same effect in two patients, both of advanced age.