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THE ELECTROCARDIOGRAPHIC EFFECTS OF INTRA-VENOUS ADMINISTRATION OF NEOSTIGMINE AND ATROPINE DURING CYCLOPROpane ANESTHESIA

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Several instances of sudden death have been reported following the intravenous administration of neostigmine and atropine in anesthetized and curarized patients. Macintosh (1) described the case of a gravely ill, 38 year old man with acute suppurative appendicitis and peritonitis; the anesthetic technique used was pentothal-cyclopropane-curare with carbon dioxide absorption. At the conclusion of the operation, 2.5 mg. of neostigmine and 0.65 mg. of atropine sulfate were administered intravenously; within one to two minutes the pulse disappeared and the patient died. Hill (2) presented the case of a deeply jaundiced, 7 week old infant with congenital atresia of the common bile duct; the anesthetic technique was open drop ether with curare. At the end of the operation, 0.25 mg. of neostigmine and 0.2 mg. of atropine sulfate were given intravenously. The infant collapsed immediately, failed to respond to resuscitative measures and died. Clutton-Brock (3) recorded the case of a deeply jaundiced, 62 year old woman with common bile duct obstruction; the anesthetic technique was hemithal-nitrous oxide-cyclopropane with curare. On completion of the operation, 2 mg. of neostigmine and 0.6 mg. of atropine sulfate were injected intravenously. Shortly afterward the patient became gray, pulseless and died; cardiac massage was ineffective. Waquet (4) reported 2 cases of sudden death in adults following the use of 0.5 mg. of neostigmine as an antcurare agent; in both cases the anesthetic technique was nitrous oxide-ether with carbon dioxide absorption.

These deaths were attributed to the cholinergic action of neostigmine on the heart. Bain and Broadbent (5), however, presented an interesting and dissenting explanation as to the cause of these fatalities; they pointed out that the initial effect of atropine is central vagal stimulation with slowing of the pulse rate. They submitted, therefore, that atropine would potentiate the cholinergic action of neostigmine when given simultaneously with the latter drug. They concluded that the simultaneous administration of atropine and neostigmine was

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contraindicated and that, even if atropine did not potentiate the cholinergic action of neostigmine, it was unlikely to produce an effective immediate anticholinergic response.

We thought it desirable to obtain a clearer picture of the sequence of events following the intravenous administration of neostigmine and atropine sulfate. By utilizing the technique of continuous electrocardiographic observation, we could determine presence or absence of potentiation of neostigmine by atropine and the nature and pattern of cardiac response to these drugs in anesthetized patients.

Method of Study

Twenty adult surgical patients, in good health, were premedicated with average adult doses of morphine sulfate and atropine sulfate, and were anesthetized with cyclopropane, carbon dioxide absorption technique. The patients were maintained in lower first and upper second planes of surgical anesthesia. Ten of these patients received tubocurarine chloride to the point of intercostal paralysis and, in some cases, to the level of partial diaphragmatic paralysis. Assisted respiration was used to maintain normal respiratory tidal volumes. All operations were of an extra-abdominal nature.

Before the induction of anesthesia, the patient was connected by
Administration of Neostigmine and Atropine

TABLE 1

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Patients</th>
<th>Dose of Neostigmine, mg.</th>
<th>Type of Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Minimal</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>0.5</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>0.5 (two separate successive doses)</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>1.0</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>1.5</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>2.0</td>
<td>0</td>
</tr>
</tbody>
</table>

electrode leads to two recording devices: (a) a cardiotachoscope which afforded continuous visual observation of the pulse rate and electrocardiogram on calibrated oscillographic screens (6) and (b) a direct writing electrocardiogram which was attached in series to the cardio-

![Fig. 2. The effects of intravenous administration of atropine (0.8 mg.) in the same patient as shown in figure 1 at the height of neostigmine activity. There was no increase in the bradycardia but rather a marked irritability of the heart. Ventricular extrasystoles (strip IV) gave way to ventricular tachycardia of multifocal origin with an occasional complex of sinus origin (strip V). In VI a, a slow run of ventricular flutter can be seen. The multifocal origin of the tachycardia persisted for a considerable time. Five minutes after the injection of atropine, a bigeminal rhythm still predominated (strip VII). Ten minutes later a sinus tachycardia remained (strip VIII).](image)
tachoscope so that immediate records could be taken of the standard limb leads. Electrocardiographic tracings were taken before induction of anesthesia and after surgical anesthesia was attained. Also, tracings were made before the injection of each drug, while continuous recordings were taken thereafter.

An intravenous saline drip was in situ to afford immediate access to a vein. All drug solutions were prepared in advance and ready for instantaneous use. Following the electrocardiographic studies, the patient was kept in the operating room until his electrocardiogram was normal and cardiorespiratory condition satisfactory and stable.

![ECG tracings](image)

**Fig. 3.** Patient was 46 years of age. A mild prolongation of the P–R interval followed intravenous administration of neostigmine (1 mg.) with a 2:1 heart block in strip III. Atropine sulfate (0.8 mg.) was given (arrow in strip III); this produced a rapid shortening of the P–R interval associated with sinus tachycardia. Also, the R–T segments became somewhat depressed and the T waves iso-electric.

The 20 patients were divided into five groups according to the administered dosage of neostigmine (table 1). Atropine sulfate, 0.8 mg., was given intravenously to each patient at the height of neostigmine activity, as determined by electrocardiographic evidence. It was our premise that the height of action of neostigmine coincided with the collective cardiographic changes. Continuous electrocardiographic tracings permitted second to second observation of the effects of neostigmine; when these effects were stabilized and fixed, it was assumed that the peak of neostigmine action was reached. It was significant that in each case no further electrocardiographic changes occurred until atropine was administered intravenously.
RESULTS

Every patient showed some electrocardiographic change following the intravenous administration of neostigmine. No striking blood pressure changes were recorded; minor, transient depressor effects were seen in several cases.

The minimal electrocardiographic changes following administration of neostigmine were sinus bradycardia, first degree auriculoventricular block, increased amplitude of the QRS complex and increased prominence of the T wave. These changes were present either individually or in combination with one another. Seven of the 12 patients in the first three groups showed these minimal changes; the remaining 5 patients showed marked changes as did all of the patients in the last two groups. There was at least one patient in each group who showed marked electrocardiographic changes. Representative electrocardiographic tracings of these are presented in detail in the illustrations (figs. 1–5).
FIG. 5. Patient was 42 years of age. Intravenous injection of neostigmine (2.0 mg.) caused marked bradycardia. After the administration of atropine (0.8 mg.) there was a change to partial heart block and sinus tachycardia (strips III, IV, V). A bigeminal rhythm was recorded in strip VI.

DISCUSSION

These electrocardiographic studies indicate that intravenous administration of neostigmine in patients under cyclopropane anesthesia will produce classical cholinergic effects of varying intensity, sinus bradycardia, wandering pacemaker, all degrees of auriculoventricular block and sinus arrest. The minimal changes mentioned earlier in this paper were described by Goldfinger and Wosika (7) following the subcutaneous administration of 1 mg. of neostigmine in unanesthetized patients; they did not observe the marked changes recorded in our study. The frequent, marked electrocardiographic changes observed by us can be attributed, in part, to the cholinergic properties of cyclopropane which exaggerated the usual cardiac effects of neostigmine. Also, we used the intravenous route of administration; this permitted a full and rapid action by neostigmine in contrast to a slower and less potent effect when given subcutaneously.

There was no evidence to support the theory of Bain and Broadbent (4) that atropine potentiated the cholinergic effects of neostigmine by central vagal stimulation. Instead, in every case, atropine
Administration of Neostigmine and Atropine

Given intravenously produced opposite effects; these were heralded by reactivation of sinus activity and followed by increased auriculoventricular conduction. As the degree of muscarinic block increased, a ventricular pattern became more prominent with the appearance of sinus tachycardia, ventricular premature contractions, bigeminy and paroxysmal ventricular tachycardia of short duration. Thus, a picture of unopposed adrenergic activity was present.

It should be noted that marked electrocardiographic changes were observed in each of the five groups. Careful examination of the electrocardiographic tracings failed to demonstrate a difference in the neostigmine effects on the curarized and noncurarized patients; some differences might have been anticipated because of the vagolytic action of curare (8). It is possible that heavier curarization would have elicited some vagolytic protection against the muscarinic effects of neostigmine.

It would be pertinent to speculate at this point on the cause or nature of “neostigmine deaths.” It is clear that neostigmine alone, in a normal patient under cyclopropane anesthesia, can produce profound disruption of auriculoventricular conduction, marked depression of the sinus node and sinus arrest. These disturbances can terminate easily in cardiac arrest, particularly in patients with jaundice, perforated peptic ulcer and sinus bradycardia in whom there is increased vagal tone (9). It is significant that the deaths reported by Hill (2) and Clutton-Brock (3) occurred in deeply jaundiced patients.

The electrocardiographic responses to intravenous administration of atropine were striking. The runs of ventricular tachycardia and, in one case, a short burst of ventricular flutter are of particular interest. Johnstone (9) ascribed these atropine effects during anesthesia to an elevated arterial p carbon dioxide and suggested that “neostigmine deaths” might be attributable to ventricular fibrillation precipitated by atropine in the presence of carbon dioxide excess. This interesting hypothesis warrants further quantitative studies.

An examination of the pharmacologic actions of neostigmine and atropine offers another explanation of “neostigmine deaths.” Neostigmine, an effective inhibitor of cholinesterase, has muscarinic and nicotinic effects. Under ordinary conditions the muscarinic action predominates. In the atropinized animal the muscarinic action of neostigmine is blocked and the nicotinic effect predominates; the result is as if an adrenergic drug were administered (10). Therefore, we may speculate that the combined effect of neostigmine and atropine produces sufficient adrenergic stimulation to precipitate fatal ventricular fibrillation, particularly during cyclopropane anesthesia (9).

Considerable weight is given to this theory by Hoffman et al. (11) who showed them the action of acetylcholine on the atropinized heart was very similar to that of epinephrine. These workers presented evidence that acetylcholine releases an epinephrinelike substance in
the atropinized heart. They postulated that acetylcholine acts on certain intracardiac structures and stimulates them to liberate epinephrine or some related sympathomimetic substance. These studies were confirmed by McNamae et al. (12).

The release of epinephrine by acetylcholine or by a potent anticholinesterase substance such as neostigmine, could precipitate ventricular fibrillation during cyclopropane anesthesia which is known to sensitize the heart to sympathomimetic amines (13). The ventricular tachycardia of multifocal origin and ventricular flutter seen in our studies (fig. 2, fig. 4) lend further support to this hypothesis.

One cannot be dogmatic about the clinical implications of our studies. It does appear, however, that the intravenous administration of neostigmine during anesthesia, with or without atropine, presents significant cardiovascular hazards. It is probable that these risks are increased with cyclopropane anesthesia. Certainly, hypoxia owing to inadequate respiratory tidal exchange could enhance these risks.

This study raises several questions which remain to be answered. The effect of intravenous atropine in the presence of an elevated arterial carbon dioxide merits quantitative examination and is now under investigation. Also, there is the question of the effect of the simultaneous, rather than separate, administration of neostigmine and atropine. In the present study, the two drugs were administered separately because it was desirable to delineate the effects of neostigmine; it will be recalled that several deaths occurred following the use of neostigmine alone (4). Also, in this manner, one could determine whether or not atropine potentiated the cholinergic action of neostigmine. However, can it be assumed that atropine acts in the same fashion after neostigmine has exerted its action as atropine acts when both of the drugs are developing their pharmacological effect? This question, too, is under investigation.

Summary

The electrocardiographic effects of intravenous administration of neostigmine and atropine during cyclopropane anesthesia are described and analyzed.

Neostigmine in doses of 0.5–2.0 mg. given intravenously produces profound disruption of auriculoventricular conduction, sinus depression and sinus arrest. The addition of atropine (0.8 mg.) results in marked adrenergic activity, cardiac irritability, multifocal ventricular extrasystoles and ventricular flutter.

The possible mechanisms of "neostigmine deaths" are presented.

The electrocardiographic tracings do not support the contention that atropine, by central vagal stimulation, potentiates the cholinergic action of neostigmine on the heart.
The studies suggest that "neostigmine deaths" during anesthesia are attributable to either (1) the cardio-inhibitory action of neostigmine or (2) the adrenergic effect of neostigmine and atropine with resulting ventricular fibrillation.

ACKNOWLEDGMENT

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REFERENCES

4. Waquet, G.: Curare and Neostigmine, Two Cases of Death Caused by Cardiac Syncope after Neostigmine Administration, Marseille Chirurg. 3: 335-339 (May-June) 1951.

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