THE ANTI-CURARE AGENTS

BY

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It is a truism to say that the only safe remedy for respiratory depression due to curarizing drugs is artificial respiration. It is, however, often very inconvenient to control a patient's breathing until such time as full spontaneous respiratory activity returns. Fortunately there has long been available in "prostigmin" (neostigmine, *B.P.*) an adequate and effective antidote drug. A few years ago, however, several fatalities were recorded shortly after the administration of this agent (Macintosh, 1949; Clutton-Brock, 1949; Hill, 1949). Lately the drug "tensilon" (3-hydroxyphenyl-dimethyl-ethyl ammonium iodide) has been adopted as an anti-curare agent in the United States. It has been investigated in Britain (Doughty and Wylie, 1952; Hunter, 1952) and found to be free from the dangers of

excessive parasympathetic stimulation inherent in the action of neostigmine. Unfortunately, tensilon has a very short action, and relapse into partial curarization may occur within some 10 minutes, especially in the deeply curarized subject. Neither antidote is thus completely satisfactory. However, since neostigmine is undoubtedly the more effective of the two, it seemed a matter of some importance to try to elucidate further the dangers of its administration and the methods available for their elimination.

The Investigation

Neostigmine was given to a series of 50 patients who had been curarized with various substitution myoneural blocking agents. All cases had been anaesthetized with nitrous oxide and oxygen and a supplement. It is generally agreed that the primary danger of neostigmine administration is cardiac inhibition. The pulse rates of the patients to whom the drug was given were therefore counted repeatedly at short intervals in order to obtain information on four points: (a) the pattern of the response of the pulse rate to neostigmine given with atropine; (b) the effect on this of giving the atropine some minutes before; (c) the modification induced by giving a sympathomimetic drug with the

FIG. 1.—Pulse-rate changes after neostigmine, 1 to 1.5 mg., with atropine, 1/100 gr. (0.65 mg.)

FIG. 2.—Later pulse-rate changes after neostigmine and atropine (doses as in Fig. 1).

FIG. 3.—Pulse-rate changes after administration of neostigmine, 2.5 mg., with atropine 1/50 gr. (1.3 mg.).

FIG. 4.—Pulse-rate changes after atropine 1/100 gr. (0.65 mg.), followed some minutes later by neostigmine, 1 to 1.5 mg. The time of administration of the neostigmine is indicated by the change from a broken to a solid line in the graph.

atropine and neostigmine; and (d) the appropriate amount of atropine required to make the ordinary doses of neostigmine safe.

Pattern of the Response of the Pulse Rate

The obvious danger of the administration of neostigmine is cardiac inhibition. With this in view, the pulse rates of patients to whom this drug was given with atropine were counted every 15 seconds after the injection had been completed (Fig. 1). It will be seen, however, that in every instance such change as did appear was in fact an acceleration and not a slowing. Presently it became apparent that bradycardia developed later in some cases. The pulse rates were therefore counted every minute for as long as possible after the injection of the drugs. In every instance it was found that there occurred a progressive slowing of the pulse rate to a minimum during the first 5 to 10 minutes after the injection had been given. Typical results are shown in Figs. 2 and 3. The slowing in some cases amounted to 60 beats a minute. The ultimate rate attained was related to the initial heart rate. In patients with a tachycardia of

120 or more at the time neostigmine and atropine were given the rate tended to slow to speeds between 70 and 100 a minute. In those whose pulses were relatively slow there was a tendency to obvious bradycardia, and rates of 40 to 50 were sometimes seen.

Effect of Giving Atropine before Neostigmine

The work reported in the previous paragraph had suggested that in the anaesthetized human subject no initial period of slowing followed the administration of atropine intravenously. None the less, as the view is widely held that atropine slows the pulse by medullary stimulation before its peripheral accelerating mechanism develops, it seemed desirable to obtain direct evidence on this point. The pulse rates were therefore followed in patients to whom atropine was given at varying periods before the neostigmine. Neither with 1/100 gr. (0.65 mg.) (Fig. 4) nor with 1/50 gr. (1.3 mg.) (Fig. 5) was there any evidence of an initial bradycardia. Further, the pulse rate accelerated apparently immediately on the arrival of the drug at the heart. There was no change in the pattern of the response to the subsequently administered neostigmine even in a case in which 19 minutes elapsed between the injection of the two drugs.

Effect of Vasopressor Drugs

In the very early days of curarization in anaesthesia one of my cases became completely pulseless after the injection of neostigmine alone. For some years after that incident it was my habit to inject either 30 mg. of ephedrine or 10–20 mg. of methedrine with the neostigmine and atropine. Patients so treated were investigated in exactly the same way as those already described. It was found that the addition of a vasopressor to the antidote mixture produced a rather greater initial cardio-acceleration (Fig. 6). The pattern of the subsequent slowing of the pulse rate, however, remained unaltered (Fig. 7). There was some suggestion that the minimum pulse rate in these cases was a little higher than those in patients to whom no vasopressor had been given. The differences were

FIG. 5.—Pulse-rate changes after atropine, 1/50 gr. (1.3 mg.), followed some minutes later by neostigmine, 2.5 mg. The time of administration of the neostigmine is indicated by the change from a broken to a solid line in the graph.

FIG. 6.—Immediate pulse-rate changes after administration of neostigmine, atropine, and a vasopressor drug. Doses: neostigmine, 1 to 1.5 mg.; atropine 1/100 gr. (0.65 mg.); ephedrine 30 mg. or methedrine 10 mg.

FIG. 7.—Later pulse-rate changes after neostigmine, atropine, and a vasopressor drug. Doses as in Fig. 6.

neither statistically significant nor striking in degree. There therefore seems to be little need for the use of vasopressors with neostigmine and atropine. Further, in two of the patients to whom this combination of drugs was given the pulse became completely irregular two minutes later and then gradually returned through a period of extrasystoles to normal during the succeeding 10 minutes.

Adequate Protective Dose of Atropine

It is very difficult to define a danger point in neostigmine administration, since a pulse rate of 50 may be physiological in a tall trained athlete, yet indicate the presence of a

FIG. 8.—Pulse-rate changes after administration of neostigmine, 2.5 mg., with atropine, 1/100 gr. (0.65 mg.)

profound vagal action on the heart in a small untrained woman. None the less, it was assumed for the purpose of this study that a dangerous degree of bradycardia was present when the pulse rate reached 50 a minute after the administration of neostigmine. So far, no patient to whom 1/50 gr. (1.3 mg.) of atropine has been given with neostigmine has developed a bradycardia of less than 50 even with a dose of 2.5 mg. of this drug. Only one of a series of 20 patients to whom 1/100 gr. (0.65 mg.) of atropine has been given with 1 to 1.5 mg. of neostigmine has developed a similar bradycardia. But in the only two patients of this series who received 2.5 mg. of neostigmine with 1/100 gr. (0.65 mg.) of atropine there appeared pulse rates of less than 50 (Fig. 8). In one of these cases methedrine was injected because the interval between the beats became so long that asystole seemed imminent. It is therefore suggested as a tentative working arrangement that 1/50 gr. (1.3 mg.) of atropine should be used when 2.5 mg. of neostigmine is given.

Discussion

The main finding of interest in this study was the absence of an initial slowing of the pulse in the patients to whom atropine was given. It has been believed for years that the first action of this drug is to stimulate the cardio-inhibitor centre in the medulla oblongata. Various studies of different features of its action have demonstrated this, and it has been repeatedly shown that when the drug is injected subcutaneously the first result is beyond question a slowing of the pulse rate (Sturgis *et al.*, 1919, McGuigan, 1921; Harris, 1921; Platz, 1922). This result occurs even with doses of 2 mg. (Bain and Broadbent, 1949). The findings of the present study are not, however, entirely without precedent. There is sound reason to believe that in the human subject, when atropine is rapidly injected intravenously, the initial cardio-inhibitor phase of its action is not in evidence. Thus Platz (1922) found that this was so provided that the dose was greater than 0.5 mg. Smith *et al.*

(1928) report that 1.2 mg. of the drug injected intravenously caused a prompt rise in pulse rate. They also comment that slowing sometimes occurred during the injection. If this was so they must have given the drug very slowly, as it requires at least 15 seconds for the transfer of any substance given intravenously at the elbow to the brain, and this interval must have elapsed before the drug they gave could produce any central slowing of the pulse. Shearer (1951), in his study of the action of intravenously injected atropine and scopolamine, found no slowing of the pulse five minutes after the drugs had been given. By contrast, it has become apparent in this study that the maximum effect of neostigmine on the pulse rate is not immediate. It requires at least five minutes for its development. It is thus clear that there is very little danger of summation between the cardio-inhibitor action of neostigmine and atropine injected intravenously in the same syringe.

It is apparent from the degree of bradycardia which has been noted in some of the patients that, even when apparently suitable doses of atropine with neostigmine are given, considerable degrees of cardiac inhibition can still occur. It is thus by no means improbable that the deaths which are reported as having occurred subsequent to the administration of neostigmine were in fact largely due to it. On the other hand, cardiac inhibition due to neostigmine does not occur suddenly and without warning. It is preceded by a gradually increasing bradycardia. If such a phenomenon is observed it is quite safe to inject an additional dose of atropine to accelerate the heart, provided that at least 1/100 gr. (0.65 mg.) is given, and that quickly. There is a corollary to this study. It is impossible to forecast the exact degree of bradycardia which will be produced by a dose of neostigmine. No patient, therefore, to whom this drug has been given should be left unwatched for the succeeding 10 minutes at least.

Summary

The pulse rates of a series of patients to whom neostigmine had been given with atropine, with or without vasopressor drugs, were counted at frequent intervals. It was established that the immediate effect of the intravenous injection of these drugs was a cardio-acceleration. In the subsequent five minutes or so the pulse rate slowed, often a great deal. It may well be that this slowing is an indication that in inadequately atropinized patients cardiac inhibition to the point of standstill may occur.

It is suggested that 1/50 gr. (1.3 mg.) of atropine should be given when 2.5 mg. of neostigmine is used for purposes of decurarization, and even when this amount of atropine is used patients should not be left alone until it has been established that excessive bradycardia is not going to develop—that is, until some 10 minutes has elapsed.

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In the January issue of *Endeavour* (Vol. XII, No. 45) there is an attractive colour plate showing the blotched African genet nursing her kittens. The genet is the only mammal in which cystinuria is known to be a normal condition. Research on the metabolism of the genet now in progress is hoped to reveal new information that will be of value in treating this condition in man.