THE INTRA-ARTERIAL INJECTION OF NEOSTIGMINE AS A
DIAGNOSTIC TEST IN MYASTHENIA GRAVIS

BY

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Harvey, Lilienthal, and Talbot (1941) and Harvey and Lilienthal (1941) reported that the effects of the injection of both acetyl choline and neostigmine into the brachial artery of patients with myasthenia gravis differed profoundly from those in the normal subject. Their results with acetyl choline could not be repeated by Wilson and Stoner (1947) or by Acheson, Langohr, and Stanbury (1948), but the intra-arterial injection of neostigmine is now recommended in standard textbooks as a diagnostic test for myasthenia gravis (Brain, 1951; Nattrass, 1952). Harvey and Lilienthal (1941) found that in all their cases of myasthenia gravis the power in the injected arm, which they imply was clinically myasthenic, improved after the injection, in contrast to the paralysis and fasciculation produced in the normal. The current theories of the pathogenesis of myasthenia gravis postulate an abnormal agent circulating in the blood, either with a curare-like action (Wilson and Stoner, 1944) or with the power to inhibit the synthesis of acetyl choline (Torda and Wolff, 1944). Presuming the existence of some such generalized metabolic defect, and despite the often extremely localized clinical manifestations of the disease, it would at least be reasonable to suppose that the intra-arterial neostigmine test might bring to light abnormalities in clinically unaffected muscles. It had come to our notice that the test was in fact being used in this way and that deductions as to the cause of oculomotor and bulbar palsies were being made from the response of clinically unaffected muscles to intra-arterial neostigmine. It was, therefore, decided to examine the results of such injections in myasthenic patients in whom the injected arm was affected and in those in whom it was not. As the paralysis produced in normal subjects has been presumed to be due to the accumulation of excessive amounts of acetyl choline, and therefore only quantitatively different from the response in myasthenia, the effects of graded doses were also studied in some of these patients.

Methods

Neostigmine methylsulphate was injected in doses of 0.25 to 1.5 mg. in a 0.25% solution, in all cases the initial dose being 1.0 mg. For subsequent injections the dose was reduced if paralysis had occurred with 1.0 mg. and increased if it had not. The injections were made with a tuberculin syringe and a hypodermic needle into the brachial artery at the elbow. The venous return from the arm was occluded with a sphygmomanometer cuff during the injection and for four minutes afterwards. During the actual injection the artery was occluded by digital compression immediately above the site of the injection. The release of the arterial flow on the completion of the injection ensured as far as possible the arrival of the neostigmine at the muscles in maximum concentration. The same arm was used throughout in each patient, and although no adverse effects on the vessel were observed, it was not thought justifiable to make more than two injections into the same artery. Both of us had gained considerable experience in the technique of the injection before the start of the present investigation, and no results are included in which there was doubt as to the injection being intra-arterial. Atropine, gr. 1/100 (0.6 mg.), was given subcutaneously 15 minutes before the injection.

The strength of the grip was measured on a mercury dynamometer before and at varying intervals after the injection. The possible effects on the grip of venous occlusion and of the discomfort of the arm-band were checked in each patient and were found to be negligible. When any doubt existed as to the clinical involvement of the injected arm the response of the grip to the subcutaneous injection of 2.0 mg. of neostigmine was recorded on a separate occasion.

Clinical Material

Ten patients were examined. In all the diagnosis of myasthenia gravis had been established by the usual clinical means and by the response to subcutaneous and oral neostigmine. In five patients signs of the disease were confined to the muscles supplied by the cranial nerves, while in the other five the injected arm was clinically myasthenic. All patients who were taking neostigmine omitted it before the test for as long as seemed to us safe.
Results

The results are shown in Table I. It can be seen that when the injected arm was not clinically myasthenic the intra-arterial injection of 1-0 mg. of neostigmine invariably produced great loss of strength of grip accompanied by coarse fasciculation. In contrast, when the arm was clinically myasthenic this effect never occurred but power either increased or showed no significant change. With smaller doses in patients without clinical myasthenia in the arm, there was either no change in power or a reduction of less degree than with 1-0 mg. In three patients in whom the injected arm was myasthenic 1-5 mg. produced an increase in power, although in one patient this increase was less than that produced by 1-0 mg. Fasciculation was never seen in this latter group of patients. The only adverse effect noted was a syncopal reaction in two patients. In both this occurred before the release of the sphygmomanometer cuff around the arm and therefore before the escape of any neostigmine into the general circulation. The effect must, therefore, have been due to the circumstances of the test and the insertion of the needle rather than to any pharmacological action.

Discussion

As neostigmine is known to exert a direct action on muscle quite distinct from its anti-cholinesterase activity (Riker and Wescoe, 1946), it was not thought that these results would contribute to the controversy on the sensitivity of myasthenic muscle to acetyl choline (Harvey and Lilienthal, 1944; Wilson and Stoner, 1947). We have confirmed, however, that myasthenic muscle reacts to the same dose of intra-arterial neostigmine in a manner different to that of apparently normal muscle. An attempt to show that this was only a quantitative difference was not wholly successful. The inability to control the distribution of the injected dose between the skin and the muscles and between the individual muscles precludes any precise deductions, but it was shown that 0-25 mg. of neostigmine will not always produce paralysis in non-myasthenic muscle. We did not demonstrate the reverse, which we thought to be theoretically possible, the paralysis of myasthenic muscle with large doses of neostigmine, but the range of dosage was possibly not sufficiently wide. It is worth noting that in one myasthenic subject Harvey and Lilienthal (1941) produced transient fasciculation with the very large dose of 3-0 mg.

The conclusions with regard to the usefulness of the test in the diagnosis of myasthenia gravis are more definite. If the symptoms of the suspected case include weakness of the arms the test may be an aid to diagnosis, but unless the injected arm is clinically myasthenic the response will be that of normal muscle. As it is precisely in those cases in which there is weakness of muscles supplied by the cranial nerves alone that doubt about the diagnosis is most likely to arise, the usefulness of the test appears to be extremely limited.

Summary

Graded doses of neostigmine were injected into the brachial artery of five patients with myasthenia gravis in whom the injected arm was weak and of five in whom it was unaffected. In all the latter five patients the injection of 1-0 mg. caused great loss of strength of grip, while in the former strength increased or was unaffected.

Smaller doses in patients in whom the arm was not myasthenic sometimes failed to produce paralysis.

Paralysis of clinically myasthenic muscle was not produced with larger doses, but the range of dosage was small.

It is concluded that the intra-arterial injection of neostigmine does not assist in the diagnosis of myasthenia gravis unless the injected arm is itself weak.

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References


