THE ESTIMATION AND COMPARISON OF HISTAMINE RELEASE BY MUSCLE RELAXANTS IN MAN

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IN READING the literature on muscle relaxants one is struck by the emphasis laid on histamine release. As each new muscle relaxant appears on the market, the manufacturers claim that it releases no histamine or that the amount it does release is less than that released by other relaxants.

Generalized histamine release in man causes broncho-spasm or fall in blood-pressure or both. These manifestations can be of serious import in anaesthesia. They can, however, occur in cases where no muscle relaxant has been used. For example, both bronchospasm and fall in blood-pressure can follow intubation in light anaesthesia. It would be unjustifiable, therefore, to use either of these manifestations in the assessment of histamine release in man.

Blood-pressure fall, however, has been used to investigate histamine release in animals. MacIntosh and Paton (1949) have used cats in their investigations. They have found that, after blocking the autonomic ganglia with nicotine tartrate or tetraethylammonium iodide to prevent side effects, the injection of d-tubocurarine chloride or dimethyltubocurarine iodide releases histamine as shown by the fall in the cat's blood-pressure.

In man a simpler method is available. The intradermal injection of histamine or a substance which releases histamine produces a wheal and flare at the site of injection. The writer's attention was drawn to this manifestation by witnessing an anaesthetist inadvertently injecting d-tubocu-
rarine chloride into the skin instead of the vein. Within a minute a wheal and flare appeared at the site of injection. On consulting the literature it was found that Comroe and Dripps (1946) and Grob et al. (1947) had used this manifestation in their examination of histamine release by muscle relaxants in man. A similar technique has been used in this investigation.

METHOD

The muscle relaxants used were the commercial preparations of d-tubocurarine chloride, dimethyltubocurarine iodide, gallamine triethiodide, and decamethonium iodide. Fifteen milligrams of d-tubocurarine chloride were taken as equivalent in potency to 6 mg. of dimethyltubocurarine iodide, 120 mg. of gallamine triethiodide, and 3 mg. of decamethonium iodide. It was necessary, in order to obtain them in equal volumes, to dilute the preparations of d-tubocurarine chloride and decamethonium iodide with sterile water.

Sterile water was also used as the control. Two minims (0.13 ml.) of one of the muscle relaxants or the sterile water control were used in each patient.

At first it was decided to use Evans blue to measure the histamine production. Evans blue is a blue dye which when injected intravenously does not easily pass out of the blood-vessels.

Where histamine has been released, however, the permeability of the blood-vessels is increased and Evans blue passes out into the tissues at the site of histamine release where it is easily seen and the extent of its deposition can be measured.

The dye was used on the writer himself. In one forearm a sample of d-tubocurarine chloride was injected intradermally and in the other forearm an equal volume of sterile
water was injected, also intradermally, as a control. The skin was swabbed only lightly with spirit beforehand, as too vigorous cleansing results in an area of erythema which might interfere with the interpretations of the results. Eight millilitres of 0.24% Evans blue were injected intravenously.

Within one minute a wheal and flare developed at the site of the d-tubocurarine chloride injection and Evans blue was deposited in the wheal. At five minutes the wheal was at its maximum and filled with the dye. The area of the wheal and flare was traced out, transferred to graph paper and measured. In the case of the sterile water no wheal or flare developed but Evans blue was deposited in the wheal raised by the injection itself, and the dye was localized to this area, which was much smaller than that resulting in the arm in which d-tubocurarine chloride was injected. It was presumed to be due to histamine produced as a result of the local trauma inflicted.

About six hours later it was noticed that a delicate blue tinge was appearing in the face. This was at its maximum about fifteen hours later and took about six weeks to disappear. It was thought that this was due to too large a dose of Evans blue having been given or to the fact that a hot bath was taken shortly after the injection and that the resultant vasodilatation allowed the dye to pass out of the blood vessels. No ill-effects were felt although the apparent cyanosis caused a great deal of comment.

In view of this bizarre side-effect, it was decided to dispense with the use of Evans blue as an indicator of histamine release. Subsequently the injections of the muscle relaxants and the sterile water control were made intradermally as described above but Evans blue was not used.

Ten patients were used for each muscle relaxant and for the control. In each case the anaesthetic was thiopentone, nitrous oxide, oxygen, and trichlorethylene and the opera-
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tion performed was cystoscopy and any necessary intraves-
ical procedure. Readings were taken after five minutes. As the flare in each case was found to be proportional to the wheal, only the wheal was measured.

\begin{table}
\centering
\caption{Results of Histamine Release by Muscle Relaxants}
\begin{tabular}{lccc}
\hline
Relaxant & Size of the wheal in square mm. \\
& Maximum & Minimum & Average \\
\hline
d-Tubocurarine chloride & 270 & 160 & 192 \\
Dimethyltubocurarine iodide & 220 & 150 & 190 \\
Gallamine triethiodide & 190 & 125 & 153 \\
Decamethonium iodide & 115 & 70 & 91 \\
Control & 55 & 28 & 36 \\
\hline
\end{tabular}
\end{table}

From the above table it can be seen that d-tubocurarine chloride releases the largest amount of histamine. Next come dimethyltubocurarine iodide, gallamine triethiodide, and decamethonium iodide in that order. In each case the wheal area is much larger than that of the control area.

d-Tubocurarine chloride and dimethyltubocurarine iodide are almost equal in their ability to release histamine.

Various other substances produce a wheal and flare when injected, amongst these are morphine and atropine (Wright, 1945). In two cases, in whom a definite wheal and flare followed the injection of morphine and atropine given as premedication, a sample of d-tubocurarine chloride was injected as described above. These patients might have been expected to show a greater response than the others. In fact, however, the resultant wheal was no larger.

\section*{DISCUSSION}

The investigation which has been described was conducted from a pharmacological point of view. No investi-
gation has been made into its clinical significance. Nevertheless one has noted that it is easier to perform intubation and also bronchoscopy in patients given gallamine triethiodide, than in those given d-tubocurarine chloride. One would be tempted to attribute this to the fact that gallamine triethiodide releases less histamine than d-tubocurarine chloride with a lesser tendency, consequently, to produce bronchospasm. This, of course, is a subjective clinical impression. There is, however, a technique now being used in anaesthesia which admits of a more objective analysis. This is “controlled hypotension” using hexamethonium or pentamethonium salts. These drugs act by blocking the autonomic ganglia and so one has a state of affairs analogous to the experiments carried out by MacIntosh and Paton on cats. It would be interesting, therefore, to know if anyone has found, using this technique, that the injection of a muscle relaxant causes a further fall in blood-pressure, due to histamine release, as occurred in the cats.

SUMMARY

(1) A method of estimating and comparing histamine release by muscle relaxants in man is described.

(2) The results of a series of experiments using this technique suggest that d-tubocurarine chloride releases the largest amount of histamine and next come dimethyltubocurarine iodide, gallamine triethiodide, and decamethonium iodide in that order.

(3) The controlled hypotension technique affords an opportunity of examining these facts clinically.

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REFERENCES


