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THE EFFECT OF MORPHINE AND HYOSCINE ON DYE CONCENTRATION CURVES IN PLASMA VOLUME DETERMINATION

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When Evans blue is injected into the circulation of normal individuals a constant dye concentration is reached within 20 min. and this concentration is maintained for a further 40 min. Subsequently it diminishes at a rate of about 5 % per hour [Crooke & Morris, 1942]. In the course of investigations upon the plasma volume in patients with shock, however, unaccountable alterations in the concentration of dye were sometimes found. A systematic examination of the factors which might be responsible for such anomalous dye concentration curves has therefore been made.

At first the anomalous results were thought to be associated with shock, but this was disproved by a normal curve occurring in a patient with severe traumatic shock, and whose systolic blood pressure was consistently below 60 mm. Hg (Fig. 1*a*). In contrast to this, a moderately shocked patient with second and third degree burns of the hands and face, whose systolic blood pressure varied from 140 to 150 mm. Hg, had an anomalous curve (Fig. 1*b*).

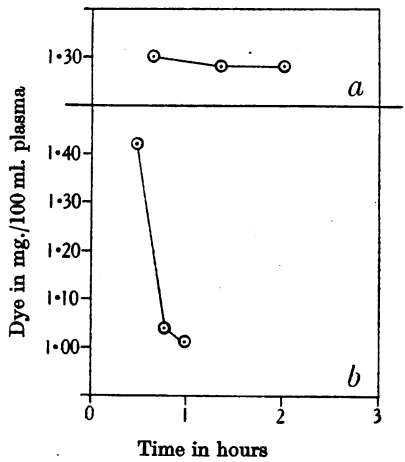

Fig. 1. Dye concentration curves in shock. Injection of dye at 0 hours. 35 mg. injected.

In order to investigate the problem under more controlled conditions, the dye concentration curves were examined in fourteen patients undergoing various major operations. The patients were given an injection of dye before the operation and the concentration curve determined throughout the operation. A second injection of dye was then given in order to correct for the loss of dye from

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the circulation since the first injection, and the concentration curve again determined. About half of the dye concentration curves so obtained were anomalous. Anomalous second curves were not related to the second injection of Evans blue because we found that when two successive injections were given to normal individuals and correction made for the dye already in the circulation, normal flat dye concentration curves were obtained (Fig. 2).

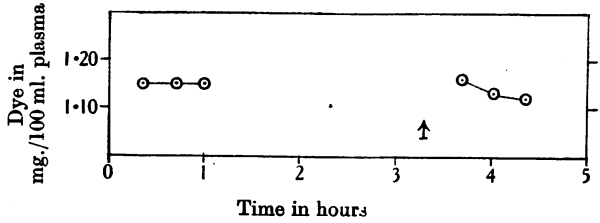

Fig. 2. Dye concentration curves in a normal subject. First injection of dye at 0 hours (35 mg.). Second injection of dye at the arrow (35 mg.).

The anomaly was also found to be unrelated to the type or severity of the operation. Nor was the anaesthetic responsible for it, because an anomalous curve began in one patient before the anaesthetic was started, and in another a normal curve was obtained immediately after a long period of anaesthesia. In all cases a hyoscine-morphine-atropine mixture had been given and in some cases the injection of these drugs preceded the injection of dye. It was therefore decided to study the effect of these drugs on the dye concentration curve in the normal subject. Twenty normal volunteers were examined.

Experimental

The effect of a hyoscine-morphine-atropine mixture on the dye concentration curve in the normal subject

The technique of plasma volume determination has been described previously [Crooke & Morris, 1942]. Seven normal volunteers were injected with 5·0 ml. of a 0·17 % solution of Evans blue and the dye concentration curve determined in the usual way. A normal control curve was obtained in every case. An injection of morphine sulphate 16·2 mg., hyoscine hydrobromide 0·65 mg., and atropine sulphate 0·65 mg. was then given. After a variable period of time, a second injection of the same amount of Evans blue was given and the dye concentration curve again determined. Generally the curve showed a preliminary fall followed by a rise which was most marked 1–1·5 hr. after the second injection of dye. There was then a second fall which ultimately flattened out at a level significantly lower than that of the control curve. This type of curve is illustrated by Fig. 3*b*. It is very similar to that shown by

the patient with burns (Fig. 1*b*), who had received an injection of morphine sulphate 90 min. before the injection of Evans blue. Individual variations in the shape of the second curve were sometimes observed (Fig. 3*a*, *b*).

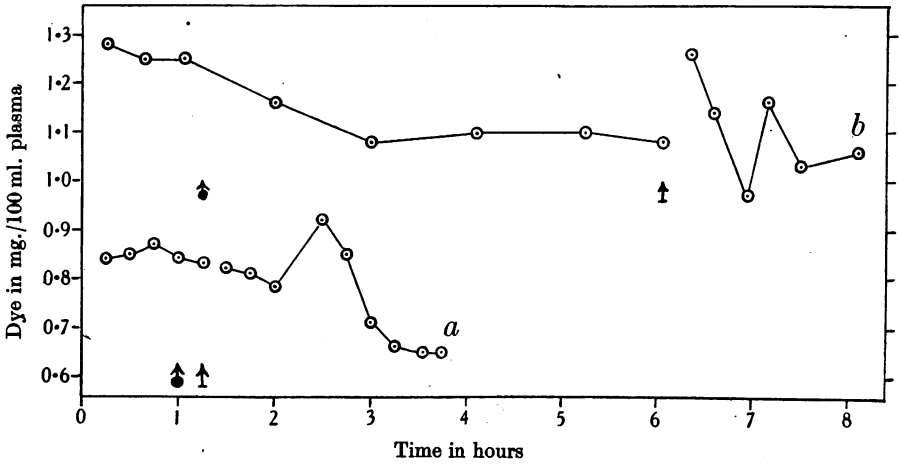

Fig. 3. Anomalous curves in normal subjects. *a*, after morphine. *b*, after morphine-hyoscine-atropine mixture. First injection of dye at 0 hours (35 mg.). Injection of drug at ↟. Second injection of dye at ↥ (35 mg.).

The individual effects of morphine, hyoscine and atropine on the dye concentration curve

The course of these experiments was similar to that described above, the drugs being administered separately. Eight normal volunteers were examined; three with morphine sulphate, two with hyoscine hydrobromide and three with atropine sulphate. Morphine sulphate and hyoscine hydrobromide had similar actions and typical anomalous curves were produced. Atropine sulphate had but little effect.

The persistence of the effect in the normal subject

A series of experiments was carried out in order to establish the duration of the effect in the normal subject. In one volunteer an anomalous curve was observed 5 hr. after the injection of morphine sulphate. This is seen in Fig. 3*b*, which also shows that when the dye is injected before the drug a normal curve is obtained for 5 hr. after the administration of the drug. This effect was observed invariably, even when only 10 min. had elapsed between the injection of the dye and the drug.

Simultaneous studies of the effect by different methods of plasma volume estimation

The possibility that the anomaly was due to the method of estimating Evans blue in plasma was suggested by the work of Bonnycastle [1942]. He used the direct method of estimation and found no alteration in plasma volume fol-

lowing the injection of morphine. A healthy fasting volunteer was therefore subjected to the experimental procedure already described, an injection of the morphine-hyoscine-atropine mixture being given. The dye concentration in the plasma was measured by the direct method of Bonnycastle, by the method of Harington, Pochin & Squire [1940] and by our own method. The second curve was found to be anomalous by all three methods (Fig. 4).

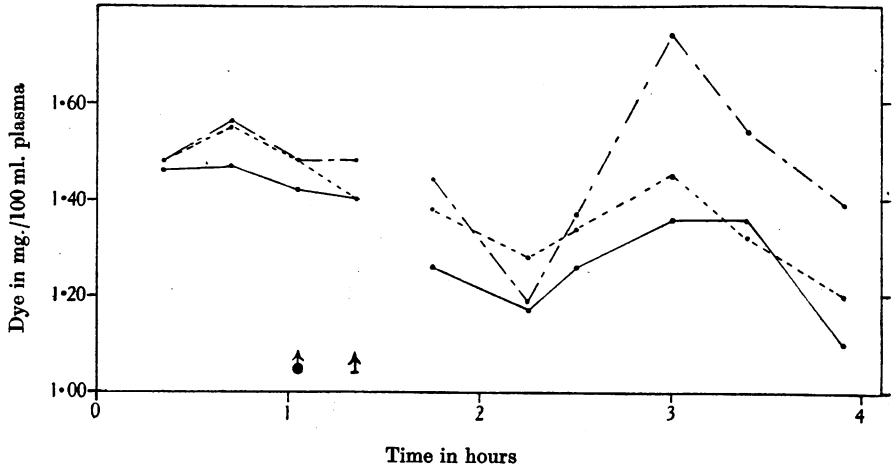

Fig. 4. Anomalous curves in a normal subject. Plasma volume estimated by three methods. —— Crooke & Morris [1942]. ---- Bonnycastle [1942]. ——— Harington, Pochin & Squire [1940]. First injection of dye at 0 hours (35 mg.). Injection of drug at ↟. Second injection of dye at ↟ (35 mg.).

Discussion

It is probable that at least two factors are concerned in the production of anomalous dye concentration curves. The first is unequal distribution of Evans blue in the circulation. This is suggested by the initial fall and subsequent rise which occurs in most anomalous curves. The delayed return of dye to the peripheral circulation can hardly be explained by any hypothesis other than that of unequal distribution. Rein [1929] has shown that the partition of blood between the peripheral and visceral regions of the circulation can vary widely in dogs with small alterations in temperature within the physiological range, and also under the influence of certain drugs. Morphine and hyoscine may influence the distribution of blood to different parts of the circulation. The small volume of blood in the antecubital vein containing the whole of the injected dye will then be distributed according to the rate of flow in the different parts of the circulation, those areas with the greater perfusion rate receiving the larger quantity of dye. Eventually the distribution will become uniform. The second factor is an abnormally rapid elimination of Evans blue from the circulation. The amount of dye lost varies markedly in different subjects, but

it has never exceeded the amount given at the second injection. After the period of abnormally rapid elimination the dye concentration again becomes relatively constant. This may be obscured however in subjects showing the most rapid elimination because the concentration then becomes so low that accurate estimation is impossible. Abnormally rapid elimination has never occurred when the dye was given before the drug so that the dye was uniformly distributed. The cause of this abnormally rapid elimination of dye is uncertain, since the normal mechanism of elimination is still obscure. Gibson & Evans [1937] have suggested that dyes of this class are mainly taken up by the reticulo-endothelial system and stored there until their eventual degradation. In the normal subject we have found that the rate of elimination is roughly proportional to the concentration of dye in the blood. If therefore, as a result of abnormal mixing, relatively high concentrations of dye persist for an appreciable time in certain parts of the circulation, it is probable that abnormally rapid elimination will occur in these areas. Probably mixing eventually becomes complete as is shown by the flattening of the curve. The dye concentration is now however at a lower level than in the initial control curve, indicating a falsely high plasma volume. This explanation of abnormally rapid elimination of dye which occurs only during the period of abnormal mixing is consistent with the observation that dye which is already normally mixed prior to the injection of the drug is eliminated at the normal rate.

Normal flat curves are invariably obtained if the injection of Evans blue precedes the injection of morphine or hyoscine by a period (about 20 min.) sufficiently long to allow of normal mixing. Plasma volume may be determined satisfactorily in shocked patients provided this precaution is observed.

Summary

1. Anomalous dye concentration curves have been found in plasma volume determinations following the administration of morphine and hyoscine.

2. The mechanism responsible for this anomaly is discussed.

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