CARDIAC FAILURE WITH RESERPINE

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Reserpine ("serpasil") is a colourless crystalline ester-alkaloid derived from the roots of *Rauwolfia serpentina*, and is useful both as a hypotensive agent and as a sedative in psychiatric practice. During the treatment of out-patients attending hospital we were surprised to discover two cases of cardiac failure occurring apparently in association with the administration of this drug. The two relevant case histories are presented. The results of the investigations suggest that reserpine causes a retention of fluid in the body, a factor which may result in heart failure in susceptible subjects.

Case 1

A housewife aged 38 developed severe hypertension following toxæmia of pregnancy, and on account of rapid deterioration in her condition had been subjected to bilateral sympathectomy during 1953. She had, in addition, a past history of depressive episodes necessitating treatment with electroplexy, having been only recently discharged from hospital for this reason. At a follow-up 0.25 mg. of reserpine three times a day was prescribed, and over the next seven weeks she again became depressed, with the appearance of minimal ankle oedema.

On examination the jugular venous pressure was not raised, the blood pressure being 170/110. The apical impulse was heaving in character and lay in the sixth left intercostal space outside the mid-clavicular line. The liver was not palpable, there was no ascites, and the lung bases were clear.

Two weeks later she became much more depressed and complained of breathlessness on exertion. The jugular venous pressure was 3 cm. above the sterno-clavicular angle and the bilateral ankle oedema had greatly increased. However, she refused further examination and failed to attend after this. Although at the time the association of cardiac failure following the administration of reserpine, particularly in the absence of any other precipitating factors, was suspicious, it was not until a further case developed failure that this association became indictable.

Case 2

A married woman aged 63 had been attending the out-patient department over a period of a year for the treatment of Parkinson's disease, receiving a total daily dose of "artane," 12 mg. A month before the onset of cardiac failure reserpine, 0.25 mg. twice a day, was prescribed.

When next seen she was in cardiac failure with cyanosis of the lips and dyspnoea at rest. On examination marked

atherosclerosis was found, the blood pressure being 110/75 with a pulse rate of 92 a minute. The apical impulse lay in the fifth left interspace outside the mid-clavicular line and a loud presystolic triple rhythm could be heard over the lower end of the sternum. In addition there were crepitations at both lung bases. The jugular venous pressure was raised 4 cm. above the sterno-clavicular angle, the liver edge being palpable two fingerbreadths below the right intercostal margin. There was no ascites, although pitting oedema of both ankles was present.

Reserpine was withheld. She was advised to rest in bed but refused to do this, remaining fully ambulant. When she returned again four weeks later no evidence of failure remained, and the presystolic triple rhythm had disappeared.

Investigation

Data were collected in order to assess the possibility of fluid retention in patients receiving reserpine. Nine patients suffering from mild psychiatric disorders were given reserpine in increasing doses for three weeks. The drug was then stopped and the investigations were continued for a further three weeks. As the patients were also having weekly injections of acetylcholine, it was necessary, in addition to using the patients as their own controls, to have a control group of patients receiving acetylcholine alone. Six similar patients on weekly injections of acetylcholine were therefore studied concurrently over five weeks. Both groups of patients were selected at random.

Dosage varied from patient to patient, depending upon the side-effects of the drug. The mean daily dosage in the first, second, and third weeks was 1.6, 2.5, and 3.3 mg. respectively. The maximum individual daily dosage was 9 mg.

Blood was withdrawn at the beginning of the investigation and weekly thereafter, estimations being carried out for haemoglobin, plasma portion of the haematocrit, mean corpuscular haemoglobin concentration, and serum sodium. In addition the patient was weighed at each visit.

It is readily acknowledged that the assessment of these indirect indices for fluid retention provides no accurate picture of alterations in either extracellular or total body fluid, but it is hoped that the presentation of these results will serve as a stimulus for a more elegant survey of the problem.

Results

The accompanying charts show the changes in weight (Fig. 1), plasma portion of the haematocrit (Fig. 2), haemoglobin (Fig. 3), mean corpuscular haemoglobin concentration (Fig. 4), and serum sodium (Fig. 5) in nine patients before and after reserpine, and in six control patients. All patients were receiving once-weekly injections of acetylcholine.

Weight.—Controls: The weight gradually increased over the five weeks of the test, the mean increase at the fifth week being 2 lb. 1 oz. (0.94 kg.) ($P>0.05$). **Reserpine:** The increase in weight was pronounced during the three weeks in which the patients were taking reserpine, the mean gain in weight being 3 lb. 1 oz. (1.4 kg.) ($P<0.005$). When reserpine was stopped the weight remained steady. When the gains in weight for the groups of controls and subjects

FIG. 1.—Changes in weight. FIG. 2.—Plasma portion of the haematocrit. FIG. 3.—Haemoglobin. FIG. 4.—Mean corpuscular concentration. FIG. 5.—Serum sodium.

receiving reserpine were compared statistically, $P>0.1$. Thus, although there was a definitely significant increase in weight among patients on reserpine, the control group also showed an insignificant gain in weight, but the difference of this weight gain between the two groups was not statistically significant.

Plasma Portion of the Haematocrit.—Controls: Apart from an unexpected and transient decrease during the first week, the values for the plasma portion of the haematocrit remained steady. **Reserpine:** During the three weeks on reserpine there was a constant increase in the values for the plasma portion of the haematocrit, the mean increase being at the 2% level ($P<0.02$). When the reserpine was withheld the plasma portion of the haematocrit fell rapidly to below normal levels before returning again to its normal value. This fall was most pronounced two weeks after the withdrawal of reserpine, and when compared with the value obtaining at the height of reserpine therapy it was found to be significant at the $P<0.01$ level. When the controls and the subjects on reserpine were compared with regard to changes in the plasma portion of the haematocrit at the third week of the investigation it was found that the values for the two groups differed significantly— $P<0.05$. Thus the administration of reserpine results in a significant increase in the plasma portion of the haematocrit.

Haemoglobin.—Controls: The haemoglobin showed a gradual increase over the five weeks under test apart from the fourth week, when the mean value inexplicably fell. This increase was not statistically significant, the mean increase being 3.5% ($P>0.1$). (The mean haemoglobin before the investigation was 80.8%.) **Reserpine:** In contrast to the control series, whilst the patients were on reserpine a statistically insignificant decrease of haemoglobin occurred, the mean fall being 2.2%. When reserpine was stopped, however, the haemoglobin returned immediately to normal levels, and two weeks after cessation of the drug the increase was significant at the $P<0.005$ level. (The mean haemoglobin before the investigation was 82%.) When the controls were compared with the patients at the height of reserpine therapy the curves were significantly different at the level $P<0.05$. Thus there is a statistically significant fall in haemoglobin values as the result of reserpine treatment as compared with control subjects.

Mean Corpuscular Haemoglobin Concentration.—There was no significant change in either the controls or the patients receiving reserpine. This implies that the decrease of the haemoglobin values found in the patients receiving reserpine was not due to altered haemopoiesis, but rather to haemodilution.

Serum Sodium.—Controls: The serum sodium values showed little change in these patients. **Reserpine:** In all patients there was an immediate decline in the serum sodium after starting reserpine, but thereafter the values remained fairly constant. The mean fall of serum sodium during the first week of treatment was 14 mg./100 ml., the decrease being statistically significant ($P<0.005$). When the control group were compared with the patients on reserpine the significance of the decline in serum sodium was confirmed ($P<0.05$).

Comment.—To summarize, the administration of reserpine results in an increase in the plasma portion of the haematocrit, a fall in the haemoglobin, and some evidence of an increase in weight. The mean corpuscular haemoglobin remains unaltered. These changes are compatible with the suggestion that reserpine is associated with retention of fluid. In addition, a significant fall in the serum sodium, maximal during the first week, occurred after reserpine was given.

Discussion

The gist of these investigations is that the administration of reserpine is associated with either water or salt-and-water retention. This would account for some of the increase in weight and for the 4% increase of the plasma portion of the haematocrit seen in the above series. If one

assumes that this roughly approximates the gain in extracellular fluid, then the estimated gain in weight should be 1.01 lb. (460 g.) (Gamble, 1947). In fact, the difference between the mean gain in weight for the patients on reserpine and that for the controls was 1.9 lb. (860 g.), a discrepancy that could be accounted for by a concomitant but slight alteration in the total extracellular fluid. This gain in weight has been noted previously, for Locket (1955) commented that an increase in both appetite and weight occurred three times as often in a group of patients whilst on reserpine as compared to that observed when the same patients were receiving inert tablets.

More recently Foote (1955) and McNeill (1955) reported that treatment with reserpine may be followed by the appearance of oedema, some of Foote's patients developing oedema of the face as well as of the ankles. This phenomenon was not associated with cardiac failure, nor was a renal origin of the oedema evident. It is of interest, then, that Gaunt *et al.* (1954), who studied the pharmacology of reserpine, suggested that in rats the latter stimulates the production of antidiuretic hormone by the posterior pituitary. If the same mechanism is found to be valid for human beings this could possibly account for the retention of fluid. The augmented appetite may equally as well be related to the action of the drug on the near-by hypothalamus. No cases of oedema or cardiac failure occurred in those patients comprising our series actually under investigation, and in all instances these patients were young and with normal cardiovascular systems.

The two patients who developed cardiac failure but who were not subjected to serial investigations were obviously more liable to failure than the normal, the retention of body fluid by reserpine being presumably sufficient to swamp their minimal cardiac reserve. The daily dose of reserpine administered to these patients was quite small. This is of importance, as the drug is in vogue as a hypotensive agent, being also combined with pentolinium tartrate for the treatment of hypertension (Smirk *et al.*, 1954; Bain *et al.*, 1955; Doyle *et al.*, 1955). Furthermore, Smirk and McQueen (1955) reported that reserpine therapy had to be abandoned in one of their patients on account of fluid retention with recurrence of the manifestations of congestive cardiac failure.

It is pertinent that an increase in weight has also been observed during treatment with hexamethonium (Persson, 1951). The same result followed the administration of pentapyrrolidinium bitartrate, and was attributed by Rønnow-Jessen (1955) to salt-and-water retention, this being sufficient for three of his patients with relative heart failure to develop absolute failure. He therefore emphasized the hazard of administering hexamethonium salts in the presence of borderline cardiac compensation or manifest failure. However, it was possible to forestall such an eventuality by frequent weighing of cases at risk during the early stages of treatment.

Finally, it is worth referring to the aggravation of depression by reserpine that occurred in our first case. Since this association was noted, Moore and Martin (1955) have advocated that endogenous depression should be regarded as a contraindication to the use of reserpine. In fact, Wilkins (1954) has reported the development of agitated depression in hypertensives treated with reserpine. Wallace (1955) also commented on the liability to melancholia of hypertensives receiving reserpine.

Summary

Two cases of cardiac failure associated with the administration of small doses of reserpine are recorded. These patients were more liable to failure than normals. The results of a series of investigations suggest that treatment with reserpine is associated with retention of fluid in the body. Thus there was a significant increase in the plasma portion of the haematocrit, a fall in the

haemoglobin, an increase in weight, and a decline in the values for the serum sodium, although the mean corpuscular haemoglobin remained unaltered.

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REASSESSMENT OF VALUE OF OXYGEN MASKS THAT PERMIT REBREATHING

BY

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The therapeutic value of oxygen inhalation is well established, and it may be given safely with immediate benefit to the patient in a number of conditions. In patients with carbon dioxide retention due to chronic disease of the chest, however, oxygen therapy may accentuate the retention by depressing ventilation (Donald, 1949; Richards, 1950) and lead to coma. This danger is reduced when oxygen is given intermittently or in small amounts (Barach, 1948). Carbon dioxide retention may occur even when equipment with minimal deadspace is used for oxygen administration (Prime and Westlake, 1954). The oxygen mask itself may aggravate this tendency by permitting the re-breathing of exhaled air from the oxygen reservoir bag.

The present investigation into the effect of rebreathing was provoked by the observation that some dyspnoeic patients for whom oxygen therapy seemed desirable were unable to tolerate a mask operating on the re-breathing principle, whereas they did benefit from the same flow of oxygen given by a mask of the Haldane type.

Historical

The oxygen reservoir bag was introduced by Haldane in 1917 to prevent wastage of oxygen during expiration. Exhalation into the bag was prevented by a non-return valve in its neck. When wearing the Haldane mask (Fig. 1) the subject inspires first all the oxygen in the reservoir bag and then air through a hole in the facepiece. The expired gas passes out through this hole.

The rise in alveolar oxygen concentration of normal subjects, using this and other types of oxygen equipment, is shown in Fig. 2, using published data (Davies and Gilchrist, 1925; Hilton, 1928; Poulton and Adams, 1936; Christie, 1938; Card *et al.*, 1940; Christensen *et al.*, 1946; Burns and Hall, 1953). The Haldane mask, with an oxygen

flow of only 2 to 3 litres a minute, has been found to restore to normal the arterial oxygen saturation in desaturated subjects (Meakins, 1920, 1921). The mask proved less efficient when used with high oxygen flows calculated to raise to a maximum the alveolar oxygen tension (Davies and Gilchrist, 1925); some air was inevitably inspired through the hole in the facepiece, and alveolar oxygen concentrations of more than 60% were seldom attained (Fig. 2, Haldane mask A). An expiratory valve in place of the air-mix aperture overcame this difficulty, and the Haldane mask then became effective at all oxygen flows (Fig. 2, Davies-Gilchrist mask). The mask was not widely used, however, as it was expensive, heavy, uncomfortable, and difficult to sterilize and maintain (Campbell and Poulton, 1935).

The Boothby, Lovelace, and Bulbulian (B.L.B.) mask, introduced in 1938, overcame a number of these limitations. This mask was essentially an improved light-weight version of the Haldane mask, with a more comfortable and better-fitting facepiece, but it differed in having a smaller reservoir

FIG. 1.—Haldane mask.

FIG. 2.—Alveolar oxygen concentrations in normal subjects wearing different types of personal oxygen equipment.

bag and no valve between the bag and facepiece. The effectiveness of this design was claimed to be due both to the rebreathing of oxygen-enriched expired air and to some increase in ventilation on account of the carbon dioxide accumulation (Boothby, Lovelace, and Uihlein, 1940). However, since the oxygen is mainly inspired at the beginning of inspiration, and the gas conserved and used again is that expired at the beginning of expiration, no useful economy over the Haldane type is to be expected. Carbon dioxide accumulation in the bag occurs, especially at high respiratory frequencies, but Boothby and his colleagues have claimed that the inspired carbon dioxide is less than 1% in the total inspire; the estimate has, however, been disputed (Barach, 1940). Other factors which affect efficiency equally in the B.L.B. and Haldane masks are the flow characteristics of the orifices and tubes, and the rigidity of the bag. When these are similar the efficiency of both masks is the same (Card *et al.*, 1940; B.L.B. and Haldane B, Fig. 2). However, all these studies have been made on normal subjects.