OUABAIN IN THE TREATMENT OF SHOCK

BY

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The use of ouabain in the treatment of shock was first reported by Sankey and Crawford (1950), acting upon a suggestion by Wiggers (1947) that cardiac stimulants might reverse circulatory failure in cases of shock in which transfusion fails.

We have been using ouabain for this purpose for the past three years. This paper reports the results of the administration of ouabain in 73 cases.

PHARMACOLOGY

Ouabain (strophanthin G) is a cardiac glycoside obtained from the seeds of strophanthus gratus; it consists of small colourless crystals, or a white crystalline powder with a bitter taste. It is soluble in water (1 part in 100) and in dehydrated alcohol; and may be sterilized by heating in an autoclave or by filtration (Martin-dale, 1952).

"Ouabaine Arnaud", the preparation which we use, contains 0.25 mg. ouabain in 1 ml. of water suitable for intravenous injection.

Ouabain has an action similar to strophanthin K, but it is twice as potent. It has a rapid action, is quickly excreted and its effect is short. It is said to be dangerous to give ouabain to patients who have been digitalized during the previous 14 days.

The intravenous dose of ouabain is 0.25–0.5 mg. The maximum permitted dose in 24 hours varies between 0.25 mg. and 5 mg. according to various authorities.

INDICATIONS FOR THE USE OF OUABAIN

Myocardial depression is one of many possible factors involved in the mechanism of surgical shock. It may exist even under otherwise normal circulatory conditions, the heart being near the limit of its reserve, and, when other factors are added, shock and circulatory failure may quickly follow. We believe that the myocardial stimulating properties of ouabain are of value in the following circumstances:

1. In shock, to aid the effect of volume replacement, before, during, and after operation.
2. To restore the blood pressure without volume replacement (i.e. without coincident transfusion), especially where there is peripheral vasoconstriction or tachycardia, and when vasopressor drugs might thus be contra-indicated.
3. In patients with hypertension when there is a sudden fall in blood pressure due to induction of anaesthesia, peritoneal stimulation, etc.
4. To correct the circulatory depression caused by altering the patient's position, etc.
(5) Prophylactically in cases where indications (3) and (4) may be expected to occur.

(6) In certain cases of cardiac arrhythmia, especially when associated with a falling blood pressure or venous engorgement.

RESULTS

Ouabain (0.25 mg.) has been given intravenously to 73 patients during anaesthesia for a variety of surgical procedures, the majority of which were major intra-abdominal or abdominothoracic operations. In addition, it has been used on a number of occasions with benefit during pre- or post-operative resuscitation. Only the former group is analysed here, as the details recorded were more precise.

Total number of administrations = 100 (73 patients).

Of these, the circulatory state showed improvement in 79, no change in 7, and continued deterioration in 10. (Details were insufficient in 4.)

On 80 occasions when ouabain was given, full details were recorded upon the anaesthetic charts, and accurate analysis was possible. The following study was made in these cases. The blood pressure before the administration of ouabain, and for the two successive readings after, was noted, and the mean blood pressure calculated (mean B.P. = diastolic B.P. + \( \frac{1}{3} \) pulse pressure) for each reading. The mean blood pressure before the administration and that closest to 10 minutes after were taken for comparison. This time was chosen as that at which the maximum effect of ouabain on arterial blood pressure is to be expected (McMichael, 1950), though the cardiac output might be expected to be increased later, even if the blood pressure had again fallen.

On this basis:

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<th>EFFECT OF OUABAIN ON MEAN BLOOD PRESSURE</th>
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<td>Rise ... ... ... ... ... ... ... 67 (84 per cent)</td>
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Of the 67 cases showing a rise in mean blood pressure:

Mean percentage rise = 32.4; standard deviation of the mean = ± 29.1; standard error = 3.5.

Of these 67 cases showing a rise in the mean blood pressure after the administration of ouabain, there were ten occasions in which fluid replacement was not given.

Of the 9 cases showing a fall in mean blood pressure:

Four patients were still bleeding, and improved with adequate blood replacement.

Five patients improved with a further injection of ouabain (0.25 mg.), suggesting that the initial dose was inadequate.

In five cases, the fall in the mean blood pressure after the administration of ouabain was also associated with the induction of anaesthesia, movement of the patient into the theatre, or the administration of depressant drugs, such as pethidine.

Of the 4 cases showing no change in mean blood pressure:

Two cases showed a rise in systolic blood pressure with increase in pulse pressure; one showed a transient rise in mean blood pressure which had passed off at 10 minutes, and in the fourth case the final blood pressure reading was taken too soon after the administration of ouabain for the full effect to have been achieved.
ILLUSTRATIVE CASE REPORTS

A. Use of ouabain to aid moderate blood volume replacement in shock, and to avoid circulatory depression consequent upon anaesthesia and operative manipulation.

Case I. B.C. Male, 70 (fig. 1).

Normal B.P. 185/90 mm. Hg. Perforated peptic ulcer of 20 hours duration. Shocked. B.P. 100/80. Dextran 500 ml., blood 250 ml. and ouabain 0.25 mg., given intravenously 30 minutes before arrival in theatre. On arrival B.P. 120/80, pulse 100. Ouabain 0.25 mg. intravenously at O. Oxygen inhalation for 15 minutes before induction of anaesthesia. Further improvement in blood pressure to 150/100. Premedication, atropine 1/100 grain (0.65 mg.). Induction with nitrous oxide, oxygen, ether; intubation; maintenance with cyclopropane, oxygen; relaxation by 0.1 per cent suxamethonium drip. Blood pressure level maintained well during operation.

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NOTE: In all the illustrations time is shown in minutes from beginning of anaesthesia:

- X = Incision; O = ouabain 0.25 mg. I.V.

B. Marked effect of ouabain following moderate rise in blood pressure gained by transfusion.

Case II. A.M. Female, 80 (fig. 2).

Pre-operative blood pressure 170/110. Partial gastrectomy for haematemesis, bleeding continuing and patient receiving blood. Premedication: morphine 1/6 grain (10 mg.), atropine 1/120 grain (0.5 mg.). On arrival in theatre, blood pressure 110/60. Induction with thiopentone and suxamethonium; intubation; maintenance with cyclopropane-oxygen; relaxation by 0.1 per cent suxamethonium drip. Severe haemorrhage at 75 and 150 minutes. Blood pressure fell to unrecordable levels. Ouabain 0.25 mg. given at O, with blood given rapidly. Excellent response on each occasion.

C. Use of ouabain to aid intravenous transfusion after massive blood loss.

Case III. H.G. Female, 62 (fig. 3).

Carcinoma of splenic flexure; excision and anastomosis, splenectomy. Premedication, pethidine, 75 mg., atropine 1/120 grain (0.5 mg.). Induction with thiopentone and suxamethonium; intubation; maintenance with cyclopropane-oxygen; relaxation by 0.1 per cent suxamethonium drip. Severe haemorrhage at 75 and 150 minutes. Blood pressure fell to unrecordable levels. Ouabain 0.25 mg. given at O, with blood given rapidly. Excellent response on each occasion.

D. Use of ouabain alone to correct blood pressure fall due to induction of anaesthesia, abdominal manipulation, etc.

Case IV. A.H. Male, 77 (fig. 4).

Biliary fistula—excision of fistula, cholecystectomy, choledocho-hepaticostomy. Premedication, morphine 1/6 grain (8 mg.), atropine 1/120 grain (0.5 mg.). Induction with nitrous oxide, chloroform, ether; intubation; maintenance with cyclopropane and oxygen; relaxation with 0.1 per cent suxamethonium drip. Severe fall in blood pressure with early intra-abdominal exploration. Ouabain 0.25 mg. given at O. B.P. rise to 130/70.

Case V. A.C. Male, 47 (fig. 5).

Gastric ulcer, partial gastrectomy. Premedication, morphine 1/6 grain (10 mg.), atropine 1/120 grain (0.5 mg.). Induction with thiopentone 300 mg., suxamethonium 40 mg.; intubation; maintenance with nitrous oxide, cyclopropane and oxygen; relaxation with 0.1 per cent suxamethonium drip. Fall in blood pressure to 70/50 mm. Hg after induction and initial abdominal exploration. Ouabain 0.25 mg. at O. Blood pressure restored to initial level in 10 minutes without other supportive therapy.
E. Occasional transient action of ouabain upon blood pressure in shock.

Case VI. M.C. Female, 74 (fig. 6).
Obstructive jaundice, laparotomy, inoperable. Premedication, pethidine 50 mg., atropine 1/120 grain (0.5 mg.). Induction with thiopentone 150 mg., nitrous oxide, oxygen, ether; intubation. Maintenance with nitrous oxide, oxygen, ether; relaxation with 0.1 per cent suxamethonium drip. Profound fall in blood pressure to 80/50 mm.Hg after induction and initial intra-abdominal exploration. Ouabain 0.25 mg. at O. Good response: blood pressure rose to 140/90 mm.Hg, but then fell to previous level 20 minutes later, illustrating a limited duration of action of ouabain in this case.

Case VII. F.W. Male, 70.
Appendicectomy for acute appendicitis. Premedication, morphine 1/8 grain (8 mg.) atropine 1/120 grain (0.5 mg.) Induction with cyclopropane, nitrous oxide, and ether; intubation; maintenance with nitrous oxide, ether and d-tubocurarine chloride. After 15 minutes, the heart was irregular ("dropped beats"). Ouabain 0.125 mg. was given, and the pulse became regular within 2 minutes.

Case VIII. M.E.P. Female, 76.
Excision of axillary metastasis nine years after
radical mastectomy. Premedication, morphine 1/6 grain (10 mg.), atropine 1/120 grain (0.5 mg.). Induction with nitrous oxide, chloroform and ether; intubation; maintenance with nitrous oxide and ether (light first plane). There was very little blood loss. Blood pressure began to fall after 15 minutes. At 40 minutes, it was 90/40, pulse rate 80, and irregularly irregular. The veins were distended. No intravenous fluid was given. Ouabain 0.25 mg. was administered at 42 minutes. At 52 minutes, the blood pressure was 125/45, pulse rate 100, but regular, save for occasional extrasystoles.

**DISCUSSION**

Wiggers (1947), in an article upon the role of myocardial depression in shock, mentioned the possible state of affairs where cardiac reserve mechanisms are already fully in play to compensate for myocardial depression, and where a reduction in venous return (as from blood loss or vasodilatation) or further depression of the heart muscle (from hypoxia or anaesthesia) might rapidly lead to circulatory failure. He suggests the possibility that "cardiac stimulants used in proper dosage and at the proper time might reverse the circulatory failure where transfusions fail". This suggestion was followed up by Sankey and Crawford (1950), who used intravenous ouabain as an aid to the treatment of traumatic shock. Ouabain had been used experimentally by Kohlstaedt and Page (1944), who had observed that cardiac dilatation after prolonged hypotension was an important sign of impending terminal shock when transfusion alone failed, and by Glasser and Page (1948), who, however, found that ouabain did not affect the survival rate in their animals, though it lessened the harmful effects of over-transfusion. Similarly, the effect of digitalis on the hypodynamic failing myocardium may be lost in the terminal stages of failure (McMichael, 1952).

The usual demonstrable action of digitalis is to strengthen the contraction of the failing ventricle, and full intravenous doses cause a rise in arterial blood pressure, due to a rise in peripheral vascular resistance (McMichael, 1952). Both digitalis and strophanthin preparations have similar properties of myocardial stimulation when dosage is comparable (Walker, Lourie and Burn, 1950).

Ouabain appeared to be the drug of choice for the purpose which we had in mind because its action is rapid. Its effect upon the blood pressure occurs within 3-8 minutes, and may pass off in 15-30 minutes (McMichael, 1950), as we noted clinically. This action may precede the beneficial effects upon the myocardium (McMichael, 1952), so that clinical improvement in the myocardial depression of shock may be expected to remain even if the blood pressure returns to the level present before the administration of the
drug. When the dosage is adequate, the initial blood pressure rise may be maintained in shock as the myocardial stimulant effect takes over after the initial effect on blood pressure has passed off, and circulatory improvement continues. If the dose is inadequate the initial rise is transient or negligible.

The effect upon blood pressure may not be seen with doses below 0.75 mg. of ouabain (McMichael, 1950). In some of our cases an initial dose of 0.25 mg. produced no response, whereas, when the dose was repeated after 10 minutes, there was a definite rise in blood pressure, suggesting that the initial dose was inadequate. We had chosen the smaller initial dose as our standard, because it was in keeping with the generally accepted therapeutic dose; with further experience, and the conviction of the safety of the drug, we are now prepared to give 0.5 mg. of ouabain initially.

We feel that the use of ouabain, either alone or in conjunction with transfusion, is a valuable aid in the treatment of hypotension occurring during surgical anaesthesia, and in pre- and post-operative resuscitation. We have seen no untoward effects following its use.

When confronted with a case of shock, whether haemorrhagic or otherwise, which fails to respond to intravenous blood-volume replacement, it is now our practice to try the effect of ouabain before proceeding to employ intra-arterial transfusion. In most cases, the response has been so gratifying as to render the more drastic procedure unnecessary, and we feel that this sequence of therapy should always be followed.

**SUMMARY**

The use of ouabain (intravenously in a dose of 0.25 mg.) in the treatment of shock, with or without replacement of blood-volume, is described in 73 patients (100 administrations). Improvement of the circulatory state followed in 84 per cent; in the remaining cases, failure to respond was associated with continued or renewed trauma or to inadequate dosage of ouabain.

We recommend strongly the use of ouabain in cases of shock in which the response to intravenous fluid replacement is disappointing, whether before, during, or after operation, and as a prophylactic in cases in which deterioration is expected to occur on induction of anaesthesia, movement of the patient, etc.; in those cases in which improvement does not occur, the drug appears to do no harm.

**ADDENDUM**

Recently, we have administered ouabain on a number of occasions in a dose of 0.5 mg., with even more encouraging responses. This second series is still too small to be worth reporting, but we incline to the belief that the larger dosage will, in future, become routine with us.

**REFERENCES**