BRITISH MEDICAL JOURNAL

LONDON SATURDAY MAY 8 1943

DESOXYCORTICOSTERONE IN ADDISON'S DISEASE A COMPARISON OF DIFFERENT METHODS OF ADMINISTRATION

BY

D. M. DUNLOP, M.D., F.R.C.P.Ed.

(From the Clinical Laboratory, the Royal Infirmary, Edinburgh)

It is well established, that desoxycorticosterone acetate (D.O.C.A.) is highly effective in the treatment of Addison's disease when given intramuscularly or implanted in pellets under the skin. The drug is ineffective when swallowed. The repeated injection of an oily solution, however, is inconvenient, especially for thin patients with poor muscles, who form the majority of those suffering from Addison's disease; in addition such an injection usually involves a visit to the doctor, and for the uninsured this may add considerably to the already high cost of the drug. The implantation of a big single dose of D.O.C.A. practically eliminates these drawbacks, since such an implantation may suffice for many months. Once implantation has been made, however, there is no means of controlling dosage. Thus dangerous toxic effects such as massive oedema and hypertension are theoretically possible from the excessive absorption of the active principle, and these have been noted by Loeb (1940).

Anderson, Haymaker, and Henderson (1940) reported good results from the sublingual administration of D.O.C.A., comparable to those obtained by injection. Two to six mg. of the drug dissolved in propylene glycol were given daily in divided doses, the drops being retained under the tongue for as long as possible. The D.O.C.A. so administered appeared to be a satisfactory form of replacement therapy for six patients over a period of six to eight weeks. Similar good results were obtained by Turnoff and Rowntree (1941) in two cases. Wilson (1942), on the other hand, found the sublingual use of D.O.C.A. dissolved in propylene glycol of little or no therapeutic value. Despite the daily sublingual administration of as large a dose as 10 mg. the four patients studied showed an alarming tendency to relapse into Addisonian crisis, though they had all previously been maintained satisfactorily by smaller intramuscular doses.

During the last year and a half an investigation has been undertaken into the effectiveness of D.O.C.A. when absorbed from the buccal cavity, and a comparison has been made between its potency when administered in this way and when given by implantation or intramuscular injection. Seven patients suffering from characteristic and unequivocal Addison's disease have been studied.

Criteria of Potency

Some initial difficulty was experienced in determining the clinical criteria to be adopted in assessing the potency of the drug. The mere subjective sensations of the patient were obviously unsatisfactory and unreliable; the blood pressure in Addison's disease often remains low in spite of considerable clinical improvement, and is not an accurate expression of the progress of a case; the blood chemistry is also an inadequate index of the effectiveness of treatment (Dryerre, 1939) since

it is often quite normal during the more chronic phases of Addison's disease (Snell, 1934) and it is only at the onset of crisis that significant changes take place in the urea, sodium, and potassium content of the blood (Allott, 1936). D.O.C.A. has, however, such a potent effect in causing retention of sodium that oedema is easily produced even in Addison's disease when it is administered along with salt. The development of oedema may therefore be taken as an indication that the drug is potent, since salt alone in doses up to 15 g. a day will not produce oedema. Even in the absence of actual oedema a steady gain in weight will suggest that the drug is active, especially if the weight falls again when its administration is discontinued.

Sublingual and Sublabial Methods

Fig. 1 shows the effect of the daily sublingual administration of 10 mg. of D.O.C.A. on the weight of two patients suffering from Addison's disease. The drug was dissolved in propylene glycol, and administered by a special dropper under the tongue, being left there without swallowing for 15 minutes. Seven applications of four

Fig. 1.—Effect of sublingual administration daily of 10 mg. of D.O.C.A. dissolved in propylene glycol. The dotted line represents the administration of salt alone; the continuous line represents the administration of salt and D.O.C.A.

drops were given each day, equalling a total dosage of 10 mg. Throughout the observation 7.5 g. of salt were given daily. The ease with which oedema was produced in the first case was due to the fact that the patient had previously been well hydrated by the use of salt and intramuscular D.O.C.A.

As oedema was produced in both cases these two experiments seemed to prove that D.O.C.A. was successfully absorbed when given sublingually. In propylene glycol the taste of the drug was not objectionable, being like that of the crushed pips of apples, but the method was excessively tedious and laborious. It is true that the smaller doses required for simple maintenance treatment would not have involved so much trouble, but a less cumbersome administrative technique was obviously desirable.

In consequence Organon Ltd. supplied small tablets of D.O.C.A., each containing 2.5 mg. of the drug, which could be held without difficulty between the upper lip and gum for a long time, even after they had begun to crumble. It was hoped that in this situation there would be so little salivary washing of the tablet that any escaping steroid would be absorbed from the oropharynx and pharynx, and that scarcely any would reach the gastric mucosa.

Figs. 2 and 3 represent the effects produced on the weight of five cases of Addison's disease by the drug administered in this way. It will be seen that oedema occurred in only two of the patients. Both of these had received very adequate treatment by intramuscular D.O.C.A. and salt before the experiment began. The other three patients were untreated cases of Addison's disease; starting in a dehydrated state, they had to leave hospital before oedema was produced. In each of these latter cases, however, a significant gain in weight occurred when sublabial D.O.C.A. was given, and weight was lost as soon as it was stopped, in spite of the fact that the daily dosage of 7.5 g. of salt was continuous. Clinical improvement paralleled the gain in weight, and in one case crisis developed when the drug was withdrawn.

FIGS. 2 and 3.—Effect of D.O.C.A. in doses of 5 or 10 mg. daily, administered sublabially in tablets.

These experiments seemed to leave no doubt that D.O.C.A. given in tablets sublabially is effective in the treatment of Addison's disease. Using 2.5 mg. tablets in this way, 10 mg. can easily be administered daily without any of the inconvenience of the sublingual method, and without the disadvantage of making the patient dependent on a doctor or nurse for frequent intramuscular injections of an oily solution.

Deep Subcutaneous Implantation

The late Dr. Henry Dryerre, working in this department, was among the first to observe the effect of D.O.C.A. in Addison's disease when implanted in pellets in the deep subcutaneous tissues. During the past four years we have treated three patients successfully in this way, seven separate implantations having been made. Two of them are in good health. One has died owing to the administration of a general anaesthetic, to which patients with Addison's disease are notoriously intolerant. The implantation of a single dose of 200 mg. of D.O.C.A. kept these patients in good health for periods varying from six to eight months. Subsequent implants then became necessary. The technique is perfectly simple, and no untoward effects, such as those recorded by Loeb, have been produced during the course of seven implantations. It is quite possible that a larger initial implantation—say of 400 mg.—would be safe and would last twice as long as 200 mg., but so far we have not had an opportunity of confirming this possibility.

Comparative Dosage

Owing to the considerable cost of D.O.C.A. it seemed important to ascertain how it could be administered most economically. In one case a comparison has been possible between the minimum dosage required to maintain the patient's weight and to keep him in good clinical condition when the

drug was administered by implantation, by intramuscular injection, and by the sublabial method. Similar comparisons have been made in two other cases between two of the techniques—either the implantation and intramuscular or the intramuscular and sublabial methods. The results are shown in the following table:

	Method	Duration in Months	Total Dose in Mg.	Average Requirement per Week in Mg.
Case 1	Implantation	7	200	6.9
	Intramuscular	6	200	7.7
	Sublabial	6	240	9.2
	Sublabial	1½	170	28.3
Case 2	Implantation	6½	200	7.1
	Intramuscular	3	120	10.0
Case 3	Intramuscular	4	120	7.5
	Sublabial	1	155	38.8

It will be seen that D.O.C.A. is rather more economical when implanted than when injected intramuscularly. It is also more convenient for maintenance purposes, though the intramuscular method should be used in the treatment of Addisonian crisis and in the initial control of an untreated case. Both methods are much more economical than the sublabial technique, which requires from three to five times as much of the drug to produce the same therapeutic effect. It is true that the pharmaceutical packing of the drug in phials or ampoules and the bacteriological sterility tests involved may increase the cost of the parenteral preparations by a few shillings. Such pharmaceutical packing and bacteriological work, however, are relatively so inexpensive in comparison with the cost of the original materials and the chemical processing as to make little difference to the total cost of the final product.

Summary and Conclusions

D.O.C.A. has proved effective in two cases of Addison's disease when administered sublingually dissolved in propylene glycol. The method is very cumbersome and wasteful.

D.O.C.A. has proved effective in five cases of Addison's disease when administered sublabially in tablets. The method is convenient but very wasteful.

Three cases of Addison's disease have been treated by implantations of D.O.C.A. Seven implantations in all have been made, each of 200 mg., without untoward effects. Each implantation has sufficed to keep the patient in good clinical condition for periods varying from six to eight months. It is suggested that implantation is the method of choice on the grounds both of economy and of convenience.

The intramuscular injection of D.O.C.A., though very effective, is rather less economical than its implantation and much more inconvenient. It should be reserved for the initial control of untreated cases and for the treatment of Addisonian crisis.

I am indebted to the Moray Research Fund of Edinburgh University for a grant in aid of the purchase of the D.O.C.A. pellets for implantation, and to Organon Ltd. for supplying the tablets of D.O.C.A. for sublabial use.

BIBLIOGRAPHY

- Allott, E. N. (1936). *Lancet*, 1, 1406.
 Anderson, E., Haymaker, W., and Henderson, E. (1940). *J. Amer. med. Ass.*, 115, 2167.
 Dryerre, H. W. (1939). *Edinb. med. J.*, 46, 267.
 Loeb, R. F. (1940). *Bull. N.Y. Acad. Med.*, 16, 347.
 Snell, A. M. (1934). *Proc. Mayo Clin.*, 9, 57.
 Turnoff, D., and Rowntree, L. G. (1941). *J. Amer. med. Ass.*, 116, 2016.
 Wilson, A. (1942). *Lancet*, 1, 762.

Dogs depleted of protein are very susceptible to injurious agents, especially to chloroform. L. L. Miller and G. H. Whipple (*J. exp. Med.*, 1942, 76, 421) find that methionine administered to dogs shortly before chloroform anaesthesia gives them complete protection against this drug. Similar protection against liver injury is also afforded if methionine—an essential sulphur-containing amino-acid—is given three to four hours after chloroform anaesthesia. They point out that in the past, and often in the present, cases of liver injury are treated with a high carbohydrate diet. Agreeing that there is good reason for this, they state that on the basis of modern work the correct treatment is to give a diet which is high in protein as well.