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CLINICAL USES OF INTRAVENOUS HYDROCORTISONE

BY

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Cortisone therapy is now an important part of day-to-day therapeutics. Whatever the argument may be for its use in rheumatoid arthritis, ulcerative colitis, and asthma, there is little difference of opinion when it comes to adrenal insufficiency; for in Addison's disease, Simmonds's disease, and in the adrenalectomized subject it is the most useful drug now available. In acute adrenal insufficiency, however, oral cortisone may not be enough; though the drug is rapidly absorbed from the intestinal tract when taken by mouth, in adrenal crisis a vomiting and dehydrated patient may need rapidly effective parenteral therapy. It is to meet this need that intravenous hydrocortisone has been produced, for the ordinary issue of cortisone or hydrocortisone acetate for oral, intramuscular, or intra-articular use cannot be given intravenously.

The use of intravenous hydrocortisone may be considered in the following conditions:

1. Addisonian crisis.—The dehydrated, vomiting, critically ill patient with Addison's disease may be unable to tolerate oral cortisone, and intramuscular injections may be too slow in action to help him. An intravenous drip of 10–20 mg. hydrocortisone per hour for some six to eight hours will usually effect marked improvement and allow the institution of oral or intramuscular cortisone therapy. This dosage can be increased, if response is unsatisfactory, to 30–40 mg. per hour or even higher.

2. The adrenalectomized patient, usually in the face of infection or some other form of stress, may become ill, weak,

and hypotensive. Such patients may not show the usual signs of adrenal insufficiency, but appear merely to go downhill rapidly and alarmingly. Nausea is frequent and vomiting commonly occurs. The use of intravenous hydrocortisone may be life-saving, and if in doubt the general rule should be to treat as for a probable adrenal failure.

3. The cortisone-treated patient with intact adrenal glands, whether he be a sufferer from rheumatoid arthritis, asthma, or any other condition, may, in the face of infection or any other form of acute stress, experience symptoms of partial adrenal insufficiency. One common form of stress is major operative surgery. A surgical operation may precipitate adrenal failure in a gland suppressed by weeks or months of cortisone therapy, and, if there is no time for 24–48 hours' full pre-operative cortisone treatment, intramuscular cortisone may be augmented by intravenous hydrocortisone. It is well recognized that after stopping cortisone therapy, if such treatment has lasted more than a few days, the adrenal glands may be unable to react normally to operative stress for some weeks or months subsequently. In such patients it is wise to "cover" the operation two days before and a week afterwards by full cortisone therapy. Intravenous hydrocortisone may in these instances also play a part if such "cortisone cover" has been neglected or the dosage insufficient.

4. The Waterhouse-Friderichsen syndrome.

5. Simmonds's disease.—In the face of stress these patients may develop signs of acute adrenal insufficiency. Allott and Simmons (1951) report a case of Sheehan's syndrome which responded only to cortisone. In such cases intravenous hydrocortisone should be considered. Such cases are rare, however, compared with the hypoglycaemic episodes which are common in this condition and which respond usually satisfactorily to intravenous glucose.

6. The above list of indications is not to be regarded as exclusive. Black and Harken (1954), for instance, discussing "the safe conduct of a patient through cardiac surgery," state that in a few cases intractable hypotension after operation appeared to be due to adrenal failure. The patient, alert and orientated despite the absence of a detectable blood pressure, responded to intravenous hydrocortisone though not to intramuscular cortisone or corticotrophin (A.C.T.H.). In severe status asthmaticus, acute disseminated lupus erythematosus, or overwhelming allergic reactions, the use of intravenous hydrocortisone could legitimately be considered.

The following cases are instructive.

Case 1

The patient was a woman aged 47. Bilateral total adrenalectomy was performed by Sir Stanford Cade for metastatic malignant disease secondary to carcinoma of the breast. The immediate post-operative progress was uneventful, no noradrenaline infusion being required. On the seventh post-operative day her condition deteriorated rapidly, swelling and induration became apparent at the medial end of the left incision, and her temperature rose to 104° F. (40° C.), her pulse to 150 a minute. She became drowsy, almost comatose, and her blood pressure unrecordable. As her condition was critical, intravenous hydrocortisone was started that night and 100 mg. was given over a period of six hours. After some two hours her blood pressure rose and her general condition improved dramatically; by morning her temperature had dropped to 99° F. (37.2° C.) and her pulse to 110. Oral cortisone, 25 mg. six-hourly, was given for the next six days and then gradually reduced to the usual maintenance dose of 50 mg. a day. There were no marked changes in serum electrolytes, sodium and chlorides being normal or just below normal throughout.

Comment.—In this case a wound infection rapidly precipitated a degree of adrenal insufficiency which seemed

likely to prove fatal. The improvement was sufficiently rapid and dramatic to make it probable that the hydrocortisone given was responsible for that improvement.

Case 2

This patient was a woman aged 44. Total bilateral adrenalectomy was performed by Sir Stanford Cade in April, 1954, for advanced metastatic disease secondary to carcinoma of the breast. Before operation she had been subject to occasional mild attacks of nausea and vomiting. In May, one month after discharge from hospital, she was readmitted, vomiting and ill; B.P. 85/75. Serum electrolytes were within normal limits. Only slight improvement occurred on L-noradrenaline and hydrocortisone (100 mg.) infusions, and it was felt that her gradual improvement was natural and essentially uninfluenced by therapy. Her next vomiting bout occurred in July; again it was felt that improvement was unrelated to L-noradrenaline given, but it was noted that the marked tachycardia settled only when the cortisone daily dosage was increased to 112.5 mg. by mouth.

In late November, 1954, she caught a severe cold and vomiting restarted. She became critically ill, pulse 140-150 a minute; the blood pressure dropped and became unrecordable. She became rapidly very weak and felt "numb." Her reflexes were normal. Hydrocortisone hemisuccinate, 50 mg., was given rapidly intravenously, followed by intravenous saline infusion. Within an hour she was distinctly better, blood pressure being 95/70. A further 50 mg. of hydrocortisone hemisuccinate was given intravenously three hours after the first injection, saline infusions were continued, and her daily dose of cortisone was increased to 200 mg. intramuscularly. Next morning she was much improved, the blood pressure was 120/90, and vomiting had stopped. Plasma chlorides and serum sodium, which were just below normal (93 and 131 mEq per litre respectively) on admission, dropped to 75 and 110 mEq as her condition deteriorated, then rose to 97 and 121 mEq two days after starting treatment.

Comment.—An upper respiratory infection apparently precipitated an attack of vomiting, a symptom to which this patient was predisposed. Her rapid deterioration seems to have been due partly to adrenal insufficiency and partly to dehydration and electrolyte upset. Intravenous hydrocortisone, abundant saline infusions, and an increase in the daily dose of cortisone appeared responsible for the improvement, which started soon after 50 mg. of hydrocortisone had been given intravenously and before more than a very small amount of saline had been infused. In this case it seems likely that in the previous episode hydrocortisone dosage had been inadequate.

Case 3

This patient, a woman aged 56, had had adrenalectomy performed by Sir Stanford Cade, the left side on March 16, 1954, the right on March 30. In the early morning of April 25 she suddenly collapsed and the blood pressure became unrecordable on the sphygmomanometer. She was sweating and the skin was cold; she was not cyanosed. For the previous three days her condition had been deteriorating and she had had nausea and vomiting, with some hypotension. Blood chemistry had been normal. The cause of this collapse was uncertain, and she was given 100 mg. of hydrocortisone by intravenous infusion over a period of six hours, purely empirically. She improved to some extent, but a greater improvement followed an intravenous infusion of noradrenaline subsequently. On May 2 her general condition had greatly improved.

Comment.—In this case hydrocortisone appeared to be less effective than the noradrenaline subsequently infused, though it may have initiated the improvement in the patient's condition. Many conditions apart from cortisone

insufficiency may cause sudden deterioration in these critically ill malignant cases—dehydration, electrolyte imbalance, and spread of the malignant process. Any infection, however trivial, may upset their somewhat precarious balance.

Discussion

Rukes, Orr, and Forsham (1954) have reported the use of intravenous infusion of the free alcohol of hydrocortisone at rates up to 50 mg. an hour in over 50 instances without untoward effect, though they note that epileptic seizures can be precipitated in susceptible patients. Thorn and his associates (1953) have shown that considerable sodium retention occurs in the normal subject during intravenous continuous infusion of 12 mg. an hour in saline. Over the short periods needed for the treatment of adrenal crisis, sodium retention and oedema are not a very real danger, however, and the use of 5% glucose in water will minimize this hazard. Rukes *et al.* advise that saline should be used only when an increase of blood volume is required, as in shock. They regard the use of intravenous hydrocortisone as justified in "selected cases of shock which are not relieved by transfusion or vasopressors."

Intravenous hydrocortisone is rapidly eliminated from the body; after its use oral or intramuscular cortisone must be given in full dosage. It is common practice to give a large intramuscular injection of cortisone acetate at the same time as the intravenous infusion is started so that it may gradually take effect when the infusion is discontinued. The patient should be very closely watched for some hours after the intravenous infusion has been stopped.

During the treatment of any condition in medicine or surgery with large doses of cortisone a close watch is always kept for signs of infection, and antibiotic therapy instituted as required. This applies particularly to adrenalectomized patients with metastatic malignant disease who are in such a frail condition that episodes such as post-operative infection are often poorly tolerated. If there is any possibility of cortisone deficiency playing a part resort is had to the use of intravenous hydrocortisone. We have not, to date, needed to use intravenous infusions of this drug over the operative period; we regard it as our main stand-by when any symptoms occur which might be construed as being the result of acute cortisone insufficiency after operation. The adrenalectomized patient may respond atypically to wound or chest infection, becoming hypotensive and ill, not responding satisfactorily to antibiotics, and going rapidly downhill. Cases such as Case 1 above should, I feel, be given intravenous hydrocortisone. Although only some may be helped, it is unlikely that the rest, seriously ill patients with advanced malignant disease, will be harmed by this treatment, which in some cases appears to be life-saving.

Summary

Intravenous hydrocortisone is a most useful weapon in the treatment of acute adrenal insufficiency; it marks a real advance in therapeutics. Its use is discussed in a number of different conditions. It should be always available when total adrenalectomy is performed and throughout the early post-operative period.

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