advocate the precaution, used in the present case, of observing the reversed segment for some 30 minutes at operation after the anastomosis has been completed, in order to ensure that the blood supply of the reversed segment remains adequate after its vascular pedicle has been twisted through 180 degrees.

Summary

The use of a reversed segment of small intestine in the treatment of persistent profuse ileostomy diarrhoea after colectomy

for polyposis coli is described. The value of the reversed intestinal segment procedure in patients with rapid intestinal transit time due to causes other than massive bowel resection warrants further exploration.

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Synacthen Depot—Adrenal Response in Normal Subjects and Corticotrophin-treated Patients*

J. K. NELSON, M.D., M.R.C.P.ED.; D. W. NEILL, M.SC., M.C.PATH., F.R.I.C.

D. A. D. MONTGOMERY, M.B.E., M.D., F.R.C.P.; J. S. MACKAY, B.SC.

B. SHERIDAN, A.I.M.L.T.; J. A. WEAVER, M.D., M.R.C.P.

Brit. med. J., 1968, **1**, 557–558

The synthetic polypeptide tetracosactrin, B¹⁻²⁴ (Synacthen) consists of the 24 N-terminal amino-acids of corticotrophin. Corticotrophin itself consists of a chain of 39 amino-acids, but it has been shown that biological activity resides in the first 19 amino-acids (Li *et al.*, 1960), whereas immunological activity and species specificity reside in the region of the 25th to 39th amino-acids (Li, 1961; Fleischer *et al.*, 1965).

Hitherto, Synacthen has been used as a test of adrenocortical function in which the response of plasma 11-hydroxycorticosteroids (11-OHCS) is taken as an index of adrenal activity. The effect of a single intramuscular injection of aqueous Synacthen is short-lived, lasting about 90 minutes (El-Shaboury, 1965). Recently a depot preparation (42,915-Ba, Ciba), Synacthen, complexed with zinc has been prepared, and we have investigated its use in normal subjects and also compared the response to Synacthen Depot and corticotrophin gel in rheumatoid and asthmatic patients.

Subjects and Methods

Normal controls for the dose response studies were six healthy medical students. A number of patients on long-term intermittent corticotrophin treatment (Nelson *et al.*, 1966)

volunteered to try the new preparation, and 10 were studied as ward patients. Plasma 11-OHCS were estimated by a modification of the fluorometric procedure of Mattingly (1962). Venous blood samples for estimation of plasma 11-OHCS were drawn at 7 a.m. (patients) and 9 a.m. (students), after which times the Synacthen Depot was given; further blood samples were taken at 12.30 and 5 p.m. (for both patients and students), 10 p.m. (students), and 11.30 p.m. (patients). The tests were continued on the day after the Synacthen Depot or corticotrophin administration to study the effect of the previous day's treatment on the pituitary circadian rhythm.

Results

Normal Subjects.—A single injection of 1 mg. of Synacthen Depot had a similar effect whether given by intramuscular or subcutaneous injection (Fig. 1). There was a marked increment of 27.5 and 31.6 $\mu\text{g.}/100\text{ ml.}$ respectively in the plasma 11-OHCS levels at 3½ hours, and this was sustained to even slightly higher concentrations at eight hours. The levels at 10 p.m. (13 hours after injection) were still markedly elevated at the time of the expected daily decline in plasma cortisol. On the second day the pattern of plasma 11-OHCS showed the expected fall throughout the day between 9 a.m. and 5 p.m. The dose response curves (Fig. 2) showed that with 0.5 mg. of Synacthen Depot the pattern of response in the first 24 hours was the same as that given by greater doses, though the actual plasma 11-OHCS increments were naturally less. The largest dose of 2 mg. evoked an increase at 3½ hours and eight hours approximately similar to 1 mg. Thereafter the pattern of response was markedly different, showing a greater elevation for a longer time—the 13-, 24-, and 32-hour levels demonstrating sustained augmentation of adrenal response. Four of the subjects experienced slight dis-

FIG. 1.—Mean plasma 11-OHCS levels ($\pm$ standard error) in six normal subjects after administration of Synacthen Depot 1 mg. intramuscularly or subcutaneously.

* From the Sir George E. Clark Metabolic Unit and Biochemistry Department, Royal Victoria Hospital, Belfast.

FIG. 2.—Mean plasma 11-OHCS levels ($\pm$ standard error) in six normal subjects after administration of Synacthen Depot subcutaneously at doses of 0.5, 1, and 2 mg.

comfort at the site of the subcutaneous injection, and for this reason all subsequent treatment of the patients was by the intramuscular route.

Patients.—Intramuscular injection of 1 mg. of Synacthen Depot caused a somewhat greater response than 40 units of corticotrophin gel (Fig. 3). The initial 5½-hour plasma 11-

response to corticotrophin given usually on a regimen of 40 units twice weekly (Nelson *et al.*, 1966). It has been noted that the effect of corticotrophin gel at this dosage was to produce an augmentation of the plasma 11-OHCS concentrations measured at six hours, but by 24 hours the phase of adrenal stimulation had ended. This same pattern was observed again in the pre-

FIG. 3.—Mean plasma 11-OHCS levels ($\pm$ standard error) in 10 corticotrophin-tested patients after administration of 40 i.u. of corticotrophin gel or 1 mg. of Synacthen Depot.

OHCS increment was slightly greater (49.4 µg compared with 40.9 µg/100 ml.), but the pattern throughout day one was essentially similar. On the second day after 1 mg. of Synacthen Depot the 11-OHCS levels remained higher than after 40 units of corticotrophin gel at all four times of measurement in each group.

Discussion

The dose response curves for the Synacthen Depot preparation suggest that the major factor influencing the duration of action is total dosage. An increase from 0.5 to 1 mg. has an effect in increasing the initial response at 3½ hours. When higher doses are considered, increasing from 1 to 2 mg. does not provoke a greater response but sustains the enhanced plasma 11-OHCS levels from the evening of the first day throughout the second day.

Comparing the effect of intramuscular injection with subcutaneous injection at a dose of 1 mg. the pattern of response is almost identical. The question of whether a subcutaneous or an intramuscular route of administration is preferable for long-term treatment would require further study, but as some of our normal subjects noted slight discomfort after subcutaneous administration we did not use this route in the patients.

The patients on long-term intermittent corticotrophin therapy have previously been studied in terms of 11-OHCS

sent study, which provides further details of the response since more frequent sampling was undertaken.

Summary

Synacthen Depot (42,915-Ba, Ciba) is an effective and potent stimulant of adrenal cortical function, given intramuscularly or subcutaneously, which has a prolonged duration of action lasting over 24 hours at a dose of 1 mg. It seems to have promise in the maintenance treatment of selected patients with rheumatoid arthritis or asthma.

We should like to thank Dr. T. B. Binns, of Ciba Laboratories Ltd., for providing supplies of Synacthen Depot (42,915-Ba, Ciba). Thanks are also due to Miss M. Weller and Mr. Roy Creighton.

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