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THE EFFECT OF A DIURETIC (CENTYL, LEO) ON THE OEDEMA OF THE HAND FOLLOWING SURGICAL TREATMENT OF DUPUYTREN'S CONTRACTURE

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Oedema is one of the most important complications of injury to and operations on the limbs, in particular the hands. This post-traumatic oedema has both a primary injurious effect, in that it may lead to bursting of sutures, necrosis of the skin, compression of vessels, nerves, etc., and it may also give rise to secondary sequelae, as the fluid in the tissues acts as a foreign body which rapidly causes fibrosis and is an associated factor in the development of post-traumatic dystrophy (Zachariae 1964).

The simplest means of counteracting oedema is by high elevation of the limb. However, this is rarely sufficient in itself, and attempts have therefore been made to employ various drugs of widely differing properties.

PREVIOUS INVESTIGATIONS

A number of workers have investigated the proteolytic enzyme chymotrypsin. Barclay (1960) found that "Chymar" probably had some effect on the oedema following operations for Dupuytren's contracture, as evaluated by measurements of the volume, but that the effect was poor in those patients in whom, because of their constitution, large amounts of oedema were to be expected (Barclay 1959). Bern (1964) found a satisfactory effect of alpha-chymotrypsin in patients who had undergone operations on the biliary tracts. The investigation was

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carried out as a double-blind trial, and the effect was evaluated from measurements of cutaneous oedema using Aldrich's (1924) intra-dermal test with sodium chloride. In these studies the preparation was administered intramuscularly, but Lie et al. (1967) found that there was an effect on the postoperative oedema following hand operations after oral administration of the proteolytic enzyme Chymoral (trypsin-chymotrypsin). Their material comprised various hand operations, and the effect was assessed by measurements of the circumference of the hand and the distal interphalangeal joint. Shaw (1969), who used the same preparation, Chymoral, found that it was effective in the oedema following finger fractures, as judged by the restitution of movement in the joints. In all these studies it has furthermore been demonstrated that chymotrypsin has an obvious effect on the pain; it may be merely for this reason that it is capable of inhibiting oedema since the patients, if they have no pain, find it easier to start moving the injured part.

Hydroxyphenylbutazone (Tanderil) undoubtedly has a very marked analgesic effect. Miller et al. (1960), and a number of other workers, also consider that they have been able to demonstrate a direct inhibitory action on the post-traumatic oedema itself (Wilhelmi 1955, Domenjoz 1960). However, Olesen & Zachariae (1965) did not find any reduction in the oedema following operations for Dupuytren's contracture. The investigation was carried out as a double-blind trial, and the effect was evaluated by measurements of the volume using Eccles' (1956) method. However, it was concluded that perhaps Tanderil might have been effective in oedema following more extensive trauma than that due to an operation for Dupuytren's contracture.

PRESENT INVESTIGATION

It would seem natural to attempt to reduce the oedema following trauma by administration of a diuretic drug, in analogy with the treatment of other forms of oedema, and the generalized effect of such a diuretic is of no importance, as it would be necessary for only a short period. In the Orthopaedic Hospital in Copenhagen we have investigated the effect of Centyl Leo on the hand oedema following operations for Dupuytren's contracture, using the same technique as that employed in the investigation of the effect of Tanderil (Olesen & Zachariae 1965).

MATERIAL, METHODS AND RESULTS

The investigations were carried out in a consecutive series of patients with Dupuytren's contracture who were admitted for operation in the Department of Hand Surgery. The patients were divided into two series which received different doses of Centyl, bendroflumethiazide; the first group received 5 mg t.i.d. from the day preceding operation until the oedema had disappeared (at most 10 days), while the second group received 10 mg t.i.d. for the same period. 56 patients were included in the experiments, 27 in the placebo and 29 in the Centyl groups.

The investigation was carried out as a double-blind trial, with alternate patients receiving active drug and placebo. The estimation of the oedema was carried out in the apparatus described by Olesen & Zachariae (1965), which is a modification of Eccles' apparatus (1956); the hand is dipped into water and the volume of water displaced is measured and is an expression of the volume of the hand. The measurements were made on the day before operation, the day after operation, and thereafter every fourth day until the preoperative volume was reached. The distribution according to age and sex in the groups was relatively uniform, as the majority of patients with Dupuytren's contracture are aged between 40 and 60 years. There were no complications in the group which received 5 mg Centyl t.i.d. but the double dosage led to a number of side-effects and it was necessary to withdraw treatment in four patients, three of whom had received the active drug and one of whom had received placebo.

The results of the trial have been evaluated statistically by H. Engberg-Pedersen, statistician, who gives the following report:

The investigation comprised two experimental groups, studied at different times. The first trial tested the effect of 5 mg Centyl t.i.d. from the day before operation until 10 days after operation, while the second was a corresponding test of the effect of 10 mg Centyl. In both cases a control group was treated with placebo.

The volume of the hand was measured on the day before, the day after operation, and at regular intervals of 4-5 days after operation, until the oedema disappeared. The difference between the maximum volume measured V_m , and the original volume V_o has been taken as an expression of the severity of the oedema.

Table 1 in the appendix shows the measured volumes V_m and V_o , and $\Delta = V_m - V_o$ and $x = 1000 \cdot (\log V_m - \log V_o)$. The following conclusions can be drawn from these figures:

- (1) In 30 per cent of the total material there was practically no oedema ($V_m - V_o < 10$ ml). In the placebo group the incidence of this finding was 22 per cent, while in the groups which received Centyl, taken as a whole, it was 38 per cent. This difference lies within the experimental error.
- (2) For the cases in which oedema developed, no difference can be demonstrated between the two temporary separate placebo groups. With an initial volume taken as 417 ml (the average of V_o for

Table 1. Postoperative Centyl therapy in Dupuytren's contracture Appendix.
Results of measurement

Placebo I					5 mg Centyl					Placebo II					10 mg Centyl				
V _o	V _m	Δ	x		V _o	V _m	Δ	x		V _o	V _m	Δ	x		V _o	V _m	Δ	x	
392	442	50	52		346	360	14	17		315	350	35	46		450	495	45	41	
440	470	33	70		370	390	20	23		550	580	30	23		455	475	20	19	
420	439	19	19		328	328	0	-		460	460	0	-		560	590	30	23	
515	580	65	52		460	470	10	9		400	415	15	16		430	410	-20	-	
310	360	50	65		405	440	35	36		365	415	50	56		470	470	0	-	
432	432	0	-		420	421	1	-		330	400	70	84		430	490	60	57	
405	450	45	46		460	472	12	11		355	395	40	46		430	470	40	39	
470	490	20	18		453	453	0	-		450	520	70	63		440	480	40	38	
504	530	26	22		510	510	0	-		390	450	60	62		365	405	40	45	
460	460	0	-		225	240	15	28		450	470	20	19		425	430	5	-	
425	475	50	48		300	300	0	-		290	320	30	43		445	465	20	19	
355	370	15	18		450	452	2	-		490	500	10	9		380	380	0	-	
335	335	0	-		355	380	25	30		560	555	-5	-		415	430	15	16	
470	470	0	-		405	418	13	14							345	365	20	25	
					476	476	0	-											

V_o = volume of hand before operation.

V_m = maximum volume of hand after operation.

Δ = V_m - V_o.

x = 1000 · (log V_m - log V_o).

the entire group), the most efficient estimate of the average volume of the oedema in the placebo groups: $\Delta = 42.1$ ml with 95 per cent confidence limits 31.7–53.0 ml.

- (3) For the cases in which oedema developed there was similarly no demonstrable difference between the effect of treatment with 5 mg Centyl t.i.d. and with 10 mg t.i.d. The most efficient combined estimate of the average volume of the oedema during treatment with Centyl is $\Delta = 26.7$ ml (20.9–33.4).
- (4) The difference between the volume of the oedema during placebo and Centyl treatment is statistically significant. On an average it was 15.4 ml, corresponding to a reduction by 37 per cent.
- (5) The variation in the volume of the oedema which developed is significantly greater for the placebo groups than for the groups which were treated with Centyl. This must be interpreted as indicating that Centyl first and foremost hindered the development of very severe oedema (> 50 ml).
- (6) The duration of the oedema, i.e. the length of time from the operation until the volume of the hand returned to V_0 , was not demonstrably affected by Centyl therapy.

If the results are divided according to treatment and the volume of oedema this gives the following 2×2 table:

	Placebo	Centyl	Total
< 10 ml	6	11	17
≥ 10 ml	21	18	39
Total	27	29	56

$$\chi^2 = 1.63 \text{ f} = 1 \quad \text{i.e. no significant difference.}$$

For $\Delta \geq 10$ ml x may be considered as normally distributed.

Placebo I	: $\bar{x} = 41.00$	$s^2 = 404$ with $f = 9$
Placebo II	: $\bar{x} = 42.45$	$s^2 = 549$ with $f = 10$
5 mg Centyl	: $\bar{x} = 21.00$	$s^2 = 95$ with $f = 7$
10 mg Centyl	: $\bar{x} = 32.20$	$s^2 = 187$ with $f = 9$

For the two placebo groups there is no demonstrable difference between the two estimates of the variance. A combined estimate is therefore $s^2 \geq 480$ $f = 19$.

The same is true of the two Centyl dosages: $s^2 = 147$ $f = 16$.

From $v^2 (19.16) = 3.26$ $p = \text{approx. } 0.01$ it can be seen that the theoretical variance is probably greater for placebo than for Centyl.

For the mean values there is no suggestion of difference between the two placebo groups and they are combined to give a common estimate: $\bar{x} = 41.76 \pm 4.80$.

For the mean values for the two Centyl groups it is found: $\bar{x} (10) - \bar{x} (5) = 11.20 \pm 5.76$, corresponding to $p = \text{approx. } 0.04$. Strictly speaking, 10 mg t.i.d. is less effective than 5 mg t.i.d., but it would be reasonable to regard this as a random fluctuation and use the mean: $\bar{x} = 27.22 \pm 2.86$. The difference between P and C is then 14.54 ± 5.59 , i.e. statistically significant. The 95 per cent confidence limits are $2.04 \cdot 5.59 = 11.40$ when correction is made for the difference between the two variances.

DISCUSSION AND CONCLUSIONS

From the present investigation and the statistical evaluation of the results it would seem that treatment with Centyl for a 10-day period in connection with the operation for Dupuytren's contracture is capable of reducing the tendency to oedema, such that the treatment acts in inhibiting the development of very severe oedema. This is extremely important, as it is the large volumes of oedema which mainly give rise to sequelae. No similar results have been obtained with any of the treatments mentioned earlier. Barclay (1960) in his investigation of Chymar found that that preparation had least effect in patients who were predestined to develop severe oedema, as the oedema was reduced by 10–20 ml regardless of whether it was slight or severe.

In an investigation completely comparable to that described here it was reduced by 10–20 ml regardless of whether it was slight or (Olesen & Zachariae 1965).

The optimum dose of the diuretic used in this trial, Centyl, would seem to be 5 mg t.i.d. for 10 days, as a doubling of this dosage did not increase the anti-oedematous effect, but gave rise to a number of side-effects.

The oedema following trauma to the hand will presumably be reduced by the administration of a diuretic immediately after the lesion, in a manner similar to that observed following operation for Dupuytren's contracture. We have given Centyl experimentally to two patients with very severe hand trauma and consider that there was

less oedema than would correspond to the lesion—but this is naturally difficult to evaluate, as there is no basis for comparison. However, these investigations will be continued.

SUMMARY

Oedema is one of the most serious complications of trauma and operations on the hands. Efforts have previously been made to reduce the oedema by means of various drugs, but these have had no definite effect.

In the present investigation we have studied the effect of a diuretic—Centyl Leo—on the oedema following operation for Dupuytren's contracture. The investigation was carried out as a double-blind trial, and the oedema estimated by measurements of the volume using Eccles' method.

It was found that a dose of 5 mg Centyl Leo t.i.d. from the day before operation until the volume of the hand has returned to normal has a statistically significant inhibitory effect on the development of, in particular, severe postoperative oedema, which experience has shown to give rise to the most serious complications.

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