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CONTINUED INVESTIGATIONS INTO THE EFFECT OF
DIURETICS UPON OEDEMA OF THE HAND FOLLOWING
OPERATION FOR DUPUYTREN'S CONTRACTURE:
BUMETANIDE LEO

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Oedema is one of the most important complications of extremity injuries and operations. This applies quite particularly to the hands because of their complicated structure and function. Only very slight oedema is required to compromise hand function for a long time or perhaps permanently. Such oedema may cause primary complications in the form of tightening of the sutures, causing cutaneous necrosis and compression of vessels and nerves, and it may give rise to secondary complications, viz. posttraumatic dystrophy (Zachariae 1964).

It may therefore be of use to administer drugs which, despite their systemic effect, must be considered to exert sufficient action upon the affected extremity. However, such drugs must not have side effects so severe that the systemic risk outweighs the local advantages.

Various authors have tested a number of drugs in the attempt to reduce local oedema in extremity injuries. A survey has been published by Zachariae et al. (1970). It may be mentioned that some effect has been found with Chymar (Barclay 1960) and with Chymoral (trypsin chymotrypsin) (Lie et al. 1967, Shaw 1969).

Tanderil, claimed by some to reduce posttraumatic oedema (Miller et al. 1960, Domenjoz 1960) was studied with a particular view to hand oedema by Olesen & Zachariae (1965), who did not find a corresponding effect.

Reduction of oedema by administration of a diuretic was studied by Zachariae et al. (1970), who used Centyl Leo (bendroflumethiazide). These investigations were performed double-blind using measurements

of hand volume before and after operation for Dupuytren's contracture. A significant reduction of the oedema was found in the group treated with the active substance as compared with the placebo-treated group.

It was reasonable, therefore, to try other diuretics, which possibly have a more specific action.

In continuation of the previous studies on the anti-oedematous effect upon hands operated upon for Dupuytren's contracture and treated with the diuretic Centyl Leo, similar studies were performed in the Department of Hand Surgery of the Gentofte Hospital, Copenhagen, using another diuretic, Bumetanide Leo. The technique was exactly the same as that used previously (Zachariae et al. 1970).

Bumetanide (3-n-butylamino-4-phenoxy-5-sulphamyl benzoic acid) is a new "high-ceiling" diuretic selected from a series of potent amino-benzoic acid derivatives (Feit 1971). Studies on animals (Feit 1971, Østergaard et al. 1972) as well as on healthy volunteers (Asbury et al. 1972, Feit et al. 1973) have revealed that bumetanide is characterized by an intensive and relatively short-lasting diuretic and saluretic effect, and on a weight basis 40 to 100 times as potent as furosemide. Clinical investigations have confirmed that bumetanide is an effective diuretic in the treatment of oedema of different geneses without any serious side effects (Asbury et al. 1972, Olesen et al. 1973).

MATERIAL AND METHODS

The investigations were performed on consecutive patients undergoing operation for Dupuytren's contracture.

The only selection was that all the patients were males with no other ailments. The trial was double-blind, one group receiving Bumetanide Leo in the form of 1 mg tablets, one tablet at 8 a.m., 2 p.m., and 8 p.m., starting immediately after the operation and continued for 10 days. The other group received placebo tablets, administered in the same way. When the patients were supplied with the tablets, they also received thorough written instructions about the intake of the tablets and about only taking a maximum of about 1500 ml fluid, in the form of non-alcoholic beverages, in the 24 hours. The oedema was examined by measuring the volume of the hand in an apparatus of the type used previously and described by Olesen & Zachariae (1965). The principle of the method is to immerse the hand in water and measure the displaced volume of water.

The assessments were performed on the day before the operation and on the 1st, 3rd, 5th, 7th, and 10th day after the operation. However, the measurements were discontinued earlier, if the volume had returned to preoperative values. Each group comprised 10 patients. Table 1 lists the age distribution of the patients in both groups as well as complications. Table 2 presents the results of the volume measurements.

Table 1. All the patients were males. There were no postoperative infections or nerve lesions.

Case No.	x/y	Age	Haematoma	Skin necrosis
1.	Drug	51	—	—
2.	—	49	—	+
3.	—	66	—	—
4.	—	53	—	—
5.	—	62	—	—
6.	—	52	+	—
7.	—	51	—	—
8.	—	67	—	—
9.	—	61	—	—
10.	—	63	—	—
11.	Placebo	52	—	—
12.	—	56	—	—
13.	—	52	—	—
14.	—	60	—	+
15.	—	47	—	—
16.	—	48	—	—
17.	—	52	—	+
18.	—	65	—	—
19.	—	60	—	+
20.	—	52	—	—

RESULTS

The material was analysed by H. Engberg-Pedersen, statistician, Dept. of Mathematical Statistics, whose results were as follows:

Previous investigations concerning the possible effect of Centyl Leo on the postoperative swelling of the hand have indicated that the ratio between the maximum volume of the hand, measured within the first 10 days after operation, V_m , and the volume prior to operation, V_o , that is $R = V_m/V_o$, is a convenient criterion on which to base the evaluation of the possible effect of a diuretic. The logarithmic transform of R , $x = \log R$, has been shown to behave as a normal deviate.

Table 3 lists the 10 individual values of V_m , V_o , and x for each of the two groups, bumetanide and placebo.

Each group yields an independent estimate of the variance of x with 9 degrees of freedom, f . The two estimates do not differ significantly and may be combined to $s^2 = 0.000347$ $f = 18$. With this variance, the group means are:

Table 2. Volume measurements.

Case No.	Preop.	1st day	3rd day	5th day	7th day	10th day
1.	500	480	485	500	465	495
2.	495	490	480	495	—	495
3.	470	465	470	475	—	480
4.	385	380	400	395	385	385
5.	460	460	450	460	—	460
6.	440	430	450	490	480	480
7.	460	450	435	450	450	485
8.	440	450	465	460	470	475
9.	420	435	415	410	—	410
10.	450	450	450	450	480	455
11.	390	395	395	405	395	395
12.	445	440	455	460	445	440
13.	455	460	480	475	515	470
14.	500	518	520	580	550	550
15.	410	440	460	450	450	430
16.	425	450	455	420	440	410
17.	380	420	430	425	400	430
18.	550	550	560	590	580	560
19.	400	390	410	410	415	400
20.	370	400	410	435	410	420

Bumetanide: $x = 0.0172$ $R = 1.040$ 95 % limits: (1.011–1.070)

Placebo: $x = 0.0399$ $R = 1.096$ 95 % limits: (1.065–1.128)

Pla/Bu: $R = 1.054$ 95 % limits: (1.012–1.097)

Even though the confidence limits are rather wide, due to the small number of subjects in each group, the last line shows that a difference between the two treatments exists and may be of medical interest. Given a mean value of 442 ml for a hand before operation, the maximum swelling after operation may be calculated as:

Bumetanide: 17.7 ml 95 % limits: (6.2–29.6)

Placebo: 42.4 ml 95 % limits: (26.1–59.2)

DISCUSSION AND CONCLUSIONS

From the investigations described above it is apparent that by administration of the diuretic Bumetanide Leo it is possible to reduce significantly the postoperative oedema in hands subjected to operation for Dupuytren's contracture. This agrees with the results of previous studies on another diuretic, Centyl Leo (bendroflumethiazide).

Table 3.

Bumetanide			Placebo		
V _o	V _m	x	V _o	V _m	x
500	500	0.0000	390	405	0.0162
495	495	0.0000	445	460	0.0144
470	480	0.0090	455	515	0.0539
385	400	0.0165	500	580	0.0645
460	460	0.0000	410	460	0.0500
440	490	0.0468	425	455	0.0296
460	485	0.0230	380	430	0.0539
440	475	0.0332	550	590	0.0304
420	435	0.0151	400	415	0.0159
450	480	0.0280	370	435	0.0703
452	470	0.0172	432	474	0.0399

Table 3 lists individual values of V_o, hand volume prior to operation in ml, V_m, the maximal volume measured within the first 10 days after operation and X, the logarithm of V_m/V_o for 10 patients in each group.

The difference in X between Bumetanide and placebo is statistically significant at the 95 % level.

The groups of 10 patients each may seem small. However, as the results are statistically significant and as they fit in with previous findings, this number may probably be considered sufficient.

No side effects were observed. This also applied to Centyl Leo in a dosage of 5 mg $\times$ 3, whereas a number of side effects occurred on 10 mg $\times$ 3. A number of the patients in the bumetanide-treated group complained of the frequent and increased urination, especially during the night.

As for the degree of reducing the oedema, Centyl Leo was found to be equally effective in the 5 mg as in the 10 mg dose. In the present study, Bumetanide Leo in the doses used had practically the same effect as Centyl Leo upon the oedema.

No doubt, the same effect will be obtainable by almost any diuretic. It is important to find one which is devoid of side effects and which may be administered in a way so that increased urination gives rise to as little discomfort as possible.

Neither of the present diuretics, in the doses used, had any side effects, and both reduced the oedema to the same extent. Centyl Leo has a more protracted diuretic effect, whereas Bumetanide Leo has a more rapid and time-limited action. As a rule, the diuretic effect has

run its course in 3 or 4 hours, thus causing the patients less discomfort, especially after the evening dose.

Concerning the indication for using diuretics to counteract post-traumatic oedema of the hand, the authors do not feel that it is indicated for routine preoperative administration to patients undergoing operations for Dupuytren's contracture and other similar procedures.

On the other hand, it seems indicated to use a diuretic—preferably Bumetanide Leo—in cases of severe hand injuries or operations causing widespread traumatization of the tissues.

SUMMARY

Oedema is one of the most serious complications of hand injuries and operations. Therefore, constant attempts have been made to find means of reducing this oedema, in addition to elevation.

In a previous trial, the diuretic Centyl Leo (bendroflumethiazide) was found to reduce significantly the oedema after operations for Dupuytren's contracture. The present trial was a continuation of the former one, but using another diuretic, Bumetanide Leo.

The trial was performed double-blind, and the oedema was assessed by a volume measurement, immersing the hand in water.

Bumetanide Leo, in a dosage of 1 mg 3 times daily for 10 days, was found to exert approximately the same reducing effect as Centyl Leo upon the oedema. No side effects occurred and, compared to Centyl Leo, Bumetanide is more convenient, as it has a less protracted diuretic effect. It is emphasized that it is not planned to administer a diuretic routinely in connection with minor operations on the hand, only in cases of major, traumatizing operations and severe injuries. Judging by the present investigations, this is believed to have a beneficial effect upon the final result.

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