Coppersulphate and Pimozide For Anorexia Nervosa

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Summary

Starting from symptom analysis, a case can be made for a pathophysiologic model of dopaminergic hyperfunctioning and noradrenergic hypofunctioning in Anorexia Nervosa.

In this model, lowered activity of dopamine-beta-hydroxylase, the enzyme that converts dopamine to noradrenalin is crucial, and a copper deficiency is ecologically important in lowered activity. Eight female cases were studied. A copper deficiency was confirmed and a lowered activity of dopamine-beta-hydroxylase was made very probable; clinical improvement after 10 weeks treatment with copper sulphate and pimozide was good. Further study along this treatment line is warranted; the more so because pimozide can block the dopaminergic hyperfunctioning directly, and probably raise serum-copper levels as well. This last property needs confirmation in humans, but may be important, because in this way pimozide can influence noradrenergic hypofunctioning.

The beneficial effects of pimozide in Anorexia Nervosa are disease specific, since on current clinical indications, anorexia is described as side-effect of pimozide.

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Introduction

The diagnosis of anorexia nervosa is based on three positive criteria (Morgan and Russell, 1975; Russell, 1970). First, the feeding disorder, be it anorexia or bulimia; second, amenorrhea in girls; and third, neuropsychiatric disturbances such as, disorder of feeding behavior, lack of motivation, dysphoria, body perception disorders, inefficiency, hyperactivity, and behavioral stereotypy; the last one expresses itself also in the inability of the patients to stop eating. As a pathophysiologic model for anorexia nervosa, some authors have proposed a hyperfunctioning of the cerebral dopaminergic systems (Barry and Klawans, 1976; Mawson, 1974; Plantey, 1977). Starting from an analysis of the stated symptomatology, one might however differentiate for their pathophysiologic mediation. Inefficiency, hyperactivity and behavioral stereotypy can be regarded as symptoms of dopaminergic hyperfunctioning, but for the feeding disorder, some hormonal anomalies, the disorder of feeding behavior, the dysphoria, and the perception disorder a plea can be made for hypofunctioning of the noradrenergic cerebral systems, as pathophysiologic mechanism (Hoes, 1976). In the body, dopamine is converted to noradrenalin by the enzyme (Evans, 1973). So, copper-deficiency may be etiologically involved in anorexia nervosa (Hoes, 1976). Clinical and biological data on eight female anorexia nervosa patients who

fulfilled the stated criteria, and treatment results according to the proposed pathophysiological model of dopaminergic hyperfunctioning, noradrenergic hypofunctioning and etiologically a copper-deficiency, are presented. Their significance is discussed.

Patients and Methods

The eight female cases studied were all hospitalized. They fulfilled the stated positive criteria. Their body weight was below the criterion of 80 percent (absolute height in cm-110) kg.

E 1 DATA ON ANOREXIA PATIENTS

Patient		Age (yrs)	Duration illness (yrs)	Body-weight (kg)	Criterion" (kg)	Body height (cm)
1 2 3 4 5 6 7 8		29	15	48	48	170
		15	1.5	45	47.2	169
		17	1.5	37	38.2	159
		14	1	30	36	155
	A	18	3	39	44	165
	B	18	3	38	40	160
	L	17	2	36	39.2	159
		16	1	38	41.6	162
MEAN				38.9	41.8	

"Body-weight criterion: weight 0.8 x (absolute value of height in cm — 1101 kg.

As biologic parameters, serum-copper, the 24 hour-excretion in urine of the metabolite of dopamine (homovanillic acid = HVA) and (nor)adrenalin (vanillylmandelic acid = VMA) were determined. The sum of the HVA and VMA values (HVA + VMA; reference values: 16 + 24 = 42 /umol/ 24 hours urine) is used as an indication of the feeding disorder and the ratio VMA/HVA (24/16 = 3/2) as an indication of the functioning of the DbH. The biologic measurements were repeated after five weeks treatment with coppersulphate, 5 mg ti.d. in capsules. Patient number three had received lyndiolR until admission; this was stopped, and she did not receive medication during these five weeks. After five weeks, case number three and four others received for the next five weeks 1 mg ti.d. of pimozide, a specific dopamine-receptor
blocker (Pinder et al, 1976). Coppersulphate was continued in all seven patients who had received it initially. The stated symptomatology was rated at a three points scale: state at admission, improvement, or recovery.

Serum-copper was determined by atomic absorption, HVA fluorometrically and VMA photometrically.

Results

On admission patient number three showed a high serum-copper and high values of HVA and VMA, and a high VMA/HVA ratio; but she had taken lyndiolR. The other seven cases however, showed low serum-copper values, low HVA and VMA excretion and a low VMA/HVA quotient as expected (Table 2).

After the five weeks of copper-sulphate treatment the symptomatology ascribed to noradrenergic hypofunctioning had improved as scored on a three points scale; this was also the case in patient number three. Menstruation had not resumed. In four patients on CuSCty and in patient number three however the symptoms, **as** presumably mediated by dopaminergic hyperfunctioning did not show satisfactory improvement. The biologic measurements were repeated after the first five weeks treatment and showed very clear improvement (Table 2).

After a total treatment period of 10 weeks, all eight patients had clinically improved very well for all the criteria including

TABLE 2

VALUES OF BIOLOGIC PARAMETERS BEFORE (1) AND AFTER (21 FIVE WEEKS COPPERSULPHATE, 5 mg p.o. t.i.d.

Patient	$CuS0_4$	Serumcopper /umol/1 (1)	(2)	VMA + HVA /umol/24 hrs urine (11)	(2)	VMA/HVA ID	12)
1	+	12	20	24	45	1/4	4/1
2	+	12	18	26	42	1/3	3/1
3	-	30	17	52	38	3/1	2/1
4	+	11	16	19	46	1/7	3/1
5	+	12	15	23	51	1/3	4/1
6	+	12	16	17	37	1/6.5	3/1
7	+	11	17	20	39	1/4	2/1
8	+	12	18	17	41	1/3	3/1
Reference Values	m±s.d.	17.0 ±3,5		24 + 16 = = 42		24/16 = = 3/2	

menstruation. Their body weight showed excellent recovery. If one takes as improvement criterion a gain of 0.5 Kg/week, there was for the ten-week treatment period in all cases a highly significant gain (p=0.0000048: student's t-test)(Table 3).

At ten weeks after admission, all patients could be discharged.

Discussion

Only the third patient had on admission biologic values, contradictory to the expected values, and yet had anorexia nervosa. However she had received lyndiolR until then; estrogens raise serum-copper (Evans, 1973) and are able to suppress feeding (Simpson and Dicara 1973; Wade, 1974). The VMA/HVA ratio was not very high, probably because of inhibition of DbH by estrogens (Redmond, Murphy and Baulu, 1975). Why the sum of HVA + VMA is high in this case, remains elusive. The other seven cases had biologic values as expected, low serum-copper values, low HVA + VMA sum and low VMA/HVA quotient. On the copper supplementation the clinical parameters of noradrenergic hypofunctioning improved well, with exception of menstruation. Resumption of menstruation appears however to be correlated with the attainment of a critical body weight (Boyar et al. 1974; Johanson, 1974). After the first five weeks this could not be expected to have been reached. But after the 10 weeks it had, and menstruation did indeed start again. In accordance with the clinical improvement, the biologic values were normalized after the first five weeks of treatment.

It was no surprise that under pimozide treatment, during the second five weeks, the symptoms of dopaminergic hyperfunctioning cleared up. The symptoms ascribed to noradrenergic hypofunctioning were further improved, which might be surprising. Pimozide has (only very weak) noradrenergic receptor blocking properties (Pinder et al. 1976), but it may raise serum-copper and -ceruloplasmin levels, as demonstrated in rats (Schreiber and Pribyl, 1976). This effect might have contributed to the continuous improvement of the symptoms of noradrenergic hypofunctioning.

The beneficial effects of pimozide in Anorexia Nervosa are disease specific, since on current clinical indications, anorexia is described as a side-effect (Pinder et al. 1976).

The results obtained appear to validate the pathophysiologic proposal of cerebral dopaminergic hyperfunction and noradrenergic hypofunctioning for anorexia nervosa; the proposed etiological role for copper deficiency is in accordance with the results. The biological measurements performed are in peripheral compartments. More direct measurements of the cerebral processes involved are highly desirable. But at the root of this model is a metabolic disorder. And the measurements performed are relatively adequate as such.

TABLE 3

BODY - WEIGHT AFTER 10 WEEKS COMPARED WITH CRITERION BODY - WEIGHTS

5 mg coppersulphate t.i.d. was supplied for 10 weeks; during the last 5 weeks 3 mg pimozide t.i.d. was added.

Patient	$CuS0_4$	Pimozide	48	42
			39	35
1 2 3 4 5 6 7 8			47	44
Body-weight (kg)	Criterion (kgl		45	43
59	53		48	41
53	50		47	43
Mean			48.3	43.9

"Criterion body-weight for therapeutic results is defined as the sum of the pre-treatment body-weight and a gain of 0.5 kg/week, which is, for **ten weeks, 10** x 0.5 **kg** = **5.0 kg.**

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REFERENCES

PINDER, R.M., BRODGEN, R.N., SAWYER, P.R., SPEIGHT, T.M., SPENCER, R. and AVERY, G.S.: Pimozide: a Review of its Pharmacological Properties and Therapeutic Uses in Psychiatry. Drugs, 12; 1-40,1976.

BARRY, V.C., and KLAWANS, H.L.: On the Role of Dopamine in the Pathophysiology of Anorexia Nervosa. J. Neural. Transm., 38; 107-122, 1976.

BOYAR, R. M,, KARZ, J., FINKELSTEIN, J.W., KAPEN, S., WEINER, H,, WEITZMAN, E. D., and HELLMAN, L: Anorexia Nervosa. Immaturity of 24-hour Luteinizing Hormone Secretory Patterns. New Engl. J. Med., 291 ,-861-865,1974.

EVANS, G.W.: Copper Homeostasis in Mammalian Systems. Physiol. Rev., 53; 353-570,1973.

HOES, M.J.A.J.M.: Psychoneurobiologische Aspecten van de Anorexia Nervosa. Tijdschr, Psychiat., 18; 680-712,1976.

JOHANSON, A.: Critical Body Weight in Anorexia Nervosa. New Engl. J. Med, 291; 904-905,1974.

MAWSON, A. R.: Anorexia Nervosa and the Regulation of Intake. Psychol. Med., **4;** 289-304,1974.

MORGAN, H. G. and RUSSELL, G. M. F.: Values of Family Background and Clinical Features as Predictors of Long-term Outcome in **Anorexia Nervosa; four-year follow-up study of 41 patients. Psychol. Med.,5; 355-371,1975.**

PLANTEY, F.: Pimozide in the Treatment of Anorexia Nervosa. Lancet, 1; 1105,1977.

REDMOND, D. E., MURPHY, D. L, and BAULU, M. J.: Menstrual Cycle and Ovarian Hormone Effects on Plasma and Platelet Monoamine Oxidase (MAO) and Plasma Dopamine-beta-hydroxylase (DBH) Activities in the Rhesus Monkey. Psychosom. Med., 37; 417-428,1975.

RUSSELL, G.F.M.: Anorexia Nervosa: its Identity as an Illness and its Treatment. In: Price, J. H. Ed. Modern Trends in Psychological Medicine, Chapter 6,131-164, Butterworths, London, 1970.

SCHREIBER, V. and PRIBYL, T.: Dopaminergic Control of Adeno-hypophyseal Weight and Serum Caeruloplasmin Levels in Rats. Neuroendocrinoiogy, 21; 58-67,1976.

SIMPSON, C.W. and DICARA, L.V.: Estradiol Inhibition of Catecholamine Elicited Eating in the Female Rat. Pharmacol. Biochem. Behav., 1; 413-419,1973.

WADE, N.: Interaction Between Estradiol-17 and Growth Hormone in **the** Control of Food Intake in Weanling Rats. J. Comp. Physiol. Psychol., 80; 359-362,1974.