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Fenfluramine in Prader-Willi syndrome: a double blind, placebo controlled trial

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Abstract

A double blind trial was conducted to determine the effect of fenfluramine on the weight and behaviour of patients with the Prader-Willi syndrome. Fifteen subjects, aged 5·5 to 27 years, received the placebo and the active drug, each for a period of six weeks. The dose of fenfluramine varied according to the age of the patient. Treatment with fenfluramine was associated with significant weight loss, improvement in food related behaviour, and a decrease in aggressive behaviour directed towards others. Skin picking and other self mutilation were unaffected by the drug. None of the subjects suffered from any side effects while taking the drug.

These findings suggest that short term treatment with fenfluramine may have a role in the management of some patients with Prader-Willi syndrome. It could be used during periods when exposure to large amounts of food cannot be avoided and aggressive behaviour is particularly difficult to contain. It may also be useful in those whose lives are threatened by the complications of obesity.

Prader-Willi syndrome is a congenital disorder that was first described in 1956.[1] It has a prevalence estimated at one in 10 000,[2] and is usually sporadic.[3] The condition is characterised by infantile hypotonia, hypogonadism, and facial dysmorphism. The characteristic hyperphagia, and abnormal behaviour and intellectual functioning, usually do not become evident until after 2 years of age. The hyperphagia associated with Prader-Willi syndrome is severe and chronic, and is responsible for the early mortality of people with the condition. Behavioural difficulties are a prominent feature of the disorder during adolescence and adulthood.[4] These behaviour difficulties include aggressive outbursts and picking at minor skin lesions, such as insect bites. The hyperphagia, together with the behavioural difficulties, make Prader-Willi syndrome one of the most serious and pervasive conditions with respect to its impact on the family unit.[5 6]

The mainstays of the treatment of Prader-Willi syndrome are control of the environment, particularly in relation to the availability of food, and the implementation of behaviour management techniques.[7] These methods are helpful, but have not proved completely successful, and the prognosis once adulthood is reached remains poor.[8] This justifies a search for other forms of treatment that may be used in conjunction with these techniques.

Reviews of Prader-Willi syndrome have stated that anorexic drugs have no place in its management.[7–10] Nevertheless, none of these reviews refers to a controlled trial of an anorexic drug, and we were unable to find any report of such a trial. Naloxone, an opiate antagonist, was given by subcutaneous injection to three patients with Prader-Willi syndrome in a double blind, placebo controlled trial, but with equivocal results.[11]

Fenfluramine (Ponderax) is an anorexic drug that has been in clinical use for over two decades and has few side effects.[12] We present the results of a double blind, placebo controlled trial to assess the effect of short term fenfluramine on the weight and behaviour of children and young adults with Prader-Willi syndrome.

Patients and methods

The patients taking part in this study were randomly selected from the 38 attending our clinic, who were over the age of 5 years, and conformed to the accepted diagnostic criteria of Prader-Willi syndrome. Informed consent was obtained from the parents and from the patients if they were old enough to give it.

They were randomly assigned into one of two groups. During the period of the trial, caregivers were instructed to continue with the same diet, exercise, and behaviour management techniques that were being followed before the trial started.

There was an initial two week period during which observations were made to obtain baseline data. Thereafter one group received the active drug for a six week period, followed by the placebo for a six week period. At the same time the other group received the placebo for the first six weeks and the active drug for the second six weeks.

Placebo and active drug were prepared in identical opaque capsules by a pharmacist who took no further part in the trial. The placebo capsules contained lactose. No one else knew which capsules contained the active drug and which contained the placebo until after data collection was complete.

The dose of fenfluramine in the capsule varied according to the age of the subject. Children from 5 to 7 years of age received 10 mg three times a day; those from 8 to 15 years received 10 mg three times a day for the first week and 20 mg three times a day thereafter, and those over the age of 15 years received 20 mg three times a day for the first week and 40 mg three times a day thereafter.

Weight was measured at the end of the base-

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Table 1 Observed behaviour in 15 patients with the Prader-Willi syndrome

Food related behaviour
Gorging: placing more food in mouth without swallowing first
Overeating: eating more than usual for age
Stealing food
Eating unusual materials
Aggressive behaviour
Physically aggressive acts
Verbally aggressive acts (including prolonged screaming)
Nagging and other preoccupations
Temper tantrums
Self directed behaviour
Skin picking
Self mutilation (excluding skin picking)

line period and at the end of each treatment period using the same scales and with the subject wearing the same underclothes. Changes in weight were compared using the Wilcoxon signed rank test.

Behaviour was observed throughout the baseline period and the last two weeks of each treatment period. Observers attended a training session before the trial during which they were instructed on how to record their observations of the subject's behaviour (table 1). Observers were unaware of which capsules the subjects were taking. Observation sessions took place at the patients' homes while they were going about their usual activities. The duration of the observation sessions was constant for each subject and always occurred at the same time of the day. Because of differences in family routines, the duration of the daily observation session differed slightly among subjects; it was, however, never less than two hours/day (mean 4·1 hours/day).

For statistical analysis, the number of times each type of behaviour was displayed in one hour was converted into a score using a behaviour rating scale from 0 to 5 (0=behaviour absent, 1=one to five episodes, 2=six to 15 episodes, 3=16 to 20 episodes, 4=21 to 40 episodes, 5=more than 40 episodes; 5 included 'behaviour continually present'). An average daily behaviour score for each type of behaviour was then calculated for the baseline period and for each treatment period. Average daily behaviour scores for related types of behaviour were combined to provide a single pooled score for each of the three groups of behaviour: food related, aggressive, and self directed. The pooled scores obtained for each patient during treatment with fenfluramine were compared with those obtained while taking placebo using analysis of variance.

Results

Fifteen patients (seven males and eight females) took part, their ages ranged from 5·5 to 27 years, mean 14·2. All patients were overweight and had problems resulting from their hyperphagia and other behaviour. None were receiving medication before the trial, or had any other diseases. One subject was functioning in the average range of intellectual ability, 12 were intellectually mildly disabled, and two were intellectually moderately disabled. The characteristic deletion on chromosome 15 was present in five.

WEIGHT

The weight of one subject was not recorded because of non-compliance. The changes in weight of the other 14 subjects are shown in table 2. Eight subjects lost weight while receiving the drug, while only two subjects lost weight while taking the placebo. The maximum weight loss was 7% (6 kg). For several patients this was the first time they had ever lost weight according to their recorded weights in our clinic records. There was a significant difference between the weight changes during the two periods ($p=0·02$, Wilcoxon signed rank test).

BEHAVIOUR

The behaviour of two patients was not analysed because of incomplete observations resulting from disruption to family routine. The behaviour observation records for the remaining 13 were converted into a pooled behaviour score for each of the three groups of related behaviours (table 3). The higher the score, the more frequently the behaviour occurred. The maximum possible score for either food related or aggressive behaviour was 20, and for self directed behaviour 10.

When these scores were compared using analysis of variance, food related and aggressive behaviour showed significant improvements during the period the drug was being taken

Table 2 Weight changes in patients when receiving placebo and fenfluramine

Case No	*When receiving placebo*			*When receiving fenfluramine*		
	Weight before (kg)	*Weight after (kg)*	*Change (%)*	*Weight before (kg)*	*Weight after (kg)*	*Change (%)*
1	20·5	20·5	0	20·5	20·5	0
2	98	98	0	98	98·5	+0·5
3	74	74	0	74	78	+5·4
4	62	62	0	62	62	0
5	46	46	0	46	43	−6·5
6	42·5	43	+1·2	43	43	0
7	24	25	+4·2	25	24	−4
8	88	90	+2·3	88·5	88	−0·6
9	48	50	+4·2	49	48	−2
10	18	18	0	18·5	18	−2·8
11	71	70	−1·4	74	71	−4·1
12	20	19	−5	20	20	0
13	92	95	+3·2	94	92	−2·1
14	80	80	0	86	80	−7

Table 3 Pooled behaviour scores for each of the three groups of behaviour measured during the baseline period and when receiving placebo and treatment with fenfluramine

Case No	Food related behaviour			Aggressive behaviour			Self directed behaviour		
	Baseline	Placebo	Fenfluramine	Baseline	Placebo	Fenfluramine	Baseline	Placebo	Fenfluramine
1	0·14	0·07	0	1	0·28	0·35	0·14	0·14	0·64
2	20	6	8·3	0·2	0·5	0	0·51	3·9	10
3	2	0	0·7	3·5	0·2	2	4·2	2·7	1·6
4	1·5	1·4	2·7	6·2	15·2	5	0·57	0·2	1
5	2·1	1·1	0	17	17	0·7	5·5	10	2
6	0·57	0·6	1·2	3·1	2	2·9	0	0	0
7	0·4	0·14	1	9·2	1·0	4·7	1	1·3	4·7
8	0	0	0	0	11·2	10	0	0	1
9	2·4	4	0·5	7·8	15·5	9·3	0·4	5·2	0·57
10	0	0	0	1	2·7	0·4	10	10	9
11	3·2	3·2	0·07	17·7	14·6	11	10	7·6	2·07
12	3·5	2·2	1·07	0·57	0·2	0·2	0·8	0·14	0·28
13	1	2·7	1·8	0·8	2·6	1·3	0	1·6	0·2

($p<0·05$ and $<0·025$, respectively). There was, however, no significant change in self directed behaviour ($p>0·10$).

In addition to the changes in scores, parents (and in some cases the patients themselves) frequently reported pronounced qualitative changes during the period the drug was being taken. Some patients quickly realised when they were taking the drug and made statements such as 'these are the real ones'. Some parents reported that this was the first time that they had seen their children refuse food. Some particularly noted behaviour changes, with statements such as 'he is a different child' and 'the best time ever'.

Discussion

Fenfluramine caused significant weight loss and behaviour improvement in some patients with Prader-Willi syndrome, when given for a period of six weeks. Though it is not unexpected that weight loss and improved food related behaviour occurred while the drug was being taken, the reason for the decrease in episodes of aggressive behaviour is less clear. Fenfluramine may have modified this behaviour by reducing the frustration associated with insatiable hunger, or by a direct sedative effect on the brain.[12] The hunger felt by people with Prader-Willi syndrome is similar in some ways to chronic pain, and control of this unpleasant sensation may reduce suffering and frustration even when weight loss is not significantly altered.

We were unable to find any distinguishing characteristics among patients who responded to the drug. The degree of obesity and intellectual impairment did not correlate with weight loss. The presence of the deletion on chromosome 15 also did not seem to play a part. We used a conservative, standardised dose of the drug during this trial, and some patients may require larger doses to control their hunger.

In this study we assessed the effect of a short course of fenfluramine, and suggest that such treatment may be helpful for difficult periods such as holidays, when access to food cannot be controlled and aggressive behaviour is particularly difficult to contain. It may also be useful in cases of severe obesity in which problems such as poorly controlled diabetes and respiratory acidosis (pickwickian syndrome) make urgent weight loss imperative. Whenever possible fenfluramine should be used in conjunction with other established forms of treatment.

The results of this study raise the question of a possible role for treatment with fenfluramine for periods of longer than six weeks. Long term use of anorexic agents is to be avoided in the management of obesity in general, but it must be remembered that Prader-Willi syndrome is a severe, incurable disorder that takes a devastating toll on affected patients and their families. A double blind placebo controlled trial to determine the efficacy of a longer course of fenfluramine in patients with Prader-Willi syndrome warrants consideration.

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