Treatment of Depression With Cyproheptadine

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We evaluated the antidepressant activity of cyproheptadine HCl in six patients diagnosed with major depression. This was a double-blind, placebo-controlled, crossover trial with treatment order balanced and randomly assigned. The patients received 4 weeks of treatment with cyproheptadine HCl 4 mg 4 times/day or placebo, followed by 4 weeks of cyproheptadine HCl 8 mg 4 times/day or placebo, followed by a crossover to cyproheptadine HCl or placebo. Each subject had a Hamilton Depression Rating Scale assessment and a 1-mg dexamethasone suppression test completed immediately before treatment and at 4-week intervals throughout the study. Two patients had nonsuppressible dexamethasone suppression tests and could not tolerate cyproheptadine due to anxiety and irritability. Four patients had suppressible dexamethasone suppression tests and had lower scores on the Hamilton Depression Rating Scale during treatment with cyproheptadine ($p<0.01$, Student's t test for paired observations). Cyproheptadine HCl may be useful in treating a subset of patients with major depression who have a suppressible dexamethasone suppression test.
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Burgeoning evidence points to an association between the endocrine system and psychopathology, in particular, the affective disorders. Cushing's disease, an endocrine dysfunction in the hypothalamic-pituitary-adrenal axis, has associated depression and elevated basal levels of adrenocorticotropic hormone (ACTH) and cortisol, and failure to suppress ACTH secretion and plasma cortisol after low-dose dexamethasone.[1] Some affective disorders, especially depression, are characterized in the laboratory the same way. Approximately one-half of seriously depressed patients have an abnormal dexamethasone suppression test.[2]

It is reasonable to assume that an effective treatment for Cushing's disease may have some impact on depression. Cushing's disease can remit with cyproheptadine HCl treatment.[3] It is assumed that this drug is effective because it is a potent serotonin receptor ($5\text{-}HT_2$) antagonist, and serotonin plays an excitatory role in the hypothalamic-pituitary-adrenal axis. Serotonin also is a neurotransmitter significant in depression. Changes in central nervous system metabolites of serotonin have been noted in affective disorders, and certain antidepressant drugs block its reuptake in the intraneuronal cleft.[4] New $5\text{-}HT_2$ antagonists still in development have antipsychotic properties, suggesting that the serotonin receptor may also play a central role in psychiatric disease other than depression.

It was our hypothesis that cyproheptadine HCl would alter the affect of a depressed person. In a pilot study to test that hypothesis, we treated six depressed patients with cyproheptadine HCl in a controlled, double-blind fashion.[5] Although the results seemed difficult to explain at the time, new information regarding the serotonin receptors and their various subtypes suggest that cyproheptadine may be used to explore the effects of inhibiting the $5\text{-}HT_2$ receptor.[6] We therefore detail our findings in hope that they will stimulate investigation and understanding of

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the role played by the 5-HT_2 receptor in depression, and also stimulate investigation into the role played by cyproheptadine and the receptor in other psychiatric diseases.

Methods

Six healthy outpatients between 21 and 50 years of age, previously taking no drugs for depression, were informed of the nature of our study and consented to participate. The study and consent form were approved by the Washington Medical Center Institutional Review Committee, and were in accord with its ethical standards on human experimentation. Each patient was diagnosed by at least two experienced clinicians as having a major depressive disorder, based on the Diagnostic and Statistical Manual III[7] criteria. A nonstructured clinical interview was conducted, and a Hamilton Depression Rating Scale[8] assessment to quantify change throughout the study was administered immediately before treatment and at 4-week intervals thereafter. Dexamethasone suppression tests were performed following the same schedule. Each person was given dexamethasone 1 mg at 11:00 P.M., and plasma cortisol was measured by radioimmunoassay 17 hours later at 4:00 P.M. Nonsuppression was defined as a plasma cortisol equal to or greater than 5 µg/dl.[8]

The drug schedule was a double-blind, 8-week, single-crossover design, with 8-week drug and placebo treatment periods assigned randomly. During the first 4 weeks (period 1) of cyproheptadine HCl (Periactin; Merck Sharp & Dohme, West Point, PA), each subject received 4 mg orally 4 times/day. If at the end of this period the patient was still depressed and tolerating the drug without troublesome side effects, the dosage was increased to 8 mg 4 times/day for another 4 weeks (period 2), but not to exceed 0.5 mg of cyproheptadine/kilogram of body weight/day. Identical placebos were administered the other 8 weeks of the study. Hamilton Depression Rating Scale results were subjected to statistical analysis using Student's *t* test for paired observations.

Results

Subjects A, B, and C had single-episode major depression (296.2). Subjects D, E, and F had recurrent-episode major depression (296.3). Subjects E and F had nonsuppression of the dexamethasone suppression test (cortisol ≥ 5 µg/dl) and could not tolerate cyproheptadine HCl due to anxiety and irritability that commenced when starting the drug. In subjects A, B, C, and D dexamethasone suppression test was suppressed and remained so on repeat testing throughout the study. Subjects A and B received placebo first and were crossed over to drug; subjects C and D received drug first and were crossed over to placebo. Subject B stopped cyproheptadine HCl after 4 weeks due to weight gain and dry mouth; subject C stopped placebo after 4 weeks due to return of depression. Thus, it was possible to analyze only the first 4 weeks of treatment (period 1) with cyproheptadine and placebo in these two subjects.

Table 1. Hamilton Depression Rating Scale Scores

Patient	Placebo	Cyproheptadine HCl	Length of Treatment (wks)
A[a]	18.5	3	8
B	37	25	4
C	16	2	4
D[a]	10.5	7.5	8

$p<0.01$.
[a]Mean Hamilton Depression Rating Scale scores were obtained twice, over each 4-week period.

Subject D had the dose of cyproheptadine HCl reduced to 6 mg/day for the entire 8 weeks of treatment due to sedation with higher doses. Subjects A, B, C, and D reported subjective improvement in depression symptoms during the first week of active treatment. All four had lower scores on the Hamilton Depression Rating Scale during the cyproheptadine treatment period than during the corresponding placebo period ($p<0.01$, Student's *t* test for paired observations) (Table 1).

Discussion

Several instances of thymolepsis have been reported in response to cyproheptadine HCl.[9,10] Our depressed patients with normal dexamethasone suppression tests self-reported antidepressant action within the first week of drug administration that seemed to increase over the 8-week study. Side effects of the drug in this group included sedation, weight gain, and nocturnal myoclonus, which were severe enough to cause reduction in drug dosage in one subject, and early discontinuation of the drug in another (50%). In a study of patients with anorexia nervosa, weight gain and an antidepressant effect were more frequent with cyproheptadine than with both amitriptyline and placebo; however, the authors did not correlate the response to a dexamethasone suppression test.[11]

It is interesting that in our two subjects (E and F) with abnormal dexamethasone suppression tests who could not tolerate cyproheptadine, the side effects were different from those reported in the literature.[9, 10] Both complained of intense irritability and anxiety due to the drug. In the two published cases citing treatment of depression with the agent, both patients had abnormal dexamethasone suppression tests, and both responded to therapy by advancing from depression to mania.

Of the five 5-HT receptor subtypes that exist in humans, 1A, 1C, 1D, 2, and 3, 5-HT_{1A} and 5-HT_2 are associated with depression.[6] Successful pharmaceuticals for the treatment of depression are 5-HT_{1A} agonists and 5-HT_2 antagonists. Tricyclic antidepressants increase postsynaptic receptor sensitivity of 5-HT_{1A}, and therefore increase its transmission. Other types of antidepressants such as serotonin reuptake inhibitors are also responsible for increased 5-HT_{1A} transmission. Some of the tricyclic antidepressants such as imipramine and amitriptyline behave as 5-HT_2 antagonists in addition to their role as 5-HT_{1A} agonists.[12] Currently, clinical studies are being conducted on antidepressants such as ritanserin, which also behave as 5-HT_2 antagonists.[13] It was postulated that serotonin may block ACTH release in both Nelson's and Cushing's syndromes, and these conditions were treated successfully with cyproheptadine HCl.[3, 14] Depression and a nonsuppressible dexamethasone suppression test were associated with increased serotonergic function.[9] Although cyproheptadine's action as an antidepressant probably is by antagonizing 5-HT_2, it can be inferred that it may also be a 5-HT_{1A} antagonist due to its reversal of fluoxetine's effect on depression.[15]

These observations suggest that depression mediated by the 5-HT_2 receptor may have a negative dexamethasone suppression test and respond to cyproheptadine HCl. On the other hand, depression mediated by the 5-HT_{1A} receptor alone or combined with the 5-HT_2 receptor may have a positive dexamethasone suppression test and show intolerance to the drug.

Of seven depressed patients treated with cyproheptadine HCl, only three responded with improvement of depression.[16] In contrast to our series, only in patients with a nonsuppressible dexamethasone suppression test did the agent improve depression. Although the reason for this discrepancy in results is not clear, it is possible that patients with a positive dexamethasone suppression test are more sensitive to the antidepressant effect of cyproheptadine, and therefore, if not severely depressed, may advance past euthymia into a mania-like state. If the other subjects were more severely depressed than ours, one might expect to see a positive response to cyproheptadine only in the most sensitive, those with the positive dexamethasone suppression test. Further studies with depression of various severities are necessary to evaluate this possible explanation.

Cyproheptadine may treat depression by selective antagonism of the 5-HT_2 receptor. All other presently available antidepressants have agonistic actions on the 5-HT_{1A} receptor. Thus, cyproheptadine HCl may offer a way to influence the 5-HT_2 receptor in the treatment of depression while other 5-HT_2 antagonists are being developed. Chlorpromazine and mesoridazine are both 5-HT_2 antagonists and can be used to treat schizophrenia.[17] Clozapine, also a 5-HT_2 receptor antagonist, has been used to treat drug-resistant schizophrenia.[18] The new 5-HT_2 antagonists still in development possess antipsychotic properties, but without accompanying movement disorders.[13] It is therefore possible that cyproheptadine may also have relevance in the treatment of psychotic disorders.

Our study demonstrates that the drug may be beneficial in the treatment of some depressed patients with a negative dexamethasone suppression test. There are also theoretical reasons to believe that it may be useful to probe the 5-HT receptor complex in depression and possibly other psychiatric diseases as well.

References

1. **Krieger DT, Glock SM.** Growth hormone and cortisol responsiveness in Cushing's syndrome. Am J Med 1972; 52:25–40.
2. **Carroll BJ, Feinberg M, Greden JF, et al.** A specific laboratory test for the diagnosis of melancholia. Arch Gen Psychiatry 1981;38:15–22.
3. **Krieger DT, Amorosa L, Linick F.** Cyproheptadine-induced remission of Cushing's disease. N Engl J Med 1975;293:893–6.
4. **Van Hiele LJ.** 1-5-Hydroxytryptophan in depression. Neuropsychobiology 1980;6:230–40.
5. **Pack AT, Greenway FL.** The successful treatment of depression with cyproheptadine HCl in subjects with negative dexamethasone suppression test [abstr]. Clin Res 1983;31:26A.
6. **Cowan PJ.** Serotonin receptor subtypes: implications for psychopharmacology. Br J Psychiatry 1991;159(suppl 12): 7–14.
7. **American Psychiatric Association.** Diagnostic and statistical manual of mental disorders, 3rd ed. Washington, DC: Author, 1980.
8. **Hamilton M.** A rating scale for depression. Neurol Neurosurg Psychiatry 1960;23:56.

9. **Price J, Ward G.** Cyproheptadine HCl in bipolar affective illness with cushingoid features. Aust N Zeal J Psychiatry 1977;11:201–2.
10. **Gold PW, Extein I, Ballenger JC, et al.** Rapid mood cycling and concomitant cortisol changes produced by cyproheptadine HCl. Am J Psychiatry 1980;137:378–9.
11. **Halmi KA, Eckert E, Falk JR.** Cyproheptadine HCl, an antidepressant and weight inducing drug for anorexia nervosa. Psychopharmacol Bull 1983;19(1):103–5.
12. **Wander TJ, Nelson A, Okazaki H, Richardson E.** Antagonism by antidepressants of serotonin S_1 and serotonin S_2 receptors of normal human brain in vitro. Eur J Pharmacol 1986;132: 115–21.
13. **Reyntjens A, Gelders YG, Hoppenbrouwers M-LJA, Bussche GV.** Thymosthenic efforts of ritanserin (R 55667), a centrally acting serotonin S_2 receptor blocker. Drug Dev Res 1986;8:205–11.
14. **Krieger DT, Luria M.** Effectiveness of cyproheptadine HCl in decreasing plasma ACTH in Nelson's syndrome. J Clin Endocrinol Metab 1976;43:1179–82.
15. **Feder R.** Reversal of antidepressant activity of fluoxetine by cyproheptadine HCl in three patients. J Clin Psychiatry 1991;52(4):163–4.
16. **Bansal S, Brown WA.** Cyproheptadine HCl in depression. Lancet 1983;2:803.
17. **Wander TJ, Nelson A, Ozaki H, et al.** Antagonism by neuroleptics of serotonin $5HT_{1A}$ and serotonin $5HT_2$ receptors of normal human brain in vitro. Eur J Pharmacol 1987; 143:279–82.
18. **Meltzer HY.** Clinical studies on the mechanism of action of clozapine: the dopamine-serotonin hypothesis of schizophrenia. Psychopharmacology 1989;99:S18–27.