

The Cholinolytic Biperiden in Depression

An Acute Placebo Controlled Study

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Summary. Clinical and experimental work indicates that cholinergic functions might play a role in modulating affectivity in man. In this acute double-blind study either the cholinolytic agent biperiden or placebo infusions were administered to six depressed females. The Janke and Debus self-rating questionnaire (EWL-K), the modified Hamilton depression scale (HAM-D), and the Montgomery and Asberg depression scale (MADRS) were used for documentation of psychopathological change.

There was an acute antidepressant effect during infusion of the active drug in comparison to placebo as measured on the global MADRS and EWL-K, but not on the modified HAM-D. Single items such as depressed mood, work and interests (HAM-D), sadness, concentration difficulties, inability to feel (MADR-S), and depressiveness (EWL-K) responded selectively and significantly to the biperiden infusion. It is concluded that cholinergic activity might be involved in the regulation of affectivity in man.

Key words: Depression – Biperiden – Anticholinergic activity

Zusammenfassung. Es gibt klinische und experimentelle Hinweise dafür, daß cholinerge Funktionen an der Modulation von Stimmung und Verhalten beteiligt sind. In einer akuten Doppelblindstudie wurde sechs depressiven Patienten das Anticholinergikum Biperiden oder physiologische Kochsalzlösung infundiert. Zur Dokumentation der psychopathologischen Veränderungen wurde die Eigenschaftswörterliste (EWL-K; Janke und Debus), die modifizierte Hamilton-Skala (HAM-D) und die Montgomery-und-Asberg-Skala (MADRS) benutzt.

Unter Biperideninfusion ergab sich im Vergleich zu Kochsalzinfusion ein akuter antidepressiver Effekt auf der MADRS, der Subskala Depressivität der EWL-K, jedoch nicht auf der modifizierten HAM-D-Skala. Einzelne Symptome wie gedrückte Stimmung, Beschäftigung und Interessen (HAM-D), Traurigkeit, Konzentrationsstörungen, Unfähigkeit zu empfinden (MADRS) verbesserten sich selektiv und signifikant.

Es wird hierin ein weiterer Hinweis gesehen, daß cholinerge Funktionen in die Steuerung der Affektivität beim Menschen eingreifen.

Schlüsselwörter: Depression – Biperiden – anticholinerge Aktivität

Introduction

Clinical observations indicate that anticholinergic agents of different chemical structure might have at least some antidepressant activities (Hoch and Mauss 1932; Abood and Meduna 1958; Flügel 1959; English 1962; Malatray and Simon 1972; Wirth 1979; Ungvari et al. 1981; Schmauss and Beckmann 1981). Biperiden is a mainly centrally active anticholinergic drug, which is widely used in the treatment

Table 1. Data of investigated patients (ICD-9: International Classification of Diseases, 9th revision; PAD: Primary Affective Disorder according to Feighner et al. 1972; MDD: Major Depressive Disorder according to Spitzer et al. 1975)

Patient/ age/sex	Diagnosis	Duration of illness	Number of phases	Age of onset	Further treatment
1/47/F	Unipolar depression ICD-9 296.1 PAD/MDD retarded	4 Months	3	44	Recovered and discharged after 28 days of treatment with approx. 175 mg/day amitriptyline
2/49/F	Unipolar depression ICD-9 296.1 PAD/MDD agitated	3 Months	4	44	Recovered and discharged after 53 days of treatment with 225 mg/day amitrip- tyline and 30 days with 60 mg/day opipramol
3/43/F	Unipolar depression ICD-9 296.1 PAD/MDD agitated	4 Months	2	43	Recovered and discharged after 40 days of treatment with approx. 200 mg/day amitriptyline
4/62/F	Unipolar depression ICD-9 296.1 PAD/MDD agitated	15 Days	12	21	Recovered and discharged after 41 days of treatment with approx. 175 mg/day amitriptyline
5/56/F	Bipolar depression ICD-9 296.3 PAD/MDD retarded	18 Days	9	17	Recovered and discharged after 25 days' treatment with approx. 175 mg/day amitriptyline. 2 weeks later switch into mania
6/42/F	Neurotic depression ICD-9 300.4 PAD/MDD	2 Months	3	28	Recovered and discharged after 69 days of treatment (approx. 200 mg/day maprotiline)

Table 2. Design of the double-blind infusion protocol

Patient	Day					
	1	2	3	4	5	6
1	B ^a	B ^a	B	PL ^a	PL ^a	B
2	PL ^a	PL ^a	B ^a	B ^a	B	B
3	PL ^a	B ^a	B ^a	B	B	PL ^a
4	B ^a	B ^a	PL ^a	PL ^a	B	B
5	B ^a	B ^a	B	B	PL ^a	PL ^a
6	B	PL ^a	PL ^a	B ^a	B ^a	B

B: biperiden

PL: placebo

^a Used for statistical evaluation

of Parkinson's disease and neuroleptic-induced extrapyramidal motor side effects (Haas and Klavehn 1955). In behavioral tests it antagonizes reserpine-induced rigor and immobilization in the swim test (Porsolt 1977) similar to the tricyclic antidepressants (Kreiskott 1981).

This acute double-blind placebo-controlled study attempts to contribute to the ongoing investigation of the role of cholinergic mechanisms in affective disorders.

Patients and Methods

Six consecutively admitted, markedly to severely depressed females were diagnosed as having primary affective disorder according to the Research Diagnostic Criteria of Feighner et al. (1972), as revised by Spitzer et al. (1975). Their ages ranged from 42 to 62 years, with a mean age of 49 years. Further ethnographic and clinical data are summarized in Table 1. Prior to the study all patients were drug free for at least 7 days. After a detailed description of the protocol, a written informed consent was given by each patient.

On six consecutive days (at 9:00 a.m.) patients received either 10 mg biperiden by infusion in 500 ml saline over 3–4 h, or just 500 ml saline during this period on two consecutive, randomly distributed days. The design of the study is described in Table 2. The nature of the infusion was unknown to both the psychiatrists and patients. A modified Hamilton depression scale (HAM-D) without items 14–21, the Montgomery and Asberg depression scale (MADRS; Montgomery and Asberg 1979) and the adjective list (EWL-K; Janke and Debus 1977) were used for documentation of psychopathological change.

Data obtained at the end of placebo infusions and from the end of the first two consecutive biperiden infusions were selected for statistical evaluation (Table 2). As four dependent measurements existed for each of the subjects, the Wilcoxon tests were not applicable for either paired data or independent samples. Therefore, we used a statistical test described by Lehmann (1975). Intraindividual rank sums were calculated for each treatment method and summed to form one rank sum. By standardization of this rank sum, a test statistic was achieved which was nearly normally distributed.

Results

Figure 1 depicts the total scores of the MADRS and the depressiveness score of the EWL-K self-rating questionnaire, which both showed a statistically significant

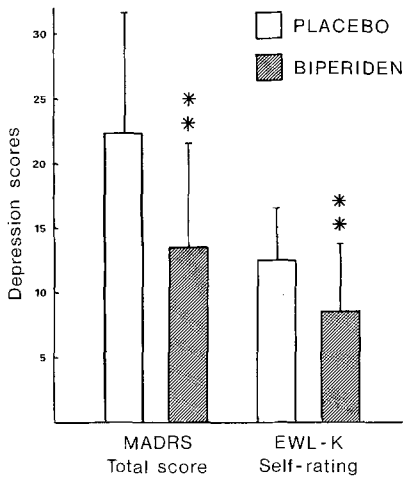


Fig. 1. Total scores of the Montgomery and Asberg depression scale and of the subscale "depressiveness" of the adjective list of Jahnke and Debus subsequent to two placebo or two biperiden infusions. ** $P < 0.01$

Table 3. Montgomery and Asberg depression rating scale (MADRS). Scores after infusion on days 1 and 2 of placebo or biperiden (mean \pm standard deviation)

Variable	Placebo	Biperiden	P corrected
Global score	23.1 \pm 10.3	14.8 \pm 8.1	0.01
Apparent sadness	3.4 \pm 2.0	1.2 \pm 1.0	0.01
Reported sadness	3.2 \pm 1.9	1.3 \pm 1.2	0.01
Inner tension	2.7 \pm 1.6	1.8 \pm 1.3	NS
Reduced sleep	3.3 \pm 2.4	3.2 \pm 1.8	NS
Reduced appetite	3.2 \pm 1.4	2.0 \pm 1.5	0.01
Concentration difficulties	3.0 \pm 1.3	2.4 \pm 1.3	0.01
Lassitude	3.0 \pm 1.4	2.7 \pm 1.2	NS
Inability to feel	3.0 \pm 1.4	2.2 \pm 1.0	0.01
Pessimistic thoughts	0.7 \pm 0.9	0.7 \pm 1.0	NS
Suicidal thoughts	0.9 \pm 0.8	0.6 \pm 0.8	NS

NS = not significant

Correction of P -values based on Bonferroni inequality ($P \times 46$ variables); Lehmann's intra-individual rank sum test for dependent variables

($P \leq 0.01$) reduction at the end of the biperiden infusions as compared to the placebo infusions.

Results of single symptoms of the MADRS scale are described in Table 3. As can be seen, these items were significantly improved by biperiden: apparent and reported sadness, concentration difficulties, reduced appetite, and inability to feel.

Table 4 shows the comparison between biperiden and placebo infusions as rated on the modified HAM-D scale (without items 14–21). The global score decreased to 13.7 ± 5.6 under placebo infusions and to 8.9 ± 5.4 under biperiden, but did not reach statistical significance. The factors retardation and agitation improved significantly, as did the symptoms depressed mood, work and interests. None of the other factors and symptoms changed markedly.

Table 4. Hamilton-depression-scale modified (without items 14-21) for measurement of short-term changes in psychopathology

Variable	Placebo	Biperiden	<i>P</i> corrected
Global score	13.7 ± 5.6	8.9 ± 5.4	NS
Factor retardation	3.3 ± 1.8	1.7 ± 1.3	0.01
Factor agitation	2.0 ± 1.9	1.2 ± 0.8	0.05
Factor anxiety	4.7 ± 3.2	2.7 ± 2.3	NS
F. somatic complaints	2.4 ± 1.6	1.8 ± 1.3	NS
Depressed mood	2.2 ± 1.5	0.7 ± 1.0	0.01
Guilt	0.2 ± 0.4	0.2 ± 0.4	NS
Suicide	0.2 ± 0.4	0.1 ± 0.3	NS
Insomnia: initial, middle and delayed	3.7 ± 2.6	3.2 ± 2.0	NS
Work and interests	1.8 ± 0.9	1.3 ± 0.9	0.05
Retardation	0.7 ± 0.9	0.6 ± 0.5	NS
Agitation	1.3 ± 1.5	0.4 ± 0.7	NS
Anxiety, psychic	1.9 ± 1.4	1.2 ± 1.1	NS
Anxiety, somatic	1.4 ± 1.0	1.0 ± 0.8	NS
Somatic symptoms, gastrointestinal	0.9 ± 0.5	0.7 ± 0.4	NS
Somatic symptoms, general	1.0 ± 0.8	0.8 ± 0.7	NS

NS = not significant

Correction of *P*-values based on Bonferroni inequality ($P \times 46$ variables); Lehmann's intra-individual rank sum test for dependent variables

The results of the EWL-K self-rating questionnaire are depicted in Fig. 2. Significant responses were found for depressiveness and for the factors introversion, emotional irritability and anxiety. As can be seen, the majority of the items were significantly improved by the acute biperiden treatment.

No psychic or somatic side effects occurred. Clinical data such as blood pressure, pulse, temperature and laboratory results did not change significantly during the study. After the protocol all patients were further treated with tricyclic antidepressants, as indicated in Table 1.

Discussion

Biperiden's mood-elevating and drive-enhancing effect has been observed earlier in schizophrenics (Flügel 1959; Jellinek 1977), parkinsonian patients (English 1962), and healthy volunteers (Schneider et al. 1975).

Degkwitz (1966) described two cases of self-medication with biperiden in healthy volunteers. After a 5-6 day period of neuroleptic like apathy and sedation, he noted an increase of drive and mood that lasted 2-3 days. Thereafter, emotional normalization occurred. These effects were similar to those found with tricyclic antidepressants in volunteers.

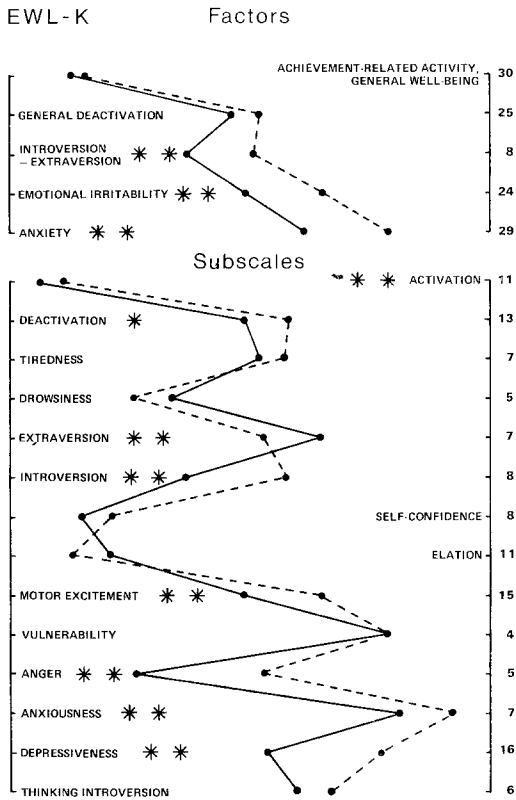


Fig. 2. Factors and subscales of the adjective list of Janke and Debus subsequent to two placebo or two biperiden infusions. (●—●) placebo; (●----) biperiden

This placebo-controlled study presents evidence that the anticholinergic biperiden has acute antidepressant effects in markedly to severely depressed patients. This is in line with another study our group performed with this compound (Kasper et al. 1981). The possibility exists that the reported effects are unspecific, as no "active" placebo with purely sedative or stimulant properties was used. However, since depressive core symptoms such as depressed mood, retardation, agitation, and anxiety were predominantly influenced and other symptoms remained unaffected, there is no strong support for this view.

It is not clear whether biperiden's antidepressant activity is solely due to its central anticholinergic effects or whether other pharmacological properties like catecholamine reuptake inhibition (Horn et al. 1970) might be involved. New-generation antidepressants such as nomifensine and mianserin, which seem to be clinically effective, are reported to be completely free from anticholinergic effects. Furthermore, no unequivocal correlation seems to exist between the cholinolytic properties of the antidepressants and their clinical efficacy. However, it may not be without significance that amitriptyline, the most widely used antidepressant, is the most potent of these compounds to bind to the muscarinic receptor in the CNS (Snyder and Yamamura 1977). Lack of correlation between the antidepressants' efficacy and their anticholinergic activity seems to be comparable to cholinolytic antiparkinsonian drugs. Their anticholinergicity, though thought of as being the

decisive mechanism, also does not always correlate with clinical efficacy (Shader and Greenblatt 1972).

Furthermore, neuroleptics with marked anticholinergic activity such as thioridazine and levopromazine are known to have antidepressant properties, whereas neuroleptics with less or no anticholinergic activity such as fluphenazine or haloperidol sometimes cause depression in schizophrenic patients. Other support that cholinergic mechanisms might be involved in modulation of mood is derived from experimental work with the cholinomimetic physostigmine, which has recently been reviewed by Janowsky and Davis (1979).

It is noteworthy that sporadic misuse and dependence on this and other anticholinergics have recently been reported (Marriott 1976; Beil 1980), though no manifest addiction seems to occur (Rapp 1974). Nevertheless, further evidence would seriously preclude biperiden's regular administration in depression.

Clearly, it is felt that anticholinergic activity is only one major antidepressant mechanism that might interact with catecholaminergic or other neurotransmitter functions in order to reestablish a functional balance, which seems to be lost in affective disorder.

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