Arch Psychiatr Nervenkr (1982) 231:213–220

Archiv für Psychiatrie und Nervenkrankheiten
Archives of Psychiatry and Neurological Sciences

The Cholinolytic Biperiden in Depression

An Acute Placebo Controlled Study

H. Beckmann and H. W. Moises

Psychiatrische Klinik des Zentralinstituts für Seelische Gesundheit (Direktor: Prof. Dr. Dr. H. Häfner), Postfach 5970, D-6800 Mannheim 1, Federal Republic of Germany

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.

0003-9373/82/0231/0213/$ 01.60

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 amitriptyline 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

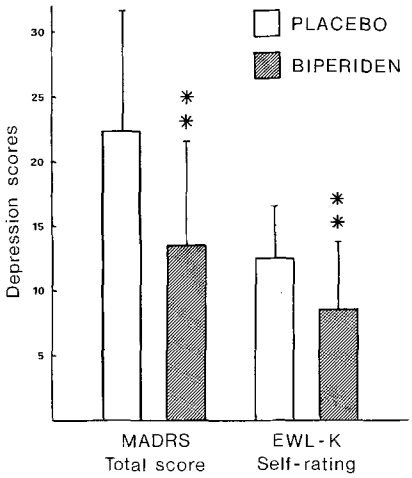

Fig. 1. Total scores of the Montgomery and Asberg depression scale and of the subscale "depressiveness" of the adjective list of Jahnke and Debus subsequent to two placebo or two biperiden infusions. ** $P<0.01$

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

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

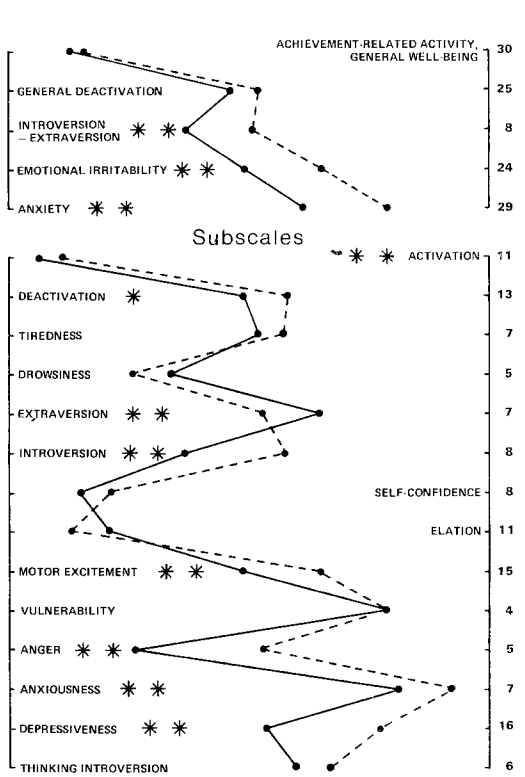

Fig. 2. Factors and subscales of the adjective list of Janke and Debus subsequent to two placebo or two biperiden infusions. (●———●) placebo; (●----●) biperiden

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 anticholinergicity 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.

Acknowledgement. Gratitude is expressed to Dr. B. Krumm for statistical advice and analysis of the data.

References

Abood LG, Meduna LJ (1958) Some effects of a new psychotogen in depressive states. J Nerv Ment Dis 127:546–550

Beil H (1980) Mißbrauch von Biperiden und Trihexyphenidyl. Dtsch Med Wochenschr 105: 1585–1586

Degkwitz R (1966) Die psychische Eigenwirkung der Psycholeptika. Hippokrates 8:285–290

English DC (1962) Reintegration of affect and psychic emergence with ditran. J Neuropsychiatr 3:304–310

Feighner JB, Robins E, Guze S, Woodruff RA, Winokur G, Munoz R (1972) Diagnostic criteria for use in psychiatric research. Arch Gen Psychiatry 26:57–63

Flügel F (1959) Die medikamentöse Therapie der endogenen Psychosen. Nervenarzt 30:241–245

Haas H, Klavehn W (1955) Über 3-Piperidino-1-phenyl-1-bicycloheptenyl-propanol-(1) (Akineton). Arch Exp Path Pharmakol 226:18–35

Hamilton M (1960) A rating scale for depression. J Neurol Neurosurg Psychiatry 23:56–61

Hoch P, Mauss W (1932) Atropinbehandlung bei Geisteskrankheiten. Arch Psychiatry 97: 546–552

Horn AS, Coyle JT, Snyder SH (1970) Catecholamine uptake by synaptosomes from rat brain. Mol Pharmacol 7:66–80

Janke W, Debus G (1977) Die Eigenschaftswörterliste (EWL-K). Ein Verfahren zur Erfassung der Befindlichkeit. Göttingen

Janowsky DS, Davis JM (1979) Psychological effects of cholinomimetic agents. In: Davis KL, Berger PA (eds) Brain acetylcholine and neuropsychiatric disease. Plenum Press, New York, pp 3–14

Jellinek T (1977) Mood elevating effect of trihexyphenidyl and biperiden in individuals taking antipsychotic medication. Dis Nerv Syst 38:353–355

Kasper S, Moises H-W, Beckmann H (1981) The anticholinergic biperiden in depressive disorder. Pharmacopsychiatr 14:195–198

Kreiskott H (1981) The antagonistic action of biperiden on states of immobility in various animal species. Models for catatonic stupor. III World Congress of Biological Psychiatry, Stockholm

Lehmann EL (1975) Nonparametrics: Statistical methods based on ranks. McGraw Hill, New York, p 132

Malatray J, Simon P (1972) Effets «psychotropes» de quelques antiparkinsoniens. J Pharmacol (Paris) 3:325–342

Marriott P (1976) Dependence on antiparkinsonian drugs. Br Med J 1:52

Montgomery SA, Asberg M (1979) A new depression scale designed to be sensitive to change. Br J Psychiatry 134:382–389

Porsolt RD, Lepichon M, Jalfre M (1977) Depression: a new animal model sensitive to antidepressant treatments. Nature 266:730–732

Rapp W (1974) Bewirken anticholinergische Antiparkinsonmittel eine Abhängigkeit? Minor Symposium II om extrapyramidala biverkningar i samband med neuroleptikabehandling, Göteborg, pp 61–65

Schmauss M, Beckmann H (1981) Clinical study about efficacy and efficacy-profile of the tricyclic antidepressant amitriptyline. III World Congress of Biological Psychiatry, Stockholm

Schneider E, Jacobi P, Maxion H, Fischer P-A (1975) Neuropsychologische Untersuchungen zur Kurzzeitwirkung von Biperiden (Akineton) beim Parkinsonsyndrom. Arch Psychiatr Nervenkr 221:15–28

Shader RI, Greenblatt DJ (1972) Belladonna alkaloids and synthetic anticholinergics. In: Shader RI (ed) Psychiatric complications of medical drugs. Raven Press, New York, pp 103–147

Snyder SH, Yamamura HI (1977) Antidepressants and the muscarinic acetylcholine receptor. Arch Gen Psychiatry 34:236–239

Spitzer RL, Endicott J, Robins E (1975) Research diagnostic criteria for selected groups of functional disorders. Biometric research. New York State Psychiatric Institute, New York

Ungvari G, Karczag I, Gerevich J, Pethö B (1981) Clinical notes on the possible anticholinergic reversal of depressive syndromes. Pharmacopsychiatr 14:71–73

Wirth J-F (1979) Utilisation des antiparkinsoniens de synthèse comme antidépresseurs. Ann Med Psychol 137:245–250

Received September 23, 1981