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Clinical Investigations into Antidepressive Mechanisms

I. Antihistaminic and Cholinolytic Effects: Amitriptyline Versus Promethazine

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Abstract. It is assumed that established antidepressants exert their clinical efficacy by potentiation or decrease of central noradrenergic and serotonergic neurotransmission. However, recent experimental work suggests that antihistaminic and/or cholinolytic effects may also be involved.

This double-blind controlled study compared amitriptyline (catecholamine potentiating, antihistaminic, cholinolytic) with promethazine (antihistaminic, cholinolytic) in 50 severely depressed inpatients over a 30-day treatment period.

Analysis of the Hamilton depression rating scale revealed significant clinical superiority of amitriptyline over promethazine in such major depressive symptoms as depressed mood, suicidal ideation, psychic anxiety, and sleep disturbances. No significant difference was evident as far as autonomous side effects were concerned. Similar results were found by analysis of the AMP rating system.

It is concluded that antihistaminic or cholinolytic effects *per se* do not explain the antidepressants' efficacy. However, potentiation of noradrenergic neurotransmission by cholinolytic activity might be the major antidepressive mechanism.

Key words: Antidepressive mechanisms – Amitriptyline – Promethazine – Antihistaminic-cholinolytic properties

Zusammenfassung. Gegenwärtig wird angenommen, daß die gebräuchlichen Antidepressiva klinisch durch eine Potenzierung oder eine Verringerung zentraler noradrenerger und serotoninerger Neurotransmission wirken. Allerdings lassen neuere experimentelle Arbeiten erwarten, daß auch antihistaminerge und/oder cholinolytische Effekte beteiligt sein könnten.

Diese kontrollierte Studie verglich Amitriptylin (katecholamin-potenzierend, anthihistaminerg, cholinolytisch) mit Promethazin (antihistaminerg,

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cholinolytisch) bei 50 stark depressiven Patienten über eine 30tägige Behandlungsperiode.

Die Analyse der Hamilton Depressionsskala ergab eine signifikante klinische Überlegenheit des Amitriptylin über Promethazin bei depressiven Kernsymptomen wie: gedrückte Stimmung, Suizidneigung, Angst und Schlafstörungen. Bezüglich der vegetativen Nebenwirkungen ergaben sich keine signifikanten Unterschiede. Ähnliche Befunde wurden mit Hilfe des AMP-Systems erhoben.

Es wird geschlossen, daß antihistaminerge oder cholinolytische Wirkungen *per se* nicht die klinischen Effekte der Antidepressiva erklären. Vielmehr scheint die Potenzierung noradrenerger Neurotransmission durch cholinolytische Aktivität der wesentliche antidepressive Mechanismus zu sein.

Schlüsselwörter: Antidepressive Mechanismen - Amitriptylin - Promethazin - Antihistaminerge-cholinolytische Wirkungen

Introduction

At present it is thought that the therapeutic actions of classical antidepressant drugs are related to their inhibition of biogenic amine reuptake into presynaptic neurons, thus enhancing (Schildkraut 1965; Bunney and Davis 1965) or decreasing (Sulser 1978) central noradrenergic neurotransmission. However, the advent of the "new generation" antidepressants has questioned the validity of this concept. It is becoming increasingly evident that, in addition, other neurotransmitters or even quite different biological mechanisms are involved in the antidepressive efficacy.

The antihistaminic activity of almost all tricyclic and "new generation" antidepressants has only recently been hypothesized to be involved in their clinical efficacy (Kanof and Greengard 1978). Specifically, it has been proposed that blockade of histaminic transmission mediated by cerebral H_2 receptors might represent the molecular mechanism of therapeutic action of various antidepressants, and further that blockade of central H_1 receptors might be responsible for their sedative properties (Kanof and Greengard 1978; Schwartz et al. 1981). Moreover, antihistamines have previously been described as having antidepressive profiles in various pharmacological and behavioral tests (Porsolt et al. 1977). Recently, Wallach and Hedley (1979) using the behavioral despair test assumed that various antihistamines including promethazine might have antidepressive properties.

There is an ongoing investigation of the role of cholinergic mechanisms in affective disorders (Janowsky and Davis 1979; Snyder and Yamamura 1977; Beckmann and Moises 1982). It has been speculated by several authors that the anticholinergic potencies of the common antidepressants might contribute to their antidepressant actions.

Promethazine, which has no pharmacological influence on catecholaminergic or serotoninergic metabolism in the central nervous system has long been used as a sedative and antihistaminic. No additional antidepressant and/or neuroleptic effects have been reported in the literature. Data from Kanof and Green-

gard (1978) and Dam Trung Tuong et al. (1980), however, indicate that promethazine and amitriptyline have comparable potencies as inhibitors of the H_2 receptor-mediated stimulation of cyclic AMP formation in slices and homogenates from brain tissue. In addition, sedative properties which have been viewed as being correlated with occupation of H_1 receptors in brain (Tran et al. 1978; Schwartz et al. 1981) are comparable in both amitriptyline and promethazine. The anticholinergic activity in amitriptyline and promethazine seems to be comparable (Gouret 1973).

In order to investigate whether the antihistaminic and anticholinergic component of the antidepressants contribute to their clinical efficacy, a comparison between amitriptyline and promethazine was performed in a double-blind controlled study.

Patients and Methods

Fifty consecutively admitted patients were randomly assigned to either amitriptyline or promethazine treatment. In the amitriptyline group there were 25 females (17 from the Psychiatric Hospital Kaufbeuren, 8 from the Psychiatric Hospital Munich), aged 32 to 68 years, with a mean age of 54.6 years. Duration of illness was between 2 and 20 years. Number of previous phases was between 2 and 10.

In the promethazine group there were 25 females (19 from the Psychiatric Hospital Kaufbeuren, 6 from the Psychiatric Hospital Munich). Ages were between 33 and 68 years, with a mean age of 50.4 years. Duration of illness was between 2 and 26 years. Number of previous phases was between 3 and 10.

All patients were diagnosed according to the International Classification of Diseases (ICD) by two experienced psychiatrists.

Diagnoses were as follows (in the promethazine group):

	ICD	*n*
Endogenous depression, unipolar type	296.1	23
Endogenous depression, bipolar type	296.3	2
Total		25

Diagnoses were as follows (in the amitriptyline group):

Endogenous depression, unipolar type	296.1	23
Endogenous depression, bipolar type	296.3	2
Total		25

Care was taken that patients with only two previous depressive and/or manic phases were included. The Hamilton depression rating scale (HAM-D) and the AMP-system were used for rating of psychopathological and neurological change. Only patients with HAM-D scores over 16 were included in the study. Informed consent was given by the patients after the nature of the study had fully been explained. There were 7 patients who refused to participate or ended their participation before day 5, and they were not included in either study group.

Drugs were given in identical capsules, so that neither the patient nor the clinican were aware of the identity of the drug. Dosage was initially 25 mg tid of either drug for 3 days and

then increased by day 5 to 50 mg tid. According to tolerance, dosage was increased to 200 and 250 mg/day until day 10 and then maintained until the end of the study. Analysis of variance and McNemar's test of significance of change were used for statistical evaluation.

Results

In the amitriptyline group 23 out of 25, and in the promethazine group 21 out of 25 patients completed the study, with all losses occurring between days 14 and 21. There were no pretrial group differences as far as sex, mean age and psychopathology on the HAM-D global score or on single items. As noted in Table 1 there were 11 responders in the amitriptyline and only 5 responders in the promethazine group.

Table 1. Global clinical response: (very) good = < 10; moderate = < 15; poor = > 16 on HAM-D scale at the end of the study

Drug	(Very) good	Moderate	Poor	Failure
Amitriptyline	11	4	8	2
Promethazine	5	5	11	4

Overall (as shown in Fig. 1) there was a statistically significant reduction of depressive symptomatology over the 4-week treatment period for both the amitriptyline group ($P < 0.01$) and the promethazine group ($P < 0.05$) as measured on the HAM-D scale. However, a highly significant group difference occurred in favor of amitriptyline ($P < 0.001$). Analysing the factors 1 to 4 of this rating system, it became evident that the factor agitation and the factor somatic complaints responded in both treatment groups, but, again there was a significant difference in favor of the amitriptyline group ($P < 0.001$; Table 2). Inspection of single items of the HAM-D scale such as depressed mood, suicidal ideation,

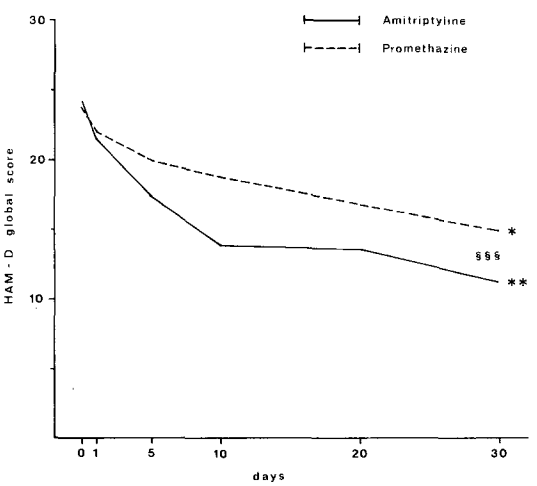

Fig. 1. Global score of the Hamilton depression scale for the amitriptyline and the promethazine treatment group over the 30-day treatment period. Analysis of variance: time: * = $P < 0.05$, ** = $P < 0.01$; group: §§§ = $P < 0.001$

Table 2. Hamilton rating scale: analysis of global scores and of the factors retardation (F1), agitation (F2), anxiety (F3) and somatic complaints (F4)

Ratings	Drugs	Day 0	D 1	D 5	D 10	D 20	D 30	P	
Global score	AMI	24.1±4.5	21.5±6.0	17.3±6.7	13.8±6.0	13.5±7.3	11.2±7.6	**	§§§
	PRO	23.9±3.9	22.1±4.0	20.0±4.5	18.8±5.5	16.8±6.3	14.9±7.2	*	
F1	AMI	3.8±2.2	3.9±2.7	3.3±2.4	2.4±2.1	2.7±2.7	2.2±2.8		NS
Retardation	PRO	3.5±1.6	3.7±1.5	3.6±1.6	2.9±1.4	2.6±1.7	2.2±1.7	*	
F2	AMI	4.0±1.6	3.0±1.2	1.9±1.1	1.3±1.3	1.4±1.2	1.0±1.3	***	§§§
Agitation	PRO	4.4±1.6	3.3±1.5	3.0±1.8	2.8±1.7	2.1±1.3	1.9±1.6	***	
F3	AMI	5.0±2.3	4.6±2.1	3.9±2.1	3.1±1.9	3.5±2.3	3.0±2.3	**	NS
Anxiety	PRO	4.6±2.2	4.4±2.4	3.9±1.8	4.0±2.1	4.0±2.4	3.4±2.3	NS	
F4	AMI	5.6±1.4	5.3±1.9	4.0±1.6	3.3±1.7	2.8±1.6	2.4±1.7	***	§§§
Somatic complaints	PRO	5.5±1.3	5.3±1.6	4.7±1.2	4.6±1.4	4.1±1.4	4.0±1.5	**	

AMI = Amitriptyline; PRO = Promethazine; Mean ± SD; ANOVA Program BMCP2V: group diff.: §§§ = $P < 0.001$; time: * = $P < 0.05$; ** = $P < 0.01$; *** = $P < 0.001$

Table 3. Selected items of the HAM-D scale for both treatment groups and their change during the 3-day study

Ratings	Drugs	Day 0	D 1	D 5	D 10	D 20	D 30	P	
Depress. mood	AMI	2.2±0.8	2.0±0.8	1.8±0.8	1.5±0.8	1.6±1.0	1.1±1.1	**	§§§
	PRO	2.5±0.8	2.4±0.9	2.4±0.8	2.0±0.7	1.9±1.0	1.6±1.0	*	
Insomnia delayed	AMI	1.4±0.6	1.2±0.7	0.6±0.7	0.3±0.4	0.3±0.6	0.1±0.3	***	§§§
	PRO	1.7±0.4	1.4±0.6	1.1±0.7	1.0±0.7	0.8±0.7	0.9±0.7	**	
Work and interests	AMI	3.3±0.4	3.0±0.8	2.9±0.7	2.6±0.9	2.1±0.8	1.8±1.1	***	§
	PRO	3.3±0.5	3.3±0.5	3.3±0.6	3.1±0.7	2.9±0.8	2.6±1.2	**	
Retardation	AMI	0.8±1.0	0.9±1.2	0.7±0.9	0.3±0.6	0.3±0.7	0.4±0.3	NS	NS
	PRO	0.5±0.9	0.6±0.8	0.6±0.7	0.5±0.6	0.3±0.5	0.2±0.3	NS	
Agitation	AMI	0.7±0.7	0.5±0.5	0.4±0.5	0.2±0.4	0.4±0.6	0.3±0.5	NS	NS
	PRO	0.7±0.6	0.5±0.6	0.5±0.6	0.4±0.5	0.3±0.5	0.3±0.5	NS	
Anxiety, psychic	AMI	2.0±1.0	1.7±0.7	1.4±0.9	1.3±0.8	1.5±0.9	1.2±1.0	NS	§
	PRO	1.9±0.9	1.7±1.0	1.7±1.0	1.5±0.9	1.8±1.1	1.3±1.2	NS	
Anxiety, somatic	AMI	1.6±0.9	1.5±0.9	1.3±0.8	0.9±0.8	1.1±0.9	1.1±1.2	*	NS
	PRO	1.5±0.9	1.6±0.9	1.4±0.9	1.4±0.8	1.4±0.9	1.3±0.9	NS	
Som. sympt. gastroint.	AMI	1.2±0.7	1.1±0.6	0.8±0.6	0.5±0.5	0.5±0.6	0.3±0.5	***	§§
	PRO	1.3±0.5	1.1±0.5	1.1±0.5	0.9±0.6	0.7±0.5	0.5±0.6	***	
Som. sympt. general	AMI	1.6±0.5	1.6±0.4	1.3±0.4	1.4±0.5	1.0±0.4	0.8±0.6	***	NS
	PRO	1.8±0.3	1.8±0.3	1.7±0.5	1.4±0.5	1.5±0.6	1.3±0.8	**	

Mean±SD; ANOVA Programm BMDP2V: group difference §=$P<0.05$; §§=$P<0.01$; §§§=$P<0.001$; time: *=$P<0.05$; **=$P<0.01$; ***=$P<0.001$

Table 4. Selected syndromes from the AMP-system and their change over the treatment period

AMP-syndrome	Drug	D 0	D 1	D 10	D 20	D 30	*P*
Apathetic	AMI	4.857	5.048	3.476	2.048	1.810	*
	PRO	5.632	5.211	4.842	4.105	3.632	
Hallucination	AMI	0.143	0.190	0.238	0.190	0.190	0.107
	PRO	0.0	0.0	0.0	0.053	0.053	
Hostility	AMI	0.952	0.952	0.905	0.762	1.095	0.143
	PRO	0.316	0.263	0.421	0.158	0.316	
Mania	AMI	0.238	0.238	0.143	0.095	0.048	>0.5
	PRO	0.105	0.211	0.158	0.053	0.158	
Somatic-depressive	AMI	9.619	8.238	4.524	3.714	2.762	**
	PRO	11.211	9.684	6.947	5.368	5.421	
Paranoid	AMI	0.286	0.286	0.429	0.619	0.762	0.158
	PRO	0.053	0.053	0.0	0.0	0.105	
Catatonic	AMI	0.429	0.381	0.0	0.095	0.048	0.432
	PRO	0.421	0.368	0.316	0.211	0.263	
Retarded-depressive	AMI	5.333	5.286	4.095	2.714	2.571	NS
	PRO	5.316	5.263	5.000	4.947	3.895	
Hypochondria	AMI	5.238	5.143	4.524	3.667	2.952	0.050
	PRO	5.895	5.789	5.579	4.684	4.579	
Psychoorganic	AMI	1.571	1.476	1.143	0.429	0.476	>0.5
	PRO	1.105	1.000	0.895	0.684	0.842	
Autonomous	AMI	5.048	5.810	6.000	4.762	4.048	NS
	PRO	5.579	6.105	6.263	5.105	4.316	
Neurologic	AMI	0.0	0.0	0.0	0.048	0.0	>0.5
	PRO	0.0	0.0	0.0	0.053	0.053	

*$= P < 0.05$; **$= P < 0.01$; analysis of variance: group difference

Table 5. Comparison of autonomous side effects as measured with the AMP rating system

	Promethazine before/after	Amitriptyline before/after
Thirst increased	0.65/0.42***	0.65/0.13***
Dry mouth	0.03/0.11*	0.01/0.03 NS
Appetite increased	0.65/0.21***	0.06 /0.08***
Blurred vision	0.47/0.23***	0.53/0.16***
Sweating	0.05/0.07 NS	0.03/0.06 NS
Autonomous side effects	0.08/0.04 NS	0.08/0.0*

* = $P< 0.05$; ** = $P< 0.01$; *** $P< 0.001$
McNemar test of significance of change

insomnia and psychic anxiety revealed a significantly better outcome for the amitriptyline as compared to the promethazine group (Table 3).

Formation of selective syndromes from the AMP rating system (Baumann and Angst 1975) demonstrated an advantage of amitriptyline over promethazine in the treatment of the apathetic syndrome ($P< 0.05$) and the somatic depressive syndrome ($P< 0.01$). The "hostility", "retarded depressive", "hypochondriac" and "vegetative" syndrome responded similarly in both treatment groups (Table 4). Side effects such as dry mouth, blurred vision, and dizziness showed no significant differences between either group (Table 5). No possibility existed of identifying clinically any of the drugs by their side effects.

Discussion

This study was designed to further explore the biological mechanisms by which the established antidepressants exert their clinical efficacy.

Since promethazine possesses potent antihistaminic and cholinolytic effects, and both of these pharmacological properties have been suggested to be causally related to the antidepressive effects of psychotropic drugs, this investigation was justified from an ethical point of view. However, results of this controlled study clearly favor amitriptyline over promethazine as an antidepressive agent, influencing the major depressive symptoms with a comparable incidence of autonomous side effects. This permits the following tentative conclusions with respect to the role of antihistaminic, anticholinergic and noradrenalin-enhancing properties for the antidepressive efficacy of amitriptyline.

A. Histaminic Function

Since the potencies of both promethazine and amitriptyline to inhibit the H_2 receptor-mediated stimulation of cyclic AMP formation are comparable (Green and Maayani 1977), the results of this clinical study do not support the view that blockade of H_2 receptors per se might be a decisice antidepressant mechanism.

Difference in absorption and distribution do not seem to account for the difference between both drugs since sedative and other centrally induced side effects were similar in both treatment groups.

The effect on insomnia, although observed with both drugs was more marked with amitriptyline. This is of interest with relation to the proposal of Schwartz et al. (1981) that H_1 antihistaminic effects have sedative properties. Since amitriptyline and promethazine seem to be comparable with respect to their H_1 antagonistic effects (Tran et al. 1978), our results suggest that other pharmacological properties are also involved in the production of sedation. Among those which might come into consideration are α_1 antagonistic effects (U'Prichard et al. 1978) or effects on serotonergic transmission. It is of interest to note in this respect that amitriptyline appears to be at least twice as potent as an α_1 antagonist than promethazine (U'Prichard et al. 1977).

B. Cholinergic Function

Several investigators (Janowsky et al. 1973; Modestin et al. 1973; Beckmann and Moises 1982) have suggested that the central cholinergic system has a role in normal affect and in the etiopathogenesis of affective disorders. On the other hand, the anticholinergic activity of antidepressants might have implications in patients possibly affected adversely by anticholinergic effects. However, the superiority of amitriptyline found in our study does not favor the view that anticholinergic activity per se has unequivocal antidepressive properties. This is in agreement with the report of Sitaram and Gillin (1980) who were unable to find acute antidepressive effects of scopolamine, a strong centrally active cholinlytic. Conversely, reports exist on the partially beneficial effects of cholinolytics in depressive disorders (Malatray and Simon 1972; Gisselmann et al. 1975; Ungvari et al. 1981). Beckmann and Moises (1982) and Kasper et al. (1981) reported that the anticholinergic biperiden has antidepressive effects during both acute and chronic treatment. However, it is not clear whether biperiden's antidepressant activity is solely due to its central anticholinergic effects or whether its slight inhibitory effects on catecholamine reuptake might be involved.

C. Catecholaminergic Function

Selective enhancement of central noradrenergic neurotransmission seems to be one of several possible mechanisms to achieve an antidepressant effect. However, it should be noted that tandamine, a selective noradrenaline reuptake inhibitor (Pugsley and Lippmann 1979) devoid of anticholinergic activity, reported to be a clinically effective antidepressant (Saletu et al. 1977), was in our hands less than convincing in severely depressed inpatients (Beckmann and Höcherl, in preparation). Furthermore, drugs which predominantly enhance dopaminergic transmission like the amphetamines or L-Dopa, or do so in addition to an enhancement of noradrenergic transmission like nomifensine and methylphenidate, are not of particular value in severely depressed inpatients but may be of help in milder depressive and apathetic states (Beckmann 1983).

Amitriptyline, with its strong anticholinergic properties, is still one of the most frequently used antidepressants. Biperiden which is an anticholinergic in the first place, processing in addition catecholamine potentiating effects, seems to exhibit certain antidepressant effects (Beckmann and Moises 1982). This together with other findings might indicate a synergism between catecholamine enhancing and anticholinergic actions.

D. The Catecholaminergic-Cholinergic Homeostasis

A potentiation of dopaminergic function by anticholinergic mechanisms has been found in various pharmacological designs (Tripod et al. 1954; Carlton 1962, 1963). Klawans et al. (1972) showed a lowering of the threshold dosage of amphetamine, a catecholamine releasing agent, required to produce stereotyped behavior. Conversely, the cholinergic compound physostigmine strongly antagonized the onset of amphetamine induced stereotyped behaviour.

With respect to noradrenaline-acetylcholine interactions, it is of interest that Fibiger et al. (1971) found a biphasic action of central cholinergic stimulation on behavioral arousal with an initial inhibitory phase and a consecutive phase of marked psychomotor excitation. They proposed that the rebound hyperactivity reflects a change in the level of functional synaptic activity in an adrenergic arousal system brought about by prolonged cholinergically mediated behavioral depression. The hemeostasis of an antagonistic inhibitory and excitatory brain function which might be represented by adrenergic-cholinergic mechanism seems well established in both laboratory work (Hess 1957) and clinical experience (Selbach 1949).

Whereas amitriptyline and its metabolite nortriptyline produce clear reuptake inhibition for both neurotransmitters noradrenaline and serotonin, promethazine is virtually devoid of any reuptake inhibition properties (Carlsson et al. 1969). Hence a potentiation of adrenergic mechanism by anticholinergic effects might be lacking and thus explain its minor efficacy at least in severely depressed patients.

In conclusion from this clinical investigation and data from the literature it appears that: H_2 receptor blockade and cholinolytic properties of the antidepressants *per se* seem not to be responsible for the antidepressant's efficacy. Instead, noradrenergic potentiation might further be enhanced or specifically influenced by associated anticholinergic activity.

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