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Clinical Observations with Pizotifene (Sandomigran) in the Treatment of Nonmigrainous Depressed Women

Csaba M. Banki

The County Neuropsychiatric Institute, H-4321 Nagykálló, Pf: 18., Hungary
(Head of the Institute: Dr. G. Lesch)

Summary. Based on earlier clinical experiences a group of 52 nonmigrainous depressed women were treated with 3—6 mg/day pizotifene (*Sandomigran*-Sandoz) in order to evaluate a presumed antidepressant action. The Bunney-Hamburg behavior-rating scale was employed to quantify the results. Thirteen patients showed marked improvement and 22 patients partial improvement after three weeks' treatment. Involutional and psychoreactive depressions responded better than endogenous forms. Symptomatically, anxiety and dysphoria were significantly more favorably influenced than retardation or paranoia. No serious side effects were observed.

Key words: Pizotifene – Depression – Anxiety.

Zusammenfassung. Aufgrund früherer klinischer Erfahrungen wurde eine Gruppe von 52 depressiven Frauen, die frei von Migräne waren, mit Pizotifene (Sandomigran-Sandoz) in Tagesdosen von 3—6 mg behandelt, um eine vermutete antidepressive Wirkung zu untersuchen. Zur Quantifizierung der Resultate wurde die Bunney-Hamburg Behavior Rating Scale verwendet. Nach 3wöchiger Behandlung zeigten 13 Patienten eine ausgeprägte und 22 Patienten eine partielle Besserung; involutive und psychoreaktive Depressionen sprachen besser an als endogene. Unter den Einzelsymptomen wurden Angst und Dysphorie signifikant günstiger beeinflußt als Hemmung und Wahnhaftigkeit. Ernsthafte Nebenwirkungen wurden nicht beobachtet.

Schlüsselwörter: Pizotifene – Depression – Angst.

Introduction

A rapidly increasing number of our patients, having found relief from their recurrent migraine attacks, provide further evidence for the therapeutic value of pizotifene in various forms of functional vascular headaches. In the course of the treatment, besides the common side effects of a mild sedation and weight gain due

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to an increased appetite [4, 8, 9, 22, 24—27, 30], we regularly observed an elevation of mood and a decrease in anxiety states. This phenomenon did not appear to be closely related to the prophylactic effect of the drug on the frequency and intensity of headache attacks, but seemed rather to depend on the severity of pretreatment psychopathology. This observation prompted us to postulate a direct anxiolytic or antidepressant effect of pizotifene, independent of its migraine-prophylactic property. Other reports [1, 17, 20, 34] had already raised this possibility, which could be further confirmed by pharmacologic considerations. Antagonists of serotonin, e.g., cinanserin, have been reported to yield anxiolytic effects [16], and benzodiazepines, the most widely used anxiolytic drugs, are also supposed to act by antagonizing brain serotonin [6, 7, 35]. Therefore we decided to test whether pizotifene has any antidepressant or anxiolytic effect in true depression.

Material and Methods

Fifty-two female patients with primary depression were included in this study. Thirty-seven of them were hospitalized for the first time, and the others had two or more prior admissions due to former manic or depressive episodes. Their age ranged from 26 to 51 years, with an average of 44 years. The diagnosis of depression was established according to the usual criteria [18], the most frequent symptoms being depressed mood, loss of energy and interest, ideas of guilt and insufficiency, motor retardation or agitation, anxiety, suicidal thoughts, insomnia, weight loss, etc. The current depressive phase had usually begun 5—20 days before admission.

After medical examination and psychiatric exploration, all patients were scored on the Bunney-Hamburg (BH) behavior-rating scale [5], which has proven to be sufficiently reliable for longitudinal observations. Further, patients were divided into subgroups according to two separate aspects: pathogenetically (involutional, psychoreactive, and endogenous) and symptomatically (anxious-agitated, dysphoric-hypochondriac, retarded, delusional-paranoid). This latter differentiation is somewhat arbitrary, but roughly corresponds to that created in drug selection and has many advantages in clinical practice.

Treatment was initiated with 3×1 tablets of *Sandomigran* (0.5 mg pizotifene) and gradually elevated according to clinical response up to 3×2 to 3×4 tablets (3—6 mg) daily. If no beneficial effect was seen with 6 mg/day during 10—14 days, or even earlier, if the severity of the symptoms made it necessary, the treatment was changed to standard tricyclic therapy and/or electroconvulsion (ECT). During the trial, we carefully avoided administering other major psychotropic drugs, particularly tricyclic antidepressants, and therefore only tranquilizers of the benzodiazepine type and nonbarbiturate hypnotica were given when necessary.

At the end of the third week, each patient was scored again on the BH scale and therapeutic ratings calculated as follows: 50% or more decrease of the initial BH score was given 2 points, 20—50% decrease 1 point, and less than 20% decrease 0 point. Zero was also given for those patients who could not end the trial.

Results

Thirteen patients of the total 52 showed clear (2-point) improvement, and another 22 substantially benefited from the pizotifene treatment (Table 1). These two groups represent 67% of the total patient population. In the table, we calculated the number of markedly or moderately improved patients separately for the diagnostic subgroups: significant differences were revealed between

Table 1. Therapeutic response to pizotifene after three weeks' treatment

	N	Therapeutic rating (points)		
		0	1	2
Endogenous	13	8	4	1
Psychoreactive	16	4	7	5
Involutional	23	5	11	7
Total	52	17	22	13
				35 (67%)

endogenous depression and the other two groups with respect to their average therapeutic response (Table 2). In the evaluation of these data it has to be considered that this population consisted of cases severe enough to require psychiatric haspitalization. Symptoms often included recurrent delusions, paranoid ideation, repeated suicide attempts, etc.

Statistical comparison of the symptomatically differentiated subgroups (Table 3) clearly demonstrated that anxious and dysphoric-hypochondriac forms of depression showed more favorable therapeutic response than retarded or paranoid-delusional forms. These differences are statistically highly significant [19].

Clinical observation of the patients during the trial confirmed the findings obtained by the formalized rating scale. In responder patients, marked improvement of the vegetative symptoms occurred on the second to the fourth day. Sleep and appetite returned first, accompanied usually by a transient sedation.

Table 2. Average therapeutic ratings after treatment in different subgroups of depressed patients

	$\bar{x} \pm$ S.E.M.	*N*
Endogenous	0.461 ± 0.18[a]	13
Psychoreactive	1.062 ± 0.23	16
Involutional	1.087 ± 0.10	23

[a] Significantly different from the other two groups ($P < 0.05$)

Table 3. Average therapeutic rating after pizotifene in the symptomatic subgroups

	N	$\bar{x} \pm$ S.E.M.
Anxious-agitated	19	1.316 ± 0.13[a]
Dysphoric-hypochondriacal	14	1.214 ± 0.18[a]
Paranoid	12	0.417 ± 0.16
Retarded	7	0.143 ± 0.14

[a] Significantly different from nonmarked groups ($P < 0.01$)

Anxiety decreased after the end of the first week, while mood elevation became evident in the majority of cases during the second half of the second week.

Undesirable side effects were moderate and infrequent. Initial drowsiness did not cause complaints and gradually decreased in the course of the second week. In some cases a marked increase of appetite led to rapid weight gain, even to an undesired degree. Three patients mentioned 'restless legs,' two patients obstipation, and one a transient dysuria.

Discussion

Elevation of mood in the course of pizotifene treatment has been observed by other authors [20, 34] in migrainous patient populations. In such cases, however, there always arises the question whether it can be attributed indirectly to the alleviation of the migraine, or to some direct pharmacologic effect. In the present study we intended to provide additional data on this subject, since after a literature survey we were not aware of any other publication dealing with pizotifene effects in nonmigrainous but depressed patients. In our female patient group (although they were too few in number to permit definite conclusions), pizotifene proved markedly or moderately effective in about two-thirds of the patients. However, the employed doses were somewhat higher than those recommended for migraine prophylaxis.

Some theoretical considerations about the mechanism of an antidepressant action may arise from the investigations of the last two decades aimed at clarifying the biochemical background of depressive illness. Among these, a large and still continuously growing body of data seems to support the so-called 'serotonin hypothesis,' i.e., the involvement of pathologic changes in brain-serotonin metabolism in the development of depression [12, 28, 31—33]. The most widely accepted version of this hypothesis postulates a decrease in free serotonin level at certain central receptor sites. In fact, tricyclic antidepressants can elevate biogenic amine levels at receptors by inhibiting their reuptake into the presynaptic vesicles; monoaminooxydase inhibitors, the other major group of effective antidepressants, have the same final effect through blocking the disposition of the brain amines. Pizotifene is also a tricyclic drug [10] with amine reuptake-inhibiting properties [23], which can also play a part in its migraine-prophylactic action [1, 34]. In this way some antidepressant effect of this compound seems to be expected. Further, depletion of brain serotonin results in a state characterized by anxiety, increased locomotor activity, insomnia, and decreased appetite [15, 21]. Some of these manifestations, strikingly similar to certain symptoms of depressive illness, can be reversed by administration of the serotonin precursor L-tryptophan, which is also sometimes therapeutically effective in clinical depression. Pizotifene has opposite effects to those of serotonin depletion (sedation, sleepiness, increased appetite, anxiety reduction). These are often referred to as side effects of the migraine-prophylactic treatment.

Some recent observations suggest the involvement of altered serotonin metabolism in both migraine and the development of depression. In a preliminary study we combined a daily dose of 4.5—6 mg pizotifene with 120 mg/day

pyridoxine for depressed patients. Synergic action was found, and therapeutic responses were more rapid and strong than with pizotifene alone. As pyridoxine itself has profitable effects in milder forms of depression, probably due to increased biogenic amine synthesis [2, 29], the deviation of newly synthetized serotonin from the periphery toward the CNS may account for this synergism. Alternatively, pizotifene can interrupt the feedback loop by blocking serotonin receptors, thus leading to increased synthesis, which can be further supported by exogenic pyridoxine supplementation.

Independent of these highly speculative aspects, we found pizotifene remarkably effective in certain forms of authentic depression, an observation that seems to warrant further trials. As most of the common antidepressants have considerably numerous adverse effects [13, 14], we believe there is clearly a need for new and safe compounds for treating depression, one of the most common psychiatric illnesses.

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