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Is Phosphodiesterase Inhibition a New Mechanism of Antidepressant Action?

A Double Blind Double-dummy Study between Rolipram and Desipramine in Hospitalized Major and/or Endogenous Depressives

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Summary. Unlike conventional antidepressants, rolipram (a new approach in the treatment of depression) stimulates both the presynaptic and the postsynaptic component of monoaminergic transmission. Several double blind trials are under way to assess the clinical efficacy and safety of this compound. The present study was a randomized, 4-week interindividual double blind double-dummy comparison with desipramine in inpatients with major (DSM-III) and/or endogenous (ICD-9) depressions. After a minimum washout period of three days the patients received either 0.50 mg rolipram or 25 mg desipramine orally t.i.d. for the first three days, then 0.75 mg rolipram or 50 mg desipramine t.i.d. until day 28. Rating tests were based principally on the AMDP-system and the HAMD scale. The study showed no differences between the two drugs as regards the efficacy, but a definite trend in favour of rolipram as regards the side effects and, in particular, anticholinergic effects.

Key words: Antidepressants – Phosphodiesterase inhibitors – Rolipram

Introduction

According to a widely accepted hypothesis of biological psychiatry deficient cerebral monoaminergic transmission plays an important role in the aetiology of endogenous depression (Schildkraut 1965). This hypothesis is based on the pharmacological mechanism of the action of antidepressants to enhance central monoaminergic neurotransmission. Classically this is achieved by inhibition of monoamine (MA) reuptake and of monoamine oxidase (MAO), by blockade of central alpha$_2$-receptors or by enhancement of MA release. Thus, all drug treatments currently used in the therapy of endogenous depression rely on interactions with neuronal target sites located *presynaptically* to increase the concentrations of MAs (first messengers) in the synaptic cleft with consequent greater stimulus to postsynaptic receptors.

An alternative approach to enhance monoaminergic neurotransmission is to increase the availability of the second messenger adenosine cyclic 3′, 5′-monophosphate (cAMP) within the postsynaptic neuron generated by noradrenaline (NA) stimulation of postsynaptic receptors i.e. to influence noradrenergic neurotransmission *beyond postsynaptic first messenger receptors.* In pursuit of this approach, rolipram, a chemically novel stereoselective inhibitor of a neuronal calmodulin-independent cAMP phosphodiesterase (PDE) isoenzyme (Fig. 1) has been predicted to exert antidepressant activity at 100 times lower dosages than conventional antidepressants (Wachter 1982, 1983; Przegalinski and Bigajska 1983). Rolipram has no MAO inhibitory activity and does not inhibit reuptake of MAs into the presynaptic neuron (Kehr et al. 1985). It is also devoid of anticholinergic effects (Wachtel et al. 1988; Ross CE, Toon S, Rowland M, Murray GH, Meya U: A study to assess the anticholinergic activity of Rolipram in healthy elderly volunteers. Pharmacopsychiatry (submitted for publication)). The potential usefulness of rolipram was

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Chemical name: 4-(3-cyclopentyloxy-4-methoxy-phenyl)-2-pyrrolidone.

Structural formula:

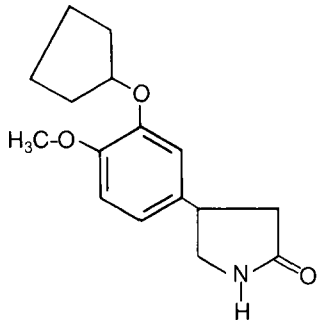

Fig. 1. Rolipram: Chemical name and structural formula

suggested on the basis of its pronounced efficacy in classic animal tests predictive of antidepressant action (Wachtel 1982, 1983; Przegalinski and Bigajska 1983). It was assumed that its antidepressant effect is based on enhanced central NA transmission brought about by the ability of rolipram to increase the turnover of NA and, at the same time, to enhance the postsynaptic cAMP-generating effect of NA via its intrinsic cAMP PDE inhibitory action (Wachtel 1982, 1983). Thus, unlike conventional antidepressants, rolipram stimulates both the *presynaptic and postsynaptic* components of monoaminergic transmission. It is assumed that its presynaptic action is also due to an increase of intraneuronal cAMP availability following cAMP PDE inhibition. The enhanced NA turnover is thought to result from synthesis stimulation following cAMP mediated activation of tyrosine hydroxylase and from facilitated release following elevated cAMP levels in the presynaptic neuron (Kehr et al. 1985). Evidence in support of the preponderance of the postsynaptic mechanism of antidepressant action of rolipram and related compounds has recently been published (Wachtel and Schneider 1986).

Open clinical phase I/II studies conducted in nearly 200 depressed patients (predominantly endogenous or chronic depression, often resistant to conventional drugs) at 20 separate and independent centers confirmed the predicted antidepressant activity and safely of rolipram (Zeller et al. 1984; Horowski and Sastrey-Hernández 1985).

The aim of the present study was to determine the antidepressant efficacy and safety of rolipram in comparison with desipramine in patients with major depressive disorder, Preliminary results of the present study were presented at the 15th CINP congress, Puerto Rico (Guiot-Goffioul et al. 1987).

Methods

The 4-week interindividual, double blind double-dummy study involved 35 patients aged from 18 to 70 years undergoing hospitalized treatment for an endogenous or typical major depression (ICD-9 296.1/296.3 or DSM-III 296.22/296.23/296.32/296.33/296.52/296.53). In the first three days following a wash-out period of at least two days, the patients received either 0.50 mg rolipram or 25 mg desipramine orally 3 × daily by randomized allocation. The maintenance dose administered from day 04 to day 28 of the study was 3 × 0.75 mg rolipram/day versus 3 × 50 mg desipramine/day. The dose of rolipram was selected on the basis of the human pharmacological and clinical results available at the time, whereas the dose of desipramine was an average dose selected to suit the double-dummy design of the study.

Table 1. Schedule for the rating and biological tests

	Study day					
	00	03	07	14	21	28
Clinical Global Impressions (CGI)	×	×	×	×	×	×
AMDP Mania-Depression Scale (AMDP-MD)	×	×	×	×	×	×
AMDP Somatic Scale (AMDP-5)	×		×	×	×	×
AMDP Psychopathology Scale (AMDP-4)	×		×			×
AMDP Syndromic Scale (AMDP-SY)	×		×			×
Hamilton Depression Scale (HAMD)	×	×	×	×	×	×
Medication protocol			×	×	×	×
AMDP Anamnesis (AMDP-1 to AMDP-3)						×
Patient Termination Record Form (DT2)						×
ECG	×					×
Laboratory status	×		×			×

The schedule for the ratings and biological tests is summarized in Table 1.

All parts of the AMDP-System were employed in their official French adaptation (Bobon 1981; Troisfontaines and Bobon 1987). The CGI was applied in its official French version (Bobon 1977).

The total score for the HAMD scale (24-item version) had to be at least 23 on admission to the study. The exclusion criteria included fertile women, MAOI in the last two weeks, electroconvulsive therapy in the last three months and desipramine nonresponders. The only concurrent psychotropic medication allowed was bromazepam as an anxiolytic and flunitrazepam as a hypnotic.

Statistical Analysis

Two-way ANOVA for repeated measures were computed on the target symptoms.

In the event of inhomogeneity of variance matrices, the degrees of freedom were adjusted using the HUYNH-FELDT method.

The programmes employed were the ANOVA/GLM from the SAS Package with the repeated option.

Table 2. Scores of the predetermined target scales, factors and items (HAMD = Hamilton Depression Scale; AMDP-SY = Syndromic scale of the AMDP; AMDP-MD = Mania-Depression subscale of the AMDP; CGI = first item of the Clinical Global Impressions). R = Rolipram; D = Desipramine. Numbers in brackets: standard deviation

Day	HAMD		AMDP/DEP		AMDP/ APA		AMDP-SY/ Dep		AMDP-SY/ Ap. Ret		CGI-1		AMDP-MD/ Dep	
	R	D	R	D	R	D	R	D	R	D	R	D	R	D
00	27.5 (5.2)	32.4 (5.7)	29.9 (5.5)	31.8 (9.9)	12.1 (0.1)	10.1 (5.5)	3.1 (0.6)	3.1 (0.5)	2.1 (1.5)	1.4 (1.1)	4.73 (0.59)	5.0 (0.55)	29.00 (6.20)	31.71 (10.4)
03	23.0 (4.6)	26.7 (9.3)									4.47 (0.64)	4.29 (0.99)	23.93 (5.61)	26.43 (12.66)
07	22.0 (7.7)	23.0 (10.7)	23.5 (6.0)	23.1 (14.3)	9.4 (4.6)	7.9 (6.2)	2.6 (0.7)	2.1 (1.4)	2.0 (1.1)	1.4 (1.2)	4.07 (0.80)	3.71 (1.27)	22.33 (5.89)	21.29 (13.62)
14	18.3 (9.0)	21.9 (11.8)									3.67 (1.11)	3.64 (1.50)	17.27 (6.84)	19.71 (14.96)
21	17.9 (10.1)	18.5 (11.2)									3.53 (1.25)	2.92 (1.61)	18.53 (8.60)	18.85 (14.69)
28	17.3 (9.5)	18.6 (13.5)	16.9 (10.7)	17.7 (16.7)	6.3 (4.4)	4.2 (4.9)	2.1 (0.9)	1.6 (1.4)	1.3 (1.1)	0.5 (0.9)	3.20 (1.37)	2.82 (1.89)	17.00 (10.24)	18.36 (17.43)

For quantitative data, the variables included in the statistical analysis were the differences calculated between the values observed on a specific day and the baseline values.

The CHI squared test was used to compare the qualitative variables.

Results

Twenty-nine patients completed the 28-day treatment and six patients dropped out. Three patients dropped out of the study after less than 14 days: one patient from the rolipram group because the nurse broke the code prematurely, another from the same group because the depression switched to mania after 7 days of treatment and one patient from the desipramine group because of a massive increase of the liver transaminases. Another three patients dropped out of the study between day 14 and 28: two from the desipramine group because of early discharge from the hospital and one patient from the same group who died of an adenocarcinoma.

The statistical analysis is confined to the 29 patients (15 from the rolipram group and 14 from the desipramine group) who completed the study. The sex and age distribution were 11 male and 18 female patients aged from 27 to 70 years (mean value: 54 years in the rolipram group and 49 years in the desipramine group). The indications were recurrent major depression without melancholia (DSM-III 296.32) in 15 patients, a single episode of a major depression without melancholia (DSM-III 296.22) in 4 patients, a single episode of a major depression with melancholia (DSM-III 296.23) in 4 patients, recurrent major depression with melancholia (DSM-III 296.33) in two patients, recurrent major depression with psychotic features (DSM-III 296.34) in one patients and a depressive bipolar disorder without melancholia (DSM-III 296.52) in 3 patients.

On study day 00, the HAMD score was 27.5 in the rolipram group and 32.4 in the desipramine group ($P < 0.05$). With the exception of this difference, the randomly created groups were homogeneous.

All the target symptoms and parameters employed for the assessment of the efficacy (Total HAMD score, Depression factor of the AMDP-4 and 5 scales, Depression item of the AMDP Syndromic Scale, Apathy factor of the AMDP-4 and 5 scales, and Apathy item of the AMDP Syndromic Scale) displayed a distinict improvement over time compared with the initial value in both the rolipram group (cf. Table 2) and the desipramine group without any differences between the two treatments being discernible. The same is true for the results documented with the CGI and Mania-Depression scales. Table 3 gives the F values for all AMDP factors. These data indicate

a) a global improvement without drug differences not only for Depression (DEP) and Apathy-Retardation (APA) but also for Psycho-organic Symptoms (ORG) and Insomnia (INS);

b) a global improvement with a significant difference between both drugs for Anxiety (ANX) in D patients, without any difference in the mean consumption of benzodiazepines; this difference is probably due to a higher initial anxiety score in D patients before treatment;

c) no significant variation as regards Hostility-Irritability (HOS), Somatic Complaints (SOM) and Vegetative Symptoms (VEG);

Table 3. F values and level of significance of the differences between rating days and between the two drugs for the factors of the AMDP-4 and -5 scales

Factor:					
1	OBS	F (1.24)	=	0.09	$P < 0.77$
2	DRA	F (1.24)	=	5.40	$P < 0.03$
3	ANX	F (1.24)	=	6.35	$P < 0.02$
4	DEP	F (1.24)	=	0.02	$P < 0.90$
5	APA	F (1.24)	=	0.06	$P < 0.82$
6	ORG	F (1.24)	=	0.37	$P < 0.55$
7	DIS	F (1.24)	=	0.16	$P < 0.69$
8	DEL	F (1.24)	=	0.78	$P < 0.38$
9	MAN	F (1.24)	=	2.59	$P < 0.12$
10	HOS	F (1.24)	=	1.15	$P < 0.29$
11	SOM	F (1.24)	=	2.02	$P < 0.17$
12	VEG	F (1.24)	=	0.23	$P < 0.64$
13	INS	F (1.24)	=	1.90	$P < 0.18$
14	NEU	F (1.24)	=	0.05	$P < 0.82$

Table 4. Relevant side effects (the figures represent the overall number of complaints occurring under active treatment)

Symptoms	Rolipram	Desipramine
Dry mouth	19	32
Constipation	8	18
Hypotension	1	11
Orthostatic hypotension	3	11
Blurred vision	0	5
Nausea	5	2

d) low values, therefore not analyzed, for the factors Obsessions, Dramatization, Dissociation, Delusions, Mania and Neurological Symptoms.

Side effects were recorded more frequently in the desipramine group than in the rolipram group (a total of 110 separate reports of concomitant symptoms in the desipramine group compared with 50 in the rolipram group). Table 4 presents the incidence of the most frequent symptoms in the two groups. It can be seen that supposedly anticholinergic side effects are more frequent with desipramine, while nausea is more frequent with rolipram.

The following findings from the analysis of the somatic or clinical and clinico-chemical parameters employed to assess the safety of the test substances are worth mentioning:

- An increase of weight in the rolipram group to an average of 73.1 kg on study day 28 compared with 71.8 kg on day 00 ($F = 5.64$, $p = 0.02$).
- A decrease of the systolic blood pressure measured in standing in the desipramine group to an average of 103 mmHg and 106 mmHg on study days 07 and 28 compared with 122 mmHg on day 00 ($F = 5.51$, $p = 0.007$).
- An increase of the serum uric acid values in the rolipram group to 59.2 mg/l and 61.3 mg/l on study days 07 and 28 compared with 55.6 mg/l on day 00 ($F = 3.55$, $p = 0.04$).
  However, a look at the pertinent individual values shows that the change compared with the initial value is not clinically relevant in any of the patients.
- A reversible increase of SGOT and SGPT in the rolipram group to an average of 23.4 U/l and 31.4 U/l on study day 07 compared to 20.0 U/l and 24.6 U/l respectively on day 00, without a simultaneous change of the OCT values. Here, again, the changes in the individual patients were of no clinical relevance.

No clinically relevant changes were observed in any of the other clinical and clinico-chemical parameters studied in either group.

Conclusions

The most important conclusions to be drawn from this study can be summarized as follows:

- Both substances were clearly effective as antidepressants. No differences were demonstrable between the treatments.

- Statistical analyses did not show that rolipram has a shorter onset of action than desipramine. However, it must be borne in mind that, in this study, the dose of rolipram was stepped up gradually as with the classical antidepressants.

- Anticholinergic and hypotensive side effects were reported more frequently under treatment with desipramine than under rolipram treatment. Otherwise, there were no serious side effects at all under either of the treatments.

- The present data on the clinical and clinico-chemical parameters examined do not give rise to any reservations about the safety of rolipram.

Since the sample in this study is a small one (15 vs. 14 patients), the risk of type II or beta error is greater than 80%. Therefore, it was not possible to show significant differences between both treatment groups.

Because of the lack of anticholinergic effects and indications of nootropic properties in animal experiments (Randt et al. 1982), rolipram may be particularly suitable for the treatment of depression in the elderly.

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