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Roxindole, a dopamine autoreceptor agonist, in the treatment of major depression

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Abstract. Roxindole is a potent autoreceptor-"selective" dopamine agonist originally developed for the treatment of schizophrenic syndromes. The drug also inhibits 5-HT uptake and has 5-HT_{1A} agonistic actions. In this open clinical trial 12 in-patients suffering from a major depressive episode (DSM-III-R) were treated with roxindole for 28 days in a fixed dosage of 15 mg per day. A reduction of at least 50% in HAMD-17 total scores was observed in 8 out of 12 patients after 4 weeks (mean HAMD-17 reduction of 56% in all patients), while 4 patients did not respond to roxindole treatment. Half of the patients showed a complete psychopathological remission (HAMD-17 < 8). Roxindole's onset of antidepressant action was remarkably rapid. Seven out of eight responders improved within the first 2 weeks of treatment (at least 50% decrease in HAMD-17 total score), and four patients were nearly asymptomatic within 1 week. Our results indicate that roxindole may possess potent antidepressant properties and that its efficacy should be further evaluated by double-blind controlled studies against reference drugs.

Key words: Roxindole – Dopamine autoreceptor agonist – Dopamine – Depression – Prolactin

There is some evidence of a decreased dopamine turnover measured by CSF levels of homovanillic acid (HVA) in at least a subpopulation of depressive patients with psychomotor retardation (Post et al. 1978). Likewise, the antidepressant efficacy of the dopamine uptake inhibitor nomifensine and antidepressive properties of dopamine agonists like bromocriptine or piribedil in some depressive patients, particularly those with psychomotor retardation and low pretreatment CSF HVA levels (Post et al. 1978; Waehrens and Gerlach 1981), indicate a possible etiological and therapeutical relevance of dopaminergic mechanisms in depression. However, in other investigations in depressed patients synthesis, storage and catabolism of dopamine were normal and studies of receptor function examined by neuroendocrinological investigations have not shown consistent abnormalities (Jimerson 1987).

Dopaminergic neurotransmission is controlled by negative feedback mechanisms mediated by D_2-like autoreceptors (Carlsson 1988). Stimulation of those autoreceptors leads to a decreased neuronal impulse rate and reduced release and synthesis of the neurotransmitter (Roth et al. 1987). Dopamine autoreceptor agonists were originally designed for the hypothesized hyperfunctional dopaminergic state of positive schizophrenic symptomatology. However, in open clinical trials with "selective" dopamine autoreceptor agonists like talipexole (B-HT 920) or roxindole (EMD 49980) in positive schizophrenia, these compounds revealed no clear-cut antipsychotic efficacy (Wiedemann et al. 1990; Wetzel et al. 1992). Nevertheless, roxindole moderately alleviated symptoms like energy loss, apathy, anhedonia, and depressive mood in patients with negative schizophrenia (Wetzel et al. 1992). However, as in the case of roxindole (Seyfried et al. 1989), autoreceptor agonists are known to also posses agonistic activity at supersensitive postsynaptic receptors (Arnt and Hyttel 1984).

The indol-alkyl-piperidine roxindole is not only characterized by its high affinity—and high selectivity, if postsynaptic receptors are normosensitive—for dopamine autoreceptors in the low nanomolar range, but also marked 5-HT reuptake inhibiting and 5-HT_{1A} agonistic actions. Thus, the drug may have extraordinary properties as an antidepressant combining both dopaminergic and serotonergic actions. Affinities to other receptors such as D_1-like, $alpha_1$ and $alpha_2$, muscarinic and 5-HT_2 binding sites are negligible. Binding characteristics to the cloned D_2, D_3, and D_4 receptors have not yet been determined.

According to the hypothesized deficiency of dopamine turnover in at least a subpopulation of depressive patients, and considering the moderate improvement of a circumscribed subset of negative symptoms of schizophrenia under roxindole treatment, we conducted an open clinical trial with roxindole in depressive in-patients in order to evaluate the efficacy and safety of the drug at a fixed

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dosage. Concomitant investigations of prolactin secretion were performed to further study the pharmacodynamic properties of the drug in relation to its clinical effects.

Patients and methods

Twelve depressive in-patients (five male, seven female) newly admitted to hospital treatment gave written informed consent to participate in the study. Eleven patients suffered from a recurrent major depression (DSM-III-R no. 296.33, melancholic type) and one patient was categorized as complaining of a single major depressive episode (DSM-III-R no. 296.23, melancholic type; Table 1). The age of the patients ranged from 36 to 64 years with a mean of 53.25 years. In order to be included in the study, patients had to present with a total score of the Hamilton Depression Scale (HAMD-17) of at least 18 points at baseline and a severity of illness of at least "moderately ill" in the Clinical Global Impression (CGI).

Exclusion criteria comprised relevant medical and neurological disorders and pretreatment with depot neuroleptics.

After a wash-out period of 4–7 days, roxindole was administered in increasing doses in a fixed schedule for a total treatment duration of 28 days. Daily doses were 3.0 mg at days 1 and 2, 7.5 mg at days 3 and 4, and 15 mg from day 5 to the end of treatment. As adjunct medication, only chloral hydrate was allowed in case of need of sedation or sleep induction.

Psychopathological ratings included the HAMD-17, the Hamilton Anxiety Scale (HAMA), the Bech-Rafaelsen Melancholia Scale (BRMS), the Global Assessment Scale (GAS), the CGI and the UKU side effects rating scale, and were assessed by a trained research assistant at days 0, 7, 14, 21, and 28.

For investigation of prolactin secretion, before and under subchronic roxindole treatment blood was withdrawn at days 0, 7, 14, 21, and 28 at 8.00 a.m. in fasting patients.

All statistical evaluations were made by two-sided Wilcoxon rank analyses for paired data comparing baseline rating scores to the respective endpoint values at termination of treatment for both completers and drop-outs ("intention-to-treat analysis") using P-values of 0.05 as levels of significance.

Results

Intention-to-treat analysis showed a significant reduction of the mean HAMD-17 score from 26.6 ± 5.5 (mean $\pm$ SD) at day 0 to 11.8 ± 9.1 at day 28 (Table 1; $P < 0.005$). BRMS total scores revealed a similar decrease from 18.3 ± 5.3 at baseline to 8.2 ± 7.1 at the end of treatment (Table 1; $P < 0.005$). Moreover, the HAMA total score was reduced from 20.6 ± 5.4 (day 0) to 9.7 ± 8.4 (day 28; $P < 0.005$), while GAS scores increased from 39.1 ± 8.0 at baseline to 65.0 ± 20.8 at day 28 ($P < 0.005$).

As far as categorical criteria for treatment outcome are concerned, a reduction of at least 50% in HAMD-17 total scores was observed in 8 out of 12 patients after 4 weeks' roxindole treatment, while in 6 patients the HAMD-17 score was reduced below 8 points at the end of treatment. Seven out of these eight patients showing a satisfactory treatment response (i.e. a HAMD-17 decrease of at least 50%) improved within the first 2 weeks of treatment. Four patients demonstrated a remarkably rapid amelioration of depressive symptoms, i.e. a HAMD-17 decrease below 8 points within the first 7 days under roxindole.

Noteworthily, three of the four roxindole non-responders did not respond to a subsequent standard 200 mg imipramine treatment within 4 weeks. In one patient (no. 11), imipramine dosage had to be raised to 400 mg per day and response occurred after another 4 weeks under plasma levels of 350–400 ng/ml. In two roxindole nonresponders (nos. 7 and 12), a sufficient treatment effect could only be achieved by potentiation of imipramine by sleep withdrawal and lithium co-administration. In patient no. 9 who was withdrawn from the study at day 7 due to psychomotor activation and non-improvement. Because of incapacitating anticholinergic side effects including urine retention under previous tricyclic administration, mianserine (120 mg/day) and tranylcypromine (60 mg/day) were administered for 4

Table 1. Patient characteristics with respect to HAMD-17 and BRMS total scores at baseline and after 4 weeks' roxindole treatment in 12 depressed in-patients. All patients with the exception of patient 4, who suffered from a single major depressive episode (DSM-III-R no. 296.23), were categorized as complaining of a recurrent major depression (DSM-III-R no. 296.33)

Patient number	HAMD-17 baseline/ endpoint	BRMS baseline/ endpoint
1	22/ 1	15/ 0
2	22/ 6	12/ 3
3	21/ 4	13/ 1
4	22/ 0	13/ 0
5	28/14	14/ 7
6	19/ 7	17/ 4
7	31/21	27/18
8	25/ 6	20/ 5
9*	28/29	17/18
10	36/16	25/11
11	32/20	22/13
12	33/18	25/18

*Drop-out due to psychomotor activation and non-improvement

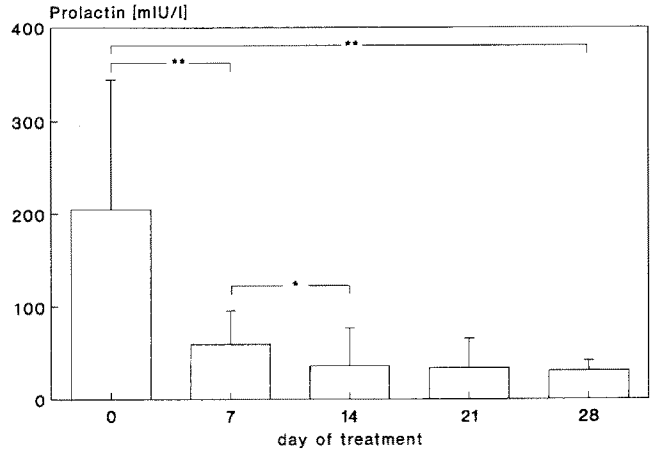

Fig. 1. Prolactin secretion before and under 28 day roxindole treatment (mean $\pm$ SD). Blood was withdrawn at days 0, 7, 14, 21, and 28 at 8.00 a.m. in fasting patients for determination of prolactin plasma levels. Prolactin secretion was significantly diminished to about 29 % within the first week and to 18 % of baseline levels in the second week of treatment. Prolactin release was further reduced significantly after 4 weeks' treatment to 15 % of baseline levels. $*P < 0.05$; $**P < 0.01$

weeks each, with lorazepam as adjunct medication. However, psychopathological improvement was only observed under a subsequent clomipramine treatment (225 mg/day).

Roxindole was well tolerated and did not cause any sedative or anticholinergic side effects. Nausea of mild degree in seven patients and severe nausea in one patient was observed during rapid dose increase in the first few days of treatment but did not require any antiemetic medication. One patient complained of marked delay of sleep onset even when depression had improved completely, and three reported slight dizziness when rising. Blood pressure and pulse rate, EEG and ECG recordings as well as laboratory findings did not reveal any clinically relevant changes.

Basal prolactin secretion was significantly reduced to 29% and 15% of baseline levels by roxindole treatment for one and 4 weeks, respectively (Fig. 1; $P < 0.01$).

Discussion

In this open clinical trial, treatment of 12 inpatients suffering from a severe major depressive episode, melancholic type, with roxindole in fixed dosage of 15 mg per day for 4 weeks resulted in a marked improvement of depressive symptoms. The observed response rate of nearly 70% is comparable to that of standard antidepressants like imipramine. Moreover, one third of patients demonstrated a surprisingly fast improvement, i.e. a HAMD-17 decrease of at least 50%, within the first 7 days of treatment. The tolerability of the drug was generally very good, with only minor side effects during the initial dose increment phase.

Our results are in line with earlier observations, that dopamine autoreceptor agonists can alleviate depressive symptoms in schizophrenic patients (Wiedemann et al. 1990; Wetzel et al. 1992). It has been hypothesized that in both schizophrenia with negative symptomatology and in depression with psychomotor retardation a relative deficiency of dopaminergic transmission is to some extent causative. Thus, depression should be improved by compounds that enhance dopaminergic transmission. Roxindole's antidepressive and antianergic effects therefore may be due to stimulation of postsynaptic dopamine receptors which may have become supersensitive due to reduced dopaminergic function rather than to presynaptic actions (Wetzel and Benkert 1992). On the other hand, the antidepressant effects of low doses of the D_2-like antagonist sulpiride have been referred to an indirect stimulating effect on dopaminergic function by a preferential blockade of presynaptic dopamine autoreceptors (Benkert and Holsboer 1984).

The marked attenuation of prolactin secretion known to be under control of an inhibitory dopaminergic tone is due to an extrasynaptic roxindole effect; dopamine receptors on the lactotrophs of the anterior pituitary are localized extrasynaptically and therefore have characteristics similar to supersensitive receptors. Because prolactin secretion can be stimulated through a serotonergic mechanism by 5-HT agonists and 5-HT reuptake inhibitors, the decrease of prolactin levels demonstrates that the dopaminergic effects of roxindole might prevail over its serotonergic actions. However, the attenuation of prolactin secretion by roxindole does not necessarily reflect the stimulation of postsynaptic dopamine receptors in other dopaminergic brain systems. In schizophrenic patients growth hormone release was elevated by subchronic roxindole treatment (Wetzel and Benkert 1992) probably also due to a dopaminergic effect of roxindole.

Roxindole's antidepressant properties may also be explained by its 5-HT reuptake inhibiting and 5-HT_{1A} agonist actions or more likely by a unique combination of both dopaminergic and serotonergic effects. Since the withdrawal of nomifensine from the market due to neuroimmunological side effects, a non-MAO inhibitor antidepressant with a dopaminergic component of action is lacking. New antidepressants with pharmacodynamic profiles different than standard tricyclic drugs could be of clinical utility in treatment-refractory patients and as tools for delineating depressive subtypes according to a differential drug response as in the case of MAO inhibitors and "atypical" depression (Liebowitz et al. 1988).

With respect to autoreceptor-selective dopaminergic drugs, it has been hypothesized that autoreceptor antagonists like (+)-AJ76 and (+)-UH232 rather than dopamine autoreceptor agonists might act as antidepressants (Carlsson 1988). Since we suggest that the antidepressive properties of roxindole might be, at least partially, due to a stimulation of supersensitive postsynaptic dopamine receptors, our findings are not contradictory to that notion. However, this question can only be resolved by clinical trials with dopamine autoreceptor antagonists in depression which to our knowledge have not yet been performed.

In conclusion, our results indicate that roxindole may indeed combine antidepressive efficacy with a rapid onset of action and justify further double-blind controlled studies against reference antidepressants.

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