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ORIGINAL PAPER

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# Savoxepine versus haloperidol

## Reasons for a failed controlled clinical trial in patients with an acute episode of schizophrenia

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**Abstract** Savoxepine, an atypical neuroleptic compound developed in the 1980s, was believed to act via selective limbic dopamine $D_2$-receptor blockade. The results of the presented double-blind, randomised, controlled clinical trial comparing savoxepine (n = 58) with haloperidol (n = 29) did not confirm the preclinical data suggesting that savoxepine would produce fewer extrapyramidal symptoms than the comparator. Animal data and PET-results obtained *a posteriori* suggested that this unfavourable outcome may have been due to the conventional, step-wise dose increase strategy used in the study leading to a high dopamine $D_2$-receptor occupancy in the striatum thus eliciting EPS. Using either a slower dose-titration or a high, single loading dose followed by a low maintenance dosing may have offered the possibility to obtain a good antipsychotic effect together with low incidence of EPS. In future clinical trials with new neuroleptics, the preclinical data should be carefully evaluated, and drug brain kinetic parameters taken into consideration.

**Key words** savoxepine · atypical neuroleptic · controlled clinical trial · pharmacokinetic

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## Introduction

The concept of "atypical" neuroleptics has been much used in recent. The most widely accepted characteristics include a good antipsychotic efficacy associated with a low incidence and severity of extrapyramidal symptoms (EPS). It is not unusual, however, to include other desirable characteristics such as a low incidence of tardive dyskinesia, no increase in plasma prolactin levels and a beneficial effect on negative symptoms. Different mechanisms may underlie these properties: the binding characteristics at the dopamine (D)-receptor complex (balanced binding to $D_1$ and $D_2$ receptors [Farde et al. 1989; Meltzer et al. 1989], selective binding to $D_3$ or $D_4$ receptors [Snyder 1990; Van Tol et al. 1991], a preferential binding to limbic dopamine receptors [Farde et al. 1989; Xiberias et al. 2001]), and a combined $D_2$-/5-hydroxytryptamine (5-$HT_2$)-receptor antagonism (Dewey et al. 1995; Meltzer et al. 1989) have been hypothesised. Clozapine, the "prototype" atypical antipsychotic compound, exhibits most of these properties: marked $D_4$-binding, balanced $D_1$- and $D_4$-receptor occupancy, a preferential binding to mesolimbic dopamine-receptors, and a balanced affinity for $D_2$ and 5-$HT_2$ receptors. The characteristics of the new "atypical" neuroleptics risperidone, olanzapine, and sertindole are attributed to a combined $D_2$/5-$HT_2$ antagonism, with sertindole showing in addition preferential limbic $D_2$-blockade.

In the late 1980s, the former Ciba-Geigy (now Novartis Pharma) was developing an antipsychotic drug displaying limbic dopamine receptor selectivity. This development was stopped after completion of the first dose-ranging trials because of toxicological findings (potential carcinogenicity). In these trials savoxepine demonstrated antipsychotic activity but failed to show a lower incidence or severity of EPS in comparison to classical antipsychotics. In the present article the results from one of these dose-ranging trials are reported and discussed with regard to the failure of the study to demonstrate a lower incidence of EPS with savoxepine

than with haloperidol; the relevance of preclinical data and the appropriateness of the clinical trial design are considered.

## Experimental procedures

### Savoxepine preclinical data

Savoxepine (CGP 19486) is a lipophilic tetracyclic cyano-dibenzoxepine-azepine derivative. It displays very potent *in vitro* $D_2$-receptor blocking activity ($IC_{50}$: 0.5 nM*). In vivo*, savoxepine blocks [$^3$H]spiperone-binding in the rat brain, with a high $D_2$ regional selectivity: the $ED_{50}$ is 0.04 mg/kg i. p. for hippocampal $D_2$-receptors and 0.7 mg/kg i.p for the striatal receptors, a ratio of 1:17 (Bischoff et al. 1988). Savoxepine also inhibits dopamine-stimulated adenylate-cyclase, indicating a strong interaction with $D_1$ receptors. It exhibits pre- and postsynaptic dopaminergic blockade with approximately the same potency at both. Savoxepine activity at the $D_3$ and $D_4$ receptors is unknown, as these receptor subtypes had not been identified when the drug development was discontinued.

Beside its dopamine-receptor blocking characteristics, savoxepine is a potent blocker of $\alpha_1$-, $5HT_2$-, and histamine–1-receptors, as well as a moderate to weak blocker of $\alpha_2$-, histamine-2-, $5HT_1$-, and cholinergic-muscarinic receptors (Waldmeier et al. 1986). Savoxepine shows almost no interaction with benzodiazepine- or opiate-receptors or β-adrenoceptors.

In animal models the potency of savoxepine in inhibiting amphetamine-induced stereotypies in rats, a model for antipsychotic efficacy, is similar to that of haloperidol ($ED_{50}$: 0.1 mg/kg p. o.) but the duration of the effect is twice as long. The capacity of the drug to induce catalepsy (a model for the propensity to induce EPS) is about 10 times lower than that of haloperidol (Bischoff, 1992).

### Clinical trial protocol

In order to ensure double-blind conditions, validate the trial, and provide comparative tolerability data, haloperidol was used as an active comparator.

Male and female inpatients aged 18 to 55 years were eligible for inclusion in the trial if they met DSM-III-criteria for an acute episode of schizophrenia. A predominance of productive symptoms was required, with a minimum score of 35 on the 18-item Brief Psychiatric Rating Scale (BPRS). All psychotropic medications had been discontinued for 1–3 days before the start of the trial.

The patients were randomised in a ratio of 2:1 to either savoxepine or haloperidol (unbalanced design). A fixed-flexible dose regimen with a stepwise titration was applied: savoxepine and haloperidol were titrated to a daily dose of 0.75 mg and 15 mg respectively, within one week. Individual dosage adjustments of 0.25 mg and 5.0 mg were possible thereafter at weekly intervals. The total treatment duration was 28 days. Permitted concomitant medications included benzodiazepines (clonazepam or diazepam) for hypnotic use if necessary and the antiparkinson drug biperiden in case of severe EPS.

Assessments were made at baseline and after 3, 7, 10, 14, 21 and 28 days of treatment. Psychiatric symptomatology was assessed by means of the 18-item BPRS, the Clinical Global Impressions (CGI), and the Nurses' Observation Scale for Inpatient Evaluation (NOSIE). At the end of treatment an overall evaluation of the therapeutic effect was made. All adverse events (AEs) were assessed for severity, duration, and presumed relationship to treatment. The EPS were assessed by means of the Simpson-Angus Scale (SAS) total scores, the akathisia and dystonia scores from the scale of the Scandinavian Society of Psychopharmacology, Committee of Clinical Studies (UKU) and the concomitant use of the antiparkinsonian biperiden was employed as an indirect measure of EPS severity. An overall assessment of the global tolerability of the study drug was made at the end of the trial using a 4-point scale.

## Results

A total of 87 patients from 2 centers were recruited into the study (58 in the savoxepine- and 29 in the haloperidol-treated groups). There were no statistically significant or clinically relevant differences between the two groups in terms of demographic data. The reasons for premature discontinuation are summarised in Table 1. There were no significant differences between the groups in terms of frequencies or reasons for discontinuation. The most frequent maximal dose in the savoxepine group was 4 tablets (2.0 mg) administered in 24 (41 %) patients. The corresponding values in the haloperidol group were 4 tablets (20 mg), administered in 10 (35 %) patients. The final doses of the two drugs in individual patients are given in Fig. 1.

At baseline, the severity of the illness was similar in both groups as illustrated by the mean BPRS total scores of 43.9 ± 10.8 in the savoxepine group and 46.8 ± 9.6 in the haloperidol group. Pronounced reductions of the BPRS total scores, reflecting an antipsychotic effect, were observed at the end of the trial in both groups, with

**Table 1** Reasons for premature discontinuation (number, percentage)

| | Savoxepine (n = 58) | Haloperidol (n = 29) |
|---|---|---|
| Early cure | 2 (3.5) | 1 (3.5) |
| Inefficacy | 2 (3.5) | 2 (6.9) |
| Poor tolerability | 3 (5.2) | 2 (6.9) |
| Inefficacy and poor tolerability | 4 (6.9) | 2 (6.9) |
| Other | 10 (17.2) | 3 (10.3) |
| Total | 21 (36.2) | 10 (34.5) |

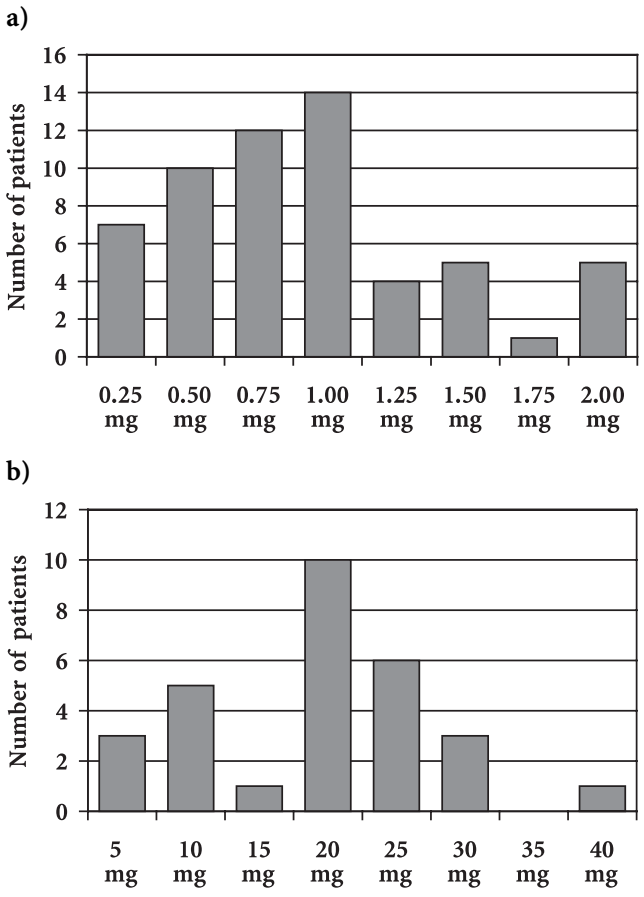


**Fig. 1** Number of patients with respective final doses (mg/day) at day 28 of savoxepine (**a**) and haloperidol (**b**).

a slight advantage for savoxepine that did not reach statistical significance (23.6 ± 13.9 for savoxepine vs. 29 ± 17.6 for haloperidol). These results were confirmed by the CGI data and by the evaluation of the global efficacy. For the NOSIE scale, patients treated with savoxepine and haloperidol showed comparable reductions in the total scores.

There was no statistical difference between the two groups in the incidence and severity of EPS as measured by the SAS total score (savoxepine: 0.6 ± 1.8 at day 0, 3.5 ± 4.5 at day 28, haloperidol 1.8 ± 3.7 and 5.4 ± 5.5, respectively). No differences were apparent between savoxepine and haloperidol in terms of dystonia or salivation scoring. During the course of the investigation 38 (66 %) of the savoxepine-treated patients and 27 (93 %) of those treated with haloperidol received treatment with biperiden for the control of Parkinsonian symptoms (statistically significant difference). Signs of akathisia were observed in only 33.3 % of the savoxepine-treated patients, compared to 58.6 % in the haloperidol group: 15.8 % vs. 31 % complained of slight akathisia, 15.8 % vs. 13.8 % of moderate akathisia, and 1.8 % vs. 13.8 % of severe akathisia. There was however a marked centre effect regarding this parameter which reduced the implications of this finding. In the global assessment of tolerability, 68.4 % of the savoxepine-treated patients were scored as "very good" or "good" compared to 58.6 % in haloperidol-group (not statistically significant). Forty-four patients on savoxepine (75.9 %) complained of an AE, as did twenty-one patients (72.4 %) in the haloperidol group. Reported AE were comparable in nature and severity in both treatment groups.

## Discussion

The efficacy results obtained in the two treatment groups are similar to those reported in the literature for well-conducted trials of antipsychotic treatments in this patient category (Dixon et al. 1995); they demonstrate that the haloperidol and savoxepine doses given in this trial were adequate. Thus to find no consistent statistically significant differences regarding the incidence or severity of EPS between the two treatment-groups was unexpected in the face of the promising preclinical data obtained with savoxepine.

One question is whether the clinical trial design and sample size could have played a role in the failure to obtain a statistically significant difference between the two treatment-groups in terms of EPS. The statistical assumptions to detect a difference were based on a total number of 120 evaluable patients to be recruited in two parallel trials; similar total numbers of patients have been recruited in other trials which were able to successfully differentiate between haloperidol and "atypical" antipsychotics in terms of tolerability (Petit et al. 1996). The data provided by the sister trial were unfortunately of poor quality and could not be employed for the evaluation of the tolerability. This resulted in an under-powered statistical analysis which may have been further jeopardised because of the 2:1 unbalanced design: the reduction in patient numbers may have appreciably affected the variability of the haloperidol arm. However, the incidence and severity of the EPS observed in the haloperidol treatment group were no different from those usually observed in clinical practice at the doses administered (Lavin and Rifkin 1992). On the other hand, although savoxepine was somewhat less prone to induce akathisia and the patients treated with savoxepine may have suffered less from EPS as reflected by the lower use of the rescue medication biperiden, the overall picture for savoxepine did not reveal a clinically, relevantly lower incidence of EPS, compared to patients treated with haloperidol. The possibility of a carry-over effect from a previous neuroleptic medication due to a too-short wash-out period (1–3 days for oral neuroleptics) could be ruled out in view of the steady increase in the SAS total scores over the first 2–3 weeks of the treatment in both treatment-arms.

An explanation for the unexpected incidence of EPS in the savoxepine-treated group may lie in the doses given, which, in this dosing trial, may have been too high.

Savoxepine was first tested in three small open clini-

cal trials yielding contradictory results: whereas in the 8 patients included by Butler and Bech (1987) no EPS were observed in a dose range of 0.4 to 2.0 mg/day, this was not the case in 10 of 16 patients investigated by Möller et al. (1989); the dose-range in this study was however 0.5 to 10.0 mg/day and the EPS incidence could be lowered by reducing the daily dose. In the trial reported by Wetzel et al. (1991), a dose range of up to 20 mg/day was administered. Although the authors state that there was no clear-cut relationship between the dosage of savoxepine and EPS, their data show that the incidence of EPS was higher in patients receiving high doses. Wetzel et al. (1991) reported that all responders were treated with a low dose regimen (0.5 mg/day), and higher doses did not increase the antipsychotic efficacy. Butler and Bech (1987) and Möller et al. (1989) made the same observation. Wetzel and co-workers speculate that the absence of EPS in the trial of Butler and Bech could be due to the patient selection method as patients were included only if they had no severe EPS during previous treatment with perphenazine at doses of 16 to 48 mg/day. The expectation that only the higher doses induce EPS was not fulfilled in the trial reported here where most patients in the savoxepine group received 1 mg/day or less and no patient was treated with more than 2 mg daily.

Hoffman and Donovan (1995) re-examined the EPS-inducing potential of savoxepine, haloperidol, olanzapine, ORG 5222, raclopride, and risperidone using two rodent catalepsy models. As a measure for clinical efficacy the authors used the inhibition of amphetamine-induced hypermotility. Dose-dependent catalepsy was observed with all drugs except clozapine. For each compound, the minimum effective dose producing catalepsy was greater than or equal to the $ED_{50}$ for antagonising amphetamine-induced hyperactivity (a dose inducing a 50 % reduction in hyperactivity). Clozapine showed the widest separation between the doses required to produce catalepsy and those required for the reduction of amphetamine-induced hyperactivity, followed by raclopride. A one- or two-fold separation was observed with the other drugs. These results are in sharp contrast with those of Bischoff (1992) showing with savoxepine a 58- to 166-fold separation between the antagonism of amphetamine-induced hyperactivity and potency to induce catalepsy. This discrepancy may be attributed however to methodological differences: in the models used by Hoffman and Donovan, no separation is made between sedation and catalepsy, and savoxepine has been shown to be strongly sedative in animals and humans.

The antipsychotic effects of savoxepine may be attributed to a long-lasting, possibly cumulative $D_2$-blockade occurring in the striatum and particularly in the hippocampus. The possible role of the hippocampus in schizophrenia has been emphasised over time, and Bischoff et al. (1986, 1988) suggested that the antipsychotic effect of a drug may be linked to a hippocampal $D_2$ receptor occupancy while the EPS could be elicited by the blockade of $D_2$ receptors in the striatum. According to Bischoff (1992), the pharmacokinetic profiles of savoxepine are very different in these two crucial brain regions, presumably in relation to its regional selectivity. In the rat, the inhibition of the $D_2$-specific [$^3$H]spiperone binding in the striatum returned to zero within 24 to 48 h with a dose of 3 mg/kg i. p., in the hippocampus a 55 % inhibition was still present after 48 h, and a statistically significant inhibition of [$^3$H]spiperone binding persisted for up to 72 h after savoxepine administration. Based on these observations, the author suggested two treatment schedules the use of which should ensure that most $D_2$-receptors in the hippocampus are occupied with only a weak effect on striatal receptors. One approach would involve a slow titration with savoxepine, an inconvenient solution in patients in need of a fast control of their symptoms. Another dosing regimen was proposed, which should produce a rapid antipsychotic effect and sedation in these agitated subjects while avoiding EPS: it consisted of a "loading" dose followed by a washout period and then a maintenance dose regimen. Using this treatment schedule in rats, after an initial loading dose of 3 mg/kg i. p., the hippocampal $D_2$-receptor occupancy was stabilized after 5 days of treatment with a very low dose of 0.3 mg/kg i. p. once daily. At that stage, the striatal $D_2$ occupancy was 40–50 % 2.5 h after drug administration, returning to zero 24 h later. In the hippocampus however the $D_2$-receptor occupancy was 80–90 % 2.5 h after drug administration, and still 40–60 % after 24 h.

In this context the results of a positron emission tomography (PET) studies seem very interesting. Leenders et al. (1993) analysed the extent and duration of striatal $D_2$-receptor occupancy by savoxepine (0.1, 0.25, 0.5 mg single doses) in humans in a [$^{11}$C]raclopride displacement study. The authors found a 50 to 70 % $D_2$-receptor occupancy in the putamen and caudatum depending on the dose of savoxepine administered. A pharmacokinetic simulation showed a persistence of the blockade for 6 days. Another simulation of 6 repeated once daily dosing (again 0.1, 0.25 and 0.5 mg) led to basal ganglia $D_2$ occupancy up to 90 % at day 5, reflecting a possible propensity for cumulating. This means for the given trial that the used dosages (Fig. 1) were much too high to avoid a high $D_2$-blockade in the striatum.

Another reason for the high EPS-liability of savoxepine in the presented trial might be that this compound is characterised by a very potent $D_2$-receptor blockade ($IC_{50}$ *in vitro*: 0.5 mM) (Bischoff et al. 1988) which is long lasting (Leenders et al. 1993, see above). As Kapur and Seeman (2001) based on a survey and critical analysis of molecular, animal model, neuroimaging, and clinical aspects of typical and atypical neuroleptics argue, the atypical antipsychotic effect is dependent on a rapid dissociation from the $D_2$ receptor at a molecular level; however, blockade of $D_2$ receptors by savoxepine is very potent and long lasting.

## Conclusion

Although methodological flaws (underpowered trial, unbalanced design, short neuroleptic wash-out period) may have prevented the demonstration of the qualities of a novel neuroleptic compound, in the present case, the failure of savoxepine to show a reduced propensity to induce EPS may be in relation to its particular pharmacological profile at the $D_2$ receptors in the striatum and the hippocampus. It is very tempting to speculate that with a dosing regimen quite different from those used traditionally and in the present trial, it would have been possible to obtain a significant antipsychotic effect without, or at least with considerably reduced EPS. At the time of the trial initiation, it was not possible to utilise an untested treatment schedule in the presence of incomplete information concerning the efficacy of savoxepine. Had the compound survived, it would have been possible to test a new therapeutic approach and a new dosing regimen, thus possibly confirming an innovative concept for the treatment of schizophrenia.

In future clinical trials with new psychoactive compounds, a careful evaluation of all preclinical data taking into particular consideration the drugs' kinetic parameters at the receptor level may lead to the design of novel dosing approaches. Usage of modern imaging techniques may then confirm and allow optimization of the proposed dosing regimen.

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