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The Sequential Treatment Approach to Resistant Schizophrenia with Risperidone and Clozapine: Results of an Open Study with Follow-Up

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In this paper we extend and test with long-term follow-up the results of a previous paper on the usefulness of a sequential treatment protocol with risperidone and clozapine in resistant schizophrenia. Twenty-four patients diagnosed as resistant schizophrenics according to DSM III R and Kane *et al.*'s (1988) criteria were treated with risperidone for 3 months. Eight patients responded (according to *a priori* criteria: improvement of basal BPRS, SAPS and SANS total scores over 20 per cent at 3 months observation), while of the remaining 16 patients two dropped out and nine responded to clozapine treatment within the next month. Five patients had partial or no response to clozapine. Follow-up lasting up to 37 months (mean 22·4 months for risperidone responders and 18·3 months for clozapine responders) showed good stability of response, no significant differences in relapses and re-hospitalizations between risperidone and clozapine responders and no tardive responses. © 1998 John Wiley & Sons, Ltd.

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KEY WORDS — schizophrenia; drug-resistant; treatment; risperidone; clozapine

INTRODUCTION

The treatment of resistant schizophrenia (RS) is possible in a large proportion of patients since the reintroduction of clozapine (CLOZ) in the late 1980s. While the critical ratio between D2 and 5HT2 blockade seems to be clearly one of the key features for clinically effective/low EPS-inducing drugs, that may be classified as 'atypical' (Meltzer, 1994), it is not yet clear which pharmacodynamic feature or profile is directly related to clinical efficacy in RS. The complex pharmacodynamic profile of CLOZ makes it difficult to answer this question. Nevertheless it is not yet clear if RS is related to a homogeneous physiopathology or not, as not all patients respond to clozapine.

Clinical studies testing the effects of new drugs sharing with clozapine only a part of its pharmacodynamic profile may be useful to narrow the field of research on CLOZ key pharmacodynamics for RS physiopathology. However, most of the studies available are based on comparisons between classical and novel antipsychotics that involve random assignment to parallel groups design and that test the effects of each drug on different groups of patients. In contrast, a sequential design, in which two or more treatments with different and progressively more complex pharmacodynamic profiles are given consecutively in the same subject unless a clinical response is found, may be useful to separate possible, discrete, physiopathologically homogeneous subgroups.

We have already published the results of a sequential treatment of resistant schizophrenia with risperidone (RIS) and CLOZ (Cavallaro *et al.*, 1995a,b), two drugs chosen because of the partial overlap in a 'key' pharmacodynamic feature of an atypical profile that is serotonin/dopamine antagonism (SDA) (Meltzer, 1994). In that study RIS was able to treat successfully 50 per cent of 16 neuroleptic-resistant schizophrenics (diagnosed with Kane *et al.*'s criteria). We concluded that SDA target brain circuits should be involved at some

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level in the expression of the illness in at least a subgroup of patients and suggested that etherogeneous dysfunctions might underly RS.

The best way to check these first hypotheses was to follow up patients in their clinical course after the attribution to the RIS or CLOZ acute response groups, to test response stability both as relapse prevention and reproducibility at rechallenge, if relapse occurred. Past response to a specific drug is still a leading criterion of pharmacological choice in psychiatry and the only evidence supporting a possible clinical difference between classical neuroleptics (Kane and Marder, 1993; Kane, 1996), not yet checked for RS (to the best of our knowledge).

In this study we will show the results of the sequential treatment of RS with RIS and CLOZ in a sample of 24 patients with a follow-up lasting up to 34 months.

MATERIALS AND METHODS

Twenty-four patients (13 F), with a mean age of 34·2 years (SD 10·2) and a mean duration of illness of 12·7 years (SD 6·6) were included in the study. Patients had to meet diagnostic criteria for schizophrenia according to DSM III criteria and the definition of refractory schizophrenia according to Kane *et al.*'s criteria (1988). Exclusion criteria were the presence of any contraindication to RIS and CLOZ treatment and previous treatment with any of these drugs. Patients gave their informed consent to the study and were hospitalized for the first month of the study period and then discharged in case of efficacy and established compliance.

RIS monotherapy started after a 1- to 3-day washout from conventional neuroleptics and 1 month after the last depot injection. Doses could be titrated up to 16 mg/day within the first month, according to clinical picture, and were then fixed for the next 2 months. Non-responders to RIS at the last observation were switched to CLOZ for the next month at free doses (up to 600 mg/day), that were fixed for the next 3 months, and then re-assessed after 1 and 3 months of treatment; clinical evaluations and response criteria were as follows. Clinical assessment was performed by the same observer before and after 1 and 3 months of treatment by means of the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) (18-item version scored 0–6) and of the Scales for the Assessment of Positive and Negative Symptoms of Schizophrenia (SAPS-SANS) (Andreasen, 1983, 1984). SAPS-SANS total scores did not include 'global rating' items of each subscale. Only rescue, p.r.n., medication for agitation (diazepam) and insomnia (flurazepam) was allowed. Compliance with treatment was checked directly by nurses during the hospitalization treatment, by tablet count and relatives' cooperation during the remaining period with additional measurement of plasma levels for CLOZ.

Patients were considered responders if total scores of all rating scales improved by at least 20 per cent and BPRS total score was less than 35 after 3 months of treatment with RIS. A partial response was considered when only the improvement of at least two parameters was obtained (i.e. 20 per cent improvement of SAPS and SANS scores but BPRS still over 35). The same criteria were applied to assess the response to CLOZ. Moreover, response had to be sustained for at least 12 weeks at follow-up to be finally attributed.

After the end of the acute study patients were followed up monthly with ambulatory visits and a complete clinical assessment with the same rating scales every 3 months, or more frequently in case of significant deterioration, with two aims. The first was to check the last response criteria of sustained response after 12 weeks, the second, to follow the long-term outcome of full, partial and non-responders.

To assess long-term follow-up outcome we decided to define as 'relapse' the return of all clinical parameters to the starting level. Minor changes were not considered, while a judgement on the result of the follow-up, that is positive (with maintenance of a positive result), negative (with loss of positive or maintenance of a negative result) or increased improvement (further improvement of 20 per cent of final, acute period BPRS score), was recorded and is indicated at the last follow-up. Hospitalizations during the follow-up period were recorded and divided as a consequence of relapse or other (social, family or other not strictly psychopathological reasons). Rates of relapse and hospitalization by month were then calculated.

Drug treatment during follow-up was maintained as monotherapy with the possibility of adjusting doses according to clinical status and side-effects. If relapses occurred in responders to one of the drugs, they were treated with one trial of the same drug lasting at least 4 weeks at doses (unchanged, reduced or increased) of the same drug decided upon by the clinician, with patients hospitalized, if necessary. Causes of non-inclusion

in follow-up were missing at follow-up visits for one CLOZ responder and one CLOZ non-responder.

RESULTS

All 24 patients completed the acute RIS treatment phase. Demographic and clinical characteristics at baseline are shown in Table 1. Eight patients were responders to RIS at a mean dose of 9·5 mg/day (median 9; SD 1·7): six patients (75 per cent) fulfilled all response criteria after 1 month of treatment and two patients (25 per cent) after 3 months of treatment due to delayed response at SANS evaluation. Of the sixteen RIS non-responders (mean RIS dose 13 mg/day; median 14·5; SD 3·2) nine patients had a positive full response to CLOZ treatment at a mean dose of 355·5 mg/day (median 400; SD 76) by 1 month, while three had a partial response to CLOZ at a mean dose of 416 mg/day (median 450; SD 104). Two RIS non-responders dropped out at the end of RIS treatment because of withdrawal of consent to be treated with CLOZ. Two patients did not respond to either treatment (RIS dose 16 mg, CLOZ doses 450 and 600 mg/day). One of these two patients was successively diagnosed as having a severe hypoperfusion of the frontal and deep temporal lobe by single photon emission computed tomography.

Basal clinical and demographic characteristics of the four groups of patients who completed the study (RIS responders, CLOZ responders, CLOZ partial responders and non-responders to both treatments) were not significantly different. Mean RIS doses of CLOZ responders and non-responders were significantly higher than those of RIS responders (respectively 13 and 16 mg/day versus 9·5 mg/day ANOVA $p < 0{\cdot}01$ *post-hoc* comparisons with Tukey test $p < 0{\cdot}05$).

Repeated measures of non-parametric ANOVA of responders and partial responders outcome (Friedmann ANOVA and Wilcoxon matched pairs test for *post-hoc* comparisons) showed a statistically significant improvement in both RIS responders and CLOZ full responders, but not among CLOZ partial responders. Tables 2 and 3 show mean values of each assessment at each evaluation and statistics for the three groups. A temporary, marginally significant improvement occurred for SAPS and BPRS values between basal assessment and the first month of RIS treatment also in RIS non-responders: at the next evaluation, after 3 months of RIS treatment values worsened back to the basal values.

Mean percentage improvement of SAPS, SANS and BPRS scores at the last acute protocol observation did not differ significantly between RIS and CLOZ full responders being respectively 65 per cent (SD 23) and 63 per cent (SD 21) of SAPS basal values, 47 per cent (SD 18) and 43 per cent (SD 21) of the basal SANS values and 52 per cent (SD 9) versus 40 per cent (SD 14) of basal BPRS values (*t*-test).

Diazepam p.r.n. medication for agitation, measured as mean weekly cumulative doses, did not differ significantly between treatment response groups during the whole acute period (median 25 mg/week), but it was actually used in a minority of cases (one case in the RIS responder group, two cases in the RIS non-responder group then responding to CLOZ, one case in the CLOZ

Table 1. Demographic, baseline clinical, treatment and follow-up characteristics of the sample

	N	Mean	Median	Range	SD
Age	24	34·2	32	23–65	10·2
Duration of illness (yrs)	24	12·7	10·5	5–30	6·6
RIS dose (mg)	24	11·9	12	8–16	3·2
CLOZ dose (mg)	14	392·4	400	200–600	99·7
BPRS score	24	53·0	50	36–88	13·2
SAPS score	24	42·6	42·5	14–80	18·1
SANS score	24	68·0	70	32–100	18·1
Follow-up (months)	20	18·5	10·6	3–37	10·3
N of hospitalizations during follow-up	19	1·0	1	0–5	1·4
N of relapses during follow-up	19	0·8	1	0–4	1.0

Table 2. Mean BPRS, SAPS and SANS total scores ±SD at basal observation and after 1 and 3 months of RIS treatment of RIS responders ($n = 8$)

	BPRS basal	BPRS 1 month	BPRS 3 months	SAPS basal	SAPS 1 month	SAPS 3 months	SANS basal	SANS 1 month	SANS 3 months
Score	54·1 ± 8·4	33 ± 10·5*	25 ± 4·8†	50 ± 23·2	23·7 ± 10·7*	16·3 ± 13·6†	67·1 ± 21·4	47·3 ± 21·8*	38 ± 19·8*‡

Statistics: repeated measures Friedman ANOVA $p < 0{\cdot}005$ for all variables. Wilcoxon test for *post-hoc* comparisons: *$p < 0{\cdot}01$ versus pre; †$p < 0{\cdot}01$ versus pre and t1; ‡$p < 0{\cdot}05$ versus t1.

Table 3. Mean BPRS, SAPS and SANS total scores ±SD at basal observation and after 1 and 3 months (m) of RIS treatment and 1 month of CLOZ treatment of RIS non-responders, partial or full responder to clozapine ($n = 12$)

	RIS treatment				RIS treatment				RIS treatment			
	BPRS basal	BPRS 1 month	BPRS 3 months	BPRS CLOZ	SAPS basal	SAPS 1 month	SAPS 3 months	SAPS CLOZ	SANS basal	SANS 1 month	SANS 3 months	SANS CLOZ
CLOZ full responders $n = 9$	48 ± 8·4	43·4 ± 9·57	47·8 ± 11·1	27·2 ± 4·9*†	35·2 ± 12·1	30·8 ± 13·9	38·0 ± 12·8	13·1 ± 8·5‡§	64·6 ± 9·8	60·6 ± 8·8	63·0 ± 13·4	35·0 ± 15·2‖
CLOZ partial responders $n = 3$	60 ± 13·7	55·6 ± 12·5	60·3 ± 4·9	41·6 ± 4·7	55·6 ± 14·6	50·0 ± 17·3	53·3 ± 12·4	28·3 ± 9·4	88·6 ± 10·5	82·0 ± 16·3	85·6 ± 15	68·6 ± 9·6

Statistics, full responders: repeated measures Friedman ANOVA $p < 0{\cdot}001$ for all variables. Wilcoxon test for *post-hoc* comparisons: *$p = 0{\cdot}01$ versus t1; †$p < 0{\cdot}01$ versus pre and t3; ‡$p < 0{\cdot}05$ versus pre and t1; §$p < 0{\cdot}01$ versus t3; ‖$p < 0{\cdot}01$ versus pre, t1 and t3. Statistics, partial responders: repeated measures Friedman ANOVA not significant for all variables.

non-responder group, one case in the CLOZ partial responder group). Compliance during the acute study was complete for all patients.

A total number of 20 patients, eight RIS responders, eight CLOZ responders and three CLOZ partial responders were followed up for a mean period of respectively 22·4 months (SD 11·4 range 6–36 months), 18·3 months (SD 10·5 range 10–37 months) and 12 months (SD 8·1 range 3–16 months). The only non-responder patient to both treatments with an organicity component reported above was followed up for 8 months.

Causes for dropping out during the follow-up were missing at follow-up visit for two RIS responders and one CLOZ partial responder after respectively 12, 6 and 3 months; one patient was dropped for lack of response in a further episode in the RIS responder group after 30 months and one CLOZ non-responder was dropped for the same reason after 8 months.

Follow-up analysis was then performed on 19 patients, RIS responders and CLOZ partial and full responders. RIS dose decreased at last follow-up visit to a mean of 8·1 mg/day (SD 0·35), while CLOZ dose increased to 418·8 mg/day (SD 125) for full responders and to 566·6 mg/day (SD 57) for partial responders.

An overall positive follow-up (positive responses were at least maintained) was found in 14 patients (73·7 per cent) of which six (75 per cent) were among the RIS responders and eight (100 per cent) among CLOZ full responders. None of the CLOZ partial responders fulfilled response criteria, or significantly improved after a follow-up duration of 3–16 months.

Five patients (31·3 per cent) showed relapses (not related to non-compliance): three were RIS responders (37·5 per cent) and two CLOZ full responders (25 per cent).

Of the three RIS responders with reacutization, one had a resolution of the relapse occurring after 12 months and continued the follow-up after an increase in dose (from 8 to 10 mg/day); one had a resolution of the relapse occurring after 12 months with a decrease in dose and one did not respond to dose reduction after an episode occurring after 30 months (dose was decreased from 10 to 8 mg/day in an attempt to increase the 'atypical' effect of RIS). Of the two CLOZ responders both improved after dose increase.

One RIS responder and three CLOZ responders, had a single episode due to non-compliance with spontaneous drug withdrawal, with a positive outcome after reintroduction of the drug therapy and good compliance confirmed.

The rate of episodes by months of follow-up did not differ significantly between the groups of RIS and CLOZ responders being 0·025 ($\pm$0·04) versus 0·014 ($\pm$0·02).

Reflecting relapses, two hospitalizations were required for both RIS and CLOZ full responders, with a hospitalization rate by month of follow-up of 0·047 ($\pm$0·06) versus 0.062 ($\pm$0·06). Included in this analysis were CLOZ partial responders, who needed five hospitalizations with an index of 0·29 ($\pm$0.34), statistically greater than that of the other two groups (*t*-test $p < 0{\cdot}05$).

Last, a further improvement, as defined by *a priori* criteria, was found in three of the RIS responders (37·5 per cent) and seven of the CLOZ responders (87·5 per cent) at the end of follow-up. This difference was statistically significant (chi square 4·3, $p = 0{\cdot}03$).

DISCUSSION

Results from our study confirm our previous data and several recent reports on the RIS efficacy in subpopulations of patients with variously defined RS. In fact, several open studies, case review studies and a double-blind study versus CLOZ, reported either equal response to CLOZ and RIS or positive response to RIS in a proportion varying from about 25–40 per cent of patients treated (see Mendelowitz and Liebermann (1995) for a review). In a peculiar report of Raza *et al*. (1995) RIS was effective in two of three previous CLOZ responders and none of five CLOZ non-responders. Anyway, to our knowledge, our study is the only one including the RS criteria definition from Kane *et al*. (1988), following a specific sequential treatment design and performing a long-term follow-up. Follow-up duration is consistent or superior to that of most prospective (all open) studies on CLOZ response available, ranging from 6 months to 1 year (Buchanan, 1995). Follow-up data are here mainly presented and discussed only with the view to check with a naturalistic observation stability of acute response to RIS or CLOZ in RS.

The increase in sample numerosity reduced, in comparison to previous data (Cavallaro *et al*., 1995a,b), the relative importance of acute RIS responders to acute CLOZ responders, being 33 per cent of the whole sample versus 64 per cent of CLOZ full responders among the RIS

non-responders. Overall success rates are not greatly different between treatments, but while about one-third of the population benefits from the simple prominent SDA, about two-thirds of the remaining patients needed the more complex pharmacodynamic profile of CLOZ to improve.

The findings substantiate our hypothesis (Cavallaro *et al.*, 1995a,b) of etherogeneous physiopathology of RS (underlying a common clinical phenotype) that may be discriminated by pharmacological response to different pharmacodynamic profiles. Unluckily, the pharmacological response to each pharmacological class could not be predicted by any clear clinical variable; nevertheless the sequential treatment using a SDA before CLOZ may be successful in a significant proportion of RS patients that would then not be exposed to agranulocytosis risk.

More patients (100 versus 75 per cent) reached clinical response criteria at first observation (1 month) among CLOZ responders than RIS responders. This difference, if clinically significant with these numbers, may be related to many factors, including delayed response to RIS, but also study design and treatment order. RIS responders who did not fulfil response criteria in the first month of RIS treatment failed only to reach the required SANS score improvement. It is possible that in these patients psychopathology was still negatively influenced by the residual effects of previous neuroleptic treatment. Nevertheless at least part of the effects seen may be aspecitical and related to recent neuroleptic withdrawal or to placebo effect rather than to a clear drug-induced improvement. Anyway, a marginal first month improvement was not maintained in time in RIS non-responders, as the statistical analysis of each level of the repeated measure analysis excluded a clinical 'carry-over' of the neuroleptic withdrawal effect in RIS non-responders that could shorten CLOZ response time. With regard to a possible placebo response, this could be excluded in RIS responders because the response was found to be stable in the next long-term follow-up in most patients.

Follow-up analysis confirms acute study data with lasting stable, homogeneous specific responses for both treatment responders according to parameters statistically evaluated. Long-term results point also to two additional and related topics of discussion. None of the CLOZ partial or non-responders reached, in a follow-up period up to 16 months, response criteria, neither did they improve further, while CLOZ full response, obtained in all responding patients within 4 weeks of treatment was followed by a further global improvement in seven of eight follow-ups. Our sample is limited, but results seem to support Carpenter and other authors' recent views on CLOZ maximum response in the first months of treatment (Carpenter *et al.*, 1995; Wilson, 1996). The further improvement among CLOZ responders is probably directly related to the fitting of CLOZ pharmacodynamics to a specific core physiopathology. In fact the similar time-lasting follow-up of the RIS responders group showed a significantly lower number of patients improving further, despite similar acute improvement.

Persisting poor or non-response at follow-up of the four patients only partially or not responding to CLOZ in the acute treatment suggest they belong probably to another biological group in which the pharmacodynamic activities of CLOZ and RIS are insufficient.

In conclusion the sequential treatment of RS with an SDA such as RIS or CLOZ is confirmed as a rational clinical approach to RS, able to improve significantly nearly 80 per cent of patients and reducing in about 35 per cent of cases the risk of exposure to agranulocytosis risk, with sustained response. Response to different atypical agents seems to be confirmed to be a useful tool able to discriminate subpopulations of RS, probably related to physiopathological variants of this disease.

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