Combining ECT and clozapine in the treatment of clozapine-refractory schizophrenia and schizoaffective disorder – a pilot study

L Koen, MB ChB, MMed (Psych)
C E van den Berg, MB ChB
D J H Niehaus, MB ChB, MMed (Psych), FCPsych, DMed
Ngaphakathi Workgroup, Department of Psychiatry, Stellenbosch University and Stikland Hospital, W Cape

Schizophrenia is considered to be among the most severe, debilitating and persistent of all psychiatric disorders. Although the adult prevalence is approximately 1%, studies have indicated that sufferers constitute close to 10% of the permanently disabled population. As such, schizophrenia is a major public health problem and the negative economic consequences underscore the urgent need to develop strategies to improve treatment effectiveness.

Despite great advances in the understanding and management of the disease, a significant portion of individuals with schizophrenia do not respond well to drug treatment. Management of these treatment-refractory patients is particularly challenging as they often require longer periods of hospitalisation, with their care ultimately amounting to a disproportionately high share of the total cost of schizophrenia. Although the advent of the second-generation antipsychotic drugs has been regarded as a breakthrough owing to improved side-effect profiles and patient satisfaction, claims of their superior efficacy in treatment-refractory patients still remain unproven.

To date, in terms of evidence base, clozapine remains the undisputed treatment of choice for patients with severe treatment-refractory schizophrenia. Unfortunately, even though clozapine remains the gold standard, recent data show that 40 - 70% of sufferers from treatment-refractory schizophrenia treated with clozapine monotherapy, of adequate dosage and duration will continue to experience disabling symptoms, i.e. positive, negative or residual symptoms. Several factors have been implicated in patient failure to respond to clozapine monotherapy, including patient non-compliance and intolerable and/or serious side-effects such as agranulocytosis, seizures, sedation, hypersalivation and metabolic issues. However, for patients in whom these can be managed and who show at least partial response to monotherapy, effective clozapine augmentation treatment strategies need to be developed.

Numerous different clozapine augmentation strategies have been described in the literature, but there is currently no actual evidence supporting one strategy over another, with research consisting mostly of case reports and small open-label, unreplicated
Methods

Subjects

Ten known clozapine-refractory patients with a diagnosis of schizophrenia or schizoaffective disorder were recruited from the acute wards of Stikland Psychiatric Hospital, Western Cape. In order to be included patients had to meet the following criteria: (i) admission for relapse due to non-compliance (≤ 1 month); (ii) DSM-IV-TR diagnosis of schizophrenia or schizoaffective disorder; (iii) known to be clozapine-refractory (see criteria below); (iv) the decision to restart clozapine and augment with ECT made independently by the patient’s treating clinician; and (v) age 18 - 60 (extremes included). Patients were excluded if (i) they had another Axis I diagnosis (excluding substance abuse); and (ii) if they had a significant unstable medical condition.

Patients were regarded as clozapine-refractory if they met the following criteria: (i) previously treated with clozapine because of being regarded as treatment resistant (continued psychosis despite adequate trials of at least two antipsychotics of two different groups with the dosage equivalent of 10 mg of haloperidol [or maximum tolerable dose]); and (ii) despite being treated with clozapine at a dosage of at least 400 mg/day, or the maximum tolerated dose, for at least 6 weeks, the patient had previously exhibited continued psychosis. (Continued psychosis was defined as clinical symptomatology that rated a score of at least 4 on one item of the positive scale of the Positive and Negative Symptom Scale (PANSS). [2])

Procedures

All patients who met the inclusion criteria were screened by the primary investigator after ECT had been discussed with the patient’s treating clinician. The patients who consented to the study were divided into two groups (depending on whether they gave consent for ECT or not). The treating clinician obtained consent for ECT and performed all additional investigations required for ECT as well as the necessary haematological monitoring prior to starting clozapine, independently of the study team.

Clozapine was started by the treating clinician (as per normal treatment protocol) at 25 mg/day and the dose was titrated up every 2 days by 25 mg until a dose of 150 mg was reached. Thereafter the dose was titrated up by 50 mg every 2 days until 250 mg was reached, whereafter titration of the dose continued according to ward protocol (50 mg/week until response or maximum tolerated dose was reached).
ECT was started by the treating clinician between days 8 and 10 after admission and administered as per the usual Stikland Hospital protocol on alternate days for three sessions per week for six sessions in total. Concomitant medications were only considered (at the sole discretion of the ward clinicians) after clozapine dosage had reached 400 mg or the maximum tolerated dose.

**Data collection**

Patients were screened 4 - 6 days before the first administration of ECT (those who did not consent to ECT were screened 7 days before clozapine was started); if they met inclusion criteria and consent was obtained, the baseline visit took place during that same visit. All data were collected on data sheets which included all demographic data, information on previous admissions and medication history. A PANSS was performed at baseline (day 0), day 21 and day 42. Clinical case notes were retrospectively accessed after discharge and any documented adverse events, the exact length of stay and the medication data (including concomitant medications) were noted. The investigators were not involved in the primary treatment of any of these patients and had no contact with them other than the study visits.

**Statistical analysis**

The data were entered into Excel sheets and data analysis was performed using the Software Package for Social Sciences (SPSS). Chi-square and Student’s t-tests (Fisher’s exact) were utilised depending on the tested variables.

**Ethical considerations**

The study was approved by the Committee for Human Research of Stellenbosch University and their prescribed ethical guidelines were strictly adhered to.

**Results**

Ten patients were enrolled in the study. Five patients consented to concomitant ECT treatment (EG), whereas the other 5 were started on clozapine only as per the usual treatment protocol (CG). Of these patients 8 were male and 7 reported an educational level of Grade 8 or higher. Nine patients were unemployed and received disability grants. Seven had a diagnosis of schizophrenia and 3 of schizoaffective disorder.

The average number of previous admissions was 3.8 (5.2 EG; 2.4 CG; p=0.245). The mean age of onset of illness in the EG was 26.6 years (SD 6.58) and that in the CG 22.8 years (SD 5.805) (p=0.362), with mean illness duration in the EG being 8.2 years (SD 5.357) and that in the CG 4.1 years (SD 3.578) (p=0.198).

The average PANSS scores in both groups dropped over the 42-day study period for all three of the subscales measured (i.e. positive, negative, general). No statistically significant differences could be observed between the two groups at any point for any of the subscales or for the total score. Table I shows a comparison between the two groups’ PANSS scores over the course of the study period.

On discharge the average length of stay for both groups in comparison with their most recent admission had decreased, but the difference between the two groups was not statistically significant. With regard to the EG the average calculation was limited to only 4 patients as one patient’s most recent previous admission had been in a long-term ward where he had spent almost 7 years. The average clozapine dosage for both groups in comparison with their most recent admission had increased, and once again the difference was not statistically significant. This change amounted to an increase of 20 mg in the EG and an increase of 170 mg in the CG (p=0.352). Table II shows a full comparison of both the average length of stay and clozapine dosage values.

In addition to clozapine, concomitant psychiatric medications were used at discharge in the EG only (with 1 exception) and included valproate (4 cases in EG and 1 in CG), orphenadrine or benzhexol (3 cases), haloperidol (1 case) and sulpiride (1 case). Other concomitant medications during admission comprised

---

**Table I. Comparison of PANSS scores in the two groups over the course of the study period**

<table>
<thead>
<tr>
<th>Time point</th>
<th>Positive</th>
<th>Negative</th>
<th>General</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EG</td>
<td>CG</td>
<td>EG</td>
<td>CG</td>
</tr>
<tr>
<td>Day 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>29.4</td>
<td>30</td>
<td>25.8</td>
<td>28.6</td>
</tr>
<tr>
<td></td>
<td>p=0.85</td>
<td></td>
<td>p=0.287</td>
<td></td>
</tr>
<tr>
<td>Day 21</td>
<td>24.8</td>
<td>25.8</td>
<td>20.6</td>
<td>21.6</td>
</tr>
<tr>
<td></td>
<td>p=0.188</td>
<td></td>
<td>p=0.386</td>
<td></td>
</tr>
<tr>
<td>Day 42</td>
<td>20.8</td>
<td>22.2</td>
<td>21.8</td>
<td>18.6</td>
</tr>
<tr>
<td></td>
<td>p=0.84</td>
<td></td>
<td>p=0.64</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>44</td>
<td>44.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p=0.215</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>37.6</td>
<td>35.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p=0.144</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>36.4</td>
<td>34.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p=0.093</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>79</td>
<td>75.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>99.2</td>
<td>103.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p=0.508</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>83</td>
<td>82.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p=0.305</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>79</td>
<td>75.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p=0.36</td>
<td></td>
</tr>
</tbody>
</table>
benzodiazepines (7 cases), anti-emetics, promethazine and sorbitol.

Adverse events documented during admission were constipation (1 case), hypersalivation (2 cases), seizures (1 case from the CG and 2 cases from the EG, 1 of which occurred during an ECT session, see below), sedation (1 case) and nausea (1 case). In the EG all but 1 patient had six sessions of ECT. For this patient the last ECT session was cancelled owing to a prolonged seizure during his fifth ECT session which had to be aborted with intravenous diazepam.

**Discussion**

The management of patients with schizophrenia has proved to be challenging in various aspects, and especially relevant to this study is the problem of clozapine refractoriness. In this pilot study, ECT-clozapine bitherapy was investigated as one strategy to manage such patients in a resource-constrained setting.

No statistically significant advantage of ECT-clozapine bitherapy above clozapine only could be demonstrated for any of the variables measured in our study setting. However, numerical advantages in terms of decreased length of stay as well as a lower clozapine dose at discharge were observed in the bitherapy group. Although this suggested numerical advantage for the EG in terms of the above variables could probably be attributed to the increased use of concomitant medication in this group, it would be important to note a comparison of the baseline data for the two groups. While not statistically significant, baseline data seemed to suggest that as a group the EG were more severely ill than the CG, as evidenced by (i) higher average length of stay at baseline, and (ii) a higher average clozapine dose on the most recent previous discharge. They also had more previous admissions, but this could just be in keeping with their longer duration of illness.

To date, no prospective control studies have been reported in the literature and the only studies that can possibly be used for comparison are that of Kho et al. 18 and James and Gray.26 However, in James and Gray’s prospective open trial on 6 patients with treatment-resistant schizophrenia, patients received six ECT sessions before initiation of clozapine treatment, making comparisons with an ECT-clozapine bitherapy trial difficult.26

Kho et al. conducted an open trial with no control group.18 A few similarities do exist between our methodology and theirs. In both, the study population consisted of a clozapine-refractory schizophrenia group in an inpatient setting. The study groups were both small (11 v. 10 (5 in the combination group (EG) and 5 in the control group (CG)) and the PANSS was used as a primary outcome measure. However, in addition to the absence of a control group, other significant differences in methodology also existed. Kho et al. conducted at least three PANSS assessments before commencing ECT, only starting when the baseline scores remained stable or increased. During this time patients were continued on their clozapine and were adherent for an average of 11.2 weeks before the ECT. PANSS assessments (by two raters) were done weekly and ECT was continued until no further improvement in positive and total PANSS scores were seen, so patients received a mean of 10 ECT sessions during their treatment. Ultimately 8 patients met criteria for remission (a drop of at least 30% from baseline total and positive PANSS scores).

During the course of the study only 1 significant adverse event occurred that could be directly related to the ECT-clozapine bitherapy, in that 1 patient suffered a prolonged seizure during the fifth session of ECT. The seizure was successfully aborted with intravenous diazepam and the patient suffered no further sequelae. To date, no life-threatening side-effects or deaths have been reported in the literature for the combination of ECT and clozapine.27 Prescription of ECT-clozapine bitherapy therefore appears to be well tolerated and may be considered reasonably safe with few adverse effects.6

Although clozapine blood level measurement could be an important tool in this research setting, it is currently not routinely available in South Africa. It could be helpful in diagnosing clozapine refractoriness, in explaining different responses to treatment and for explaining and monitoring side-effects of clozapine. Future studies of this nature should consider doing clozapine blood level measurement for these reasons.

| Table II. Comparison between average length of stay and clozapine dosages in the two groups |
|---------------------------------|-----------------|-----------------|
|                                 | Most recent previous admission | Current admission |
|                                 | EG               | CG              | EG               | CG              |
| Length of stay (days)           | 146.3 (p=0.328)  | 81.8 (p=0.174)  | 100.5 (p=0.628)  | 70.2 (p=0.409)  |
| Clozapine dosage (mg)           | 550 (p=0.409)    | 480 (p=0.409)   | 570 (p=0.409)    | 650 (p=0.409)   |
The main limitation of this study was the relatively small number of cases and the fact that study staff were not blinded to the treatment. Factors contributing to inability to consent to ECT could also have biased the sample choice. Strengths of the study include the use of a single setting (with established treatment guidelines) as well as a single rater who conducted all assessments.

Conclusion

This pilot study represents the first controlled trial of ECT-clozapine bitherapy in a population with clozapine-refractory schizophrenia and schizoaffective disorder reported in the literature. In summary, despite the lack of statistically significant results in this study, lessons learnt from strengths and limitations could inform future study designs. The validity of our choice of current clinical practice at Stikland Hospital for the treatment of relapsed, non-compliant, known clozapine-refractory patients with a diagnosis of schizophrenia or schizoaffective disorder was not supported by our results. However, the study did provide us with preliminary evidence for the safety and efficacy of this combination. It would therefore be reasonable to continue to use this strategy in selected cases, at least until other clozapine-refractory treatment strategies become more available in our setting.

The authors would like to acknowledge Karen Cloete’s help in preparing a preliminary partial draft of the manuscript.

References