Melperone in treatment-refractory schizophrenia: a case series

Eromona Whiskey, Marta Vavrova, Fiona Gaughran and David Taylor

Ther Adv Psychopharmacol

(2011) 1(1) 19–23

DOI: 10.1177/

2045125311399800

© The Author(s), 2011.

Reprints and permissions:

<http://www.sagepub.co.uk/journalsPermissions.nav>

Abstract:

Objective: Clozapine is the treatment of choice in refractory schizophrenia, but a substantial proportion of patients experience inadequate response or tolerate the drug poorly. Melperone has been suggested as a possible alternative in such patients. This case series examines the efficacy of melperone in refractory schizophrenia.

Method: All patients prescribed melperone at the South London and Maudsley NHS Foundation Trust were identified using a pharmacy database. The main outcome was to determine the proportion of patients discharged on melperone.

Results: Three of 21 patients were discharged on melperone. The primary reason for discontinuation was lack of efficacy.

Conclusion: Melperone may be an option in a very few patients with refractory schizophrenia, but it should not be considered as an alternative to clozapine.

Keywords: schizophrenia, melperone, clozapine, antipsychotic agents

Introduction

Clozapine is the treatment of choice in patients with refractory schizophrenia with response rates of 30–60% [Meltzer *et al.* 1989; Kane *et al.* 1988]. According to the National Institute for Clinical Excellence (NICE) guidelines for the treatment of schizophrenia, clozapine should be offered to patients who have not responded adequately despite sequential use of at least two different antipsychotics [National Institute for Clinical Excellence, 2009]. Nonetheless, a substantial proportion of patients show an inadequate response to clozapine. For such patients, NICE recommends the addition of a second antipsychotic. However, evidence suggests that the addition of a second antipsychotic to clozapine results only in marginal benefits [Barbui *et al.* 2009; Taylor and Smith, 2009].

Furthermore, clozapine is associated with a significant burden of side effects and requires close haematological monitoring. Many clozapine-related side effects such as hypersalivation, sedation and hypotension are often benign and transient; metabolic disturbances such as weight gain, diabetes and dyslipidaemia are more significant and have long-term health implications.

Other adverse effects such as agranulocytosis, myocarditis and thromboembolism may be life threatening.

There is therefore a continuing need for viable alternatives to clozapine for the treatment of patients who are wholly or partially treatment refractory as well as for patients who are poorly tolerant of clozapine. Various options have been briefly investigated in trials and in clinical practice. Despite the paucity of evidence, high-dose antipsychotics and combinations are commonly used in such patients [Paton *et al.* 2008].

Melperone is a butyrophenone antipsychotic licensed as Buronil in many countries in Europe but not in the UK. It has antagonist activity at D₂ and 5HT_{2A} receptors and fulfils criteria for atypical antipsychotic drugs with its low rate of extrapyramidal side effects and tardive dyskinesia [Bjerksten *et al.* 1979]. In addition, the ratio of dopamine D₄/D₂ occupancy for melperone has been shown to resemble the binding profile of clozapine [Lahti *et al.* 1993]. Melperone has been investigated in an open trial for the treatment of patients with

Correspondence to:

Eromona Whiskey,
BPharm, MCMHP,
MRPharmS

Bethlem Royal Hospital,
Monks Orchard Road,
Beckenham, Kent, UK
Eromona.Whiskey@slam.nhs.uk

Marta Vavrova, MB, ChB

National Psychosis
Service, South London and
Maudsley NHS Foundation
Trust, London, UK

Fiona Gaughran, MD,
FRCPsych, FRCP, FRCP

National Psychosis
Service, South London and
Maudsley NHS Foundation
Trust, London, UK and
Institute of Psychiatry,
Kings College London,
London, UK

David Taylor, BSc, MSc,
PhD, FCMHP, MRPharmS

Pharmacy Department,
South London and
Maudsley NHS Foundation
Trust, London, UK and
Institute of Psychiatry,
Kings College London,
London, UK

Table 1. Patient characteristics: summary.

Parameter	Description
Sex	Male: 12 Female: 9
Age	Range 20–63 years (mean age, 36 years)
Ethnicity	White: 11 Black: 7 Asian: 3
Diagnoses (as recorded in medical notes)	Schizophrenia: 13 Schizoaffective disorder: 7 Severe depression with psychotic symptoms: 1
Mean age of onset of illness	19 years; range 12–43 years
History of clozapine treatment	Yes: 18/21
Discharged on melperone	$n = 3/21$

refractory schizophrenia [Meltzer *et al.* 2001] and shown to significantly improve overall psychiatric status as measured by the Global Assessment Scale (GAS) [Endicott *et al.* 1976] although it did not significantly affect the Brief Psychiatric Rating Scale (BPRS) scores [Overall and Gorham, 1962].

There is very little clinical experience of the use of melperone in the UK as it is currently unlicensed. Recently, there has been interest in melperone as a possible alternative to clozapine. This retrospective case series examines the outcomes for patients with refractory schizophrenia treated with melperone at the South London and Maudsley NHS Foundation Trust where it was first used in the UK.

The South London and Maudsley NHS Foundation Trust provides a range of mental health and substance misuse services in the UK. It provides care and treatment for a local population of 1.1 million people in South London. In addition, there are specialist services for people from across the country. The National Psychosis Unit is one of such tertiary referral services for the treatment of patients with refractory schizophrenia and melperone was first used here in the UK in 2005. This is thus the first published evidence of the experience with melperone in the UK.

Method

Using the pharmacy database, we identified all patients prescribed melperone from April 2005 to July 2010. From patient medical notes we extracted relevant information on past antipsychotic treatments and reasons for prescribing of melperone. For patients treated and discharged

from the National Psychosis Unit, we contacted the care team to find out what the current antipsychotic treatment was. The main outcome was to determine proportion of patients discharged on melperone: a proxy for acceptable treatment outcome.

Results

In total, 22 patients were treated with melperone. One patient was excluded as she was treated for less than a week. Tables 1 and 2 give patient characteristics.

This sample comprised patients with severe and treatment-refractory illness. The average age of onset of illness was 19 years of age. Almost all patients (18/21, 86%) had a prior exposure to clozapine. Of these, 10 patients had discontinued it because of adverse effects, 6 because of noncompliance with medication or blood tests and 2 patients because of inadequate response. Three patients had no prior exposure to clozapine. In two patients, this was because they had low baseline neutrophil counts and so they were ineligible for clozapine treatment. The third patient had not been exposed to clozapine because of a refusal to comply.

Duration of treatment

Three (14%) patients were discharged on melperone and 18 patients discontinued treatment during their stay on the unit. Of those who stopped treatment, the mean duration of treatment was 5.4 months. Of the three patients who were discharged on melperone, one was lost to follow up while two continued to take melperone at follow up, one for 4 years 11 months and the other for 4 years.

Table 2. Patient characteristics and outcome.

Sex	Age (years)	Ethnicity	Age of onset (years)	Duration of illness (years)	Previous history of clozapine	Reason for melperone	Duration of melperone treatment (months)	Reason for stopping melperone	Antipsychotic before melperone	Antipsychotic after melperone	Current antipsychotic (July 2010)
M	30	Black	14	21	Y	Intolerance to clozapine - hypertension	7	Ineffective	Clozapine	Amisulpride	Clozapine
F	51	Asian	24	23	Y	Intolerance to clozapine - seizures	3	Ineffective	Olanzapine + Amisulpride	Clozapine	Clozapine
M	26	Black	18	3	N	Low ANC* and ineligible for clozapine	11	Ineffective	Olanzapine + Amisulpride	Zuclopenthixol decanoate	Quetiapine + Amisulpride
M	33	Black	19	14	Y	Refused clozapine	3	Ineffective	Pipothiazine palmitate + Olanzapine	Clozapine	Clozapine
M	43	White	18	21	Y	Refused clozapine	3	Refused	Risperidone + Amisulpride	Aripiprazole	Clozapine + Amisulpride
F	32	Asian	21	7	Y	Intolerance to clozapine — neutropenia	9	Refused, EPSE	Olanzapine + Aripiprazole	Clozapine	Risperidone
M	38	White	24	9	Y	Noncompliance with clozapine	5	Ineffective	Amisulpride + Olanzapine	Clozapine	Consta + Olanzapine
M	60	White	43	16	Y	Hypersensitivity on clozapine	1	Adverse effects	Clozapine	Olanzapine	Risperidone
F	23	White	14	8	Y	Intolerance to clozapine — constipation	2	Ineffective	Clozapine	Olanzapine	Olanzapine
F	30	Black	14	11	Y	Insufficient response to clozapine	7	Adverse effects	Clozapine	Quetiapine	Clozapine
F	44	White	21	20	Y	Non compliance with clozapine	5	Non compliance	Haloperidol	Clozapine	Sulpiride
M	33	White	19	13	Y	Intolerance to clozapine — neutropenia	4	Ineffective	Haloperidol	Clozapine	Clozapine
F	23	White	16	2	N	Low ANC and ineligible for clozapine	6	Ineffective	Risperidone	Risperidone	Amisulpride
M	20	Black	12	5	Y	Intolerance to clozapine	11	Ineffective	Olanzapine	Clozapine	Consta
F	33	White	16	13	Y	Intolerance to clozapine pericarditis		Discharged on melperone	Zuclopenthixol decanoate	Discharged on melperone	Melperone

(continued)

Table 2. Continued.

Sex	Age (years)	Ethnicity	Age of onset (years)	Duration of illness (years)	Previous history of clozapine	Reason for melperone	Duration of melperone treatment (months)	Reason for stopping melperone	Antipsychotic before melperone	Antipsychotic after melperone	Current antipsychotic (July 2010)
F	24	White	16	3	Y	Insufficient response to clozapine	4	Discharged on melperone	Chlorpromazine risperidone	Not known	Lost to follow up
M	63	White	39	19	Y	Noncompliant with clozapine	4	Ineffective	Risperidone + Amisulpride	Clozapine	Risperidone
M	34	White	19	10	N	Refused clozapine	2	Ineffective	Zuclopenthixol Haloperidol	Clozapine	Olanzapine
M	46	Black	22	21	Y	Noncompliant	2	Refused	Risperidone	Flupentixol Decanoate	Flupentixol Decanoate
M	31	Asian	14	12	Y	Intolerance to clozapine – neutropenia	12	Ineffective	Olanzapine	Amisulpride	Amisulpride
F	41	Black	15	22	Y	Intolerance to clozapine. Sedation and weight gain		Discharged on melperone	Aripiprazole	Discharged on melperone	Melperone
ANC, absolute neutrophil count.											

Reason for discontinuation of treatment

The primary reason for discontinuation of melperone was lack of efficacy in 13/18 (72%) of patients. Four patients were poorly compliant and so melperone was stopped. In the remaining patient adverse effects were the main reason for discontinuation.

Tolerability of melperone

Melperone was reasonably well tolerated. One patient was discontinued due to ECG changes with a QTc interval of 498 ms. This patient also had akathisia. Another patient experienced extrapyramidal side effects at a dose of 300 mg daily. One patient refused to continue melperone due to gastrointestinal disturbance, eye pain and insomnia. No other serious adverse effects such as seizures or blood dyscrasias were reported.

Dose of melperone

Dose was in the range of 225–600 mg daily for all but one patient who was treated on a dose of 900 mg daily.

Discussion

Although the data on the efficacy of melperone in treatment-resistant schizophrenia are rather limited, it was initially perceived in our unit as ‘clozapine without blood tests’ and an option particularly for refractory patients who refused clozapine or those who were intolerant to the various adverse effects observed with clozapine.

The sample treated comprised a cohort of patients with severe refractory psychotic disorders, with a relatively early onset of psychotic illness and mean duration of antipsychotic treatment of 13 years. The majority of patients had been previously treated on clozapine, hence there is some selection bias although it is noteworthy that of the sample who discontinued melperone, more than half were subsequently re-exposed to clozapine with therapeutic benefits. This is in contrast to the findings by Meltzer and colleagues who found that nonresponders to melperone generally did not respond to clozapine treatment [Meltzer *et al.* 2001].

Of 21 patients treated, only three patients (14%) were discharged on melperone (the primary outcome measure). One patient was lost to follow up and two patients remain clinically stable on long-term treatment. Of these, one patient has a diagnosis of schizoaffective disorder, depressive type.

She had remained well on clozapine for 2 years but discontinued due to weight gain and sedation and suffered a relapse of her illness. She was tried on other medications without success and refused to go back on clozapine, hence the trial of melperone. She remains on melperone treatment in addition to sodium valproate, mirtazapine and venlafaxine in the community. The second patient on long-term treatment with melperone has a diagnosis of severe depressive episodes with psychotic symptoms. She was previously treated on clozapine but developed myocarditis. She failed to respond to other antipsychotic and antidepressant combinations as well as to ECT treatment. She is currently in a rehabilitation unit on treatment with melperone in combination with lithium, lamotrigine and mirtazapine.

Limitations

This is a rather small retrospective case notes review including only 21 patients. There may be bias in the sample population as more than half (13/21) the patients were treated in a tertiary referral centre and most had previous exposure to clozapine. There were no formal clinical assessments or ratings of psychopathology nor systematic evaluation of melperone tolerability and adverse effects.

Conclusions

This is the first attempt to evaluate the efficacy of melperone in the treatment of refractory psychotic illness in a naturalistic setting. Although it may be a worthwhile option in a very few patients, our results indicate a low overall success rate with melperone in patients with treatment refractory psychotic illness. Melperone should probably not be seen as an alternative for patients for whom clozapine is not suitable. Routine ECG monitoring should be considered at doses greater than 300 mg daily.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

None declared.

References

- Barbui, C., Signoretti, A., Mule, S., Boso, M. and Cipriani, A. (2009) Does the addition of a second antipsychotic drug improve clozapine treatment? *Schizophr Bull* 35: 458–468.
- Bjerkenstedt, L., Gullberg, B., Harnryd, C. and Sedvall, G. (1979) Relationships between clinical and biochemical effects of melperone and thiothixene in psychotic women. *Arch Psychiatr Nervenkr* 227: 181–192.
- Endicott, J., Spitzer, R.L., Fleiss, J.L. and Cohen, J. (1976) The global assessment scale. A procedure for measuring overall severity of psychiatric disturbance. *Arch Gen Psychiatry* 33: 766–771.
- Kane, J., Honigfeld, G., Singer, J. and Meltzer, H. (1988) Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry* 45: 789–796.
- Lahti, R.A., Evans, D.L., Stratman, N.C. and Figur, L.M. (1993) Dopamine D4 versus D2 receptor selectivity of dopamine receptor antagonists: possible therapeutic implications. *Eur J Pharmacol* 236: 483–486.
- Meltzer, H.Y., Bastani, B., Kwon, K.Y., Ramirez, L.F., Burnett, S. and Sharpe, J. (1989) A prospective study of clozapine in treatment-resistant schizophrenic patients. I. Preliminary report. *Psychopharmacology* 99(Suppl.): S68–S72.
- Meltzer, H.Y., Sumiyoshi, T. and Jayathilake, K. (2001) Melperone in the treatment of neuroleptic-resistant schizophrenia. *Psychiatry Res* 105: 201–209.
- National Institute for Clinical Excellence (2009) Schizophrenia: core interventions in the treatment and management of schizophrenia in adults in primary and secondary care (update). <http://www.nice.org.uk/>.
- Overall, J.E. and Gorham, D.R. (1962) The Brief Psychiatric Rating Scale. *Psychol Rep* 10: 812.
- Paton, C., Barnes, T.R., Cavanagh, M.R., Taylor, D. and Lelliott, P. (2008) High-dose and combination antipsychotic prescribing in acute adult wards in the UK: the challenges posed by P.R.N. prescribing. *Br J Psychiatry* 192: 435–439.
- Taylor, D.M. and Smith, L. (2009) Augmentation of clozapine with a second antipsychotic—a meta-analysis of randomized, placebo-controlled studies. *Acta Psychiatr Scand* 119: 419–425.

Visit SAGE journals online
<http://tpp.sagepub.com>

SAGE JOURNALS
Online