Asian Journal of Psychiatry 45 (2019) 50–52

Contents lists available at ScienceDirect

Asian Journal of Psychiatry

journal homepage: www.elsevier.com/locate/ajp

Short communication

How to identify and manage non-response to clozapine?

Mujeeb U. Shad[a,b,c,*], Emma Felzien[a], Kamalika Roy[a,b], Simrat Sethi[b]

[a] School of Medicine, Oregon Health & Science University, Portland, Oregon, United States
[b] Department of Psychiatry, Oregon State Hospital, Salem, Oregon, United States
[c] Samaritan Mental Healthcare System, Corvallis, Oregon, United States

ARTICLE INFO

Keywords:
Clozapine
Non-response
Identify
Manage

ABSTRACT

Clozapine is the only approved treatment for Treatment-Refractory Schizophrenia. Here we describe a case series of three hospitalized patients with clozapine nonresponse. One of them responded to clozapine after dose adjustments were made for an interaction between clozapine and ciprofloxacin. The other two cases remained clozapine nonresponders despite optimizing clozapine treatment. However, both these patients responded to other antipsychotic medications (APMs) with better tolerability than observed with clozapine treatment. This case series focuses on diagnosing a genuine from a pseudo-nonresponse to clozapine and to consider other APMs in genuine nonresponse before switching to invasive interventions, such as ECT.

1. Introduction

Since clozapine provides the only evidence-based treatment for patients with treatment-refractory schizophrenia (TRS) (Manu and Grudnikoff, 2016; Mukku et al., 2018), optimal efforts are warranted to confirm a true clozapine non-response before giving up on clozapine treatment. Failure to optimize treatment with clozapine may also explain a relatively high level of clozapine non-response in patients with TRS (Manu and Grudnikoff, 2016). This is especially true in patients, who respond unusually to the usually effective and tolerated doses of clozapine probably due to genetic variance in clozapine metabolism and/or drug-interactions between clozapine and concomitantly administered medications. The most cost-effective tool to help differentiate a true from a pseudo-non-response to clozapine is therapeutic drug monitoring (TDM) with optimal clozapine response ranging from 350 to 600 ng/mL (Greenwood-Smith et al., 2003; Schoretsanitis et al., 2018; Hiemke et al., 2018). The plasma levels may also help rule out medication non-adherence and the clozapine/norclozapine ratio can provide an estimate of cytochrome P450 (CYP) 1A2 enzyme status as it primarily mediates conversion of clozapine to norclozapine (Olsson et al., 2015). Assessment of clozapine non-adherence is one of the most important tasks at hand before making a valid diagnosis of clozapine non-response. Once clozapine nonadherence is ruled out, all efforts should be focused to optimize clozapine treatment. However, many clinicians prefer augmentation strategies even in patients with no or modest response to clozapine. This could be due to augmentation being a simpler and less risky process than switching antipsychotic medications (APMs), except in situations where bone marrow toxicity warrants clozapine discontinuation. Although augmentation strategies with APMs, glutamate modulators and mood stabilizers have been proposed in ultra-treatment resistant schizophrenia (Naguy and Alamiri, 2019), a recent metanalysis reported a low quality of supporting evidence for these clozapine augmentation strategies with the possible exception of APMs (Wagner et al., 2019).

Here we describe three cases of hospitalized patients, who did not respond to clozapine treatment and developed significant adverse effects. The first patients started responding to clozapine after dose adjustments were made to accommodate an interaction between clozapine and concomitantly administered, ciprofloxacin. The other two patients continued to be non-responders despite efforts to optimize clozapine treatment. However, these clozapine non-responders did respond to other APMs with significantly less adverse effects than those observed with clozapine treatment. These cases highlight the need to differentiate a true from a pseudo-non-response to clozapine and to consider non-clozapine APMs as one of the options to manage clozapine refractory schizophrenia.

2. Case history 1

A 45 years-old Caucasian female with a long-held diagnosis of schizophrenia was switched to clozapine after being diagnosed with treatment-refractory schizophrenia after multiple trials of APMs and hospitalizations. While clozapine was being gradually titrated up, patient developed severe urinary tract infection and was prescribed

* Corresponding author at: Oregon Health & Science University, Attending psychiatrist, Oregon State Hospital, 2600 Center St NE, Salem, OR 97301, United States.
E-mail address: shad@ohsu.edu (M.U. Shad).

https://doi.org/10.1016/j.ajp.2019.08.016
Received 10 January 2019; Received in revised form 28 August 2019; Accepted 29 August 2019

Table 1
Summary of patient demographics, diagnoses, treatment history, clozapine response versus non-response, and concomitant medications.

Pt. No.	Age/Sex	DSM-V diagnosis	Co-morbid conditions	Prior treatment failures with maximum doses for at least 4-6 weeks	Clozapine/Norclozapine Levels in ng/mL	Clozapine response versus non-response	Concomitant Medications
1	45yo/ F	Schizophrenia	Hyperlipidemia, COPD	Olanzapine, aripiprazole, quetiapine, perphenazine	− 431/207 without ciprofloxacin − 780/350 ng/mL when co-administered with ciprolfloxacin	Initial lack of response and significant adverse effects converted into response and reduction in adverse effects decreased after several dose adjustments	-Ciprofloxacin 500 mg for urinary tract infection x 2 wks.
2	32yo/ F	Schizoaffective disorder, bipolar type	Hypertension History of PTSD	Fluphenazine, ziprasidone	− 401/87 on 200 mg/day of clozapine	Sustained clozapine non-response despite optimal treatment and significant adverse effects. Eventually responded to iloperidone with good tolerability	-Clonazepam 0.5 mg in AM and 1 mg in PM for anxiety -Lithium 600 mg a day - Hydroxyzine 50 mg at bedtime for insomnia
3	41yo/ F	Schizophrenia	Hyperlipidemia	Olanzapine, fluphenazine, ziprasidone, divalproex sodium, lithium	− 440/101 on 175 mg/day of clozapine	Sustained clozapine non-response despite optimal treatment and significant adverse effects. Eventually responded to 8 mg/d of Risperidone with decent tolerability	-Divalproex sodium 1000 mg in AM and 1500 mg in PM for mood stability

500 mg a day of ciprofloxacin. The urinary symptoms responded but the patient started developing significant adverse effects, including extreme tiredness, fatigue, sedation, blurring of vision, sialorrhea and dizziness. Significant adverse effects along with lack of response with usually effective clozapine dose of 300 mg/day warranted request for clozapine and norclozapine levels, which were found to be extremely high at 823 ng/mL and 200 ng/mL, respectively. The dose was gradually reduced to 150 mg/day, which not only resolved adverse effects, but patient's psychosis and aggression also subsided within 2-weeks of the dose change. In the meanwhile, UTI resolved and ciprofloxacin was discontinued. However, within a week, patient relapsed with a significant drop in clozapine and norclozapine levels to 203 g mL and 87 ng/mL, respectively. At which point, clozapine dose was gradually increased back to 300 mg/day with clozapine and norclozapine steady state levels of 403 ng/mL and 189 ng/mL, respectively. In about 2 weeks patient regained her antipsychotic response along with a reduction in aggression without any significant adverse effects.

3. Case history 2

A 32-year-old Caucasian female with treatment-refractory schizoaffective disorder, bipolar type, continued to suffer from acute psychosis and significant behavioral disinhibitions despite clozapine/norclozapine levels of 401/187 ng/mL) at 200 mg/day for at least two months. She also suffered from heavy sedation, drooling, weight gain, retention of urine, and dizziness. This lack of efficacy along impairing adverse effects led to gradual discontinuation of clozapine and consecutive trials with fluphenazine and ziprasidone, without improvement of symptoms. Eventually, patient was gradually cross-titrated from clozapine to iloperidone. After two weeks of 12 mg two times a day of iloperidone, staff noticed discontinuation of auditory hallucinations and a significant improvement in patient's persecutory delusions along with improvement in insight into illness and active involvement in psychotherapy and social activities.

4. Case history 3

A 41-year-old Caucasian female with refractory schizoaffective disorder, bipolar type continued to have significant psychosis despite adequate treatment with several APMs and mood stabilizers. This treatment refractoriness resulted in a clozapine trial, which also failed despite achieving the recommended therapeutic clozapine/norclozapine levels of 440/101 ng/mL at a clozapine dose of 175 mg/day at steady state. In addition to lack of efficacy, increasing level of sedation and general malaise along with blurring of vision, constipation and tachycardia warranted multiple unsuccessful adjustments in clozapine dose with multiple blood draws to monitor clozapine levels, which resulted in patient refusal to take clozapine anymore. The patient had to be gradually titrated off clozapine and started on an oral dose of 3 mg a day of risperidone for efficacy and tolerability followed by a long-acting injectable, Risperdal Consta at 25 mg once every 2 weeks to address mediation nonadherence. Within a period of 3-weeks, patient showed dramatic improvement in her psychosis symptoms. Staff reported an improvement in her treatment engagement, mood regulation, and insight into her illness and need for the treatment.

5. Discussion

The first case illustrates how a clozapine non-responder can respond to clozapine after necessary dose adjustments to accommodate for altered clozapine levels due to a drug-drug interaction. In this case therapeutic drug monitoring (TDM) guided appropriate dose adjustments. Ciprofloxacin, a quinolone antibiotic, is known to competitively inhibit cytochrome P450 (CYP) 1A2 enzyme (Granfors et al., 2004), which provides primary metabolic pathway for clozapine demethylation to norclozapine (Olsson et al., 2015). Since this patient was being

treated with ciprofloxacin at the time clozapine was being titrated up, she developed toxic clozapine levels, which not only compromised its efficacy, but also resulted in clinically significant adverse effects. Multiple previous reports have described this interaction between ciprofloxacin and clozapine (Sambhi et al., 2007; Brownlowe and Sola, 2008; Raaska and Neuvonen, 2000; Meyer et al., 2016). However, clozapine dose reduction only worked while ciprofloxacin was administered, but patient decompensated after the antibiotic was stopped and the clozapine levels returned to baseline. Eventually, an increase in clozapine dose to 300 mg/day yielded therapeutic levels and a return in efficacy without significant adverse effects (Table 1).

As opposed to case 1, cases 2 and 3 demonstrate efficacy on other antipsychotic medications (APMs) after completely failing an adequate trial of clozapine. Both cases developed significant adverse effects without efficacy at an effective clozapine dose as determined by TDM (Table 1). One can argue that an augmentation strategy might have worked, but not only patients 2 & 3 lacked a response to justify augmentation, but more importantly, refused to take clozapine due to adverse effects or to allow blood draws for blood monitoring.

One of the reasons iloperidone may have been helpful in our second patient is her history of post-traumatic stress disorder (PTSD). Iloperidone is one of the most potent alpha-1 receptor blockers (Stahl, 2013), which is a mechanism that has been linked with reduction in nighttime intrusion symptoms and improvement in sleep efficiency in patients with PTSD (Green, 2014). This case exemplifies practical application of psychopharmacological profile of an APM to a patient comorbid symptom profile.

In our third case, it was risperidone that worked well. However, it is difficult to explain response to risperidone and not to a drug like clozapine, which is still considered a gold standard to manage TRS (Mauri et al., 2014). A theoretical explanation might be that our patient needed higher and more sustained blockade of D2Rs with risperidone than offered by clozapine (Mauri et al., 2014). In addition, risperidone, due to significantly lesser blockade of histamine and muscarinic receptors than clozapine is better tolerated and is less likely to result in adverse effects as commonly reported with clozapine, such as blurring of vision, constipation, tachycardia, heavy sedation and general malaise (Mauri et al., 2014).

The findings from this brief report are based on only three patient cases and should be interpreted with caution. In addition, the outcome of the trials is mostly relied on self-reports, or qualitative assessment by the patient care team lacking systematic and quantitative measurement of psychosis, such as the Positive and Negative Syndrome Scale (Kay et al., 1987). Nevertheless, to our knowledge, this is one of the few case series to underscore the need to identify a true versus misperceived clozapine non-response utilizing TDM. It is also rare to see reports of patients with clozapine non-response responding to other APMs. As reflected by case 2 & 3, a therapeutic response can be enhanced if a non-clozapine APM is matched with a patient's symptom profile and comorbidities.

6. Conclusion

This report illustrates diagnosis and management of clozapine non-response in three treatment-refractory cases with different outcomes, one of which actually converted into a responder after dose-adjustments were made using TDM, while the other two remained non-responders until switched to other APMs. Therefore, not only it is important to optimize clozapine treatment before labelling a non-response, but also not to give up on other APMs, which can be effective in some treatment-refractory patients before more invasive treatments, such as ECT are considered.

Authors' contributions

Corresponding author, Mujeeb U. Shad conceived the idea of presenting this interesting case report and all authors equally contributed to the drafting the manuscript. MS reviewed the final version of the manuscript. All authors read and approved the final manuscript.

Funding source

None.

Declaration of Competing Interest

None of the authors have any conflict of interest in relation to this case report.

Acknowledgements

Nursing and other unit staff that takes care of the patients.

References

Brownlowe, K., Sola, C., 2008. Clozapine toxicity in smoking cessation and with ciprofloxacin. Psychosomatics 49, 176.
Granfors, M.T., Backman, J.T., Neuvonen, M., Neuvonen, P.J., 2004. Ciprofloxacin greatly increases concentrations and hypotensive effect of tizanidine by inhibiting its cytochrome P450 1A2-mediated presystemic metabolism. Clin. Pharmacol. Ther. 76, 598–606.
Green, B., 2014. Prazosin in the treatment of PTSD. J. Psychiatr. Pract. 20, 253–259.
Greenwood-Smith, C., Lubman, D.I., Castle, D.J., 2003. Serum clozapine levels: a review of their clinical utility. J. Psychopharmacol. 17, 234–238.
Hiemke, C., Bergemann, N., Clement, H.W., Conca, A., Deckert, J., Domschke, K., Eckermann, G., Egberts, K., Gerlach, M., Greiner, C., Grunder, G., Haen, E., Havemann-Reinecke, U., Hefner, G., Helmer, R., Janssen, G., Jaquenoud, E., Laux, G., Messer, T., Mossner, R., Muller, M.J., Paulzen, M., Pfuhlmann, B., Riederer, P., Saria, A., Schoppek, B., Schoretsanitis, G., Schwarz, M., Gracia, M.S., Stegmann, B., Steimer, W., Stingl, J.C., Uhr, M., Ulrich, S., Unterecker, S., Waschgler, R., Zernig, G., Zurek, G., Baumann, P., 2018. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. Pharmacopsychiatry 51, 9–62.
Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276.
Manu, P., Grudnikoff, E., 2016. Clozapine for treatment-resistant schizophrenia. Am. J. Ther. 23, e1133–4.
Mauri, M.C., Paletta, S., Maffini, M., Colasanti, A., Dragogna, F., Di Pace, C., Altamura, A.C., 2014. Clinical pharmacology of atypical antipsychotics: an update. EXCLI J. 13, 1163–1191.
Meyer, J.M., Proctor, G., Cummings, M.A., Dardashti, L.J., Stahl, S.M., 2016. Ciprofloxacin and clozapine: a potentially fatal but underappreciated interaction. Case Rep. Psychiatry 2016, 5606098.
Mukku, S.S.R., Sivakumar, P.T., Varghese, M., 2018. Clozapine use in geriatric patients-Challenges. Asian J. Psychiatr. 33, 63–67.
Naguy, A., Alamiri, B., 2019. Ultra-treatment resistant schizophrenia- where do we stand? Asian J. Psychiatr. 44, 95–96.
Olsson, E., Edman, G., Bertilsson, L., Hukic, D.S., Lavebratt, C., Eriksson, S.V., Osby, U., 2015. Genetic and clinical factors affecting plasma clozapine concentration. Prim. Care Companion CNS Disord. 17.
Raaska, K., Neuvonen, P.J., 2000. Ciprofloxacin increases serum clozapine and N-desmethylclozapine: a study in patients with schizophrenia. Eur. J. Clin. Pharmacol. 56, 585–589.
Sambhi, R.S., Puri, R., Jones, G., 2007. Interaction of clozapine and ciprofloxacin: a case report. Eur. J. Clin. Pharmacol. 63, 895–896.
Schoretsanitis, G., Spina, E., Hiemke, C., de Leon, J., 2018. A systematic review and combined analysis of therapeutic drug monitoring studies for oral paliperidone. Expert Rev. Clin. Pharmacol. 11, 625–639.
Stahl, S.M., 2013. Role of alpha1 adrenergic antagonism in the mechanism of action of iloperidone: reducing extrapyramidal symptoms. CNS Spectr. 18, 285–288.
Wagner, E., Lohrs, L., Siskind, D., Honer, W.G., Falkai, P., Hasan, A., 2019. Clozapine augmentation strategies - a systematic meta-review of available evidence. Treatment options for clozapine resistance. J. Psychopharmacol. 33, 423–435.