Case Based Clinical Pearls: A schizophrenic case study

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ABSTRACT

Clinical pearls based on the treatment of a patient with schizophrenia who had stabbed a taxi cab driver are discussed in this case study. Areas explored include the pharmacokinetics of fluphenazine decanoate, strategies to manage clozapine-associated agranulocytosis, and approaches to addressing hyperprolactinemia.

KEYWORDS

Schizophrenia, fluphenazine pharmacokinetics, clozapine monitoring, hyperprolactinemia

INTRODUCTION

Forensic psychiatry is a subspecialty in the field of psychiatry in which medicine and law collide. Practiced in many facilities such as hospitals, correctional institutions, private offices and courts, forensic psychiatry requires the cooperation of health care and legal professionals with the common goal of helping patients become competent of their legal charges and returning to a productive life in the community. In contrast to general psychiatric patients, the clients in this field have been referred through court systems instead of general practitioners and are evaluated not only for their symptoms but also their level of responsibility for their actions.

These patients can be some of the most challenging to treat because of factors such as non-compliance, an extensive history of failed medication trials, and the severity of their mental illness. Some of the most severe mentally ill patients reside in forensic psychiatric hospitals and have spent much of their lives institutionalized. Treatment refractory schizophrenia, defined as persistent psychotic symptoms after failing two adequate trials of antipsychotics, is a common occurrence in forensic psychiatric hospitals and often requires extensive manipulation of medication regimens to obtain a desired therapeutic response. Like other patients, these patients may present with barriers to using the most effective treatment such as agranulocytosis, inability to obtain and maintain therapeutic drug levels due to fast metabolism, or bothersome adverse effects such as hyperprolactinemia. In treatment resistant patients, it may still be necessary to use these medications even when barriers are present due to a lack of alternative therapeutic options not previously exhausted. In addition to complex regimens, treatment plans for these patients often require trials of multiple medication combinations or unique exploitation of interactions and biological phenomena.

CASE

We report a forensic case study that exemplifies multiple clinical pearls that may be useful in patients with treatment refractory schizophrenia. A 31-year-old African American female presented to the emergency room escorted by law enforcement after stabbing a cab driver with a pencil. The patient stated she was raped by the cab driver and while in the emergency room stated that "dirty cops brought me here." She was admitted to the inpatient psychiatric unit to determine competency to stand trial for the assault of the cab driver. She had been in many previous correctional institutions with a known history of schizophrenia and additional diagnoses of amenorrhea, hyperprolactinemia, and obesity.

The patient's history was significant for auditory hallucinations and paranoid delusions beginning by age fourteen with a diagnosis of major depression with psychotic features. By age eighteen, she was diagnosed

with schizophrenia, paranoid type. She had multiple previous hospitalizations and a history of poor compliance as an outpatient. There was no known history of tobacco, alcohol, or illicit drug use. Her family history was significant for schizophrenia, diabetes mellitus, and drug use. The patient reported abusive behavior by her grandmother, who was her primary caretaker as a child.

During hospitalization, the patient continued to report sexual assaults, accusing both patients and staff of rape, and declined to participate in groups. She denied any visual or auditory hallucinations but continued to exhibit paranoid delusions. The patient was later found to be permanently incompetent to stand trial and was committed to the state's department of mental health for long term treatment of her psychiatric illness.

CLINICAL PEARL I – PHARMACOKINETICS

The patient was previously treated with fluphenazine decanoate intermittently for two years with difficulty obtaining the desired therapeutic response. After approximately two months of therapy, the patient presumably at steady state (~14 day half-life) still failed to demonstrate any clinical response. There is no conclusive evidence that fluphenazine levels correlate with clinical outcomes, however the psychiatrist had worked with this patient in the past and felt the lack of response in this situation justified a fluphenazine level.[1] The fluphenazine level was shown to be 2.2ng/ml (therapeutic range 0.5-3 ng/ml) while taking fluphenazine decanoate 50mg intramuscularly (IM) every two weeks. Increasing the target drug level to the upper edge of the normal range was warranted in this patient due to the persistent positive symptoms and a desire to continue using a long-acting injectable agent, which can ensure the delivery of medication in uncooperative and noncompliant patients. Fluphenazine is a high potency first generation antipsychotic that can improve positive symptoms of schizophrenia; however it is not effective in treating the negative symptoms. It was decided that the addition of a CYP2D6 inhibitor such as fluoxetine would not only provide increased levels of fluphenazine, but would also improve the patient's negative symptoms such as flat affect, anhedonia, social isolation and amotivation.[2] Thus, fluoxetine was given as 20 mg orally (PO) daily resulting in an increase of the fluphenazine level by 0.9 ng/ml (40%) after twenty two days of therapy to 3.1 ng/ml. One month later the fluphenazine decanoate dose was increased to 125 mg IM every two weeks (max 100mg/dose), with continued fluoxetine treatment, resulting in a supratherapeutic level of 3.6 ng/ml. Positive and negative symptoms only showed minor improvement. A 6-week study by Goff, et al. demonstrated an increase of up to 65% in fluphenazine serum concentrations in patients administered concomitant fluoxetine 20 mg/day.[2] In this case, the addition of fluoxetine safely and effectively elevated fluphenazine blood levels. Addition of an inhibitor may be beneficial in patients who are CYP2D6 ultra-rapid metabolizers, as was suspected in this patient.

Many complications, including prolonged jail time, can arise from forensic clients being non-compliant with their medications, which is the reason long acting injectables are often warranted. Our patient had a history of non-compliance and continued to experience positive symptoms despite treatment with fluphenazine. Therefore, the decision was made to try another long-acting antipsychotic injection. After reviewing the patient's chart, it was noted that a previous trial of oral haloperidol 30mg/day showed moderate improvement. Thus, after tolerability and efficacy was determined with oral haloperidol the patient was converted to haloperidol decanoate 300 mg (10-15 x oral daily dose of haloperidol) administered every three weeks beginning two weeks after discontinuation of fluphenazine decanoate 125 mg IM every two weeks. Fluphenazine levels approximately six weeks after its discontinuation (and two weeks after the discontinuation of fluoxetine 20 mg PO daily) were still supratherapeutic. Given that this patient had a fluphenazine level of 3.6 ng/ml near the time of haloperidol decanoate administration, it would be questionable whether another high potency antipsychotic would be of any additional benefit in comparison to the increased risk of extrapyramidal side effects (EPS). Data provided in one study showed fluphenazine decanoate as being detectable for up to 48 weeks after discontinuation.[3] Because fluphenazine decanoate can be detected for such an extended period of time, it leaves the patient at a continued risk for extrapyramidal side effects, especially if another antipsychotic is added shortly thereafter. In the forensic population, many patients have treatment refractory schizophrenia and the use of antipsychotics will need to be life-long. It is often common for these patients to be on multiple concurrent agents, increasing the risk for developing long-term extrapyramidal side effects. Therefore, it is important to minimize the risk of these symptoms whenever possible.

Despite supratherapeutic levels of fluphenazine, the psychiatrist felt it would be beneficial to continue haloperidol decanoate 300 mg every three weeks with increased monitoring for signs and symptoms of EPS.

CLINICAL PEARL II – CLOZAPINE AND AGRANULOCYTOSIS

During the current admission the patient continued to exhibit paranoid behavior and lack of insight, expressed anger, and disliked attending or participating in groups. Her medication history included haloperidol, fluphenazine, quetiapine, aripiprazole, asenapine, olanzapine, paliperidone, and sixteen days of clozapine therapy before leukopenia warranted discontinuation. Due to her extensive history of failed antipsychotics and the known superior effectiveness of clozapine, this patient was an ideal candidate for clozapine therapy. Additionally, because of the poor quality of life a declaration of incompetency would lead to, using the most effective possible agent is an important priority in forensic patients. Clozapine is the most effective antipsychotic based on the U.S. Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) and the UK Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS).[4,5] In regards to the significant blood draws and monitoring that is continuously required, clozapine can be a challenging medication to use in treatment refractory patients.

One strategy we are currently working on in our hospital to help increase the number of patients on clozapine is using a point of care (POC) lab device which will allow a complete blood count (CBC) plus 5-part differential to be completed by finger stick, instead of weekly blood draws that our nurses, physicians and, especially, patients dislike. The cost of the POC lab device is approximately $20,000, although upon completion of a cost analysis it was found that five CBCs per day would pay for the cost of the machine after one year. Many times, these patients can become irritated and violent when having their blood drawn, especially, if on a consistent basis. Repetitive blood draws was noted by our physicians to be the largest obstacle in using clozapine in our treatment refractory patients.

Our primary challenge in using clozapine for this patient was finding a way to maintain the absolute neutrophil count (ANC) within acceptable limits (≥1500mm^3), which is not uncommon for many patients. The Clozaril Patient Monitoring Services revealed 0.4% of patients had pre-treatment white blood cell counts (WBC) too low to allow initiation of clozapine. Of these patients, 75% were of African or African-Caribbean descent, likely due to the increased leukocyte marginalization that has been shown to be more prominent in these populations.[6] Of all neutrophils in the body, 90% reside in the bone marrow and the remainder circulates freely in the blood or deposit next to vessel walls (margination). The addition of lithium has been shown to increase neutrophil counts by 2000/mm^3 through demarginalization of leukocytes.[7] This increase is not dose –related but may require a minimum lithium level of 0.4 mmol/L.[8,9] Lithium therapy used to increase neutrophil counts may be especially effective in patients of African or African-Caribbean descent due to demarginalization of leukocytes. In this patient case, lithium 300 mg by mouth three times daily was initiated for fifteen days to increase the absolute neutrophil count from 1200/mm^3 to ≥ 1500/mm^3 for continuation of clozapine while the white blood cells continued to stay within appropriate limits of ≥3000/mm^3. It was soon realized that lithium was being cheeked, so liquid form was given, but discontinued after the patient continued to spit the medication out. Unfortunately, clozapine was discontinued thereafter as a result of noncompliance with the lithium causing failure to maintain appropriate white blood cell counts.

Another possible strategy for obtaining appropriate WBC and ANC levels that would enable clozapine continuation is to obtain blood samples later in the day. A study recently published compared the same set of patients having early morning blood draws to blood draws taken later in the day (mean sampling time - pre/post was 5 hours 24 minutes).[10] They showed a difference in the pre/post time change in WBC values being marginally significant (mean increase=667/mm^3, p=.07), with a significant difference (mean increase=1,130/mm^3, p=.003) between the pre/post time change in ANC values. ANC values were impacted to a greater extent by the time change than WBC values in this sample. Changing the time at which blood draws are taken during the day may allow for clozapine continuation by limiting the risk of pseudoneutropenia, however it remains the clinician's responsibility to discern between benign or malignant neutropenia.[10] It is recommended, for patients with WBC values trending down or below the predefined criteria, to have labs redrawn several hours after the morning lab before clozapine therapy is discontinued.[10] In this case study, obtaining the sample later in the day may have allowed our patient to continue clozapine therapy.

CLINICAL PEARL III – HYPERPROLACTINEMIA AND ASSOCIATED COMPLICATIONS

The patient in this case had additional diagnoses of amenorrhea and hyperprolactinemia. The diagnosis of amenorrhea prompted clinicians to obtain labs showing a prolactin level of 168.8 ng/ml (normal ranges: 3-20ng/ml for men; 4-25ng/ml for non-pregnant women; 30-400ng/ml for pregnant women). Lab monitoring of

prolactin levels is not necessary if the patient is not exhibiting symptoms such as disturbances in the menstrual cycle, galactorrhea, gynecomastia, retrograde ejaculation, impotence, oligospermia, short luteal phase syndrome, diminished libido or hirsutism. Monitoring guidelines published in 2004 by APA recommend screening for symptoms of hyperprolactinemia at each visit for the first year and then yearly thereafter. Mt. Sinai Conference Physical Health Monitoring Guidelines for Antipsychotics published in 2004 recommended monitoring at every visit for the first twelve weeks and then yearly.

Occasionally, practitioners are confronted with the dilemma of whether treatment of hyperprolactinemia is warranted in asymptomatic patients. In answering that question, a few things should be considered, such as the patient's risk for osteoporosis and/or cardiovascular disorders. If there are no physical issues of concern, then psychological issues should be addressed. Estrogen deficiency, which may occur with increased prolactin, mediates mood, cognition and psychopathology.[11] Results of several studies conducted in women with hyperprolactinemia have demonstrated increased depression, anxiety, decreased libido and increased hostility. Men shared similar problems but did not exhibit an increase in hostility.[12] The authors hypothesized that women demonstrated increased hostility as a protective mechanism for their offspring.

Antipsychotic medications have differing potencies in regards to hyperprolactinemia, which may help guide product selection. The most potent inducer is risperidone, followed by haloperidol, olanzapine, and ziprasidone.[13] Clozapine and quetiapine are truly sparing, and aripiprazole has even been shown to reduce prolactin levels.[14] Aripiprazole may be a viable treatment option in some patients with hyperprolactinemia. In one study, females with risperidone induced hyperprolactinemia taking therapeutic doses of risperidone 2 to 15 mg/day showed significantly lower prolactin levels from weeks 8 to 16 compared to baseline when administered aripiprazole (3, 6, 9, or 12 mg daily).[15] The mean percent reductions in prolactin concentration at 3, 6, 9, and 12 mg daily were approximately 35%, 54%, 57%, and 63%; however, there was little variability in prolactin levels above 6 mg daily of aripiprazole. Therefore, unless giving liquid form, aripiprazole 5mg daily should be an optimal dose in lowering prolactin levels. In this case, the patient exhibited the clinical symptom of amenorrhea, which correlated with an elevated prolactin level. The addition of aripiprazole 10 mg by mouth once daily decreased this patient's prolactin level by 51 ng/mL (30.3%) after twelve days of treatment.

If an elevated prolactin level is incidentally found, the patient should be monitored for symptoms and labs may be repeated. In patients exhibiting symptoms of hyperprolactinemia with a serum level <200 ng/mL, the antipsychotic dose should be reduced or the agent changed to a more prolactin-sparing drug.[13] If switching the agent is not reasonable, the addition of a dopamine agonist such as bromocriptine or cabergoline may be beneficial, as well as the antiviral agent amantadine.[16] In patients with levels >200 ng/mL, or with persistently elevated levels despite changing to a more prolactin-sparing agent, an MRI of the sella turcica should be obtained to rule out a pituitary adenoma or parasellar tumor.[13] Practitioners should be aware that prolactin levels may remain elevated for significant periods of time following discontinuation of a long acting causative agent due to continued D_2 receptor antagonism.[1] One study found elevated prolactin levels in patients who discontinued fluphenazine decanoate as much as six months after the last injection.[1,3]

CONCLUSION

In summary, we have discussed a few clinical pearls to be considered when working with treatment refractory patients with schizophrenia and outlined some unique aspects of treatment in forensic clients. First, we reviewed potential complications and concerns with using fluphenazine decanoate. In addition, we discussed that ultra-rapid CYP2D6 metabolizers may need an increase in dose when appropriate and/or an addition of an inhibitor. Secondly, patients with agranulocytosis that may benefit from clozapine may find improvement in WBC and ANC values with the administration of lithium and/or changing the time of day in which labs are drawn.

Lastly, hyperprolactinemia may result in not only physical symptoms but psychological symptoms as well. Also, health care providers should not only be cognizant regarding how and when to monitor for hyperprolactinemia, but also the various treatment options available, such as changing to less offensive agents, dopamine agonists, or adding low dose aripiprazole. This patient case exemplified multiple strategies that can be considered when managing treatment refractory patients in which alternative options for therapy are not readily available.

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