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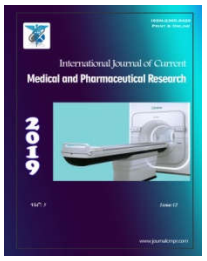

Research Article

CLOZAPINE-INDUCED PRIAPISM AND SUBSEQUENTVALPROIC ACID-INDUCED PRIAPISM A CASE OF A 40-YEAR OLD MAN WITH DIAGNOSIS OF SCHIZOAFFECTIVE DISORDER WITH NO PREVIOUS HISTORY OF PRIAPISM

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ABSTRACT

A 40-year old gentleman suffering from schizoaffective disorder since 2004, with co-morbid cocaine and cannabis abuse and parathyroidectomy was admitted to our psychiatric intensive care unit on 4th May 2018. Since admission he required eight episodes of seclusion due to extreme agitation. He failed to respond to several antipsychotics, however his mental state improved on the combination of zuclopenthixol decanoate 600mg/week, sodium valproate 2000mg/day and clonazepam 4-6mg/day. Because of the side effects of zuclopenthixol and past good response to clozapine; on 28th June 2018, he was commenced on clozapine, titrated to 300mg/day within 14 days. He made a marked progress after three weeks, however on 21st July, exactly 23 days, post clozapine he reported a prolonged, 12-hour painful erection. At the Accident and emergency (A&E) department, clozapine-induced priapism was confirmed; the patient received penile block and aspiration. clozapine was immediately stopped.

The patient refused to be re-challenged on clozapine and was instead commenced on risperidone (subsequently changed to paliperidone palmitate 150mg/monthly) alongside sodium valproate (2000mg/day). He made adequate progress, however, due to presence of negative symptoms and requiring further treatment on 20th August 2018 he was transferred to our local psychiatric rehabilitation unit. On 16th September 2018, he was taken to A&E again because of priapism that required drainage. This time, valproate-induced priapism was diagnosed; consequently, valproate was reduced from 2000mg/day to 1000mg/day. On 22nd September 2018, he had his 3rd priapism, which was again linked to sodium valproate, which was discontinued on 25th September. The patient continued paliperidone palmitate 150 mg/monthly and on 17th January 2019 discharged home. No further incidents of priapism have been reported since 22nd September 2018.

INTRODUCTION

Priapism (a prolonged, persistent and painful erection without sexual stimulation) is classified into non-ischemic (high flow) type, caused by penile or perineal trauma, cocaine, metastatic malignancy; and ischemic (low flow) type, usually caused by haematological disorders such as sickle cell anaemia, drugs, metabolic disorders and alcohol (Bivalacqua and Burnett, 2006). Among all cases of priapism, 15-41% are medication induced, out of which, 15-26% are linked to the use of antipsychotic medications (Thompson, Ware MR and Blashfield, 1990).

Clozapine, the first atypical antipsychotic developed (Crilly, 2007), has been termed atypical because, in contrast to typical antipsychotics, it does not produce significant extrapyramidal side effects, does not elevate prolactin levels, and does not induce tardive dyskinesia after long-term use (Baldessarini and Frankenburg, 1991). Clozapine is a dopamine D1, dopamine D2, 5-HT2A, alpha1-adrenoceptor, and muscarinic-receptor antagonist and in the United Kingdom (UK) is licenced for treatment of schizophrenia in patients unresponsive to, or intolerant of, conventional antipsychotic drugs (bnf.nice.org.uk).

According to the clozapine summary of product characteristics, clozapine-induced priapism is estimated <1/10,000 (Leyden-Delta, 2012). Only a few cases of clozapine-induced priapism have been reported (Seftel *et al*., 1992). The most likely mechanism of clozapine-induced priapism is an increase in parasympathetic tone through an α1-blockade obstructing the venous drainage from the corpora cavernosa of the penis (Anderson *et al*., 2010).

Valproic acid (sodium valproate) is a branched short-chain fatty acid derived from naturally occurring valeric acid.

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Valproic acid is used primarily in the treatment of epilepsy and seizures, but is also used in migraine, bipolar, mood, anxiety, and psychiatric disorders. Valproic acid acts on γ amino butyric acid levels in the brain, blocks voltage-gated ion channels (Ghodke-Puranik *et al*., 2013). In the UK, however, valproic acid is only licenced for treatment of epilepsy and treatment of manic episodes associated with bipolar disorder. Valproate is highly teratogenic and evidence supports that use in pregnancy leads to neurodevelopmental disorders (approx. 30-40% risk) and congenital malformations (approx. 10% risk). Valproate must not be used in women and girls of childbearing potential unless the conditions of the Pregnancy Prevention Programme are met and only if other treatments are ineffective or not tolerated, as judged by an experienced specialist. Use of valproate in pregnancy is contraindicated for migraine prophylaxis [unlicensed] and bipolar disorder; it must only be considered for epilepsy if there is no suitable alternative treatment(bnf.nice.org.uk).

Valproate-induced priapism is reported to be extremely rare and based on the Federal Drug Agency report from November 2019 (www.ehealthme.com/ds/valproate+sodium/priapism) of14,180people who took sodium valproate, eight (0.06%) reported priapism. A single case of valproate-induced priapism has been reported in a 48-year old gentleman with bipolar disorder (Bansel and Gupta, 2013). Altered expression of α1 adrenergic receptors or phosphodiesterase enzyme may be the possible mechanism behind sodium valproate induced priapism (Phiel, 2001).

DISCUSSION

Priapism has been reported in patients treated with various antipsychotics, including typical and atypical antipsychotics as ziprasidone, risperidone, quetiapine aripiprazole, olanzapine and clozapine. There have been several reports in which the problem reoccurred in re-challenge with another antipsychotic (Brichart *et al*., 2008). Moreover, evidence suggest there is no correlation between dosage or duration of antipsychotic medications and priapism (Thompson, Ware and Blashfield, 1990). Valproate-induced priapism is reported to be extremely rare, affecting about 0.06% of patients taking this medication. As priapism is thought to be caused by blockage of alpha-1-adrenergic receptors, it is likely to recur with another antipsychotic with an alpha-1-adrenergic capacity is used. Therefore, in patients with a history of antipsychotic-induced priapism, a drug with low peripheral alpha-adrenergic affinity should be used. It is important to stress that patients may find it embarrassing to openly discuss priapism, therefore require asking specifically about priapism. Furthermore, patients should be informed about the possibility of recurrence of priapism and if it reoccurs they should immediately seek medical advice as priapism is a medical emergency.

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