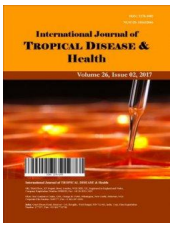

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A Report of the Ruinous Effects of Pentazocine Abuse in a Female Adult with Sickle Cell Anaemia Seen in Uyo, Niger-Delta Region of Nigeria: An Urgent Call to Action

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Authors' contributions

This work was carried out in collaboration between all authors. Author ISA contributed substantially to the conception and design of study, acquisition of images, drafting of the article, revising it critically for important intellectual content, final approval of the version to be published. Authors EHJ and EEU contributed substantially to the conception of study, acquisition of images, drafting of the article, final proofreading of the version to be published.

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Case Report

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ABSTRACT

Painful crisis is the commonest and most distressing clinical manifestation of sickle cell anaemia (SCA), thus prompt and adequate analgesia should be provided to ameliorate the suffering of the patient. Pentazocine is a potent opioid analgesic with mixed receptor activities commonly used in the management of pain in SCA patients. Its abuse among SCA patients has remained a daunting challenge in medical practice worldwide, especially in developing economies like ours. However, reports on opioid abuse or dependence among SCA patients in our environment are inexistent. This report sets out to highlight the addictive potential of pentazocine and the complications associated with its abuse in SCA patients. We report a case of a 40-year-old known SCA female with a five-year history of excessive use of parenteral pentazocine. She commenced self-injection

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of pentazocine following a previous admission in a private hospital on account of bone pain crisis. Other analgesics such as diclofenac, ibuprofen, piroxicam and tramadol were not efficacious in alleviating her excruciating pain but the administration of parenteral pentazocine provided her with quick and complete relief, hence the beginning of her dependency. She had a hankering desire to use the drug which she used on daily basis. Initially, she injected 30-60 mg (1 – 2 ampules) of pentazocine per day but in the last one month before presentation in our facility, she increased the dose of the drug to 270 mg (9 ampoules) daily. She developed multiple cutaneous and musculoskeletal complications. A diagnosis of pentazocine dependence in a sickle cell anaemia patient was made. She was admitted and jointly managed by the Haematology, Orthopaedic and Mental Health Teams. We hereby advocate effective sensitization of healthcare providers, SCA patients, their caregivers and the society at large about the risks and complications of pentazocine abuse. This is to espouse the fervid need to exercise caution with pentazocine prescription and use. As much as possible, oral formulations, when deemed necessary, should be recommended since most of the observed physical complications occurred apparently as a result of parenteral administration of the drug. Lastly, pentazocine should be categorized as a controlled drug with stringent measures in place to regulate its sales in our environment.

Keywords: Sickle cell anaemia; painful crisis; pentazocine abuse; opioid; tramadol.

1. INTRODUCTION

Sickle cell anaemia (SCA) is a form of sickle cell disease (SCD), which is a heterogenous group of autosomal co-dominant qualitative haemoglobin disorder [1]. SCA is the most prevalent and severe form and results from inheritance of two homologous haemoglobin S (Hbs) alleles, affecting 60% to 70% of people with SCD. Other SCD genotypes include haemoglobin SC disease, haemoglobin SD disease, sickle cell beta thalassaemia among others [1,2].

SCA is a chronic, monogenic disorder of increasing global health importance with highly diverse clinical manifestations traceable to its peculiar pathologic nature [3]. It is marked by acute exacerbations of bone and visceral pain secondary to vaso-occlusion and ischaemia. The pain is characteristically excruciating and debilitating, and represents an important cause of frequent hospital visits and admissions [4,5]. Elander et al. [6], in their study among SCA patients who were substance dependent, found that pain-related symptom constituted 88% of all symptoms. Similar findings have been reported by other workers [7,8]. Fluid therapy and analgesia are essential aspects of sickle cell pain crisis management [9]. Choice of analgesia depends on the severity of the pain and the patient's prior analgesic needs or history and usually includes opioids or non-steroidal anti-inflammatory drugs (NSAIDs) either alone or in combination [10]. The protracted use of NSAIDs in SCA patients is strongly discouraged because of the risk of NSAID – induced vasoconstriction of the renal vasculature and consequent chronic kidney disease coupled with the already existing background propensity to develop nephropathy [11,12]. In SCA, NSAIDs are usually prescribed in the management of mild pain while moderate to severe and chronic pain often require the opioids [9,12]. In difficult cases, where pain is unremitting after 48 hours of adequate analgesia, exchange blood transfusion is the therapy of choice [9]. Other treatment modalities for intractable pain in SCA include nerve block, physiotherapy, orthopaedic intervention or surgery, and cognitive behaviour therapy [9,13]. The clinician has the duty to ensure prompt and effective pain control and in the same vein should be wary of exceeding the medical needs of the patients [9].

Pentazocine, a synthetic opioid analgesic of the benzomorphan family [14], is usually the first choice opioid in managing acute and chronic painful episodes in sickle cell anaemia patients, followed by tramadol, dihydrocodeine and morphine in that order [9,15]. Pentazocine lactate, the intramuscular/intravenous injectable form is readily available in Nigeria and other African countries and is widely used for pain relief. It has a mixed receptor action and acts by binding to kappa, mu and delta (α,μ & δ) receptors in the sensori-neural system and other tissues [14,16]. It is worthy of mention that pentazocine was introduced in 1967 to address the problem of lack of a potent analgesic that had no unsavoury effect such as drug dependence, a goal that has been practically unachieved. Pentazocine has an estimable analgesic action although its prolonged parenteral use or abuse has been associated with several adverse effects including, skin fibrosis, ulceration, abnormal pigmentation, fibrous myopathy and contractures

[17,18,19]. In the current world health organization (WHO) analgesic ladder and guidelines in pain control, pentazocine has been omitted due to its tendency to cause dependence and the aforementioned deleterious effects as well as other notable ones [20,21]. It is interesting to note that phenotypic and genotypic variations exist among different individuals with SCA and even occur over time in the same patient [3]. This may hamper fervent efforts at achieving adequate analgesia over time with regards to management of sickle cell pain crisis.

Pentazocine abuse refers to a psychological dependence on pentazocine with associated craving, lack of capacity to limit or stop its consumption, the emergence of a withdrawal syndrome during cessation and the compulsive use aimed at achieving euphoric effects despite obvious harm [22]. This addiction may lead to devastating consequences associated with unconscionable craving in spite of adequate dosing and pain control with other analgesics. The use of pentazocine as a sole agent in the treatment of chronic pain has been identified as an important cause of addiction [23].

Cases of pentazocine abuse have been reported worldwide. The menace has also been observed among sickle cell anaemia patients in Nigeria [24,25]. Many patients with SCA already have a poor quality of life and low life expectancy [9]. Thus, unwholesome practice such as pentazocine abuse could exacerbate the bleak clinical outlook in SCA patients in a developing country like ours where access to appropriate and adequate healthcare services is suboptimal. In our environment, a significant number of these patients, purchase the drug "over the counter". Efforts have been made in some countries to exterminate the abuse of pentazocine. The intervention strategies include classifying pentazocine as a controlled drug to prevent unwarranted access to the drug and the production of pentazocine brands containing naloxone to counteract the addictive property [21,22].

In spite of the foregoing, the cases of pentazocine abuse in Nigeria, especially in SCA patients, are increasing and no tangible measures have been put in place to rein the unnerving trend. Moreover, there are no reports of pentazocine abuse as well as its associated morbidities in SCA patients in our locality probably because of low index of suspicion and due to patients' unwillingness to volunteer such information. This report is therefore designed to highlight some of the physical complications and socio-economic challenges associated with pentazocine abuse in SCA patients as well as evaluate the necessity for stringent legislation to regulate the procurement of the drug in our country.

2. CASE REPORT

A 40-year – old unemployed university graduate residing in Uyo, Nigeria presented to the Haematology clinic, University of Uyo Teaching Hospital with a history of recurrent fever, difficulty in breathing, chest pain and painful swollen arms and thighs. She was a known sickle cell anaemia patient and had an intense desire to use pentazocine which she injected intramuscularly (occasionally intravenously) herself on daily basis.

She started abusing pentazocine 5 years prior to presentation, following a bone pain crisis for which intravenous pentazocine (first ever dose) was prescribed by her family physician for pain relief. Then she received 30mg of pentazocine daily for 5 days and she reported having profound relief after receiving the injection with all her pain disappearing. After the treatment, she began to abuse the medication by self-administration; she injected the drug into her buttocks, upper limbs, lower limbs, abdomen, the chest and neck. In the last 1 month, she increased the dose of the drug from initial 30-90 mg daily to 270 mg daily.

Initially, she spent about one thousand naira (about $3.00) per day to purchase pentazocine from pharmacies without doctor's prescription which increased to about nine thousand naira (about $25,000) with increasing amount of pentazocine (30 mg to 270 mg). To sustain her drug using habit, she sourced money by stealing from her mother, or lying to strangers, friends and her three older siblings who reside in London to give her money for other purposes. She mismanaged the funds given to her and found herself unable to take care of her basic needs such as buying clothing, shoes and consistently depended on her mother and siblings for her daily needs. She had previously experienced the euphoric effect of pentazocine when it was first used by her family physician to alleviate her pains. She enjoyed this effect and was always looking forward to the next dose. Whenever she did not use the drug, she would be dysphoric, restless and insomniac. This was a distressing experience for her, so she ensured that the drug

was always handy. She had to use the drug on a daily basis to be able to have a pleasant day despite evidence of infection at injection sites which sometimes required prolonged antibiotic therapy, incision and drainage.

She was diagnosed with SCA at the age of 2 years, and was neither compliant with proguanil hydrochloride, folic acid and other prescribed medications nor regular with follow-up visit. Prior to her abuse of pentazocine, she experienced crisis about 8-9 times annually, which was relieved with tramadol or diclofenac.

The patient was admitted 2 months ago on account of similar complaints for 2 weeks at our facility and comanaged by the Haematologist, Orthopaedic Surgeon and Mental Health Physician. She was discharged to continue treatment as an outpatient with weekly psychological sessions but was not abstinent and did not keep follow-up clinic appointments.

Fig. 1. Ulcers, scars and lymphedema

Fig. 2. Flexure deformity of the spine

Fig. 3. Hyperpigmented macules, ulcers and lymphedema

Fig. 4. Lymphedema and flexure deformities of the digits

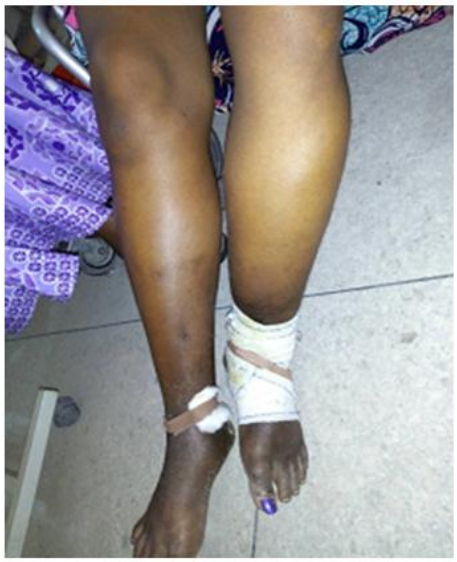

Fig. 5. Ankle ulcers and lymphedema

Figs. 1–5. Images of some of the physical complications are shown

She was the only SCA patient in a monogamous setting of four children. She lived with her mother, a 72-year-old retired primary school teacher, in a duplex. Her father died 20 years ago of unknown cause. In spite of the frequent interruptions in her school programme by sickle cell crises, she was able to graduate from the university with a Bachelor of Arts degree (Second class honours, lower division 2.2) in Nigerian languages. She was single and had no serious relationship with the opposite sex all her life which she ascribed to the disadvantages imposed by her chronic illness. She, however, maintained a good social rapport with her peers.

On mental state examination, the patient was well-groomed, extremely anxious but cooperative. She had no hallucinatory experience or behaviour suggestive of it. Her speech was coherent. There was no abnormality in stream, form, content and possession of thought. Her cognitive functions were normal. She had full insight into her problem.

Physical examination at presentation revealed a young woman, febrile (38.6%), markedly pale, icteric, dehydrated, in severe respiratory distress evidenced by nasal flaring, intercostal and subcostal recessions, respiratory rate of 40 cycles per minute, pulse rate of 110 per minute, bossing of the forehead, long spiny extremities, bilateral pitting edema of the legs and distended abdomen with tender hepatomogaly. She had discharging sinuses in the neck, anterior chest wall and both upper arms, bilateral ankle ulcers, hyperpigmented indurated macules and scars (from needle pricks) on the anteromedial aspects of both arms and massive lymphedema of the upper and lower limbs, fixed contractures and deformities of the spine, limbs (and digits) with lordotic gait and varying degrees of loss of joint movement.

The following diagnoses were made: Anaemic heart failure, chronic osteomyelitis with severe sepsis and pentazocine dependence in a sickle cell anaemia patient. She was promptly admitted and given oxygen via intranasal prongs. Urgent haemogram showed packed cell volume (PCV) of 5%, white blood cell count (WBC): 38 x $10^9/_L$, white blood cell differential: Neutrophils – 60%, lymphocytes, 35%, eosinophils – 3%, monocytes – 2%, basophils – 0%; platelet count (PC): 171 x $10^9/_L$. Peripheral blood film (PBF) review revealed numerous irreversible and reversible sickle cells, a few nucleated red cells, occasional target cells and severe neutrophilic toxic granulations with left shift up to the metamyelocyte stage.

She was transfused with packed red cells and commenced on intravenous ceftriaxone and metronidazole among other treatment plan.Urine and wound swab microscopy/culture & sensitivity (M/C/S) showed no growth. Serum urea, creatinine and electrolytes were within normal limits. Total biliribin and conjugated bilirubin were elevated, 90.3µmol/L (2-17) and 69.7µmol/l (2-7), respectively. Abdominal ultrasound scan revealed marked hepatomegaly, mesenteric lymphadenopathy and gallstones, with evidence of extrahepatic bile duct obstruction. Chest radiograph and Xray of the limbs were requested but not done. Doppler ultrasound of the upper and lower limbs revealed deep vein thrombosis involving the left common femoral vein and the superficial femoral vein. Malaria parasite test was negative. Viral serology (HIV, HBs Ag and Anti-HCV Ab) results were negative. On account of the above findings, the Cardiologist, Gastroenterologist, Orthopaedic Surgeon and Mental Health Physician were invited to review the patient. Sadly, patient's condition deteriorated and this continued till her death one hour after admission. Autopsy request was vehemently declined by the relatives because of the cultural belief that ancestral spirits prohibit mutilation of the body and that possible retaliation would take place, making the siblings die prematurely.

3. DISCUSSION

Authors across the globe have reported pentazocine abuse in different individuals including patients with SCA [17-19,24,26]. However, the phenomenon is not only underreported in patients with SCA in Nigeria but most workers have not documented the various physical complications and socioeconomic effects of parenteral pentazocine abuse on the patients with SCA. That being said, it is a major public health issue in our country, where it continues to be prescribed by clinicians for management of both acute and chronic pain in SCA patients. In the present report, majority of the complications occurred as a result of abuse of parenteral pentazocine. Oral formulations of pentazocine are barely used in our practice owing to their scarcity. Nevertheless, it is rational to deduce that these physical complications would be unlikely with oral

formulations of the drug, taking into cognizance the pathological basis of the complications [17-19,25,27]. Based on our findings, we strongly entertain the diagnosis of parenteral pentazocine abuse in any SCA patient presenting with multiple ulcers, scars and sinuses at sites other than the ankles, lymphedema, fibrous myopathy, contractures and fixed joint deformities.

The hyperpgimented macules, skin indurations, ulcers and scars observed in the patient could have resulted from poor injection techniques, precipitation of the drug [27] with local ischaemia and possibly infections culminating in tissue necrosis. Due to the repeated injections and background immunological deficiencies in SCA, the ulcers usually run a chronic course with healing by fibrosis and scarring. These findings are not uncommon in SCA patients who abuse pentazocine and have been reported by other workers [17-19,24-27]. Management of these complications usually require hospital admission, antibiotic therapy, daily wound dressing, hydroxyurea therapy, zinc therapy, skin grafting, hypertransfusion and automated red cell exchange [24-27]. It is to be noted that the patient was offered these therapeutic options but she did not make the best use of them owing to her infrequent hospital visit and non-compliance with treatment.

Massive lymphedema of the upper and lower limbs was one of the most striking and cosmetically disfiguring physical complication observed in the patient. This could have resulted from blockade of the lymphatic drainage by inflammation, myopathy, ulceration, scarring and fibrosis following repeated injection of pentazocine. This is one complication that has been extensively documented in other related works [17-19,24,25,27,28]. Systematic review of published literature shows filariasis to be the most common cause of secondary lymphedema in the developing world while cancer therapy is the leading cause of the condition in developed climes [27-29]. Regrettably, parenteral pentazocine abuse appears to be the most frequent cause of lymphedema in patients with SCA in our country [24,25,28]. There is no cure for lymphedema currently. Available therapies are essentially palliative and include physiotherapy and use of bandages to manage and reduce the swelling [30]. Surgical interventions such as volume reducing surgery and lymphatic microsurgery are not routinely performed [31].

Some form of fibrous myopathy was noted in our patient. However, we did not confirm the diagnosis using biochemical, radiological and histological investigations, but history and examination findings were highly suggestive. This complication has been grossly underreported generally in spite of its notoriety of being a common sequela of prolonged parenteral pentazocine abuse. The underlying pathogenetic mechanism is not well elucidated but easy precipitation of pentazocine in the neutral or slightly alkaline pH of extracellular fluid with attendant inflammation and fibrosis may play a role [27]. The fibrous myopathy contributed to the contractures and deformities observed in the patient. The contractures accounted for the fixed flexion and extension in some of her joints resulting in impaired movement and gait abnormality. Management of these complications comprises detoxification and withdrawal of pentazocine, use of corticosteroids or nonsteroidal anti-inflammatory drugs, collagenases, physiotherapy, myotomy or myectomy and muscle lengthening procedures [18]. However, there may be permanent disability particularly if the affected muscles are fibrotic and non-functional [32].

The patient was single and unemployed as earlier stated and we believe that her SCA status may have been responsible for these. The major physical complications of pentazocine abuse may make her unattractive to a prospective spouse or employer. Moreover, her unmarried status may engender a vicious cycle of pentazocine abuse because of the absence of a partner's restraining influence. On the other hand, the unpredictable and frequent illness episodes and hospital visits and admissions may significantly contribute to her inability to keep a relationship or job.

Astoundingly, the patient had high daily doses of pentazocine injections for a long period. The maximum dose of pentazocine that she injected daily was 270 mg (9 ampoules). She spent an insane amount of money to sustain the unhealthy habit. The highest amount she ever expended monthly on purchase of the drugs was noted to be NGN 270,000. In order to have a steady supply of the drug, the patient told a lot of lies to get money from family members, friends and even strangers. She, however, denied ever engaging in unchaste relationships or anti-social activities in return for money though she admitted to using forged prescriptions and sometimes did not present prescription papers at all to access

the drug from pharmacies and drug stores. These illicit transactions are possible because there has been apparently no stringent regulations on procurement of the drug, no effective system to verify drug prescriptions and no austere punishment or penalties for erring healthcare providers and their clients. Unfortunately, pentazocine is readily available as over-the-counter drug in our society where it is sold in almost every drug store or pharmacy illegally without medical prescription. In view of this, it is plausible to posit that the abuse of injectable pentazocine may be more common than reported. Policy makers should therefore make legislation on indiscriminate prescription and use of pentazocine. Pentazocine should be made strictly a prescription drug with stiff punishment meted out to anyone who flouts the law.

Clinicians should be cautious about prescribing injectable pentazocine. After prescribing the pentazocine, clinicians should keep careful watch for possibility of abuse. Exceedingly worrisome is the fact that many SCA patients feign pain after genuine pain has subsided in order to continue receiving prescription of pentazocine or self-inject it. At this point, the clinical acumen of the physician is highly required to differentiate genuine pain from simulated pain in SCA patients with pentazocine abuse. It is therefore germane for Health Care Providers to draw up a comprehensive guideline on how to manage the pain, by understanding the cause of the pain, recognizing the difference between acute and chronic pain and types of analgesic to prescribe. Mild forms of analgesic such as paracetamol, ibuprofen, diclofenac should be used first for acute and chronic pain before considering stronger analgesics such as tramadol, codeine, pentazocine, morphine that have been found to have high potential for addiction. And when a stronger analgesic is considered to be the preferred option due to the nature of the pain, the duration of use should be relatively brief and the patients and their relatives should be oblivious of the identity of the drug to avoid abuse of any form. To further foster these lofty preventive strategies, the patients are encouraged to attend clinics regularly, even during the steady-state periods. This helps in close monitoring and treatment of painful crises and other morbidities to prevent the patients from indulging in self-medication practices with attendant grievous consequences, which are common in adult SCA patients who use multiple prescription drugs for management of symptoms related to their disease and may not receive routine hospital care [20].

Furthermore, a comprehensive psychological assessment should always be carried out for all patients with SCA who abuse pentazocine in order to determine any behavioural problems like antisocial behaviour, malingering, drug dependence and so on. Subsequently, SCA patients who fulfill the diagnostic criteria for 'Mental and Behavioural Disorder due to use of Opioids' according to the International Classification of Mental and Behavioural Disorders (ICD-10) should be referred to a detoxification unit and thereafter rehabilitation unit in a mental health facility where their bone pain crises and drug addiction problem will be expertly managed. Patients could also be referred to a self-help group (sickle cell club) after rehabilitation program, where they would ventilate their feelings and encourage one another. This will improve their quality of life and discourage them from indulging in substance abuse.

The physical complications of pentazocine abuse pose ominous psychological and socioeconomic challenges to the SCA patients, their families and the society as a whole. Despite the huge financial outlay incurred in the management of the complications, the attainment of their complete resolution has remained an onerous task.

4. CONCLUSION

We advocate effective sensitization of healthcare providers, SCA patients and the caregivers and the society at large about the risks and complications of pentazocine abuse. This is to underpin the need to exercise utmost caution with pentazocine prescription and use. Oral formulations, whenever they are deemed necessary, should be recommended in lieu of the parenteral therapies since most of the observed complications were apparently due to the parenteral administration of the drug. Guidelines and regulations on the procurement and use of the drug in our country should be provided by the appropriate authorities with strict measures in place to enforce the punishment of anyone who runs afoul of the regulations. Lastly, any SCA patient presenting with the highlighted physical complications should be considered as a case of pentazocine abuse until there is considerable clinical evidence to the contrary.

CONSENT

The written informed consent for usage of the deceased's images for this report was provided by her mother.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the authors.

CASE HISTORY

Patient and her relatives gave the history.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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