MORPHINE-INDUCED RESPIRATORY DEPRESSION IN AN ADULT SICKLE CELL DISEASE PATIENT

Job G. Otokwala[*1], **Richard I. Oko-Jaja**[2]
[1]Intensive Care Unit, Department of Anaesthesiology, University of Port Harcourt and University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria.
[2]Renal Unit, Department of Medicine, University of Port Harcourt and University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria.

***Corresponding author:** Job G. Otokwala
Email:job.otokwala@uniport.edu.ng

ABSTRACT
Background: *Sickle cell disease (SCD) is a common genetic abnormality in Nigeria. One of the commonest complications associated with it is vaso-occlusive crisis which results in both acute and chronic painful states. Pain relief is an integral part of the management of vaso-occlusive crisis.*

Opioids such as morphine and hydromorphone, and the non-steroidal anti-inflammatory analgesics are routine analgesics in this setting due to the ease of access, global availability and cost. For such chronic painful states, one of the major concerns about the use of opioids is the risk of drug dependence and addiction. Morphine has increased plasma clearance rate from increase in hepatic blood flow, renal blood flow and glomerular filtration rate in some adult sickle cell disease patients. Therefore, risk of morphine toxicity increases in the presence of renal impairment. This was observed in this index patient (a known SCD patient) with diabetes mellitus and acute kidney injury, and had been on both hydromorphone and morphine and suddenly developed severe respiratory depression.

Conclusion: *Adult Sickle cell disease patients may be complicated by renal impairment which could affect drug clearance. This should be considered in managing sickle cell patients.*

Keywords: *Morphine, respiratory depression, sickle cell disease.*

CASE PRESENTATION

A 40-year old lady with a medical history of truncal obesity, type 2 diabetes mellitus and sickle cell disease (SCD), on holiday/social visit from overseas. She was referred for haemodialysis on account of reduced urine output, speech difficulty, sudden loss of consciousness, and left-sided body weakness. Summary report of available ancillary investigations: CT brain: mid brain infarct only, HB 8.2g%, WBC (43 x 10^3/l), HbA1c 6.6%, Urinalysis: red blood cells of 298mg/dl. Creatinine 6.35mg/dl, Urea 122.35mg/dl, Sodium 133mmol/l,

CC BY NO SA

Potassium 4.3mmol/L, Chloride 105 mmol/l, Total serum protein 6.4g/dl, Serum albumin 2.8g/dl. Alanine transaminase 308.6*iu*/l, Aspartate transaminase 575iu/l, Alkaline phosphatase 7iu/l. Total bilirubin 1.23mg/dl. Conjugated bilirubin 0.60mg/dl.

Past medical history revealed multiple blood transfusions and sessions of haemodialysis.

Drug History: SC Clexane 40mg daily, SC Regular insulin, SC Lantus insulin 33iu nocte, IV Metoclopramide 10mg OD, tablets Omeprazole 40mg BD, Dicyclomine 20mg 6hourly, Folic acid 5mg daily.
Hydromorphone 8mg 8hourly, Losartan 25mg daily, Magnesium oxide 400mg daily.
Morphine sulphate ER 100mg (a tablet) 8hourly, Trazodone 100mg nocte, Vitamin B12 100mcg daily, Aspirin 325mg daily.

Clinical examination at the intensive care unit showed an obese unconscious lady, with GCS of 9/15 (eye opening 3, best verbal response 2, best motor response 4). Pupils were pin point. She was icteric and pale. PR 104b/min. BP 80/40mmHg, RR 6cycles/min.

In view of the drug history and renal impairment, morphine toxicity was suspected. Intravenous naloxone at 800micrograms diluted and administered as a slow IV infusion was given with good effect. Respiratory rate improved spontaneously and the patient became fully conscious to give her history. The blood pressure was supported with dopamine. The patient was administered five sessions of haemodialysis. She was discharged home 4 days after the last haemodialysis session.

DISCUSSION

Sickle cell disease affects many organs in the body and has the tendency to be complicated with multisystem organ failure especially in older sicklers.[1] The kidneys are not spared as sickle cell nephropathy is common.[2] The need for routine screening of adult sicklers for renal abnormalities was advocated by Bolarinwa *et al*, found to have an asymptomatic onset in childhood with a tendency to progress to CKD in adults.[3]

Pain arising from vaso-occlusive crisis was first described by Africanus Horton 1872.[4] Is often acute and episodic or chronic caused by avascular necrosis in musculoskeletal system and other systems. Pain is a common presentation of SCD patients, and it has been reported that pain relief is often inadequate from previously utilised measures[5] necessitating the frequent combination of analgesics.

This index patient presented with sepsis on a background of chronic kidney disease as evidenced by the ancillary laboratory results. The use of dihydromophone and morphine tablets at doses highlighted above on a background of chronic renal failure resulted in the respiratory failure, often associated with morphine toxicity.

Opioid sensitivity is a key determining factor in the choice of opioids in order to avoid overdose and respiratory depression.[5] Slow release morphine is usually administered twelve hourly and should not be administered at the same time as hydromorphone but with other analgesics with different modes of action. Edward *et al*

had reported the possibility of morphine metabolism to hydromorphone in a cohort of chronically treated patients with morphine.[6,7] This observation could underlie the experience of this patient who obviously combined oral morphine and hydromorphone at the stated doses on a background of CKD.

Metabolites of both drugs are excreted through the kidneys and would lead to increased risk of toxicity. Kotila *et al* and colleagues[8] had reported the case of a SCD patient administering pentazocine along with pethidine to ameliorate pain. This highlights the problems of opioid abuse among SCD patients.[9]

The management of these patients requires a high index of suspicion and clinical experience to identify those at risk and the need for early intervention. This index patient presented with a life-threatening condition, respiratory failure and sepsis, on a background of CKD.

Morphine has increased plasma clearance rate from increase in hepatic blood flow, renal blood flow and glomerular filtration rate in some adult sickle cell disease patients. The risk of morphine toxicity increases in the presence of renal impairment. Allen *et al*[10] had observed the tendency for a disruption of the pharmacokinetic properties of the drugs with an increased tendency for a prolongation of the duration of action in an overdose.
The escalation of the dose of morphine to achieve a satisfactory clinical effect which resulted in respiratory depression in this patient, is said to occur at a much slower rate, thus narrowing the therapeutic window to predispose them to increased risk of respiratory depression.[11]

In terms of the diagnosis of morphine toxicity in this patient, important clinical signs were hypopnoea, depressed level of consciousness and miosis. However, these may be masked by renal failure and sepsis. Respiratory rate was 6-8cycles per minute, miosis was present, depressed level of consciousness (GCS 9/15) and a drug history from the referral hospital gave away the diagnosis of opioid toxicity.[12]

For treatment, naloxone, a competitive mμ opioid receptor antagonist is commonly used. In this index case, it was administered/titrated intravenously to reverse the effects of morphine overdose at a dose of 0.08mg every 2-3minutes until the respiratory rate improved above 12 cycles per minute.

Edward[13] has reported that the effective dose requirement for naloxone in this setting of drug overdose is dependent on such factors as the weight of the patient, volume of opioids already consumed by the patient, relative affinity of naloxone for the receptor and the opioid to be displaced. For want of information on the above data, naloxone was titrated to good effect in an infusion using the recommended lower initial dose regimen[14] which consisted of diluting 800micrograms (2mls) in 8mls of 0.9% sodium chloride (to 10mls) and administering it in aliquots of 1ml every 2-3 minutes until the respiratory rate improved to above 12 cycles per minute.

CONCLUSION

Adult sickle cell disease patients may have renal impairment which could affect drug clearance. Regular assessment of renal function and adaptation of drug use is strongly advised.

REFERENCES

1. Bolarinwa RA, Akinlade KS, Kuti M, Olawale OO et. Renal disease in adult Nigerians with Sickle cell anaemia: A Report of prevalence, clinical features and risk factors. *Saudi J of Kid Diseases and Transpl* 2012 Jan; 171-175.
2. Phuong-Thu TP, Phuong-Chi TP, Alan HW, Susie QL. Renal abnormalities in Sickle cell disease. *Kidney Int* 2000; **57**:1-8
3. Nnaji UM, Ogoke CC, Okafor HU, Achigbu KI. Sickle cell Nephropathy and Associated factors among Asymptomatic children with sickle cell anaemia. *Hindawi Int J of Paediatrics* 2020 doi 10.1155/2020/1286432
4. Africanus Horton JB. The diseases of tropical climates and their treatment. London: *Churchill,* 1874.
5. Okpala I, Tawil A. Management of pain in sickle cell disease. *J R Soc Med* 2002;**95**: 456-458
6. Edward JC, Howard A H, Yale HC, Douglas C. Evidence of morphine metabolism to hydromorphone in pain patients chronically treated with morphine. *J Anal Toxicol* 2006;**30**:1-5. doi: 10.1093/jat/30.1.1.
7. DePriest AZ, Heltsley R, Black DL, Mitchell JM et al. Prescription Opioids. V1. Metabolism and excretion of hydromorphone in urine following controlled single-dose administration. *J Analytical toxicology* 2016; **40**: 575-582.
8. Kotila TR, Busari OE, Makanjuola V , Eyelade OR. Addiction OR pseudoaddiction in sickle cell disease patients: Time to decide-A case series. *Annals of Ibadan Pg Med.* 2015 Jun; **13**: 44-47.
9. Makanjuola AB, Olatunji PO. Pentazocine Abuse in Sickle cell Anaemia patients: A report of two case vignettes. *Afr J Drug & Alcohol studies* 2009; **8**: doi 10.4314/aidas.v8i2.52933.
10. Allen L, Kimura K, Mackichan J, Ritschel W. Committee for pharmacokinetic nomenclature of the American college of clinical pharmacology. Manual of symbols, equations & definitions in pharmacokinetics. *J Clin pharmcol.* 1982; **22**:1S-23S.
11. Etches RC. Respiratory depression associated with patient–controlled anaesthesia: A review of eight cases. *Can J Anaes* 1994; **41**:125-32.
12. Hoffmann JR, Schriger DL, Luo JS. The empiric use of naloxone in patients with altered mental status: a reappraisal. *ANN Emerg Med* 1991; **20**; 246-52.
13. EDWARD WB. Management of opioid analgesic overdose. *N Engl J Med* 2002 Jul 12; **367**: 146-155.
14. NHS. What naloxone doses should be used in adults to reverse urgently the effects of opioids or opiates?. https://www.sps.nhs.uk/articles/about-ukmi-medicines-gas/ accessed 23/12/2020.