Drug use in porphyria: a therapeutic dilemma

Jose J, Saravu K, Shastry B A, Jimmy B

ABSTRACT

One of the most frequent precipitating factors for attacks of porphyria is the administration of drugs. Use of drugs with porphyrinogenic potential often worsens the condition and often poses a therapeutic dilemma. A 23-year-old female patient presented to the casualty room with abdominal pain, chest pain and vomiting. Her past medical history was significant with episodes of generalised abdominal pain. The patient was initially treated for her abdominal pain and vomiting. She developed seizures and was treated with diazepam and phenytoin. Based on the positive investigation reports (positive urine porphyrins, elevated urine ALA and positive porphobilinogen) and symptoms, a diagnosis of acute intermittent porphyria (AIP) was done. Before the diagnosis of AIP was made, the patient was treated with drugs which are not considered to be safe in porphyric patients, such as phenytoin, metoclopramide, and diclofenac. The use of these drugs probably contributed to the initial worsening of the patient's clinical condition. After the diagnosis of AIP was made, the patient was treated with safer alternatives; gabapentin as the antiepileptic agent, promethazine as antiemetic, and propanalol as the antihypertensive agent. Withdrawal of the unsafe agents and symptomatic management with the safer alternatives contributed to the recovery of the patient. Along with the case report and the observations made on the various drugs used in the patient, the importance of the various information sources available on the safety potential of these agents is discussed. The observations with the drugs used in our case will be a useful addition to the existing information on the safety of these agents.

Keywords: acute intermittent porphyria, drug safety, porphyria

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INTRODUCTION

The porphyrias are a heterogeneous group of disorders caused by deficiencies of specific enzymes of the haem biosynthetic pathway.[1] Acute intermittent porphyria (AIP), an acute porphyria belonging to the group of hepatic porphyrias, is the most common acute porphyria in most countries.[2] Acute attacks of porphyria are most commonly precipitated by events that decrease haem concentrations, thus increasing the activity of ALA synthetase (ALA-S) and stimulating the production of porphyrinogens.[3] Among the various precipitating factors for attacks of porphyria, one among the most frequent causes is administration of drugs. Drugs may trigger an acute attack of porphyria in many ways, most of which depend on an increased demand for haem production or a failure of haem inhibitory feedback as a final common pathway. Drugs may interfere with the haem synthetic pathway or they may increase the demand for haem by increasing utilisation, e.g. through increased demand for oxidative processes mediated through the cytochromes. It is of interest to note that the evidence of drugs associated with the causation and exacerbation of non-acute prophyrias is weak, compared to the strength of evidence for the acute forms of porphyria.[3]

Considering the various clinical manifestations during acute attacks of porphyria, it becomes always essential to manage the patient's symptoms with drug therapy, which in fact is usually a therapeutic dilemma for healthcare professionals. Data available and the recommendations of drugs as safe or unsafe in porphyria are based on anecdotal experience of the use of these agents in porphyric patients and reports of the induction of acute attacks, or on measurements of porphyrins or their precursors in urine or faeces during the use of the drug.[3] Extrapolating the data on porphyrinogenicity from animal cultures and tissue cultures may not be always possible. Data from experiences in clinical settings is more valuable, but it may not be always available. Using these data from various sources, databases and recommendations are generated by various bodies as a reference source for better patient care.[4-7] Databases, specifically on drug safety in porphyria, are available with options to search on general information on drug safety as well as patient-specific search considering the vulnerability of a patient, based on age, gender, and previous and

Department of Clinical Pharmacy, Shirdi Sai Baba Cancer Hospital, Kasturba Hospital, Manipal University, Manipal, Karnataka 576104, India

Jose J, MPharm
Lecturer

Jimmy B, MPharm
Lecturer

Department of Medicine, Kasturba Medical College

Saravu K, MD, DNB
Associate Professor

Shastry BA, MD
Professor

Correspondence to:
Mr Jimmy Jose
Department of Pharmacy Practice,
School of Pharmacy,
International Medical University,
No.126 Jalan 19/155B,
Bukit Jalil,
Kuala Lumpur 57000,
Malaysia
Tel: (60) 3 8656 7228
Fax: (60) 3 8656 7229
Email: jimmy_jose2001@yahoo.com

current disease activity.[4] Other useful resources include tertiary sources such as textbooks[8,9] and review articles.[2,3,10]

Some of the limitations with these information sources are as follows: safety information on many drugs are not available, conflicting data may be presented in different sources, quality and quantity of input information which might have been used before making the recommendations might be a concern. They serve only as a guide for prescribing. In spite of these limitations, such information sources act as a valuable source of information for making decisions regarding drug therapy. These information sources will become more informative and elaborate if practising healthcare professionals try to disseminate all the information regarding their experiences with drugs in porphyric patients. This article reports a 23-year-old female patient in whom AIP was diagnosed and was managed for her symptoms. Focus is given on the experience gained with the use (safe and unsafe) of various drugs in this patient, and the importance of careful use of drugs in this group of patients is discussed.

CASE REPORT

A 23-year-old female patient presented to the casualty room with abdominal pain, chest pain and vomiting for one day. Abdominal pain was acute in onset, burning and intermittent with no radiation, intensity of which increased with food intake. Her past medical history was significant with admission to the hospital three years previously for generalised abdominal pain. She was admitted one month previously to another hospital for cellulitis of the left foot and was treated with antibiotics (the identity of the drugs used is not clear). She gave a history of recurrent generalised abdominal pain in addition to spasmodic dysmenorrhoea and a history of sadness for the past one year. Her family history depicted one of her sisters with a history of seizures. On examination of the patient, mild pallor was present, blood pressure (BP) was 140/100 mmHg, pulse rate 60 beats/min and respiratory rate 12 cycles/min. The abdomen was soft, with mild tenderness in the epigastrium and hypogastrium. Bowel sounds were normal. Investigations showed a low Hb (10.1 g/dL) and an elevated erythrocyte sedimentation rate (35 mm/hr). Random sugar, renal and liver functions were normal. Urine pregnancy test was negative. Ultrasonography of the abdomen was also normal.

On the day of admission, the patient was given intravenous (IV) pantoprazole 40 mg OD, intramuscular (IM) drotaverine 40 mg TID, which were continued till the fifth day. On the second day, the patient had two episodes of generalised tonic-clonic (GTC) seizures and was treated with IV diazepam. IM diclofenac sodium BD for abdominal pain and IV metoclopramide for vomiting was started on the third day and were continued till the fifth day. She had another episode of GTC seizures on the same day and hence was started with oral phenytoin 300 mg HS. Computed tomography of the brain, which was done on the same day, was normal. Electroencephalography showed abnormal bilateral frequent frontal spike waves with normal background alpha activity of 8–10 cycles/sec. The patient had another episode of GTC on the fifth day. In view of her abdominal pain and seizures, urine porphyrins were tested on the fifth day. Urine porphyrins were found positive, urine ALA was 61 mg/L (0–6) and porphobilinogen was also positive. A diagnosis of acute attack of porphyria, AIP, was made, and a change in the direction of the therapy and selection of drugs used was effected. Tablet gabapentin 300 mg TID was started as the antiepileptic drug instead of phenytoin. Tablet pyridoxine 40 mg TID was started and injectable dextrose was administered at a rate of 400 g/day. Pentazocine and promethazine were given IV for her abdominal pain and vomiting, respectively. The patient became drowsy and spoke incoherently on the morning of the sixth day. In view of her elevated BP (220/130 mmHg on the sixth day), she was treated with tablet propranolol 40 mg QID. In the afternoon, she was unconscious and was not responding to any stimuli. Pupils were sluggishly reacting to light. Hypotonia was present in all the four limbs with absent deep tendon reflexes. On the eighth day, sodium was 116 meq/L, which was corrected with 3% saline.

On the ninth day, the patient started talking and she was fully alert. Her BP was well managed with propanolol, with BP readings on the 11th and 13th days being 150/100 mmHg and 130/90 mmHg, respectively. Propranolol was tapered to 40 mg BD on the 17th day. The patient's neurological weakness completely improved. On the 20th day, the patient's BP was 102/70 mmHg and propranolol was stopped. Her condition improved, and on the same day, she was discharged with the following medications; tablet gabapentin 300 mg TID and tablet pyridoxine 40 mg TID. During the time of discharge, the patient and her relatives were educated on the disease, measures to be taken to prevent acute attacks of porphyria, and a list of drugs to be avoided was provided.

DISCUSSION

Discussion is restricted to the evaluation on the use of drugs in the present case, concentrating on the related literature on the safety of drugs used and possible

effect of these drugs on the disease condition in the present case. Further, we have tried to discuss in brief the alternative treatment options for various associated conditions observed in our patient. Even though no clear conclusions could be drawn regarding the specific effect of all the drugs used in our case, as multiple drugs were used at the same time, we feel that sharing all observations made related to drug use in porphyria will be useful additions to the existing literature. Drugs which were used in treating the abdominal symptoms included pantoprazole and drotaverine, and was used before the diagnosis of porphyria. Even though there are no reports of precipitation of porphyria attacks with the use of pantoprazole, it is recommended to be used with caution in circumstances where it needs to be used.[4,5] Other agents in the class of proton pump inhibitors also have a similar safety recommendation in porphyric patients.[4-6] H_2 receptor antagonists (ranitidine and famotidine) are considered to be safer alternatives,[4] even though certain studies proposed that they be used with caution.[3,9,11] Acute attacks of porphyria have been reported with the use of drotaverin, and hence use of this drug is recommended to be avoided in porphyria.[9] Even though a clear conclusion regarding the response to the use of pantoprazole and drotaverine could not be drawn, the influence of these drugs, alone or in combination, in the development of seizure complication on the second day cannot be ruled out.

For the management of vomiting, metoclopramide was used before, and promethazine after, the diagnosis of porphyria. Metoclopramide has been associated with acute attacks of porphyria and is advised to be used with caution.[4,5] But certain studies have reported the safe use of metoclopramide during acute attacks.[11] On the other hand, promethazine is considered to be non-porphyrinogenic,[4] and its use is recommended, even though another study[9] considers its use as unsafe. Other safer alternatives for vomiting include phenothiazine drugs, such as prochlorperazine and chlorpromazine.[2,4,6] For the treatment of seizures, the patient was administered phenytoin as well as diazepam before the diagnosis of porphyria was made, while gabapentin was given after the diagnosis. Phenytoin has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.[4,5,9,12] In our case, phenytoin was used for three days and its administration did not improve the seizures and probably worsened the condition. Diazepam is considered to be probably porphyrinogenic and has to be used with caution only in strong or urgent indications.[4,5] Benzodiazepines are considered to be probably safe when used in lower doses as a sedative.[8] Safer anticonvulsant alternatives include gabapentin and vigabatrin.[10,13] In our case as well, gabapentin was probably effective in controlling the seizures without worsening the condition. Our experience reconfirms the safe use of gabapentin in porphyric patients. The fact that the withdrawal of porphyrinogenic agents used in the patient, like metoclopramide and promethazine, might also have contributed to the control of seizures needs to be considered.

For the management of pain, the patient was administered diclofenac and pentazocine. Diclofenac has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.[4,5,9] Even though narcotic analgesics in general is recommended for analgesia in pophyric patients,[8] pentazocine use is advised to be avoided during a porphyria attack.[3,9] Safer alternatives include codeine, meperidine and morphine, acetaminophen and aspirin.[3,4] The patient was given propanalol as an antihypertensive agent. Beta-blockers are safe for use in porphyric patients and considered as a drug of choice. More experience is with the use of propanalol, and atenolol, timolol, and labetalol are safe alternatives.[3-6,10] In our case, the patient's BP was adequately controlled by propanalol and its use did not affect the disease state of the patient. Our experience reconfirms propanalol as a safe antihypertensive.

No firm conclusions on the specific negative impact of many of the drugs used could be drawn as multiple drugs were used together in the patient. But it is quite prudent to consider that agents, such as drotaverine, metoclopramide, phenytoin, diazepam and diclofenac used before the diagnosis of porphyria, might have a negative impact. This observation is based on the prognosis of the patient's condition as well as the review of literature on the safety of these drugs in porphyric patients. As a useful addition to the existing literature, our experience reconfirms gabapentin and propanalol as safe agents in porphyric patients for the treatment of associated seizures and hypertension. Early diagnosis, judicious uses of drugs during acute attacks, and advising the patients on avoiding drugs with porphyrinogenic potential are of great importance in porphyric patients. Healthcare professionals could refer to information resources for guidance during this therapeutic dilemma. Clinicians should consider use of those drugs with greater safety data and less conflicting information, rather than drugs with lesser safety data and conflicting evidences. Further, sharing of experiences with the use of various agents, especially newer agents, is of prime importance for the safe use of drugs in porphyric patients.

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