Case report

Acute intermittent porphyria: analgesia can be dangerous

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SUMMARY

Acute intermittent porphyria (AIP) is a rare condition, a metabolic disorder of the haem biosynthesis. An acute crisis of AIP can present as a combination of symptoms, such as abdominal pain, autonomic dysfunction, hyponatremia, muscle weakness and neurological symptoms in the absence of others obvious causes. We report the case of a 53-year-old woman, who was previously diagnosed with AIP 5 weeks after therapeutic suspension has developed an acute disease exacerbation. During hospitalisation, further exacerbation has occurred after analgesia with metamizole. Glucose and hemin infusions resulted in slow improvement. Physical rehabilitation was crucial to peripheral polyneuropathy recovery. Taking into account the porphyrinogenic effect described for metamizole, this drug might have triggered the second attack. Clinical history was sufficient to suspect the diagnosis and to start the treatment immediately, preventing important sequelae.

BACKGROUND

Porphyrias are disorders of haem synthesis, among which acute intermittent porphyria (AIP) is the most prevalent of all eight types in European population.¹ It affects 1 in 2000 people and only 10% manifest the disease, usually young women. It is an autosomal dominant disease and results from deficiency in the third enzyme of haem synthesis, uroporphobilinogen deaminase. The enzyme defect leads to overproduction of the porphyrin precursors, delta aminolevulinic acid and uroporphobilinogen, that causes nervous system injury and explains the main symptoms.² Diagnosis of this condition is challenging because the symptoms and signs are non-specific. Pharmacological history is important not only before the crisis, but also during treatment. All health professionals who are involved should know about the potential porphyrinogenic effect of the drugs that the patient is taking, in order to enhance disease management, avoiding adverse effects.³

We report a case where the patient is already diagnosed with AIP for several years. In patients like these ones who are presented with unexplained abdominal pain, neurological complications, psychiatric features and hyponatraemia, the attention should be directed to the possibility of an acute crisis. This work reports a typical presentation of acute crisis of AIP, its management, the dangers of drug prescription (including the potential porphyrinogenic induction) and the possible sequelae of this entity.

CASE PRESENTATION

A 53-year-old Caucasian woman, diagnosed with AIP since the age of 37, was being treated with hemin 150mg every 2 weeks without exacerbation for the last 8 years. During a period of prolonged travelling vacation, the patient discontinued her medication for 5 weeks. She had no history of taking porphyrinogenic drugs. After this period of medication suspension, she has checked-in to the emergency department with a 3 days' history of generalised muscle pain, tremors, weakness, headache, constipation and altered mental status. Her blood pressure was 180/98 mm Hg, heart rate of 92 bpm and auricular temperature was at 37.4°C. She was confused and disoriented in time and space, but there were no other neurological changes. On physical examination, there was diffuse abdominal pain with no changes on the palpation. Urine had a characteristic reddish colour after prolonged light exposition (figure 1)

INVESTIGATIONS

At the emergency department, primary laboratory investigation has revealed no alterations within haemogram, renal function and arterial blood gas parameters. Blood sodium was 131 mmol/L and hepatic enzymes were slightly increased: alanine aminotransferase (ALT) of 36 U/L (reference range < 45 U/L) and aspartate aminotransferase (AST) of 45 U/L (reference range < 35 U/L). Protein electrophoresis showed a little peak of gamma globulin without monoclonal component. Urine dipstick test, thorax radiograph and abdominal ultrasound showed no alterations. The infectious hypothesis was excluded.

Investigation has proceeded in the inpatient setting, in the internal medicine department. Urine analysis revealed increased uroporphobilinogen 61.83mg/24 hours (reference range 0.0–3.4 mg/24 hours) and porphyrins 437.3 µg/24 hours (reference range < 220 µg/24 hours) with normal delta-aminolevulinic acid, uroporphyrins and coproporphyrins levels.

One week later, there was a clear symptomatic aggravation after a single metamizole administration (2000mg intravenous). Metamizole was prescribed at night by a doctor called of the emergency department for irruptive abdominal pain. The patient was already medicated with her usual analgesic medication: paracetamol, transdermal fentanyl, gabapentin and amitriptyline, and had already taken transmucosal fentanyl that she used on request. The patient developed intense muscle weakness,

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Figure 1 Reddish colour urine after prolonged light exposition.

impaired gait and generalised pain worsened. Urine analysis was repeated: porphobilinogen 28.81mg/24hours, porphyrins 124.5µg/24hours, delta-aminolevulinic 8.17mg/24hours (reference range 1.5–7.5mg/24hours) and normal uroporphyrins and coproporphyrins levels. Neurological examination revealed bilateral stocking-glove paraesthesia and distal limb symmetrical tetraparesis—grade 2 (figure 2). A four-member electromyography was performed and showed severe acute sensory-motor axonal polyneuropathy.

Figure 2 Upper limbs paralysis 1 day after metamizole endovenous administration.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of an AIP attack includes neuropsychiatric diseases and a roll of common acute abdominal pain causes such as appendicitis, cholecystitis or pancreatitis.⁴ In a patient already diagnosed with AIP, this presentation strongly suggests an acute attack. Diagnosis was settled on clinical basis, though laboratory investigation was useful to confirm the diagnosis.

TREATMENT

Continuous 5% glucose infusion (goal: 300–500 g/day) and a carbohydrate-enriched diet were started, gradually improving the patient's mental status. Hemin infusion was started within the first week of hospitalisation, at the usual patient dose (3 mg/kg) for two consecutive days. There was a clear improvement in abdominal pain and weakness. However, 3 days later, metamizole administration was followed by clinical worsening with neurological impact. After electromyography was performed, hemin was administered for two consecutive days.

Pain control was achieved using paracetamol and fentanyl according to WHO 'pain ladder'. Other analgesics (gabapentin, venlafaxine and amitriptyline) were useful as adjuvant therapy. Clinical response to treatment was monitored through the surveillance of dysautonomia symptoms, such as constipation, arterial hypertension and tachycardia.

All drugs were selected after consultation of available porphyrinogenic drugs lists and specific instructions for no administration of other medications were attached on her clinical process.

OUTCOME AND FOLLOW-UP

The patient evolved with complete remission of pain and mental confusion. Physical rehabilitation was delayed by weakness and muscular pain until the eighth day, with partial improvement of the peripheral polyneuropathy. On discharge, the patient was referred to a rehabilitation centre to maintain hemin dose of 150 mg every 2 weeks. Two months later, muscle weakness was grade 4 at four members and gait was normal, without support. Pain was controlled with a fixed dose of analgesics. No other symptom was referred and the patient was motivated.

DISCUSSION

AIP's most frequent clinical presentation is acute pain, mainly abdominal, a very common symptom among several other diseases. Though AIP is a very rare disease, the association of abdominal pain with signs of autonomic dysfunction, confusional state and hyponatremia is highly suggestive of this diagnosis.^{3 4} Acute peripheral polyneuropathy is often present. It usually takes years to establish the diagnosis. Other causes of acute abdominal pain and neuropsychiatric disorders must be excluded.⁴ In already diagnosed patients, the most common causes of exacerbation are the use of porphyrinogenic drugs and hormonal oscillations (mainly in women), but other causes should be exhaustively investigated (eg, infections and metabolic disturbs).^{2–4} A fivefold increase in 24 hours urine porphobilinogen sample sheltered from the light is the biochemical criteria for an acute attack.³ However, the treatment must not be delayed pending this confirmation in a highly suggestive case such as the presented one.

It is also important to educate the patients and health professionals about the precipitating factors that can cause exacerbations. All drugs should be carefully selected from an up-to-date

list of safe porphyria medication, that is, non-porphyrinogenic drugs (eg, <http://www.drugs-porphyria.org>).^{2,3,5} Even analgesics are susceptible to trigger an AIP attack. In this case, we believe that metamizole was the trigger for the second attack.

Metamizole (also known as dipyrone) is a pyrazolone derivative that due to its chemical structure and its analgesic, antipyretic and anti-inflammatory effects, is classified as a nonsteroidal anti-inflammatory drug. Additionally, metamizole offers spasmolytic properties.^{6,7} In combination with its mostly favourable gastrointestinal tolerability, its profile led to an extensive clinical application. Metamizole is available for oral, rectal, intramuscular and intravenous administration and it achieves an oral bioavailability of almost 100%. There are clinical and practical evidence that the intravenous administration of paracetamol or metamizole is currently the analgesics of choice in the emergency room treating patients with acute abdominal pain due to their similarity.^{8,9} Metamizole parenterally used (2500 mg) for postoperative pain is equianalgesic to 50–100 mg intravenous pethidine or to 100 mg intravenous tramadol, while a single 500 mg oral dose of metamizole appears similar to that of ibuprofen 400 mg.^{9,10} Therefore, metamizole is used in many countries for pain relief on postoperative pain, colic pain, cancer pain and migraine.^{10–13}

Metamizole has several active metabolites with an extensive hepatic metabolism mediated, not only, by cytochrome P450 (CYP) 3A4 system, but also, by CYP2B6, CYP2C8 and CYP2C9. This gives him a certain potential for interactions with other substances metabolised via these CYP systems as well as a hepatotoxic potential of metamizole seems to be possible.^{6,7,14}

Since the 1970s, some countries (Japan, UK, USA) have banned metamizole use because of an association with agranulocytosis, with an incidence that varies between 1:1 000 000 and 1:1500.^{15,16} However, potential risks associated with metamizole administration are not yet clear in the latest published studies and some also consider that in the past the risk of metamizole-induced agranulocytosis was exaggerated and may depend on dose, duration and concomitant medication.^{15,17–20} However, an increasing number of side effects of metamizole have been reported affecting the cardiovascular system (ie, hypotension and arrhythmia), the respiratory system (ie, bronchospasm, especially in asthmatic patients) and the skin (ie, maculopapular rash), among others.^{6,14,19}

Adverse reactions of metamizole, such as nausea and gastric discomfort, can be confused with an acute porphyric attack.¹⁰ In the literature, there is only one report of an attack of AIP following the use of metamizole, although the patient also used other known porphyrinogenic drugs and was suffering from a urinary infection, so causality between metamizole and the attack was not clear.²¹ European Porphyria Network reports one attack requiring hospitalisation in a previously undiagnosed female AIP patient. It even reports uneventful use of metamizole in four patients with acute porphyria. Although metamizole is considered a 'probable porphyrinogenic drug', its use has been sustained when no safer alternative exists and the indication outweighs the risks on emergent situations (<http://www.drugs-porphyria.org>).

To date, the best treatment for acute attacks includes haem preparations (hemin), symptomatic treatment for the autonomic dysfunction, pain and polyneuropathy, adequate nutrition and hydration.²² High carbohydrate diet or intravenous glucose administration may be sufficient in milder attacks or at the initial phase until the hemin is available.¹

Frequent haem infusions reduce crisis severity and frequency, leading to its use as off-label prophylaxis. However,

in the long term, this may cause exogenous haem dependence, need for progressive increase of haem dosage and iron overload with hemosiderosis. Chronic liver disease, thrombotic complications, endocrinopathies and heart failure manifest at late stages.³ To date, orthotopic liver transplantation is the only curative treatment for selected patients with severe disease and who do not respond to conventional options or have a limiting quality of life, before irreversible neuronal damage has occurred. Novel approaches on AIP treatment are emerging based on enzymatic modulation and gene therapy, giving to the patient's good expectations.^{22,23}

Learning points

- This is a classic case of a rare metabolic disease. Acute intermittent porphyria (AIP) presents as acute attacks related with overproduction of porphyrin precursors.
- Porphyrinogenic drugs frequently trigger AIP. Metamizole increasingly seems to be a porphyrinogenic drug.
- Haem preparations and carbohydrate loading are the only treatments able to downregulate haem biosynthesis and prevent porphyrin precursors accumulation.
- Multidisciplinary teamwork (internists, surgeons, psychiatrists, neurologists, physiatrists and nurses) must be involved in the diagnosis and management of this disease.

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REFERENCES

- 1 Cardenas JL, Guerrero C. Acute intermittent porphyria: general aspects with focus on pain. *Curr Med Res Opin* 2018;34:1309–15.
- 2 Stein PE, Badminton MN, Rees DC. Update review of the acute porphyrias. *Br J Haematol* 2017;176:527–38.
- 3 Pischik E, Kauppinen R. An update of clinical management of acute intermittent porphyria. *Appl Clin Genet* 2015;8:201–14.
- 4 Ventura P, Cappellini MD, Biolcati G, et al. A challenging diagnosis for potential fatal diseases: recommendations for diagnosing acute porphyrias. *Eur J Intern Med* 2014;25:497–505.
- 5 Thunell S, Pomp E, Brun A. Guide to drug porphyrinogenicity prediction and drug prescription in the acute porphyrias. *Br J Clin Pharmacol* 2007;64:668–79.
- 6 Lutz M. Metamizole (Dipyrone) and the Live: A Review of the Literature. *J Clin Pharmacol* 2019;1–10.
- 7 Rogosch T, Sinning C, Podlewski A, et al. Novel bioactive metabolites of dipyrone (metamizol). *Bioorg Med Chem* 2012;20:101–7.
- 8 Falch C, Vicente D, Häberle H, et al. Treatment of acute abdominal pain in the emergency room: a systematic review of the literature. *Eur J Pain* 2014;18:902–13.
- 9 Arellano F, Sacristán JA. Metamizole: reassessment of its therapeutic role. *Eur J Clin Pharmacol* 1990;38:617–9.
- 10 Edwards J, Meseguer F, Faura C, et al. Single dose dipyrone for acute postoperative pain. *Cochrane Database Syst Rev* 2010;9:CD003227.
- 11 Hearn L, Derry S, Moore RA. Single dose dipyrone (metamizole) for acute postoperative pain in adults. *Cochrane Database Syst Rev* 2016;4:CD011421.
- 12 de Leeuw TG, Dirckx M, Gonzalez Candel A, et al. The use of dipyrone (metamizol) as an analgesic in children: What is the evidence? A review. *Paediatr Anaesth* 2017;27:1193–201.

- 13 Reist L, Erlenwein J, Meissner W, *et al.* Dipyron is the preferred nonopioid analgesic for the treatment of acute and chronic pain. A survey of clinical practice in German-speaking countries. *Eur J Pain* 2018;22:1103–12.
- 14 Ariza A, García-Martín E, Salas M, *et al.* Pyrazolones metabolites are relevant for identifying selective anaphylaxis to metamizole. *Sci Rep* 2016;6:23845.
- 15 Ibáñez L, Vidal X, Ballarín E, *et al.* Agranulocytosis associated with dipyron (metamizol). *Eur J Clin Pharmacol* 2005;60:821–9.
- 16 Hedenmalm K, Spigset O. Agranulocytosis and other blood dyscrasias associated with dipyron (metamizole). *Eur J Clin Pharmacol* 2002;58:265–74.
- 17 Andrade S, Bartels DB, Lange R, *et al.* Safety of metamizole: a systematic review of the literature. *J Clin Pharm Ther* 2016;41:459–77.
- 18 Jasiecka A, Maślanka T, Jaroszewski JJ. Pharmacological characteristics of metamizole. *Pol J Vet Sci* 2014;17:207–14.
- 19 Kötter T, da Costa BR, Fässler M, *et al.* Metamizole-associated adverse events: a systematic review and meta-analysis. *PLoS One* 2015;10:e0122918.
- 20 Maj S, Centkowski P. A prospective study of the incidence of agranulocytosis and aplastic anemia associated with the oral use of metamizole sodium in Poland. *Med Sci Monit* 2004;10:Pi93–5.
- 21 Bianchetti J, Lipniacka A, Szlendak U, *et al.* [Acute intermittent porphyria and oral contraception. Case report]. *Ginek Pol* 2006;77:223–6.
- 22 Fontanellas A, Ávila MA, Berraondo P. Emerging therapies for acute intermittent porphyria. *Expert Rev Mol Med* 2016;18:e17.
- 23 Berraondo P, Martini PGV, Ávila MA, *et al.* Messenger RNA therapy for rare genetic metabolic diseases. *Gut* 2019;68:1323–30.

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