

Safe Usage of Isotretinoin in a Woman with Latent Acute Intermittent Porphyria

Elin Storjord¹, Ole-Lars Brekke² and Erik Waage Nielsen^{1,3}

¹Department of Anesthesiology, Nordland Hospital, NO-8092 Bodø, ²Department of Laboratory Medicine, Nordland Hospital and Institute of Medical Biology, and ³Institute of Clinical Medicine, University of Tromsø, Norway. E-mail: elin.storjord@gmail.com
Accepted August 16, 2006.

Sir,

Isotretinoin therapy for severe acne carries a risk of side-effects, including elevation of liver enzymes and hepatic toxicity (1).

Acute intermittent porphyria (AIP) is an autosomal dominant inherited disease. Due to low activity of the porphobilinogen deaminase (PBGD) enzyme, the third step in the biosynthesis of heme, excessive amounts of the porphyrin precursors porphobilinogen (PBG) and aminolevulinic acid (ALA) accumulate, particularly in the liver (2). Accumulation of ALA and PBG are thought to provoke AIP symptoms. Adjoining areas in northern Sweden and northern Norway have the world's highest prevalence of AIP (3, 4). Most of these patients carry the W198X mutation (3, 4).

Medications such as barbiturates have been reported to induce attacks in AIP (5). However, relatively few reports address the safeness of commonly used drugs in AIP. The manifest form of AIP includes attacks with serious abdominal pain, muscle pain, fatigue, renal failure, hepatic cancer and/or neuropsychiatric symptoms.

We have monitored a patient with latent AIP who needed isotretinoin treatment of acne conglobata. The main worry of the patient's local doctor was the risk of provoking acute attacks and to transform the more benign and stable latent AIP into a manifest form by exposing her for the potentially liver-toxic drug isotretinoin.

METHODS

Analysis of porphyrins and precursors in urine

Urine was collected as spot urine in light-protected containers and stored in the laboratory at -20°C until analysis. Urine excretion of total porphyrins (6), ALA and PBG (7) were analysed using kits from Bio-Rad Laboratories GmbH (München, Germany). Total porphyrins were analysed spectrophotometrically after extraction on a column containing anion exchange resin. Urine porphyrins were separated on a Merck Hitachi high-performance liquid chromatography (HPLC) system, consisting of a L-7100 pump, a L-7360 column oven and a L-7480 fluorescence detector. Samples were injected by a Merck Hitachi L-7200 auto-injector. The HPLC system was controlled using D-7000 software from Merck Hitachi. Determination of urine porphyrins by HPLC was performed using columns and reagents obtained from Recipé GmbH (München, Germany). Degassing with helium was used. Urinary reference values for total porphyrins, ALA and PBG in adults were < 200 nmol/l, < 51 $\mu\text{mol/l}$ and < 7 $\mu\text{mol/l}$, respectively.

CASE REPORT

A 22-year-old 50 kg physically fit woman suffered from acne conglobata and latent AIP. The diagnosis of latent AIP was based on absence of clinical symptoms, the analysis of initially normal porphyrin precursors in urine and normal total porphyrins in blood, stool and urine. Her mother suffered from manifest AIP with the W198X mutation. At the age of 21 years, polymerase chain reaction analysis confirmed the W198X mutation in the PBGD gene in our patient. She was treated with isotretinoin for 131 days. The total dose of isotretinoin was 6500 mg, corresponding to 130 mg/kg. She had 5 consultations with the dermatologist during the treatment period, and each time blood was drawn for analyses of liver- and kidney-function and of inflammation. After 14 days of treatment, alanine aminotransferase (ALAT) was temporarily elevated.

The influence of isotretinoin on AIP was monitored by a total of 24 urine analyses of total porphyrins, ALA and PBG (Fig. 1). The levels did not change significantly during the treatment. HPLC analysis after the study period showed that the urinary total porphyrins mainly consisted of uroporphyrin and coproporphyrin (data not shown). No symptoms of AIP developed during the treatment period.

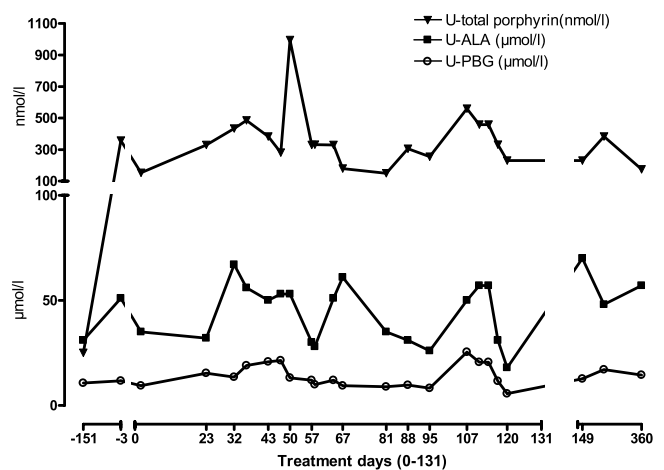


Fig. 1. Excretion of total urinary porphyrins, delta-amino laevulinic acid (ALA) and porphobilinogen (PBG) before, during and after a 131-day isotretinoin treatment in a 22-year-old woman with latent acute intermittent porphyria. Reference values of total porphyrins, ALA and PBG were < 200 nmol/l, < 51 $\mu\text{mol/l}$ and < 7 $\mu\text{mol/l}$, respectively.

DISCUSSION

A number of drugs cannot be used in patients with AIP for fear of side-effects. As this patient had a problematic, long-standing and therapy-resistant acne conglobata, the indication for an effective treatment was strong. After taking a 6500 mg course of isotretinoin, her acne was healed. The liver enzyme ALAT measured in serum also returned to normal. As this elevation in ALAT is frequently seen during treatment, we have no indication that this finding is related to AIP.

To minimize the risk of developing manifest AIP, urine analysis of porphyrin precursors and total porphyrins were performed regularly during the treatment with isotretinoin. Total porphyrins were measured to detect any development of a cutaneous porphyria in addition to AIP, which in most cases would increase total porphyrins. Isotretinoin was in fact shown to induce cutaneous pseudoporphyria in 2 persons using other drugs simultaneously. However, in these 2 persons urinary excretions of porphyrins were not elevated, and the mechanism may not have involved the heme-generating cycle at all (8).

Isotretinoin may have serious side-effects, including teratogenicity and depression (9). The most common side-effects are certain mucocutaneous, ophthalmological and laboratory abnormalities (9). The side-effects experienced by our patient, however, were limited to very dry skin and slightly elevated liver enzymes.

The clinical evaluation of the acute porphyria and the urine excretion of PBG, ALA and total porphyrins remained essentially unchanged during the treatment. The finding that total porphyrins, ALA and PBG were sometimes slightly above the reference values (Fig. 1) is not uncommon even in asymptomatic patients with AIP (10). The normal biological variation of urine ALA, PBG and total porphyrins is relatively high, in part due to the varying urine concentration (10). The biological variation can be reduced by expressing total porphyrins, ALA and PBG in urine as $\mu\text{mol}/\text{mmol}$ creatinine (10), but this was not common practice in Norwegian laboratories at the time of the study.

Although we show that isotretinoin was safely administered in a person with latent AIP, regular monitoring of ALA, PBG and total porphyrins in urine is advisable in every patient with AIP until more data are available.

ACKNOWLEDGEMENTS

Dr Kurt Andreassen, Saltdal, Norway, suggested the monitoring of this patient.

Conflicts of interest: None declared.

REFERENCES

1. Fallon MB, Boyer JL. Hepatic toxicity of vitamin A and synthetic retinoids. *Gastroenterol Hepatol* 1990; 5: 334–342.
2. Moore MR. Biochemistry of porphyria. *Int J Biochem* 1993; 25: 1353–1368.
3. Andersson C, Thunell S, Floderus Y, Forsell C, Lundin G, Anvret M, et al. Diagnosis of acute intermittent porphyria in northern Sweden: an evaluation of mutation analysis and biochemical methods. *J Intern Med* 1995; 237: 301–308.
4. Tollali G, Nielsen EW, Brekke OL. Acute intermittent porphyria. *Tidsskr Nor Laegeforen* 2002; 122: 1102–1105.
5. Moore MR, Hift RJ. Drugs in the acute porphyrias-toxicogenetic diseases. *Cell Mol Biol (Noisy-le-grand)* 1997; 43: 89–94.
6. Doss M, Schmidt A. Rapid determination of urinary total porphyrins by ion exchange chromatography. *J Clin Chem Clin Biochem* 1971; 9: 415–418.
7. Manzerall D, Granick S. The occurrence and determination of delta aminolevulinic acid and porphobilinogen in urine. *J Biol Chem* 1956; 219: 435–436.
8. Riordan CA, Anstey A, Wojnarowska F. Isotretinoin-associated pseudoporphyria. *Clin Exp Dermatol* 1993; 18: 69–71.
9. Charakida A, Mouser PE, Chu AC. Safety and side effects of the acne drug, oral isotretinoin. *Expert Opin Drug Saf* 2004; 3: 119–129.
10. Aarsand AK, Petersen PH, Sandberg S. Estimation and application of biological variation of urinary delta-aminolevulinic acid and porphobilinogen in healthy individuals and in patients with acute intermittent porphyria. *Clin Chem* 2006; 52: 650–656.