Fulminant Hepatic Failure Associated with Propylthiouracil

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OBJECTIVE: To report 2 fatal cases of fulminant hepatic failure associated with propylthiouracil treatment against hyperthyroidism.

CASE SUMMARY: Two women, 30 and 32 years old with no previous liver disease, were treated with propylthiouracil against Graves' disease. Both patients developed jaundice after a 4- and 5-month treatment period, respectively. The disease was similar to viral hepatitis, with a progressive course to severe liver dysfunction and death, along with multisystem organ failure despite extensive therapeutic measures. One of the patients was pregnant and subsequently miscarried. Neither patient had a history of alcoholism, drug abuse, blood transfusion, or exposure to hepatitis A, B, or C. Extrahepatic obstruction was ruled out with an abdominal ultrasonogram. Serologic studies and immunologic tests were negative. A submassive necrosis was shown in a postmortem histologic study.

DISCUSSION: Naranjo probability scale criteria applied to both cases confirm the adverse reactions as probable. These cases fit the requirements of drug hepatotoxicity proposed by Hanson and the Council of the International Organization of Medical Sciences. Eight deaths associated to propylthiouracil were found in our review of the medical literature up to December 2000.

CONCLUSIONS: Despite the widespread use of propylthiouracil, fulminant hepatitis with death is exceptionally rare; these 2 cases could be added to the fatal outcomes published to date.

KEY WORDS: drug-induced hepatitis, fulminant hepatitis, hyperthyroidism, propylthiouracil.

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Propylthiouracil is one of the most widely used drugs in the treatment against hyperthyroidism. Even though the risk of liver injury is rare, use of propylthiouracil could eventually lead to fatality. We present 2 fatal cases in which fulminant hepatitis was associated with propylthiouracil. In 1 of the cases, a pregnant woman presented with liver impairment previous to fetal loss. Both patients died as a consequence of multiple organ failure.

Case Reports

CASE 1

A 30-year-old woman, reporting no significant pathology before a diagnosis of Graves' disease in October 1996, presented with typical clinical features and thyroid-stimulating hormone (TSH) 0.0 µU/mL (immunoradiometric assay [IRMA]), total thyroxine (T_4) of 22.7 µg/dL (radioimmunoassay [RIA]), total triyodothyronine (T_3) >600 ng/dL (RIA), and anti-thyroid microsomal antibodies (AMA) (+) 1:1600. Treatment included propylthiouracil 450 mg/d and low doses of propranolol, with poor therapeutic adherence (skipping propylthiouracil doses or taking lower doses) according to patient records in the outpatient facility of Hospital Carlos Van Buren.

She still presented with clinical hyperthyroidism when she was admitted in March 1997 due to jaundice that began the prior 2 weeks. She also presented with diffuse abdominal malaise. Propylthiouracil was suspended 1 week prior to admission. She reported no alcoholism, drug abuse, blood transfusion, hepatitis contact, or previous liver disease.

The laboratory test results were as follows: aspartate aminotransferase (AST) 138 U/L, alanine aminotransferase (ALT) 207 U/L, total bilirubin 29.5 mg/dL, alkaline phosphatase (AP) 208 U/L, and prothrombin time (PT) 17 seconds (international normalized ratio [INR] 1.64). Results of other basic tests were normal: complete blood cell count, urinalysis, blood glucose, serum creatinine, plasma electrolytes. An abdominal ultrasonogram ruled out extrahepatic obstructive factors.

The initial course during her hospitalization was favorable, with a mild biochemical improvement. Viral etiologic and autoimmune assays were performed during this period.

Author information provided at the end of the text.

Hepatitis A IgM antibody (HAIgMAb), hepatitis B surface antigen, and Hepatitis C IgM antibody (HCIgMAb) were negative. The antinuclear antibodies (ANAs) were (+) 1:80 homogeneous and the antimitochondrial, antismooth muscle antibodies (ASMA), and antigastric parietal cells were also negative. No definitive ^{131}I therapy could be performed, and she was treated with low propranolol doses only. Ten days after admission, the women presented with progressive lethargy, mental confusion, and flapping with severe respiratory depression. She was transferred to the intensive care unit (ICU), where she had respiratory arrest, reversed with assisted mechanical ventilation. From this moment on, she went through persistent respiratory insufficiency and became less conscious, with liver function and laboratory tests deteriorating.

The woman's respiratory status became more compromised with a *Pseudomonas aeruginosa* infection diagnosed via bronchoalveolar lavage; she then developed progressive renal failure. She died due to multiple organ failure in March 1997, with no response to antibiotics, steroids, or vasoactive drugs.

A 900-g soft-consistency liver was found on autopsy. The histologic study showed extensive liver necrosis, hemorrhagic infiltration, widened portal triads, and lymphoplasmocytic infiltrate. The rest of the hepatocytes presented with perilobular cholestasis and ductal proliferation (Figure 1).

CASE 2

A 32-year-old woman, with a diagnosis of Graves' disease after clinical studies performed July 1996, presented with mild thyrotoxicosis, a 40-g diffuse goiter, minimal eye signs, and the following test results: TSH (IRMA) 0.0 µU/mL, T_4 (RIA) 15.9 µg/dL, unbound thyroxine (RIA) 3.9 ng/dL,T_3 (RIA) 194 ng/dL, and AMA highly positive (+) 1:1 638 400. Thyroid scintigraphy showed volume and isotope uptake increase. Propylthiouracil treatment was begun with 200 mg/d in August. A 10-week pregnancy was identified in November, so the dose was decreased to 150 mg/d according to the clinical and biochemical improvement during her controls at the endocrinology unit at Carlos Van Buren Hospital.

She was admitted to the obstetrics unit in January, due to abrupt jaundice with mild malaise. No previous data on hepatic or thyroid disorders were reported, and there was no alcoholism, drug abuse, hepatitis contact, or previous blood tranfusion.

During the physical examination, an accentuated icterus was found on the skin and mucosa. Neither the liver nor the spleen was palpable, and there was no ascites. Her pregnancy was normal. Laboratory test results were as follow: AST 948 U/L, ALT 686 U/L, total bilirubin 32.8 mg/dL, AP 364 U/L, and PT 19.9 seconds (INR 1.92). Other basic test results were normal. An abdominal ultrasonogram ruled out obstructive factors in the biliary ducts, showing only mild splenomegaly. Propylthiouracil treatment was suspended on hospital day 1.

Viral studies showed negative reactions for hepatitis A, B, and C. Two ANA results were determined: 1 positive, at 1:80 with a homogeneous pattern, another negative; antimitochondrial antibodies, ASMA, gastric parietal cells, DNA, extractable nuclear antibodies (ENA), and antineutrophil cytoplasmic antibodies (ANCA) were negative. No definitive ^{131}I therapy for hyperthyroidism could be performed due to the underlying pregnancy, but the woman was treated with low intermittent doses of propranolol.

A few days after the onset of symptoms, she was transferred to the ICU, where she stayed for 1 week, according to her partial response to the treatment against liver failure and a discrete improvement of laboratory test results. Ten days later, she presented with metrorrhagia and underwent an emergency Cesarean section secondary to abruptio placentae and a miscarriage.

Because liver failure was suspected during the postsurgical period, she was once again admitted to the ICU, where she developed progressive hepatic dysfunction with a minimal response to portosystemic treatment. She developed nosocomial bronchopneumonia (bronchoalveolar lavage positive for *Staphylococcus aureus*). She was sent back to the internal medicine unit where she developed multiple organ failure (progressive respiratory insufficiency, acute kidney failure, disseminated intravascular coagulopathy) and coma. There was no response to intensive therapy; she died in March 1997.

Her autopsy report showed a liver of 1140 g, with a wrinkled surface and a soft consistency. The histologic study reported a widened porta triads and lymphoplasmocytic inflammatory infiltrate. Trabeculae were disorganized and lysis of hepatocytes was seen, especially in the central lobular zone. Moderate cholestasis and ductal proliferation were found in the periphery (Figure 2).

Discussion

According to the Naranjo probability scale,[1] our 2 cases indicate a probable relationship between the liver dysfunction and propylthiouracil treatment. The causality relationship with the drug was based on (1) a clinical case after propylthiouracil intake, (2) no risk factors previous to treatment, and (3) no other illnesses that could have caused the liver lesions (biliary duct obstructions, viral infections, autoimmune pathology).

Neither of our patients had any laboratory tests performed previous to the propylthiouracil intake. The fulminating hepatitis diagnosis was based on the criteria used in liver disorders,[2,3] including jaundice, clinical evolution similar to severe viral hepatitis, abrupt development of encephalopathy, terminal multiple organ failure, and histologic hepatic injury confirmation during the autopsy. Hepatitis secondary to drug intake is difficult to diagnose. Hanson[4] proposed 6 conditions: (1) clinical evidence and hepatocellular dysfunction tests; (2) signs and symptoms related to drug intake; (3) no serologic evidence for current infection with hepatitis A or B viruses, cytomegalovirus (CMV) or Epstein–Barr virus (EBV); (4) absence of other etiologies of liver damage such as shock or sepsis; (5) no other chronic liver conditions; and (6) certainty that any other drug has not been administered, especially those with known hepatotoxicity.

The Council of the International Organization of Medical Sciences (CIOMS) proposed the terms to be applied to liver

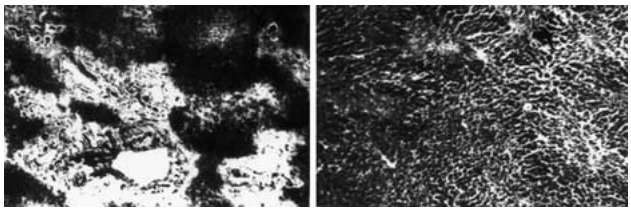

Figure 1. Extensive areas of necrosis with hemorrhagic infiltration are seen at low power (left). There are widened portal triads by edema and incipient fibrosis. At higher power (right), perilobular cholestasis and slight ductal proliferation are noticeable.

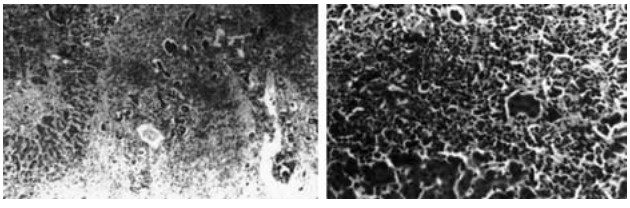

Figure 2. Low-power view (left) of the liver showing widened portal triads with lymphoplasmocytic inflammatory infiltrate that extends into the lobule. Trabecules are disorganized, with hepatocyte lysis mainly in the centrolobular zone (right). Moderate cholestasis and ductal proliferation are seen on high-power view (right).

injury and submitted terminology based on clinical data, the impairment of liver function test results, and the outcome of the biopsy or liver autopsy.[5] Requirements for the acute failure were published in order to classify a given drug in relation to the potential injury to liver cells, cholestasis, or both.

According to these criteria, our cases matched those parameters for propylthiouracil to be causative of fulminating hepatitis.

Viral hepatitis was ruled out when hepatitis A, B, and C markers were not identified. No tests were performed for CMV or EBV, but according to CIOMS these are optional. Autoimmunity tests are not a requirement, but their outcomes were negative in both patients (gastric parietal cell antibodies, ASMA, antimitochondrial antibodies); however, antinuclear antibodies were positive at a low titer. The second patient presented with tests negative for DNA, ENA, and ANCA. Thyrotoxicosis was mild to moderate in both cases and neither of the patients presented with congestive heart failure or other extrathyroidal risk factors.

The clinical analysis of 1 of the patients established a varying dose of propylthiouracil and an intermittent dose for 4 months; the other patient received propylthiouracil 200 mg/d for 5 months and a constant dose of 150 mg/d for 15 days. It took 92 days from the begining of propylthiouracil treatment to the onset of jaundice in the first patient, and 162 for the second. The first patient died 30 days after the icterus onset, while the second died at 50 days.

The second patient presented with an accentuated impairment of her liver test results with a high cytolytic pattern (a high AST increase), while the first patient presented with minor damage. Both patients presented with a cholestatic pattern (total bilirubin and AP increase) with a lengthening of PT. These impairments were compatible with liver injury secondary to drugs, even though a major hepatocellular compromise in relation to propylthiouracil has been reported.[6]

Prophylactic treatment for liver failure when toxicity was first detected and for the coma at the second stage, required hospitalization in the ICU, but antibiotics, corticoids, and other intensive therapies could not prevent development of multiple organ failure. While the first patient was being treated, liver transplantation was proposed; however, it could not be performed within the needed time period.

A review of literature on propylthiouracil liver toxicity shows a variable set of parameters for its classification. Hanson published 8 cases of hepatotoxicity, including 3 deaths[4]; Jonas and Eidson reported 14 cases of hepatotoxicity with 5 deaths,[7] and Levy reported 5 pediatric cases out of a total of 16; 3 deaths occurred in 8 patients aged <21 years.[8]

Eighteen cases of toxicity were reported by Deidiker and De Mello, with 7 children among them, with a total of 6 deaths (2 children).[9] Williams et al. reported 30 toxicity cases, of whom 7 died,[10] while Ichiki et al. presented 25 cases.[11] These lists are included among the articles reviewed that have enough data to be analyzed in relation to drugs' responsibility for toxicity.[12-17] Propylthiouracil toxicity has been evaluated as well as the etiopathology. An immunologic-based hypersensitivity could account for the hepatotoxicity.[18,19]

Eight deaths have been reported previously (Table 1).[4,7,9,10,20-23] Coldwell et al.'s[22] first fatal outcome case presented with secondary liver congestion due to heart failure in the final phase of sepsis with a high granulocytopenic component. Eisen's second case[23] developed liver toxicity after using propylthiouracil for just 1 day. It is being discussed whether these cases should be included in the list of deaths secondary to propylthiouracil, even though Lock and Sthoeger reported a severe liver toxicity case after only 1 day of propylthiouracil treatment.[24]

There are very few publications on liver toxicity associated with propylthiouracil therapy during pregnancy, because hyperthyroidism rarely has been observed and treated concomitantly.[25]

Summary

In our 2 patients with fulminant hepatic failure, previous treatment with propylthiouracil for hyperthyroidism was the probable cause of death. In both cases, the disease was similar to viral hepatitis, with a progressive course to profound liver dysfunction, encephalopathy, and death caused by multisystem organ failure, despite extensive therapeutic measures. One of the cases was associated with pregnancy and fetal loss during the phase of hepatic insufficiency.

In both patients, the clinical course, biochemical patterns, and autopsy results indicate that the hepatotoxicity was probably caused by propylthiouracil.

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EXTRACTO

OBJETIVO: Se informan 2 casos fatales de hepatitis fulminante asociados a tratamiento de hipertiroidismo con propiltiouracilo (PTU).

RESUMEN DEL CASO: Dos mujeres de 30 y 32 años de edad sin antecedentes de hepatopatía se trataron con PTU por enfermedad de Graves. En ambos casos, se desarrolló ictericia después de 4 y 5 meses de tratamiento. La enfermedad fue clínicamente similar a una hepatitis viral con insuficiencia hepática progresiva y muerte en falla orgánica múltiple a pesar de todas las medidas terapéuticas. En 1 de los casos, se asoció embarazo con pérdida fetal. En ambos casos, no había historia previa de alcoholismo, abuso de drogas, transfusión de sangre, ni exposición a hepatitis A, B, o C. Se descarto obstrucción extrahepática con ecografía abdominal. Los estudios serológicos virales y las pruebas diagnósticas de autoinmunidad fueron negativas. Los resultados de las autopsias demostraron necrosis hepática submasiva.

COMENTARIOS: Ambos casos se consideran como probables en la escala de Naranjo y cumplen la totalidad de las exigencias de hepatotoxicidad según los criterios de Hanson y del Comité Internacional de la Organización de Ciencias Médicas (CIOMS). En nuestra revisión de la literatura médica, se encontraron solo 8 muertes asociadas al uso de PTU hasta 1999.

Table 1. Cases of Fatal Hepatic Failure

Reference	Patient Gender/ Age (y)	PTU Dose (mg/d)	PTU Duration	Antiviral Antibodies	Autoantibodies	AST (U/L)	TB (mg/dL)	AP (U/L)	Liver Histology
Coldwell et al.[22] (1952)	F/60	300	29 d				10.9	1.7 BU	toxic hepatitis
Eisen[23] (1953)	F/52	300	1 d						massive necrosis
Safani et al.[20] (1982)	F/20	300	2 wk	B (–)	ANA (–)	750	22	248	submassive necrosis
Hanson[4] (1984)	F/20	800	3 mo	A (–) B (–)	ANA (+) AMA (–) ASMA (–)	714	11.4	444	
Limaye et al.[21] (1987)	F/42	300	12 mo	A (–) B (–)		1755	22	381	submassive necrosis
Jonas et al.[7] (1988)	F/13	300	7 mo	A (–) B (–)	ANA (–) AMA (+)	1565	14.7	369	massive necrosis
Deidiker et al.[9] (1996)	F/13	250	4 mo	A (–) B (–) C (–)	ANA (+) ASMA (–)	2561	13.8		submassive necrosis
Williams et al.[10] (1997)	F/54	800	12 d	A (–) B (–) C (–)	ANA (+) AMA (–) ASMA (–)	955	23.5	258	biopsy: chronic hepatitis, acute injury
Case 1 (1997)	F/30	450	4 mo	A (–) B (–) C (–)	ANA (+) AMA (–) ASMA (–)	138	29.5	208	submassive necrosis
Case 2 (1997)	F/32	200	5 mo	A (–) B (–) C (–)	ANA (+) AMA (–) ASMA (–)	948	32.8	364	submassive necrosis

AMA = antimitochondrial antibody; ANA = antinuclear antibody; AP = alkaline phosphatase; ASMA = antismooth muscle antibody; AST = aspartate aminotransferase; BU = Bodansky units; TB = total bilirubin.

CONCLUSIONES: A pesar que el PTU es uno de los medicamentos mas utilizados en el tratamiento del hipertiroidismo, la hepatitis fulminante con muerte es excepcional y se han descrito solo 8 fallecimientos, a los que se pueden agregar nuestros 2 casos presentados.

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RÉSUMÉ

OBJECTIF: Rapporter deux cas d'insuffisance hépatique fulminante fatals associés à l'administration de propylthiouracil (PTU) pour traiter une hyperthyroïdie.

RÉSUMÉ DU CAS: Deux femmes âgées de 30 et 32 ans sans antécédent de trouble hépatique ont reçu du PTU pour traiter une maladie de Graves. Les deux patientes ont développé une jaunisse après 4 et 5 mois de traitement. Les symptômes étaient semblables à ceux d'un hépatite virale, soit une évolution progressive de la dysfonction hépatique jusqu'à une atteinte sévère ayant causé la mort ainsi qu'une atteinte irréversible des organes vitaux en dépit de mesures thérapeutiques extensives. Une des patientes était enceinte et a fait une fausse couche durant sa maladie hépatique. Aucune des deux patientes n'avait d'antécédent d'alcoolisme, d'abus de drogues, de transfusion sanguine ou d'exposition à l'hépatite A, B ou C. Une échographie abdominale à confirmé qu'une obstruction extrahépatique n'était pas en cause. Les études sérologiques ainsi que les tests immunologiques se sont avérés négatifs. À l'autopsie, une coupe histologique a révélé une nécrose massive du foie pour les deux patientes.

DISCUSSION: Pour les deux cas présentés, l'algorithme de Naranjo a révélé une association probable entre le PTU et l'hépatite fulminante. Les cas décrits dans cet article répondent aux critères d'hépatotoxicité médicamenteuse émis par Hanson et le Concil of the International Organization of Medical Sciences (CIOMS). Une revue de la documentation scientifique jusqu'à 1999 a permis d'identifier 8 cas de mort associée au PTU.

CONCLUSION: Malgré l'utilisation répandue du PTU, l'hépatite fulminante mortelle est exceptionnellement rare. Les deux cas présentés dans le présent article pourront être ajoutés aux quelques cas de mort associée au PTU qui ont été publiés jusqu'à maintenant.

Esthel Rochefort