Drug-induced liver injury secondary to the use of oral contraceptives in a patient with prolonged jaundice and persistently elevated transaminases: A case report

Lesión hepática inducida por uso de anticonceptivos orales en una paciente con ictericia prolongada y transaminasas persistentemente elevadas: reporte de caso

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Abstract
Drug-induced liver injury is a diagnosis of exclusion. Typically, it occurs in patients who develop clinical and biochemical changes compatible with hepatitis, but is related to a history of the recent onset of pharmacological agents and resolves after withdrawal of the offending agent. Its development has been described with the use of some antibiotics, antituberculosis drugs, statins, herbal remedies, and nonsteroidal anti-inflammatory drugs; however, there are few reports of cases with the use of oral contraceptives, in which the emergence of idiosyncratic mechanisms can lead to the presentation of clinical features such as jaundice and laboratory abnormalities, such as elevated transaminases. This requires extensive studies to rule out other conditions that may present in this way, which represents a clinical challenge. This article presents a case report of a patient with a history of chronic use of implantable contraceptives who, after adjusting therapy with the initiation of oral contraceptives, developed an episode of marked elevation of transaminases and jaundice.

Keywords: contraceptive agents, drug-induced liver injury, hepatitis, liver toxicity, jaundice, transaminases.

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Resumen
La hepatotoxicidad inducida por medicamentos es un diagnóstico de descarte. Tipicamente, se presenta en pacientes que desarrollan cambios clínicos y bioquímicos compatibles con hepatitis, pero relacionados con el inicio reciente de agentes farmacológicos, y que se resuelven tras el retiro de la noxa. Su desarrollo se ha descrito con el uso de algunos antibióticos, antituberculosos, estatinas, herbolarios y antiinflamatorios no esteroides; sin embargo, hay pocos reportes de casos con el uso de anticonceptivos orales, en los cuales el surgimiento de mecanismos idiosincráticos puede llevar a la presentación de características clínicas como ictericia y anormalidades en laboratorios, como la elevación de transaminasas. Esto requiere estudios extensos para descartar otras patologías que pueden presentarse de esta forma, lo que representa un reto clínico. En este artículo se muestra el reporte de un caso de una paciente con antecedente de uso crónico de anticonceptivos implantables y que, tras el ajuste de la terapia con el inicio de anticonceptivos orales, desarrolla un episodio de elevación marcada de transaminasas e ictericia.

Palabras clave: anticonceptivos, daño hepático inducido por drogas, hepatitis, hepatitis tóxica, ictericia, transaminasas.

Introduction
Drug-induced liver injury (DILI) is a term used to describe the unexpected development of liver impairment secondary to drugs that are commonly used [1]. This damage can directly compromise hepatocytes, the classically affected cells, through different mechanisms such as the formation of reactive metabolites, alteration of drug transport pumps, increased immune-mediated response, mitochondrial dysfunction, and activation of stress signaling pathways, leading to apoptosis or cell necrosis [2]. Liver damage can be classified into different types: direct, which is related to the drug dose, has a rapid onset, high recurrence, and is predictable; and indirect or idiosyncratic liver damage, which is not related to the drug dose. The time of presentation varies between days, weeks, or months, and being uncommon, it is not predictable [3].

The incidence of this condition is difficult to estimate, as it is often unrecognized or unreported. Current data are mainly obtained retrospectively from pharmacological surveillance studies, and these data vary depending on the definition implemented. Additionally, the increasing use of herbal medicines in recent decades also complicates the ability to accurately determine the true incidence [4]. However, surveillance efforts have enabled the identification of drugs potentially associated with severe hepatic failure events, leading to their withdrawal from the market [5].

In a Spanish registry of 843 patients with DILI, it was found that the most prevalent drug was amoxicillin-clavulanate (22%), followed by antituberculosis drugs such as isoniazid (4.5%), certain non-steroidal anti-inflammatory drugs like ibuprofen and diclofenac (4.8%), and herbal supplements (3.4%). Other medications such as statins and azathioprine were less commonly reported [6]. There are few reported cases of DILI with the use of modern oral contraceptives. Some reports involve preparations containing levonorgestrel and ethinylestradiol, which have been linked to the development of cytolytic hepatitis [7]. There is also limited data on cases with histological confirmation related to the use of levonorgestrel 150 μg/ethinylestradiol 30 μg [8].
**Case description**

A 25-year-old female patient presented to the emergency department with generalized jaundice, macular lesions on the anterior thorax and forearms, choleuria, and abdominal pain that had been developing for 8 days. The abdominal pain was located in the epigastrium and radiated to the right hypochondrium. The patient had a previous history of hepatitis of unknown origin that occurred 4 years earlier. Additionally, she had been using contraception for 4 years with a subdermal levonorgestrel extended-release implant of 150 mg, which she had discontinued 5 months prior to her emergency department visit. It was also noted that 4 weeks before admission, she had started taking combined oral contraceptives containing dienogest 2 mg/ethinylestradiol 0.03 mg.

On admission, laboratory test results showed a complete blood count with leukocytes at 4,770/µL, neutrophils at 2,890/µL, lymphocytes at 1,370/µL, eosinophils at 60/µL, hemoglobin at 12.3 g/dL, and platelets at 278,000/µL. Additionally, there were elevated levels of alkaline phosphatase (Alk), alanine aminotransferase (ALT), and aspartate aminotransferase (AST), as well as increased levels of direct bilirubin. Tests were conducted to rule out infections such as viral hepatitis, HIV, and leptospirosis. Biliary obstruction was also ruled out after imaging tests including ultrasound and magnetic resonance imaging.

Given the persistence of elevated transaminases, autoimmune etiologies and infiltrative diseases were considered. Tests for antinuclear antibodies, anti-smooth muscle antibodies, antimitochondrial antibodies, and immunoglobulin G4 levels were negative. Diseases such as Wilson’s disease and hemochromatosis were also ruled out. In the absence of a clear diagnosis, a liver biopsy was performed to obtain more information. However, the biopsy results were inconclusive as most of the analyzed fragments corresponded to hemorrhagic clots. Only one fragment of liver tissue with a central vein, without portal spaces, showed evidence of cholestasis with a cannular biliary plug and mild to moderate focal acute inflammatory activity. The patient’s timeline is detailed in Figure 1.

Two main possibilities were considered: drug-induced liver injury (DILI) related to oral contraceptive use versus autoimmune hepatitis. The patient was treated with prednisolone and symptomatic measures. Throughout the course of treatment, a decrease in liver transaminases was observed, and the patient was discharged. The steroid dose was gradually reduced, and the patient did not experience an increase in transaminases after the steroids were withdrawn. During her subsequent medical follow-up, the patient remained off oral contraceptives.

**Discussion**

Suspicion DILI relies on a thorough clinical history. Typically, affected patients exhibit liver test abnormalities suggestive of hepatitis. While in some instances, DILI may manifest with biochemical features of cholestasis, with a normal hepatobiliary image. The use of the R-value ((ALT/ULN)/(Alk P/ULN)) can help determine the origin: hepatocellular if >5, cholestatic if <2, and mixed between 2-5 [9]. For DILI, clinical and biochemical changes occur following the initiation of a new drug or therapeutic agent, including herbal remedies. Improvement or resolution of hepatotoxicity is evident after discontinuation [10]. Often, the diagnosis is one of exclusion, as concurrent pathologies must be ruled out through studies on viral hepatitis, specific antibodies associated with hepatic involvement (such as anti-smooth muscle antibodies, antinuclear antibodies, IgG levels), and evaluation of risk factors like alcohol consumption and
metabolic diseases [11]. However, in some cases, despite thorough clinical assessment and absence of apparent risk factors or drugs with a high association with hepatotoxicity, reaching a diagnosis can be challenging. Additionally, the time required

**Figure 1.** Hepatic chemical evolution and diagnostic and therapeutic interventions performed.* Magnetic resonance cholangiography, hepatitis B surface antigen, hepatitis C antibodies, hepatitis A IgM, hepatitis E IgM and IgG, anti-smooth muscle antibodies, antimitochondrial antibodies, antinuclear antibodies, protein electrophoresis, IgG levels, ceruloplasmin, ferritin, % transferrin saturation, inconclusive liver biopsy.
Drug-induced liver injury secondary to the use of oral contraceptives: A case report

Corredor-Rengifo D, Sánchez-Romero M, Ocampo-Posada M, Gómez-Ramírez DM

152

for hepatic biochemistry normalization after discontinuing the offending drug may vary, taking several weeks to months [12].

In this case, the patient presented with jaundice and a significant elevation of transaminases upon admission. During the initial assessment, it is crucial to consider any hepatic biochemical abnormalities that may indicate a hepatocellular or cholestatic process [13]. Additionally, the timing of symptom onset is important to consider. Given the patient’s history of hepatitis four years prior to the current hospitalization, common causes such as viral hepatitis were initially ruled out. Toxic exposures related to chronic liver disease were also excluded. Furthermore, less prevalent but higher-incidence causes in young female patients, such as autoimmune and deposition diseases, were systematically evaluated, along with hepatic and biliary tract imaging, all of which yielded negative results. The possibility of DILI was consistently considered, aligning with guidelines for its management, as it remains a diagnosis of exclusion [9-11].

The patient was not undergoing pharmacological treatment with drugs strongly associated with the development of hepatotoxicity [14]. However, she was using oral contraceptives, which have been linked to other adverse effects such as hepatic adenomas, Budd-Chiari syndrome, and the risk of hepatocellular carcinoma [15], albeit with few reports of hepatotoxicity [7,8]. One notable aspect of the patient’s disease course was the persistent elevation of her transaminase levels, particularly ALT >1,000 U/L. While there is variability in the resolution time of inflammation and biochemical elevation in patients with DILI, ranging from weeks to months [12], steroids were used during the initial diagnostic and therapeutic process. Steroids have a clear indication in conditions such as autoimmune hepatitis [16], which was ruled out due to negative autoantibodies. The use of steroids in DILI is not strongly recommended due to variability in response observed in retrospective registries, along with associated risks and a lack of guidelines or standardization in doses and administration routes, without clear profiling of patients who are candidates for their use [17].

Another important consideration is the necessity of a liver biopsy. While not typically required in the evaluation of DILI and not included in guidelines, unlike autoimmune hepatitis where it is more commonly indicated [16], several factors may warrant the need for a liver biopsy. These include the presence of multiple plausible etiologies, exposure to drugs or agents with low liver injury rates, the severity of liver involvement, the need to rule out additional causes, particularly autoimmune hepatitis [18], all of which were relevant in this patient’s case. A biopsy was performed via endoscopic ultrasound, an increasingly popular technique for liver interventions [19], with a success rate in histological diagnosis of up to 93.9% and no significant differences in success rates compared to fine needle biopsy (95.8%) or tru-cut biopsy (92.7%) with p=0.59 [20]. However, the pathology results were inconclusive due to a suboptimal sample. This outcome may have been influenced by the operator’s experience, as this procedure is less commonly performed in our region.

Following clinical follow-up, the patient’s progress was favorable. Although she exhibited some characteristics of Hy’s law, such as elevation of transaminases more than three times the upper normal limit and bilirubin elevation greater than two times the upper limit without evidence of cholestasis, a situation associated with mortality rates of up to 10% [21], the patient also met the criteria of the modified Hy’s law, which has a better ability to identify mortality risk at 26 weeks [22]. This circumstance was also
fulfilled by the patient due to an R-value el-
evation >5. Fortunately, the patient’s evo-
lution was quite satisfactory, and after 10
weeks of discontinuing oral contraceptives
along with a low dose of oral steroids that
were gradually tapered off, she achieved
normalization of clinical and hepatic bio-
chemistry.

Another aspect of diagnosing DILI is the
rechallenge with the suspected causative
agent [9,10,23], a scenario that likely oc-
curred in this patient. Four years before the
current episode, she had been hospitalized
for an episode of unexplained hepatitis that
retrospectively coincided with the insertion
of a subdermal extended-release contra-
ceptive. She reported intermittent episodes
of jaundice, which seemed to improve after
removal of the subdermal device but wors-
ened after initiation of oral contraceptives.

Conclusion

The use of oral contraceptives is a com-
mon practice, with some well-known ad-
verse effects; however, descriptions of DILI
episodes from these are rare. There were
nuances in the case that suggested a possi-
bile cause-effect relationship; however, due
to the patient’s age and the need to rule
out more prevalent causes, several studies
were conducted. Liver biopsy and the use
of steroids are both controversial in this
condition. Nonetheless, both tools were
employed, but it’s important to recognize
that in many cases, the disease course
involves slow resolution, taking weeks or
months to normalize abnormalities. There-
fore, it’s crucial to systematically evaluate
the need for these interventions, especial-
ly if criteria related to increased mortality,
such as Hy’s law, are met. In this patient, af-
after removing the triggering agent and ruling
out other causes of liver damage, clinical
improvement indicates the presence of DILI
secondary to oral contraceptives. This cir-
cumstance should be considered in patients
of reproductive age who may present with
hepatitis or DILI.

Right to privacy and
informed consent

The authors declare that this article does not
contain data that would allow the identifi-
cation of the patient. The patient has given
consent for publication, and the authoriza-
tion is held by the corresponding author.

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Drug-induced liver injury secondary to the use of oral contraceptives: A case report


