Case Report
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Acute Hepatitis Due to Agomelatine Use in Elderly Women with Depression: Case Series

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Although agomelatine may be associated with an increased risk of hepatotoxicity, the incidence rate of acute hepatitis seemed divergent between clinical trials and daily practice. Whether aging or gender is a risk factor in developing hepatotoxicity due to agomelatine is not clear. We present 3 older female cases with acute hepatitis occurring due to highly probable idiosyncratic drug-induced liver injury caused by agomelatine. From these cases, regular surveillance on liver function in the older women taking antidepressants would be of benefits.

KEY WORDS: Agomelatine; Acute hepatitis; Major depression.

INTRODUCTION

Drug-induced liver injury (DILI) has an estimated annual incidence between 1 and 19 per 100,000 persons exposed to prescription medications and accounts for approximately 10% of acute hepatitis cases [1]. DILI, generally established by excluding other causes, is diagnosed on a high index of suspicion. Of the patients with DILI, 0.5–3% treated with antidepressants may develop asymptomatic mild elevation in liver enzyme levels [2]. Agomelatine, a novel antidepressant, is a melatonin (MT_1/MT_2) receptor agonist and serotonergic (5-HT2c) receptor antagonist [3]. Data in a pharmacovigilance database suggest that agomelatine is associated with increased hepatotoxic potential [4]. Gahr *et al.* [5] also reported that increased age, female sex, and polypharmacy may be risk factors for agomelatine-related hepatotoxicity. Here, we report the cases of 3 older female patients with acute hepatitis due to possible idiosyncratic DILI caused by agomelatine. All 3 patients have consented to the publication of this report on the grounds of anonymity.

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CASE

Case 1

Patient 1, a 64-year-old woman without prior history suggestive of active liver disease, was prescribed agomelatine for depression and severe sleep disturbance. Her liver function before agomelatine use was normal. The initial dose was 25 mg daily and was titrated to 50 mg daily after 5 days. Three weeks after treatment initiation, the patient returned to our clinic without advance notice and claimed she took 62.5 mg daily to improve sleep quality. The patient continued taking the same dosage and claimed she felt "brighter". At 1 month after treatment initiation, slight yellowing of skin; however, the patient, being oblivious to it, continued taking agomelatine over the next 2 months. Consequently, jaundice developed without associated abdominal pain, abdominal distension, constipation, or fever. The patient's symptoms gradually deteriorated and she ultimately experienced drowsiness.

She was admitted to our medical intensive care unit (ICU) in the aforementioned state; she also presented with icteric sclera and hand flapping tremors suggestive of hepatic encephalopathy. Laboratory testing revealed abnormal liver function, with total bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase levels of 18.57 mg/dl (direct: 12.10 mg/dl), 1,600 U/L, 1,101 U/L, and 117 U/L, respectively. Abdominal

Table 1. Clinical characteristics of the 3 cases

Variable	Case 1	Case 2	Case 3
Age (yr)	64	63	72
Body mass index (kg/m^2)	25.6	24.6	26.7
Agomelatine dose	25 mg → 50 mg → 62.5 mg at bedtime	50 mg at bedtime	25 mg at bedtime
Time of acute hepatitis after agomelatine use	One to two months	6 weeks	3 months
Clinical symptoms of acute hepatitis	Yellowish urine, jaundice, drowsy consciousness	No obvious signs or symptoms indicating liver injury	General malaise, tea-colored urine
Concomitant medications	Lorazepam 1 mg	Lurasidone 40 mg	Lorazepam 1 mg
Liver enzyme levels	Total bilirubin: 18.57 mg/dl (direct 12.10 mg/dl), AST: 1,600 U/L, ALT: 101 U/L, ALP: 117 U/L	AST: 93 U/L, ALT: 169 U/L	AST: 267 U/L, ALT: 456 U/L

ALT, alanine transaminase (reference range 11−40 U/L); AST, aspartate transaminase (reference range 15−41 U/L); ALP, alkaline phosphatase (reference range 32−91 U/L).

ultrasound revealed mild coarse liver parenchyma without a sonographically evident nodule, cyst, or mass. All tests were negative for hepatitis B surface antigen; IgM against hepatitis B core antigen; anti−hepatitis C virus antibody; as well as serologies for hepatitis A, cytomegalovirus, and autoimmune markers such as antinuclear, antimitochondrial, and antismooth muscle. Serum ceruloplasmin concentration was also within the normal range. The patient was conservatively managed in the ICU, and she resumed full consciousness on day 4. The patient's liver panel results suggested hepatocellular-type liver injury. The patient's liver function returned to normal after agomelatine use was discontinued for 1 month.

Case 2

Patient 2 was a 63-year-old woman diagnosed as having generalized anxiety disorder and delusional disorder. She had no history of major systemic illness and was prescribed lurasidone (40 mg; 1 tablet) at bedtime. After adding agomelatine (25 mg; 2 tablets) for 6 weeks, the patient's liver enzyme levels began increasing (ALT: 93 U/L, AST: 169 U/L). Testing for hepatitis A, B, and C provided negative results. Because no new medication other than the agomelatine added, under the consideration of agomelatine-related hepatitis, we tapered off agomelatine dosage, and her liver enzyme levels normalized 2 weeks after she discontinued the agomelatine regimen.

Case 3

Patient 3 was a 72-year-old woman diagnosed as having major depressive disorder for nearly two decades. She had been taking mesyrel and lorazepam for several years; otherwise, she was healthy with no medical illness. She has no habit of alcohol use. Because insomnia and depressed mood recurred, we switched her mesyrel (100 mg; 1 tablet) to agomelatine (25 mg; 1 tablet) at bedtime; she subsequently reported improvements in sleep quality and decreased anxiety. After taking agomelatine for 3 months, the patient complained of general malaise and tea-colored urine. Her liver enzyme levels increased above 3 times the upper limit of the normal range (ALT: 267 U/L, AST: 456 U/L). Liver sonography revealed mild fatty liver and benign liver hemangioma. After excluding possible physical or pharmacological causes of hepatic injury, we immediately discontinued the patient's agomelatine regimen and instead prescribed mirtazapine (30 mg; 1 tablet) before bedtime. Consequently, these liver enzyme levels decreased gradually and returned to normal after 1 month (Table 1).

DISCUSSION

In all our cases, the liver impairment symptoms developed within 1−3 months of agomelatine treatment initiation. After discontinuing agomelatine, the patients' liver functions returned to normal levels. Voican *et al.* [2] reported that even at therapeutic doses, all antidepressants are associated with hepatotoxicity risk. Hepatotoxicity symptoms are typically idiosyncratic and unpredictable, and they generally appear between several days and 6 months after treatment initiation [2].

Although all antidepressants can induce hepatotoxicity, the risk is particularly high in older patients and patients with polypharmacy [2]. In all our cases, the patients

were aged > 60 years and had not been taking multiple drugs; therefore, agomelatine-related acute hepatitis could be considered the most likely underlying condition. In terms of pharmacokinetics, agomelatine is mainly metabolized by hepatic cytochrome P450 (CYP)1A2, CYP2C9, and CYP2C19 enzymes [6]. Patients 1 and 3 continued to take lorazepam, which is not metabolized by the CYP pathway. Although patient 2 had concomitantly taken lurasidone, which is mainly metabolized by CYP3A4, drug–drug interaction was unlikely to increase agomelatine plasma level.

According to a pooled analysis of 4 prospective, noninterventional studies, the incidence of acute hepatitis after agomelatine use was 0.5% [7]. Fulminant hepatic failure has been previously reported in a woman with fatty liver after taking agomelatine [8]. According to a national health insurance database in France, agomelatine did not indicate any significant increased serious liver injury risk [1]. Furthermore, data sources from 4 European countries indicated that compared with citalopram, agomelatine is not associated with an increased risk of DILI hospitalization in routine clinical practice [9]. Compared with sertraline, agomelatine has similar efficacy with fewer side effects [10]. Notoriety bias may increase awareness among physicians; therefore, early detection with drug discontinuation may reduce agomelatine-induced liver injury severity [11]. The reason that older women are prone to DILI is unclear; however, a higher body fat content observed in older women may increase distribution volumes for lipophilic drugs; the fat serves as drug reservoirs and prolongs drug release into circulation. This could also be explained by the elevated body mass index (24–27 kg/m^2, overweight) in all 3 patients. Moreover, aging-related decrease in drug clearance may favor increased concentrations and a prolonged exposure to the toxicity of the drug or its reactive metabolites. According to our case series, agomelatine use remains an underlying cause of acute hepatic risk in patients without hepatic disease.

Varying hepatic injury levels were noted among our patients. Patient 1 exhibited more severe symptoms of acute hepatitis possibly due to the longer duration and higher dosage of agomelatine (62.5 mg per day). Moreover, the incidence of agomelatine-induced transaminase increase is dose-dependent [5]. All the 3 patients experienced clinically improvements in either mood or sleep; however, the benefits did not outweigh the risks. A prompt discontinuation of agomelatine use should be considered in patients with acute hepatitis.

Although there was no increased risk of severe hepatic involvement associated with the initiation of agomelatine use compared to selective serotonin reuptake inhibitors [1], our case series supports the recommendation of transaminase monitoring. Regular surveillance of liver function in older women taking agomelatine, particularly during the initial treatment months, is imperative. Physicians should be attentive and consider discontinuation of agomelatine regimens if acute hepatitis is suspected.

■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Conceptualization: Cheng-Chen Chang, Yen-Jen Chen, and Yi-Cheng Liao. Data acquisition: Yen-Jen Chen and Yu-An Chen. Writing–original draft: Cheng-Chen Chang, Yen-Jen Chen, Yu-An Chen, and Yi-Cheng Liao. Writing–review & editing: Cheng-Chen Chang, Yen-Jen Chen, and Yi-Cheng Liao.

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REFERENCES

1. Billioti de Gage S, Collin C, Le-Tri T, Pariente A, Bégaud B, Verdoux H, *et al. Antidepressants and hepatotoxicity: a cohort study among 5 million individuals registered in the French national health insurance database. CNS Drugs 2018;32:673-684.*
2. Voican CS, Corruble E, Naveau S, Perlemuter G. *Antidepressant-induced liver injury: a review for clinicians. Am J Psychiatry 2014;171:404-415.*
3. Wang SM, Woo YS, Kim NY, Na HR, Lim HK, Bahk WM. *Agomelatine for the treatment of generalized anxiety disorder: a meta-analysis. Clin Psychopharmacol Neurosci 2020;18:423-433.*
4. Gahr M, Zeiss R, Lang D, Connemann BJ, Schönfeldt-Lecuona C. *Hepatotoxicity associated with agomelatine and other antidepressants: disproportionality analysis using pooled pharmacovigilance data from the Uppsala Monitoring Centre. J*

Clin Pharmacol 2015;55:768-773.

5. Gahr M, Freudenmann RW, Connemann BJ, Hiemke C, Schönfeldt-Lecuona C. *Agomelatine and hepatotoxicity: implications of cumulated data derived from spontaneous reports of adverse drug reactions. Pharmacopsychiatry 2013; 46:214-220.*
6. Buoli M, Mauri MC, Altamura AC. *Pharmacokinetic evaluation of agomelatine for the treatment of generalised anxiety disorder. Expert Opin Drug Metab Toxicol 2014;10:885-892.*
7. Laux G, Barthel B, Hajak G, Lemke M, Volz HP. *Pooled analysis of four non-interventional studies: effectiveness and tolerability of the antidepressant agomelatine in daily practice. Adv Ther 2017;34:895-914.*
8. Gruz F, Raffa S, Santucci C, Papale RM, Videla MG, Fernández MG, *et al. [Agomelatine: fulminant liver failure in a patient with fatty liver]. Gastroenterol Hepatol 2014;37:92-94. Spanish.*
9. Pladevall-Vila M, Pottegård A, Schink T, Reutfors J, Morros R, Poblador-Plou B, *et al. Risk of acute liver injury in agomelatine and other antidepressant users in four European countries: a cohort and nested case-control study using automated health data sources. CNS Drugs 2019;33:383-395.*
10. Akpınar E, Cerit C, Talas A, Tural Ü. *Agomelatine versus sertraline: an observational, open-labeled and 12 weeks follow-up study on efficacy and tolerability. Clin Psychopharmacol Neurosci 2016;14:351-356.*
11. Pariente A, Gregoire F, Fourrier-Reglat A, Haramburu F, Moore N. *Impact of safety alerts on measures of disproportionality in spontaneous reporting databases: the notoriety bias. Drug Saf 2007;30:891-898.*