Spontaneous adverse drug reaction reports on patients with cirrhosis

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LETTER TO THE EDITOR

Spontaneous adverse drug reaction reports on patients with cirrhosis: analysis of the nature, quantity and quality of the reports

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Patients with cirrhosis have a high risk of adverse drug reactions (ADRs), in part due to alterations in drug pharmacokinetics [1, 2]. Less is known about pharmacodynamic alterations that could occur because of the pathophysiology of cirrhosis. For example, up to 50% of patients with cirrhosis and ascites that use ibuprofen suffer from renal impairment because ibuprofen potentiates the renal vasoconstriction occurring in cirrhosis [3]. Data on pharmacokinetic changes are obtained during premarketing studies. These are usually single-dose studies, with few participants. Patients with severe cirrhosis are frequently not included [2]. Hence, potential drug safety issues in patients with cirrhosis are often revealed in the post-marketing setting. To obtain more information on ADRs in these patients, we rely on information from clinical practice. One of the tools to do so is spontaneous reports, provided that the quality of clinical documentation is sufficient. Spontaneous reports have been studied in other populations in which pharmacokinetic and pharmacodynamic alterations could occur (e.g. infants [4], elderly [5]), yet no study focused on patients with cirrhosis. Therefore, in this study, we aim to determine the number of spontaneous ADR reports on patients with cirrhosis and the quality of documentation. Furthermore, we analysed the nature of the ADR reports.

We extracted all reports submitted between January 1990 and July 2018 to the Netherlands Pharmacovigilance Center Lareb mentioning "cirrhosis" in the medical history, clinical information or narrative. We excluded duplicate reports, reports with cirrhosis as ADR and reports with an uncertain diagnosis of cirrhosis. The diagnosis was considered uncertain if the report mentioned "possible cirrhosis" or if a liver transplantation was described with no details on disease recurrence. Moreover, the report was excluded if it mentioned "primary biliary cirrhosis", since a large part of these patients does not have cirrhosis yet [6]. The content of the included reports was quantitatively described. The suspected drugs were compared with prescribing recommendations for cirrhosis [7] to assess if any drugs with additional ADR risks were involved.

In total, 50 reports were retrieved from the Lareb database. Twelve were excluded because they were duplicates ($n = 2$), reported about cirrhosis as ADR ($n = 2$) or reported about patients with an uncertain diagnosis ($n = 8$). Table 1 shows some characteristics of the 38 included reports. The severity of cirrhosis was described in 12 reports (32%) and 7 (19%) used a validated severity classification (i.e. Child-Pugh classification).

A total of 58 suspected ADRs were reported and most frequent were as follows: thrombocytopenia, a rash and seizures (all reported thrice). The reports included 43 suspected drugs with pegylated interferon-alpha-2a as most commonly involved ($n = 3$). Of these suspected drugs, four were known to have additional risks in cirrhosis (i.e. pegylated interferon-alpha-2a ($n = 3$) and atorvastatin) [7]. Of the 66 suspected ADR-medicine combinations, the causality according to the Naranjo score was "probable" in 17% and "possible" in 83%. The ADR was mentioned in the drug label in 59% of combinations,

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Table 1 Characteristics of spontaneous ADR reports on patients with cirrhosis

Report characteristics, total number (%)	**38 (100)**
Reporter	
Physician	30 (79)
Pharmacist	5 (13)
Other healthcare professional	2 (5)
Unknown	1 (3)
Seriousness reaction	
Death	3 (8)
Life threatening	5 (13)
Hospitalization	11 (29)
Serious	4 (11)
Non-serious	14 (37)
Unknown	1 (3)
Suspected medicines, total number (%)	**43 (100)**
Number of medicines per report, median (range)	1 (1–3)
Top three most frequently reported drugs, *n* (%)	
Pegylated interferon-alpha-2a	3 (7)
Meropenem	2 (5)
Norfloxacin	2 (5)
Propranolol	2 (5)
Suspected ADRs, total number (%)	**58 (100)**
Number of ADRs per report, median (range)	1 (1–5)
Top three most frequently reported ADRs, *n* (%)	
Thrombocytopenia	3 (5)
Rash	3 (5)
Seizures	3 (5)
ADR-medicine combinations, total number (%)	**66 (100)**
Causality according to Naranjo score	
Probable	11 (17)
Possible	55 (83)
Data on ADR-drug combination	
Described in drug label	39 (59)
Reported in literature (not in drug label)	4 (6)
Not in label, nor in literature	23 (35)

ADR, adverse drug reaction

Table 2 Narrative of two spontaneous adverse drug reaction reports on patients with cirrhosis

Case 1: 64-year-old female with rhabdomyolysis

Clinical history: Cirrhosis due to alcohol use disorder, type 2 diabetes, hypertension and hypercholesterolemia.
Suspected medication: Atorvastatin (already used for 8 years and the last year in a dose of 40 mg twice daily).
Concomitant medication: Spironolactone, hydrochlorothiazide, metformin, tolbutamide, fluvoxamine, paracetamol/codeine, metoprolol, thiamine and nystatin. Nystatin (5 mg four times daily) was started 2 weeks before the event.
Event: Patient was hospitalized for rhabdomyolysis and atorvastatin was stopped. The outcome is unknown.
Previously described: Drug label
Causality (Naranjo score): Possible
Comments: Rhabdomyolysis is a well-known adverse drug reaction of atorvastatin. Atorvastatin is highly cleared by the liver which increases the risk of high plasma levels and rhabdomyolysis in patients with cirrhosis. Pharmacokinetic changes will be larger with an increasing severity of cirrhosis. However, data on the severity of cirrhosis is not provided in the report.

Case 2: 75-year-old female with lactic acidosis

Clinical history: Cirrhosis due to non-alcoholic steatohepatitis (NASH)/auto-immune hepatitis with oesophageal varices, type 2 diabetes, gout, hypercholesterolemia and a hysterectomy.
Suspected medication: Metformin (850 mg twice daily used for 4 years) and spironolactone (increased 3 weeks before the event from 50 mg per day to 200 mg daily).
Concomitant medication: -
Event: Patient was hospitalized for lactic acidosis and both metformin and spironolactone were stopped. She was recovering.
Previously described: Drug label (metformin), not found (spironolactone)
Causality (Naranjo score): Possible (for both metformin and spironolactone)
Comments: Possible interaction between the two medicines; diuretic-induced renal impairment and dehydration may increase the risk of lactic acidosis in patients using metformin. In addition, severe liver dysfunction could lead to reduced tissue perfusion and impaired lactate clearance. Important information is missing in the documentation (i.e. the severity of cirrhosis and renal function parameters).

in literature in 6% and 35% could not be found in the label, nor in literature. All these ADR-medicine combinations were unique; in Table 2, we depicted two ADR reports as example and provided comments on missing data.

To our knowledge, this is the first study examining spontaneous ADR reports on patients suffering from cirrhosis. The number of reports seemed low, suggesting selective reporting or inadequate documentation of cirrhosis as (co)morbidity. Furthermore, the quality of documentation was poor; key data on the diagnosis and severity of cirrhosis were frequently lacking. It is not only important that reporting of ADRs on these patients is encouraged, but also that sufficient patient details are requested during reporting from the treating physicians. The low quantity and quality of reports limited analyses of the nature of ADR reports to explore potential drug safety issues in cirrhosis. To gain more knowledge on ADRs in patients with cirrhosis, data from a pharmacovigilance centre could be combined with post-marketing data from other sources, such as electronic health records.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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