High Prevalence of Ibuprofen Drug-Induced Liver Injury in Spanish and Latin-American Registries

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INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are responsible for 3% to 10% of idiosyncratic drug-induced liver injury (DILI) cases in the Western world.[1–3] Ibuprofen is a widely prescribed NSAID avail- able as over-the-counter medication (OTC), and perceived as having a better safety profile than many other NSAIDs. Interestingly, striking regional differences in the frequency of ibuprofen hepatotoxicity were noted in a comparison of causative DILI agents among large DILI cohorts in 2010.[4] Based on the limited information available on this type of DILI, we aimed to analyze the clinical presentation of ibuprofen-associated hepatotox- icity in the search for a potential drug signature.

METHODS

Twenty-one ibuprofen-induced idiosyncratic hepato- toxicity cases from the Spanish DILI Registry and 5 cases included in the Latin DILI Network were analyzed and compared with 76 idiosyncratic hepatotoxicity events resulting from other NSAIDs and 844 non–NSAID-induced hepatotoxicity cases from the same databases. Only cases induced by conventional medications were included in the current study. All NSAID cases were limited to cases in which the NSAID was judged as a single-culprit drug.

RESULTS

Ibuprofen was the most frequent causative drug (29%) among the 73 NSAID DILI cases in the Spanish DILI Registry, followed by diclofenac (18%). Among the 29 Latin-American NSAID hepatotoxicity cases, nimesulide (38%) predominated, followed by diclofenac (34%) and ibuprofen (17%). Demographics and clinical features, including liver injury pattern and laboratory parameters, did not differ between the 26 ibuprofen DILI patients and those induced by other NSAIDs or non-NSAIDs (Table 1). Hypertension was less prevalent among the ibuprofen cases (10% vs 20%–29%), whereas diabetes was significantly more frequent (27% vs 7%–12%; $P = .04$). Despite not being statistically significant, the ibuprofen cases contained a higher proportion of fatal/liver transplant patients (12% vs 3%–5%) than the other 2 groups.

DISCUSSION

Ibuprofen has traditionally been considered to have very limited hepatotoxicity potential. However, a considerably higher prevalence of ibuprofen DILI cases was noted in the

Spanish DILI Registry compared with previous reports from the United States and Iceland.[2,5] The commercialized oral doses of ibuprofen available for OTC use in Spain are 200 and 400 mg. In the United States, OTC ibuprofen is available only at 200 mg. The fact that ibuprofen consumers in Spain have access to higher OTC doses raises the question of whether the difference in ibuprofen DILI frequency seen between the Spanish and US DILI registries could be related to dosage. It is believed that a threshold drug dose, which may vary between individuals, needs to be exceeded for idiosyncratic DILI to occur. Thus, larger drug doses could increase drug biotransformation rates and trigger excess reactive metabolite formation. As a result, generation of oxidative stress may lead to cellular injury by activating cell death–related signaling pathways. In fact, increased expression of c-Jun N-terminal kinases has recently been demonstrated in liver tissue of DILI patients.[6] Hence, one might hypothesize that higher available OTC dose formulation is more likely to induce a cellular injury process that may lead to ibuprofen DILI in susceptible individuals. A recent multicenter study in Italy reported a higher adjusted risk of liver damage for ibuprofen than for diclofenac.[7] It is interesting to note that ibuprofen also is available as a 400-mg OTC formulation in Italy. Nevertheless, genetic differences and variations in pattern of drug use also may contribute to differential ibuprofen DILI frequencies.

Our study did not show a characteristic drug signature for ibuprofen DILI compared with other causative agents. Although generally developing within 4 weeks from treatment initiation and presenting as a hepatocellular type of liver damage, the characteristics of ibuprofen hepatotoxicity varied considerably be- tween susceptible patients. This most likely reflects the contribution of host and environmental factors in DILI presentation.[8] We detected a trend toward diabetes mellitus being more common in patients with ibuprofen DILI. The implication of this finding is yet to be understood. Diabetes as a general DILI risk factor lacks supportive evidence. Furthermore, diabetic patients are advised to use ibuprofen at the lowest recommended dose for short durations to avoid further alteration of renal homeostasis. We also detected a lower prevalence of hypertension in the ibuprofen cases. This is likely the consequence of ibuprofen as well as many other NSAIDs being issued with a special warning in patients with hypertension because they can attenuate the ef- fects of antihypertensive agents. In conclusion, the risk of developing ibuprofen-induced liver injury is low considering the extensive use of this drug worldwide, but should not be overlooked as it can have life-threatening

consequences. The absence of a distinct drug signature highlights the contribution of individual host and environmental factors in ibuprofen DILI.

REFERENCES

1. Lucena MI, Andrade RJ, Kaplowitz N, et al. Phenotypic characterization of idiosyncratic drug-induced liver injury: the influ- ence of age and sex. Hepatology 2009;49:2001–2009.

2. Björnsson ES, Bergmann OM, Björnsson HK, et al. Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology 2013;144:1419–1425.

3. Chalasani N, Bonkovsky HL, Fontana R, et al. Features and outcomes of 899 patients with drug-induced liver injury: the DILIN prospective study. Gastroenterology 2015; 148:1340–1352.

4. Suzuki A, Andrade RJ, Björnsson E, et al. Drugs associated with hepatotoxicity and their reporting frequency of liver adverse events in VigiBase: unified list based on international collabo- rative work. Drug Saf 2010;33:503–522.

5. Schmeltzer PA, Kosinski AS, Kleiner DE, et al. Liver injury from nonsteroidal anti-inflammatory drugs in the United States. Liver Int 2016;36:603–609.

6. Cubero FJ, Zoubek ME, Hu W, et al. Combined activities of JNK1 and JNK2 in hepatocytes protect against toxic liver injury. Gastroenterology 2016;150:968–981.

7. Donati M, Conforti A, Capuano A, et al. Risk of acute and serious liver injury associated to nimesulide and other NSAIDs: data from drug-induced liver injury case-control study in Italy. Br J Clin Pharmacol 2016;82:238–248.

8. Chen M, Suzuki A, Borlak J, et al. Drug-induced liver injury: interactions between drug properties and host factors. J Hepatol 2015;63:503–514.

Table 1. Comparison of Demographic, Clinical, and Laboratory Parameters Between Hepatotoxicity Cases Induced by Ibuprofen, Other NSAIDs and Non-NSAID Drugs

	Ibuprofen (N=26)	Other NSAIDs (N=76)	Non-NSAIDs (N=844)	*p* value
Demographical data				
Female, n (%)	13 (50)	43 (57)	434 (51)	0.7
Age, mean (range)	51 (18-77)	55 (16-82)	55 (11-90)	0.4
>60 years of age, n (%)	7 (27)	33 (43)	366 (43)	0.8
BMI (Kg/m^2), mean (range)	28 (23-36)	26 (20-36)	26 (16-59)	0.06
Clinical presentation, n (%)				
Jaundice	17 (65)	53 (71)	557 (67)	0.8
Hospital admission	14 (58)	37 (52)	443 (52)	0.9
Eosinophilia	6 (24)	13 (18)	200 (25)	0.4
Lymphopenia	4 (17)	13 (19)	151 (21)	0.8
Positive autoantibodies titers	6 (27)	17 (26)	166 (24)	0.9
Treatment duration, median d (range)	16 (1-1826)	30 (3-550)	29 (1-3724)	0.2
Time to onset, median d (range)	15 (3-1767)	27.5 (3-466)	27 (1-2313)	0.2
Underlying diseases, n (%)				
Hypertension	2 (10)	12 (20)	187 (29)	0.06
Diabetes mellitus	7 (27)	6 (8)	103 (12)	0.04
Type of liver injury, n (%)				
Hepatocellular	15 (58)	51 (67)	499 (61)	0.5
Cholestatic/mixed	11 (42)	25 (33)	319 (39)	
Severity, n (%)				
Mild	9 (35)	25 (33)	263 (31)	1.0
Moderate	14 (54)	40 (53)	464 (55)	
Severe	-	6 (8)	63 (7)	
Fatal / liver transplantation	2 / 1 (12)	2 / 2 (5)	19 / 13 (3)	
Biochemical parameters at onset, mean xULN (range)				
TBL (mg/dL)	5.7 (0.4-26)	7.3 (0.6-34)	7.0 (0.2-46)	0.8
AST	14 (0.9-50)	18 (1.3-134)	15 (0.2-180)	0.7
ALT	18 (1.0-68)	21 (1.2-98)	18 (0.3-203)	0.1
GGT	9.5 (0.5-43)	8.3 (0.3-47)	8.3 (0.2-79)	0.7
ALP	2.3 (0.8-7.1)	2.1 (0.2-8.1)	2.3 0.3-22)	0.6
Cases fulfilling Hy's law criteria, n (%)	11 (42)	30 (39)	276 (33)	0.3
Outcome, n (%)				
Cases resolved in ≤ 1 year from onset, n (%)	11 (85) (n=13)	38 (88) (n=43)	358 (86) (n=418)	0.9

Percentages shown were calculated based on the total number of episodes with available information.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; d, days; GGT, g-glutamyl transferase; TBL, serum total bilirubin; ULN, upper limit of normal.