Assessment of Hy's Law in the Drug-Induced Liver Injury Network (DILIN) Database

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Background

The late Hyman J. Zimmerman observed that hepatocellular (HC) drug-induced liver injury (DILI) with jaundice had a mortality rate of ≥ 10% (Hy's Law), far higher than cholestatic/mixed (C/M) DILI.

The FDA uses Hy's Law to help identify drug applications with unacceptable risk of fatal DILI.

However, Hy's Law does not define whether to use initial or peak liver test values and what constitutes HC DILI.

Aim

To develop a more precise definition of Hy's Law using the DILIN database.

Methods

Drugs implicated in at least 10 cases of DILI in the DILIN Prospective Study were analyzed.

Jaundice was defined as a peak total serum bilirubin ≥ 2.5 mg/dL.

R value was calculated as the ratio ALT/ULN ÷ Alk P/ULN.

Four permutations of Hy's Law were applied:

- *R*≥ 5 using initial or peak ALT levels (within 30 days)
- ALT or AST ≥ 3 times ULN with Alk P ≤ 2 times ULN also using initial or peak values (FDA based criteria).

Mortality was defined as death or liver transplant within 2 years of onset that was adjudicated as primarily due to DILI.

Results

Of 2293 cases enrolled in the DILIN Prospective Study between 2004 and 2021, 1718 were adjudicated as definite, highly likely or probable.

The 30 most frequently implicated agents (10 to 190 per drug) totaled 878 cases including 662 with jaundice.

The mortality rate for jaundiced cases was 6.2% (42/662).

Using initial *R* values, the mortality rates were 11.1% for hepatocellular (HC) vs 2.0% for cholestatic/mixed (C/M) cases (Risk Difference [RD] 9.1%, p<0.001); using *R* values at peak ALT level, mortality rates were 10.3% vs 1.6% (RD 8.7%). (Figure 1)

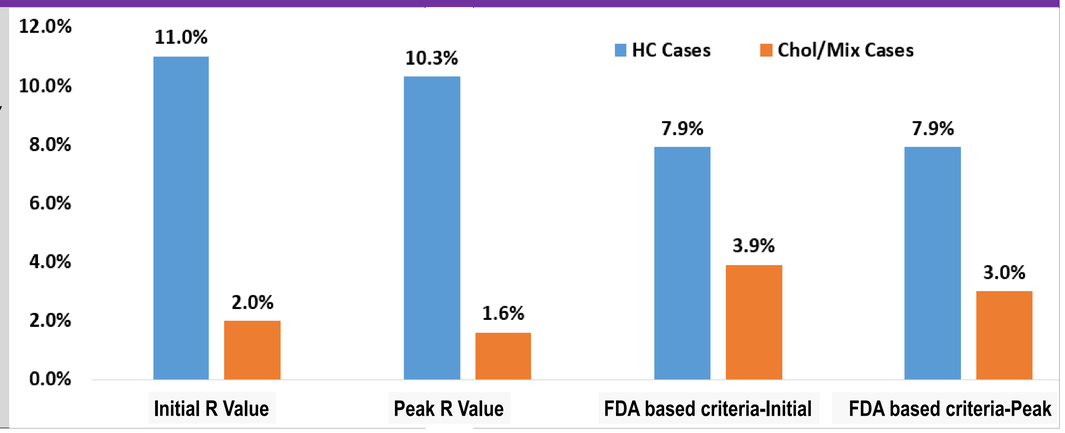
Using FDA based version of HC DILI, mortality rates were 7.9% vs 3.9% (RD 4%) using initial values and 7.9% vs 3.0% (RD=5%) using peak values. (Figure 1)

Because initial *R* identified HC cases with the highest mortality, this definition was used to assess the 30 most frequently implicated drugs individually.

Drugs that frequently caused HC injury (≥ 50% of cases) generally had mortality rates of 10% or greater; while drugs that typically caused C/M injury had low rates (Figure 2). There were, however, striking exceptions of agents with high rates of HC injury that had low mortality rates such as minocycline, lamotrigine, and atorvastatin (all 0%). (Figure 2)

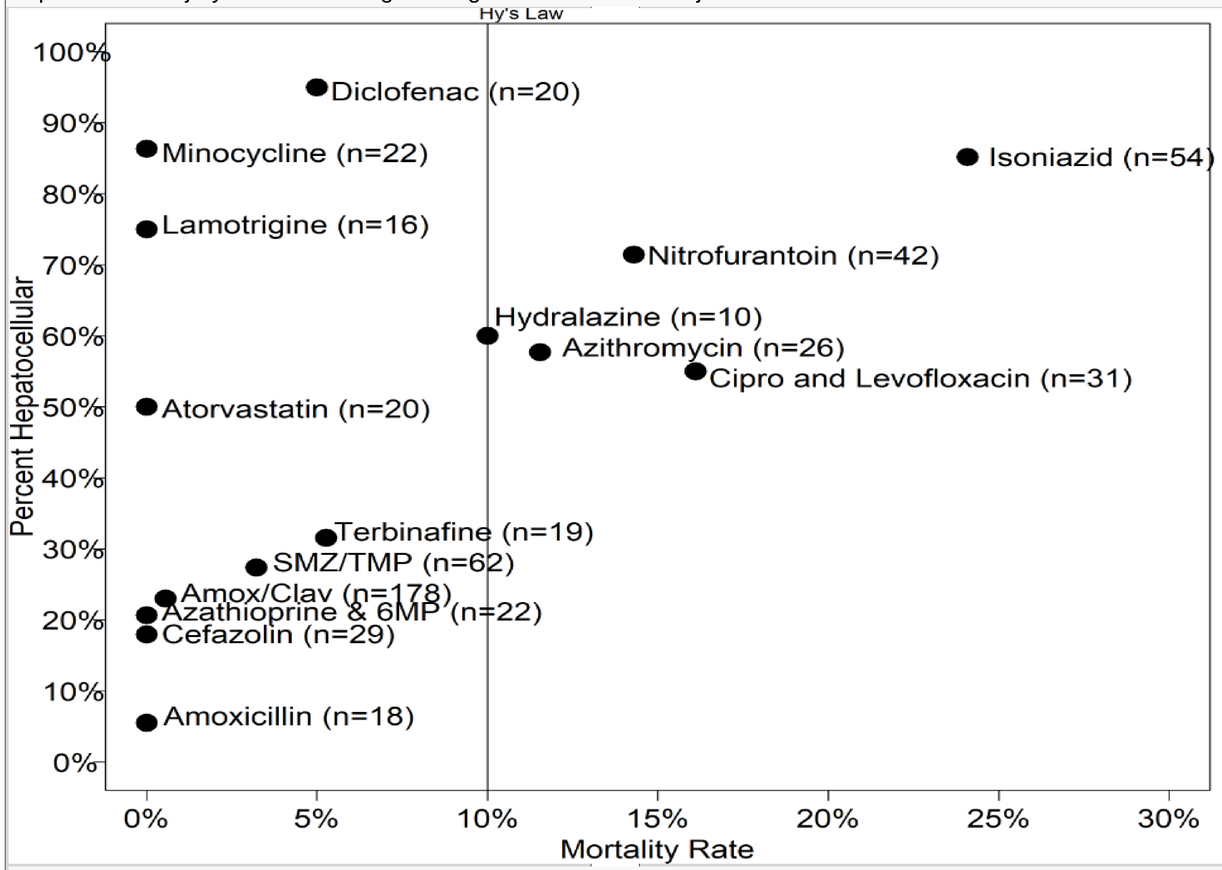
Results

Figure 1: Mortality Rate *Hepatocellular vs Cholestatic/ Mixed, Initial vs Peak*



Results

Figure 2: The mortality rate of DILI attributed to 17 frequently implicated drugs by the proportion of cases with hepatocellular injury. The remaining 13 drugs had fewer than 10 jaundiced cases



The remaining 13 frequently implicated agents all had fewer than 10 cases with jaundice: phenytoin (9), carbamazepine (9), methyldopa (9), amiodarone (9), disulfiram (8), duloxetine (8), infliximab (7), allopurinol (7), interferon beta (7), valproate (7), imatinib (6), ipilimumab (4) and sulfasalazine (3)

Summary

Initial *R* values appeared to be the most sensitive means of identifying Hy's Law cases.

Regardless of the definition used, some drugs that cause hepatocellular injury with jaundice had mortality rates well below 10%.

Conclusion

Hepatocellular DILI with jaundice defined by initial R values ≥ 5 and a initial bilirubin ≥ 2.5 are at the highest risk of mortality.

Mortality risk however remains drug specific.

Further research into drug specific mechanisms of HC DILI and recovery are needed to prospectively assess mortality risk.