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COMMENTARY

How can 'Hy's law' help the clinician?

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XIMELAGATRAN

Dr. Lewis[1] has reviewed over four decades of selected publications on the subject of drug-induced hepatotoxicity, and has summarized his opinions of the messages derived from the work of the late Hyman J. Zimmerman ('Hy' to his many friends and followers). He has also considered the impact of these messages on the current regulatory climate for new drugs under review for approval at the Food and Drug Administration (FDA). He questions what he feels were overly cautious recommendations of an FDA Advisory Committee not to approve the new anti-thrombin agent ximelagatran (EXANTA®, AstraZeneca) because of their concerns about hepatotoxicity,[2] and concludes with an editorial call for fairness, balance, and caution in not over-interpreting what has come to be termed 'Hy's Law.' He concedes that monitoring patients for serial serum activity of alanine aminotransferase (ALT) may have some weaknesses, but pleads that this form of monitoring is the best we have at present and should be kept and used for risk assessment until a better test becomes available.

In taking these positions, Dr. Lewis is well experienced and qualified to provide his opinions. Not only was he a student, colleague, and close friend of Hy Zimmerman, but he also has served often as an expert consultant both to industrial sponsors of new drug applications and at other times to the FDA as a temporary special government employee. At a meeting in April 1999 developed by the FDA's Center for Drug Evaluation and Research on 'Drugs and the Liver: What They Do To Each Other,' Dr. Zimmerman had been asked to speak but was unable, and he asked Dr. Lewis to present the lecture he had been planning since the previous summer. It was at that meeting, which was the last public appearance of Hy Zimmerman before his death in July, that Dr. Robert Temple of the FDA Office of Medical Policy first described publicly the term 'Hy's Law' (or 'Hy's Rule') for the observation that Dr. Zimmerman had discussed at a Fogarty Conference at the National Institutes of Health in 1978.[3] It had been Dr. Temple's experience over more than 20 years that Hy's observation had been valid and clinically useful in many cases, and it had not failed, at least up to then. The term is discussed in a recent review in the journal Hepatology.[4]

'Hy's Law' still is not firmly validated by extensive data analysis, nor is it exactly defined, as Dr. Lewis points out. It is of interest that two very recently published retrospective surveys, from Sweden[5] and Spain,[6] provide clinical support for the Zimmerman observation[7] that 'drug-induced hepatocellular jaundice is a serious lesion.' Hy Zimmerman never called his observation either a rule or law, nor took personal credit for it. He was too modest to do so, although even in the last months of his life he did not disagree with Bob Temple's use of the eponymic term, and he reiterated the narrative description of his findings in the second edition of his definitive text published 2 months posthumously.[8]

The genius of Hy's observation, developed out of his vast consulting experience and his encyclopedic recall of the literature, was that he realized that when enough of the liver cells were injured that the overall organ function became impaired sufficiently to disable the great capacity of the liver to extract, conjugate, and excrete bilirubin from the plasma into the bile (resulting in jaundice), the problem was serious and potentially life-threatening. Implicit in the statement

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were two-key ideas: (1) the liver injury indeed had to be caused by the drug in question and not by a disease process such as viral or other type of hepatitis, or by some other agent, and (2) the main liver injury had to be primarily hepatocellular and not cholestatic, for the latter type of injury is far less immediately threatening to life. Hy never did define quantitatively the hepatocellular injury in terms of how much serum transaminase activity increase was meant, or the jaundice as what specific level of serum bilirubin concentration was needed, nor whether he referred to total bilirubin (TBL) or direct-reacting serum bilirubin. Those numbers need to be examined carefully, determined and defined by analyses of data as to what cut-off points best maximize specificity and sensitivity of the combined test, and for further validation of the principle. But it remains that the fundamental observation is true: if there is enough hepatocellular damage to impair bilirubin excretion, there is a lot of damage and a potential threat to life.

Use of serum transaminase activity (aspartate aminotransferase, AST, formerly known as SGOT, serum glutamic-oxalacetic transaminase; and ALT, formerly known as SGPT, serum pyruvic-oxalacetic transaminase) to measure injury to organs, was first applied in the diagnosis of acute myocardical infarction,[9] before being applied more and more to liver injury. It was based on the seminal work 50 years ago of the then-medical student Arthur Karmen, who developed a rapid spectrophotometric analysis[10] to replace tedious methods using chromatography. It has become routine to measure ALT as an indicator of hepatocellular injury as a tool for both screening and monitoring, as well as for following the course of liver injury and disease. However, it is believed widely but wrongly that ALT is specific for liver cell injury. It has been forgotten that transamination reactions are extensively distributed in many tissues for linking protein and carbohydrate metabolism, and serum ALT elevations may be seen in other settings such as myocardial and skeletal muscle injury, and intestinal epithelial damage in celiac sprue. Further, ALT elevation is not specific for drug-induced injury to hepatocytes but is also seen in viral, ischemic, and autoimmune hepatic injury and in many other liver diseases. Drug-induced liver injury (DILI) is hence a diagnosis of exclusion that requires much more clinical information for correct differential diagnosis.

Measurement of serum bilirubin concentration is an even older liver test than the serum transaminase activity measurement, but it is at least a real measure of one function of the liver, the ability to clear bilirubin from the plasma as it circulates through the liver, to conjugate its two propionic chains on the central pyrroles with one or two molecules of glucuronic acid, and to excrete into the bile the more water-soluble monoglucuronide or diglucuronide derivatives of bilirubin. In contrast to this, it is not really an hepatic function to regulate the plasma activity of enzymes such as the transaminases, whose levels are the net result of the rates of release of enzymes into the blood from injured cells (liver, muscle, heart, gut, etc.) and rates of proteolytic degradation of the enzyme proteins, mainly by cells of the reticuloendothelial system, only some of which (Kupffer cells) are in the liver. It is therefore not correct to refer to serum enzyme activity measures (ALT, AST, etc.) as liver 'function' tests. Other measures, such as the concentration of serum bilirubin, or the plasma prothrombin time (or its internationalized ratio, INR) are more properly measures of overall functions of the liver.

Occurrence of drug-induced hepatocellular injury, indicated by ALT elevations, with elevated total bilirubin is therefore ominous and calls for prompt concern and action. Increases of ALT only, without rises in TBL or other measures of liver function such as INR or prothrombin time, are frequently or even usually reversible, often without even stopping drug administration, because of the great capacity of the liver to develop adaptive tolerance to xenobiotic substances such as drugs. Only in patients who are idiosyncratically hypersusceptible to the DILI, or in whom adaptive or regenerative mechanisms fail, does progressive and serious drug-induced liver damage occur. There is no exact numerical level of transaminase activity elevation alone that predicts reliably whether the injury will become serious (disabling, requiring or prolonging care in hospital, threatening life) or not.

Preclinical animal testing and controlled clinical trials in humans detect and lead to elimination of most of the obviously hepatotoxic drugs. But we are left with the rare but serious hepatotoxicity that develops in the few susceptible individuals who are idiosyncratically different than most people and are unable to adapt to or tolerate ordinary doses of drugs that may be safe for the great majority. We do not yet know how to detect these hypersusceptible persons in advance, how to avoid exposing them to a drug they cannot tolerate. Although serious drug-induced hepatotoxicity is relatively rare, drugs that cause it cannot be ignored and generally are taken off the market, as illustrated by the troglitazone (REZULIN®, Parke-Davis, New York, USA.) story mentioned by Dr. Lewis. In that example, even 1 case of drug-induced acute liver failure per 1000 to 10 000 exposed patients became a real problem when millions were treated.

The low incidence of serious DILI imposes twin problems: (1) it requires that large numbers of exposed

patients be observed in order to detect any cases of idiosyncratically susceptible people, and (2) it demands a reasonably sensitive but extremely *specific* screening test to avoid unnecessary work-up of large numbers of patients who show false positive test results. At present no single test is both sensitive enough to detect nearly all the susceptible patients and at the same time is specific enough (>99.99%) to avoid the falsely positive 'detection' of non-susceptible people. We have observed repeatedly at the FDA that finding even a few cases in a limited number of well-selected participants in controlled trials, especially if the incidence is significantly greater than on control drugs, is predictive of increased numbers of much more serious cases after approval, marketing, and widespread clinical use, when far more numerous and less well selected and observed patients are exposed to the new drug.[11] This was the case for troglitazone and bromfenac, and previously for benoxaprofen, ticrynafen, and other drugs withdrawn after initial approval for clinical use.

The value of Hy Zimmerman's observation is that the *combination* of both ALT and TBL elevations appears to be quite sensitive and is very highly specific for serious liver injury. It may be ironic that two such old tests, ALT and TBL, neither of which by itself is sufficiently specific, can be combined into a far more powerful new test. The clinical insight and inspiration of Hy Zimmerman's observation is now ready to be examined more closely, better defined, validated, and communicated. But additional clinical information beyond serum chemistries must be gathered in order to exclude various liver diseases and non-drug causes. This is best done immediately upon detection of the first abnormalities, whether symptoms or laboratory findings, with initiation of close observation. Because of the low incidence we can afford to do the prompt and thorough work-up of the few patients who show the 'Hy's Law' findings, immediately stop the probably offending drug when true liver functions are becoming impaired, follow and care for the patient as urgently needed. Even in relatively rare cases in which a drug appears to cause or aggravate liver dysfunction, it is important to be fairly sure it indeed was caused by the drug, and to consider the counter-balancing benefits of the drug treatment. One of the currently most challenging issues is accurate attribution of causality, and we do not yet have truly reliable methods to accomplish this. The sometimes-used Roussel-Uclaf Causality Assessment Method (RUCAM) developed by the Council for International Medical Sciences[12,13] is still quite cumbersome and is dependent upon collection of full information for differential diagnosis.[14]

It is becoming clear that monitoring large numbers of patients serially for serum ALT increases has not been successful in detecting or preventing DILI, is costly and inefficient, and is not done well by physicians or patients. Using patient self-monitoring daily of early symptoms, without serial monitoring of serum transaminases, to avoid serious hepatotoxicity from isoniazid prophylaxis[15] illustrates this point. Despite this, after review of the serious cases of liver injury in 6948 study participants on ximelagatran and 6230 on control agents, Lee and other consultants[16] for the sponsor of ximelagatran recommended that ALT monitoring be used. Fixed levels of ALT rise have not been shown to be reliably predictive of serious liver injury and do not allow for harmless adaptation that occurs in large numbers of patients who could continue taking the drug safely. We all would like an ideal test for DILI, but for now it appears that we already have a better test than ALT alone, namely the combined use of ALT and TBL elevations, as proposed by Hy's Law.

Dr. Lewis calls for balance and caution in applying 'Hy's Law' in both regulatory and clinical settings, and for fairness to pharmaceutical developers of new drugs. On the other hand, greater concern perhaps should be focused on the safety of the patients who will receive the new drugs. There are many difficult issues in understanding the mechanisms by which serious DILI is produced in a few susceptible persons, in making accurate attribution of causality, and in searching for biomarkers to identify and protect from exposure the idiosyncratically different persons who are at special risk. Further research is needed to study these challenging issues. It is time to consider and to take action to convene workshops, discuss and debate the issues, initiate and fund research, and conduct prospective safety studies to address these vexing problems.

BROMFENAC

Goldkind and Laine[17] in this issue consider in detail the bromfenac experience, after recently having reviewed the literature[18] on the hepatotoxicity of non-steroidal anti-inflammatory drugs (NSAIDs). Using meta-analytic methods of pooling study results on groups being treated for chronic pain of rheumatoid and osteoarthritis, they found[18] that diclofenac treatment was far more likely to lead to reported ALT elevations and serious DILI than other NSAIDS (ibuprofen, naproxen, meloxicam) or placebo, and rofecoxib more than celicoxib or valdecoxib. Elevations of serum ALT activity, more than threefold the upper limit of the normal range, were 35–90 times

more frequent than serious DILI, which had a reported incidence of 1/2000 or less. For bromfenac (DURACT, Wyeth-Ayerst), approved in July 1997 only for short-term (10 days) use for relief of acute pain, the danger of longer term use of bromfenac had been noted during FDA review[19] of clinical trial data, but it was hoped that labeling instructions for short-term use only would be followed by physicians and patients, and bromfenac was not approved for long-term use for chronic pain of arthritis.

After approval, bromfenac was used for longer periods of treatment than approved, and more severe DILI was observed, leading to withdrawal of the drug by the manufacturer in June 1998 because of reports of four deaths and eight liver transplantations.[20–23] Finding that labeling instructions were not followed in practice, for bromfenac and later for troglitazone,[24] has led to some loss of confidence in relying upon such instructions to protect patients. There is uncertainty as to whether periodic serum enzyme monitoring is fully or even somewhat effective. Despite four letters to practicing physicians in 1997–1999, ALT monitoring failed to be done in practice as instructed for troglitazone. There were reports of rapid progression of troglitazone-induced hepatotoxicity to irreversible acute liver failure, within less than a monthly ALT monitoring interval, in 19 patients.[25] Despite this, Lewis[1] and Lee *et al.*[16] still advocate ALT monitoring for ximelagatran, a new drug that has been proposed for use principally on the basis of convenience to patients in their not needing to have periodic blood testing for prothrombin times to adjust warfarin dosing, but instead would have to have periodic monitoring of ALT levels of activity.

It seems to be time also to re-think, study, and debate the uncertain hope that routine ALT monitoring, which so far has not worked satisfactorily, will protect patients significantly. The two papers[1,17] in this issue on the subject of DILI therefore raise many issues that demand our attention as to what we all should be doing together to address them.

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