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Limits of Labeling and Warnings

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Labeling and Warning

What labeling would say regarding liver injury and monitoring depends on the use of the drug, alternatives, and the nature of the injury. Some cases:

1. Clear Hy's Law cases (say ≥ 2), or severe hepatic injury, available therapy either pharmacologically similar or mechanistically distinct, and no documented advantage over alternatives.

Regulatory conclusion is non-approval (ximelagatran, lumiracoxib, dilevalol) or, upon discovery, withdrawal (bromfenac, troglitazone, pemoline, trovafloxacin); note that even attractive drugs like ticrynafen (a uricosuric diuretic) were withdrawn.

[Overcome by showing effect in non-responders]

Cases (cont)

2. Clear Hy's Law cases, but drug has worthwhile advantages over alternatives.

Drug could be approved or remain marketed with label urging monitoring (isoniazid) or required monitoring/REMS (bosentan) but the monitoring needs to be realistic. E.g., for a serious lifelong illness like pulmonary hypertension, monitoring is feasible/credible and we have seen few fatal outcomes with bosentan. Monitoring, however, did not alter outcomes at least not enough) with troglitazone, either because

- it wasn't done
- it doesn't work (deterioration too rapid)

Cases (cont)

2. Cont (Hy's Law cases but worthwhile)

An issue worth considering.

Does Hy's Law case always have the same implication? Could there be drugs that can cause fatal injury but whose injury is monitorable and, if drug is stopped, reversible essentially all the time? Note, even Hy's Law case is not always fatal (10% or more).

- Troglitazone – seems not
- Bromfenac – seems not
- Isoniazid – usually but not always
- Bosentan – seems yes

Is there a way to anticipate this from the pattern of AT elevation and bilirubin elevation? Seems worth a systematic look.

Cases (cont)

3. AT elevation but no Hy's Law.

As we know, heparin, aspirin, statins, and tacrine all cause AT elevation but rarely, if ever, cause bilirubin elevation or liver failure. Labeling has sometimes called for monitoring (statins did).

Cases (cont)

4. Severe liver injury, even fatal, but very rare, e.g., labetalol, diclofenac, cause severe injury but diclofenac not as bad as bromfenac, ibufenac, etc. and may be COX-2'ish, and labetalol has both beta-blocking and vasodilating properties (i.e., not a typical beta-blocker.

Such drugs remain with warnings and call for monitoring (diclofenac, labetalol) but cause some fatal injuries, either because monitoring doesn't work or isn't done.

Conclusion

Serious hepatotoxicity is not dealt with by labeling or monitoring unless 1) Drug has important benefit (bosentan, isoniazid) or serious injury is very rare (diclofenac, labetalol), and usually for a drug with advantage (labetalol).