Accuracy of hepatic adverse drug reaction reporting in one English health region

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The lack of specific markers for drug induced liver injury suggests that inaccurate reports of hepatic adverse drug reactions are likely to be common, with the diagnosis based on circumstantial evidence and speculation by the reporting clinician.[1] The problems of assessing the cause of drug induced liver injury have led to consensus meetings to establish a standardised framework for evaluating drug hepatotoxicity.[2 3] Using these international criteria, we aimed at evaluating the accuracy of reports of hepatic adverse drug reactions to the Committee on Safety of Medicines in the Northern region in 1992-6. When the cause of liver injury had been incorrectly attributed to a drug we also determined the frequency of missed or delayed diagnoses.

Methods and results

Altogether 188 hepatic adverse drug reactions were reported during 1992-6; 138 case records were available for review during 1997-8, with the consent of those reporting the reactions (101 reports from hospital doctors, 37 from general practitioners). Adverse drug reactions were evaluated on the basis of international consensus criteria.[3 4] Reactions were classified as drug related when there was a clear temporal relation with drug intake and likely alternative causes had been excluded. They were classified as unrelated if either the onset or the course of the reaction did not suggest drug injury[3] in the presence of a confirmed alternative cause for the reaction. Reactions were classified as of indeterminate cause when there was temporal relation between drug intake and the reaction but also a likely alternative cause or no temporal relation but also no alternative cause for the reaction.

Of 138 reactions, 52 were considered to be drug related, 65 unrelated, and 21 of indeterminate cause. Results of follow up liver tests were available 0-2114 (median 120) days after the reaction for hospital patients and 14-2555 (median 99) days after the reaction for general practitioners' patients. Among the 65 patients with reactions unrelated to a drug, the primary underlying diagnoses (table) were unrecognised by the reporting doctor in 35. The delay in reaching the primary diagnosis in these patients was often considerable: a median of 88.5 (range 2-1480) days in the hospital group and 122 (30-982) days in the general practitioner group.

Comment

Using international consensus criteria, we found that almost half of reported hepatic adverse drug reactions are almost certainly unrelated to the incriminated drug. When a new drug is introduced into clinical practice, experience of its effects is limited, so that postmarketing surveillance is essential.[5] By its nature, the reporting of suspected rather than confirmed adverse drug reactions will always lead to reports of reactions that are unrelated to the drug. In future investigations of hepatic adverse drug reaction reports the Medicines Control Agency might use the international consensus criteria as, in addition to identifying true adverse drug reactions, pharmacovigilance is essential to refute false positive reactions.[5]

Inaccurate adverse drug reaction reporting may lead to the correct diagnosis being missed or delayed as well as inappropriate withdrawal of a drug. Even though we cannot prove that the inaccurate adverse drug reaction reports delayed the correct diagnosis, this seems likely in those cases in which investigations such as ultrasound examination and autoantibody profiling were not performed during the initial evaluation.

For patient management, definitely attributing a reaction to a drug should be based on the exclusion of other causes by investigations. More emphasis on the timing of the reaction would increase the accuracy of hepatic drug reaction reports and indicate the need for further investigation where the temporal relation did not suggest drug hepatotoxicity.

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Alternative diagnoses in patients whose reactions were considered unrelated to drugs. In parentheses are numbers of cases in which primary underlying diagnosis was recognised and treated at time that reaction was reported but reaction was incorrectly attributed to a drug

Diagnosis	Hospital reports (n=49)	General practitioner reports (n=16)
Common bile duct stone	8 (0)	4 (0)
Ischaemic hepatitis	8 (7)	2 (1)
Autoimmune hepatitis	6 (1)	2 (0)
Systemic sepsis	7 (6)	5 (5)
Alcoholic liver disease	3 (1)	0
Gilbert's syndrome	3 (0)	0
Hepatitis due to Epstein-Barr virus infection	2 (1)	0
Hepatitis due to cytomegalovirus infection	2 (0)	0
Steatosis	2 (0)	1 (0)
Postictal (as indicated by raised muscle enzyme level)	1 (1)	1 (1)
Lymphoma	2 (0)	0
Paracetamol overdose	2 (2)	0
Cholangitis	1 (1)	0
Thyrotoxicosis	1 (1)	0
Hepatitis B cirrhosis	1 (0)	0
Cryptogenic cirrhosis	0	1 (0)

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