Consensus

Criteria of drug-induced liver disorders
Report of an International Consensus Meeting*

Summary

International reporting of adverse drug reactions by pharmaceutical manufacturers to national drug regulatory authorities requires internationally accepted standard definitions of reactions and criteria for assessment of causality. The Council for International Organizations of Medical Sciences (CIOMS) undertook a pilot project to prepare such definitions and criteria, and proposed to use as its model a series of expert consensus meetings organized in France by the pharmaceutical company, Roussel Uclaf, with the participation of the official French network of pharmacovigilance. Under CIOMS auspices, an international meeting was organized to test the feasibility of adapting for international use the outcome of the French consensus meetings on drug-induced liver disorders. The meeting resulted in a series of proposed standard designations of drug-induced liver disorders and criteria of causality assessment.

The need for standard definitions of adverse drug reactions

The lack of universally standardized definitions of adverse drug reactions has been a daily problem for those concerned with drug safety. To describe an adverse event occurring during clinical trials and in the post-marketing period, doctors use terms derived from their medical education or their preconceptions of the mechanisms of reactions to drugs. The regulatory authority of the pharmaceutical firm records this information in either the reporter's terms or other terms considered equivalent and chosen from an internationally agreed terminology. However, there are several international terminologies, which are not identical, and which are difficult to compare since the terms they propose have not been defined on either a scientific or a practical basis.

Medical-dictionary or textbook definitions of the most frequent or severe adverse drug reactions are often contradictory and not usable in practice. Generally, these definitions are based on findings of laboratory examinations, which are not readily available. However, an accurate term must be used for each adverse reaction to record, report or list it, and to comply with regulatory requirements concerning its labelled or unlabelled nature or severity. Assessment of the benefit/risk ratio of a drug takes into account not only the incidence but also the severity of its adverse effects. Thus, lack of a definition of the reaction and a measure of its severity may result in the use of inaccurate or misleading terms, induce bias in evaluating safety and lead to unjustified actions.

Criteria for assessing causality of adverse drug reactions

After recording the information with the help of one of the terminologies, the next step is to assess the causal re-

* This report, prepared by Dr. C. Bénichou of the Division of Pharmacovigilance of Roussel Uclaf, Paris, is the outcome of the work of an international group of experts (listed in Annex 1), which met for 2 days in Paris in June 1989 under the chairmanship of Prof. J.P. Benhamou. The meeting, held under the auspices of the Council for International Organizations of Medical Sciences (CIOMS), was organized by Dr. Bénichou and Dr. G. Danan, also of Roussel Uclaf. CIOMS gratefully acknowledges its indebtedness to Roussel Uclaf and to all the members of the group, and especially to Dr. Bénichou, whose contribution at all stages was crucial.

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relationship between the reported event and the suspected drug. This phase is intuitive for the reporter, but the specialist, in either the pharmaceutical industry or the regulatory authority, bases assessment on a defined method. There are numerous methods of assessing causality, according to criteria that refer to such factors as:

(i) The chronology of the administration of the drug, and especially the intervals between the beginning or the end of treatment, and the apparent onset of the reaction.
(ii) The course of the reaction when the suspected drug has been stopped (or continued).
(iii) The respective roles of drugs and diseases in the etiology of this type of reaction.
(iv) The response to the readministration of the drug.
(v) The results of laboratory tests.
(vi) Previous knowledge of the toxicity of the drug.

Such methods have been described by independent investigators, pharmaceutical companies and national administrations. Certain concentrate on specificity, others on sensitivity. None is accepted universally.

The degree to which reactions conform to criteria may be graded either qualitatively or quantitatively. For example, the interval between administration of a drug and onset of a reaction can be described as strongly suggestive, suggestive, compatible or incompatible, or it may be scored 0 to 3. Similarly, the observed course of the reaction may be described as being strongly suggestive of, weakly suggestive of, or incompatible with a drug etiology. The main object of causality assessment is to translate into quantitative or semi-quantitative terms the probability of a given clinical condition having been caused by a drug. This is based on the judgement of specialists. One major difficulty in setting up a universal method applicable to all types of adverse reaction is that different types of adverse reaction require different weighing of criteria. Clearly, in practice, the weighing of criteria should be adapted to the type of reaction.

Series of French consensus meetings on standardization of definitions of reactions and causality assessment criteria

An attempt to standardize definitions of reactions and criteria of assessment was undertaken in France at the instigation of the Roussel-Uclaf Group, which organized consensus meetings with the participation of representatives of the official French network of pharmacovigilance. Experts from the universities were invited for their standing in their specialties and their expertise in drug toxicity. The initial object of these meetings was to define the main types of adverse reactions. It was clearly important to take into account the average quality of information contained in spontaneous reports, since only rarely did these reports include all the clinical and biological data needed for scientific assessment. Histological data are generally absent and cannot be obtained when the report is received by the administration or the pharmaceutical industry. Therefore the proposed definitions should not be dependent on the availability of all possible data. Equally, the other extreme had to be avoided – of adopting too wide a definition, which would allow uncritical recording of any information. The consensus-meeting groups therefore had to formulate definitions that would apply to the great majority of clinical conditions associated with drug use. The objective was to provide definitions for at least 90% of cases. Once these definitions were prepared, the terms proposed by the WHO Adverse Reactions Terminology were analysed and the terminology discussed. Finally, for each type of adverse reaction, the consensus group defined the different criteria, the role of medicines in general and the main non-drug etiologies, and made a list of relevant investigations.

Different categories of adverse reactions were studied: liver and blood disorders, acute renal failure, interstitial pneumonitis, allergic vascular purpura and photosensitivity. The conclusions of the consensus meetings have been published (1–11), and for the last 2 years have been used by several French regional centres of pharmacovigilance and a number of pharmaceutical firms. Increasingly, publications describing adverse drug reactions refer to these consensus meetings for the definitions of reactions and criteria for assessing causality. This assessment has become reproducible and the use of a common language represents substantial progress.

International consensus meeting on definitions of drug-induced liver disorders

The Council for International Organizations of Medical Sciences (CIOMS), in 1986, organized a working group of representatives of multinational pharmaceutical manufacturers and regulatory authorities to devise and test a standard international report form and procedure whereby manufacturers would report to regulatory authorities adverse drug reactions occurring in foreign countries (12). In June 1989 the working group had accomplished its task and a number of countries had adopted the procedure. At the suggestion of the working group, CIOMS then undertook to implement a project to establish internationally agreed definitions of adverse drug reactions and criteria for the assessment of causality. CIOMS took as its model for the project the series of French consensus meetings described above. In view of the experience of
Roussel Uclaf with these meetings, CIOMS requested Roussel Uclaf to organize a pilot international consensus meeting of experts to adapt the conclusion of the French consensus meetings on drug-induced liver disorders, and to prepare the report of the meeting.

Accordingly, under the auspices of CIOMS, Roussel Uclaf convened the meeting in Paris on 12–13 June 1989 (Annex 1: list of participants). It discussed the conclusions of the French consensus meetings on the subject, defined the principal drug-induced liver reactions, defined and graded criteria of causality assessment, and listed the principal etiologies according to type of reaction. The conclusions of the meeting are presented below.

Designations of drug-induced liver disorders on the basis of liver-test abnormalities

I. When liver biopsy or autopsy has been performed, the lesion should be named according to the histological findings - e.g. 'cirrhosis', 'chronic liver disease', 'hepatic necrosis' or 'hepatitis'.

II. In the absence of histological data, such terms as 'hepatitis', 'hepatic necrosis', 'chronic liver disease' or 'cirrhosis' should not be used in reporting. The preferred term is 'liver injury'. The signs and symptoms of liver injury (asthenia, abdominal pain, nausea, vomiting, pruritis, jaundice) are not specific enough to ascertain a liver disorder. Confirmation of liver injury is based on results of biochemical tests of the liver. The term 'liver tests' should be used instead of 'liver function tests'.

(1) Liver injury

The term 'liver injury' should be used if there is an increase of over 2 $N$ (upper limit of the normal range) in ALT (alanine aminotransferase) or CB (conjugated bilirubin) or a combined increase in AST (aspartate aminotransferase), AP (alkaline phosphatase) and TB (total bilirubin) provided one of them is above 2 $N$. No other biochemical test is specific to liver disorder.

Liver injury is designated 'hepatocellular' when there is an increase of over 2 $N$ in ALT alone or $R \geq 5$. Where $R$ (ratio) is serum activity of ALT/serum activity of AP. (Each activity is expressed as a multiple of $N$. Both should be measured together at the time of recognition of liver injury.)

Liver injury is designated 'cholestatic' when there is an increase of over 2 $N$ in AP alone or $R \leq 2$.

Liver injury is designated 'mixed' when both ALT (above 2 $N$) and AP are increased, and $2 < R < 5$. The ratio ($R$) is of most use in patients with jaundice. $R$ may vary during the course of the liver injury.

'Acute liver injury' is considered present when these increases have lasted less than 3 months.

'Chronic liver injury' is considered present when the increases have lasted more than 3 months. (It should be distinguished from 'chronic liver disease', which may be used only on the basis of histological findings.)

The term 'severe liver injury' is used in the presence of (in order of increasing severity):

- jaundice
- prothrombin* $<50\%$ (or equivalent)**
- hepatic encephalopathy

'Pulmonary liver injury' is the term used to designate rapid (days to weeks) development of hepatic encephalopathy and severe coagulation disorders.

(2) Abnormalities of liver tests

Isolated increase even over 2 $N$ in AST, AP or TB should be considered only a biochemical abnormality and not necessarily a sign of liver injury.

When the increase in ALT, AST, AP or TB is between $N$ and 2 $N$, the term 'abnormality of liver tests' should be used and not 'liver injury'.

Causality assessment of drug-induced liver injury: acute hepatocellular liver injury

(1) Time to apparent onset of the reaction (Table 1)

<p>| TABLE 1 |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Suggestive from onset of drug administration</th>
<th>Compatible from onset of drug administration</th>
<th>from cessation of drug administration</th>
<th>Incompatible from onset of drug administration</th>
<th>from cessation of drug administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial treatment</td>
<td>5–90 d</td>
<td>&lt;5 or &gt;90 d</td>
<td>$\leq 15$ d</td>
<td>Drug taken after the onset of the reaction</td>
</tr>
<tr>
<td>Subsequent treatment</td>
<td>1–15 d</td>
<td>&gt;15 d</td>
<td>$\leq 15$ d</td>
<td></td>
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</tbody>
</table>

* Valid only after parenteral administration of vitamin K.
** May be expressed as decrease in prothrombin concentration or prolongation of prothrombin time.
(2) Course of the reaction

After cessation of the administration of the drug:

The course is very suggestive if there is decrease of ALT ≥ 50% of the excess over the upper limit of normal within 8 days and no additional elevation of ALT within a month. The course is suggestive if the decrease of ALT ≥ 50% within 30 days.

The course is not suggestive i.e., against the causal role of the drug, if the variations in level of ALT are different from above.

The course is inconclusive if there is no information regarding liver tests.

If the drug is continued:

The course is always inconclusive as regards causality assessment, i.e., no reliable conclusion can be drawn.

(3) In case of readministration of the drug

The response is positive if there is at least a doubling of ALT irrespective of date, duration or combination with other uninterrupted drugs.

The response is negative if the increase is less than N, provided the drug has been given in the same dose, for the same duration and with the same combined drugs as for the first administration.

The response is uninterpretable under other conditions.

(4) Information to be collected to permit the most accurate assessment of causality

Information about the patient.

— Age
— Sex
— Underlying disease or condition
— Weight
— Height

Important risk factors in the development of drug-induced liver injury.

— Use of one or more other drugs at the same time as the suspect drug, with accurate record of dates and times of administration.
— Use of alcohol (amount, regularity, duration).

(5) Information or results of investigations to exclude non-drug-related causes of liver injury.

— Alcohol-induced injury, which is suggested when the ratio AST/ALT ≥ 2

— IgM anti-HBe, which indicates recent infection by hepatitis B virus (HBV)
— IgM anti-HAV, which indicates recent infection by hepatitis A virus (HAV)
— non-A, non-B hepatitis: anti-hepatitis C virus (HCV) antibody (which may be present only after 1 or 2 months—sometimes 4 months—following acute phase of liver injury), and/or circumstantial evidence, including administration of blood or blood products between 2–6 months previously, or recent travel to areas where hepatitis is endemic.
— Ultrasonography of the liver and biliary tract to exclude cholelithiasis and biliary tract abnormalities.
— Episode of recent acute hypotension
— Results of tests to determine recent infection by cytomegalovirus (CMV) or Epstein-Barr virus (EBV) (optional).

Causality assessment of drug-induced liver injury: acute cholestatic or mixed liver injury

(1) Time to apparent onset of the reaction (Table 2)

(2) Course of the reaction

After cessation of the drug.

The course is suggestive if reduction of at least 50% of the excess above the upper limit of normal of AP and/or total bilirubin occurs within 6 months.

The course is intermediate if this reduction is < 50% within 6 months.

The course is inconclusive if the levels are stable or increase.

If the drug is continued:

The course is always inconclusive as regards causality assessment, i.e., no reliable conclusion can be drawn.

(3) Readministration

The response to readministration is positive if there is at least a doubling of AP irrespective of date, duration or combination with other uninterrupted drugs.

The response to readministration is negative if the increase is lower than N and if the drug has been given in the same dose, for the same duration and with the same com-

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TABLE 2
bined drugs as for the first administration.

The response to readministration is *uninterpretable* under other conditions.

(4) Information to be collected to allow the most accurate assessment of causality

--- Information on the patient.
--- Age
--- Sex
--- Weight
--- Height
--- Underlying disease or condition

--- Important risk factors in the development of drug-induced liver injury.
--- Use of concomitant drugs, with accurate record of dates and times of administration
--- Use of alcohol (amount, regularity, duration)
--- Pregnancy

(5) Information or investigation to exclude non-drug-related causes of liver injury.

--- Ultrasonography of the liver and biliary tract to exclude cholelithiasis and biliary tract abnormalities
--- History of alcohol-induced injury, which is suggested when the ratio AST/ALT is 2
--- IgM anti-HBc, which indicates recent infection by HBV
--- IgM anti-HAV, which indicates recent infection by HAV
--- Non-A, non-B hepatitis: anti-hepatitis C virus (HCV), antibody (which may be present only after 1 or 2 months—sometimes 4 months—following acute phase of liver injury), and/or circumstantial evidence, including administration of blood or blood products between 2–6 months previously, or recent travel to areas where hepatitis is endemic.

List of participants (Annex 1)

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References