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Editorial

DICLOFENAC (VOLTAREN: VOLTAROL)-ASSOCIATED HEPATOTOXICITY

The television report on Cable News Network (CNN) on 9 August 1993 on the exceptionally large numbers of reports in the USA of hepatitis and jaundice associated with intake of diclofenac leading, in an appreciable number of cases, to death is indeed of much concern. All kinds of issues are raised, namely:

(a) How many reports of adverse drug reactions (ADRs) are necessary before action should be taken?

(b) What is the nature of action in this case?

(c) What are the responsibilities, regarding proper conduct of enquiries and in taking preventive action, of the company marketing the drug, the government regulatory agencies (e.g. Food and Drug Administration (FDA)), and legal–political authorities.

(d) Why is so little known about the causes of side-effects, such as hepatotoxicity from NSAIDs, which are not uncommon.

The last question provokes a real issue: Why Medical Research Councils and organizations and companies alike do not take more action and support research on such important side-effects as hepatotoxicity from NSAIDs. The zeal with which research is sponsored on the more popular topics, such as the human genome project and the biological basis of homosexuality, contrasts with the appalling disinterest in such important issues as the side-effects of NSAIDs in general.

The 'diclofenac–hepatotoxicity' case, as it may now be known, has several important features. The human issue was exemplified by the CNN report concerning the tragic death from diclofenac hepatotoxicity in 1990 of Cheryl Fleischner whose family are now suing the Ciba Geigy Corporation, USA, for *inter alia* false advice on the hepatotoxicity of diclofenac. True enough, hepatotoxicity of the drug was well known at the time of its approval and introduction into the USA in the late 1980s [1–4]. The FDA agonized over this issue and finally agreed to a package warning of this problem, noting also that hepatotoxicity is observed with other NSAIDs [1]. Now the issue is one of 'grade' or 'severity' and frequency of the occurrence of hepatotoxicity from diclofenac compared with that from other NSAIDs. Aspirin and salicylate are well known to be associated with hepatitis but it appears to be particularly apparent in patients with systemic lupus erythematosus and severe rheumatoid arthritis [5]. The tragic story of benoxaprofen (Opren) which, in the early 1980s, was withdrawn worldwide because of hepatotoxicity, probably secondary to drug accumulation in arthritic patients with renal insufficiency, is another relevant case [6]. Many authorities and scientists agree that, in other respects, benoxaprofen

was a major advance in therapy of arthritic diseases. Had the drug been better managed by the medical profession, the conditions under which drug accumulation developed and, most importantly, the factors leading to the development of hepatotoxicity and mechanisms thereof, appropriate preventive action could have been taken. After all, we must not forget that it is a very rare drug indeed which will not be without side-effects, many of them serious, especially those drugs destined for long-term use in chronic diseases, e.g. arthritis. It could be argued that it would be better to understand the reasons for and mechanisms of side-effects of NSAIDs and devise appropriate preventive measures than to develop newer NSAIDs which often produce the same range and type of side-effects. Why must we continue to re-invent the wheel?

Returning to the diclofenac case, an FDA expert, Dr H. Zimmerman, stated, in the CNN report, that over 180 cases of diclofenac-associated hepatotoxicity had been reported to this agency, 79 of which manifested as jaundice and 18 of which resulted in death. Surely this must be a similar rate to that of benoxaprofen a decade ago? Dr Zimmerman rightly points out that these are probably considerable under-estimates of the ADR profile of diclofenac, since the reporting of ADRs is known to be low in the USA and is subject to a range of factors. The CNN report states that a Federal Grand Jury is now enquiring into the diclofenac case in New Jersey, USA and, no doubt, comments from the company and FDA will be subject to subjudice limitations for the present.

What we, as scientists, should probe in greater detail are the conditions and mechanisms underlying the development of diclofenac- and NSAID-associated hepatotoxicity. Lessons may be learnt from the benoxaprofen case and from other NSAIDs. What has always surprised me is that very little emphasis is ever placed on the analysis of clinical reports on prior and concomitant drug use, the disease state and, especially, concurrent disease(s). Some reports are notably deficient in providing these important elements. One only has to look over the reports of benoxaprofen hepatotoxicity to observe that an appreciable number of the patients had consumed paracetamol (acetaminophen), a well-known irreversible hepatotoxin.

This may be a highly significant point, worth examining with diclofenac, since it has been known for 2–3 years that, under some conditions in mice, diclofenac may interact synergistically with paracetamol (or vice versa!) to enhance its hepatotoxicity [7]. The biochemical mechanism for this has been investigated to a limited extent and, in one study, it appears that a quinine-imine metabolite of diclofenac is produced in mice [7]. It is presumed that this has the properties of the same metabolite produced in the liver from paracetamol under conditions of glutathione (GSH) deficiency [7,8]. The quinine metabolite of paracetamol covalently binds to liver proteins and nucleic acids and this appears to underly the irreversible nature of paracetamol hepatotoxicity in poisoning [2,8]. By analogy, the quinine-imine metabolite of diclofenac might also react with liver biomolecules, leading to the same consequences [7].

Given, however, the limited information available some 2–3 years ago, one wonders why cautions against concurrent therapy with paracetamol and ingestion of ethanolic beverages (which are well known to deplete glutathione and are intrinsically hepatotoxic) was not considered by the company, the FDA and indeed other authorities alike?

Also, if a drug is likely to produce a hypersensitivity reaction like hepatitis, as is suspected with diclofenac, then why is the drug, like other hepatotoxic NSAIDs, co-prescribed with immunosuppressive and other drugs which may exacerbate the hypersensitivity conditions or may affect immune surveillance in the liver?

What about the complexity of drug–drug and drug–disease interactions evident in patients receiving NSAIDs? This journal has had several articles and editorials emphasizing these points. One only has to look at a typical case report to throw up one's arms in horror at the number and type of drug combinations which have been prescribed (but about which there is very little information on the quantities given) in relation to the development of side-effects and progress of disease(s) being treated. The medical profession often prescribes combinations of drugs that overburden the liver detoxification reactions as well as other physiological and biochemical defensive reactions. The lack of care and awareness in this profession is of particular concern. It behoves those submitting case reports to be more vigilant about the above details; from the point of view of hepatotoxicity from drugs such as diclofenac and paracetamol, it should be mandatory to estimate total drug intake since these drugs may, like cytotoxic agents, display a relationship between side-effects and accummulative toxicity.

When is there going to be a qualified warning that NSAIDs should not be taken with more than say one or two units of alcohol per day? (The limit is intended to make some reasonable allowance for intake of wine which is part of the lifestyle in many countries.) Most especially, caution is required regarding NSAID intake in those with a high alcohol consumption and monitoring of these patients is especially important.

Finally, as far as diclofenac is concerned, there are other potential consequences from hepatotoxic effects of this drug which may be undetected. The recent spate of reports on the development of diaphragm-like strictures in the small and large intestine with this drug [9–12] is of particular concern. This may arise in conditions of abnormal liver function if, say, active metabolite(s) of the drug are excreted into the bile from the liver and thence accumulate in mucosal cells in the intestine.

Clearly, there are many important and emotive issues in the diclofenac case and they should be considered in the wider context of NSAID use. All aspects of medical practice must be considered in the apparently innocent process of prescribing a drug. There is clearly an urgent need for more accurate reporting of ADRs of all kinds associated with NSAIDs, and, as far as the diclofenac case is concerned, all other drugs which have been prescribed and disease factors should be sought with vigilance while they are fresh in everyone's mind. We urgently need research on the hepatotoxicity of NSAIDs. Hopefully, pressure will be brought to bear upon the research granting agencies to face the realities of the need for funding of research on all major side-effects of NSAIDs, perhaps with financial input from company sources in a manner which would remove the possibility of bias from this type of support.

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