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Incidence of hepatitis induced by non-steroidal anti-inflammatory drugs (NSAID)

Netter *et al*¹ reported the incidence of hepatitis due to NSAID after a French drug surveillance study in 1985.² This work, which is regularly cited in reference books and other publications,^{3,4} has been updated with the results of a second cooperative study carried out in the same way, by the same team, to compare and measure any changes in risk after a three year interval. As we have pointed out,⁵ this approach should minimise the bias inherent in such studies of drug surveillance.

In 1989 the drug surveillance centres collected 51 cases (30 women and 21 men) [the comparable figures for 1985 were 56 cases—37 women and 19 men] of hepatitis associated with NSAID in patients without any previous history of hepatic disorder. They comprised acute cytolytic hepatitis (7)

Changes in incidences of hepatitis (cases per months of treatment) due to NSAID in France

Group	Incidence of hepatitis	NSAID	
		1985	1989
1	> 1/50 000	Oxyphenbutazone	
2	1/50 000 to 1/100 000	Isoxicam, pirofen, sulindac	Pirprofen, fenbufen, phenylbutazone
3	1/100 000 to 1/300 000	Fenbufen, ibuprofen, indomethacin, ketoprofen	Ketoprofen, sulindac, diclofenac, mefenamic acid
4	1/300 000 to 1/500 000	Diclofenac, piroxicam	Ibuprofen, etodolac, piroxicam, tenoxicam
5	< 1/500 000	Flurbiprofen, sodium naproxen, niflumic acid, tiaprofenic acid	Indomethacin, sodium naproxen, niflumic acid, tiaprofenic acid, fenoprofen

[24], acute cholestatic hepatitis (17) [9], or mixed hepatitis (7) [15]. The remainder were subclinical biochemical abnormalities (20) [8].

In 1989 all patients recovered after the drug was stopped [in 1985 three patients died].

On the basis of the later study, NSAID were reclassified according to the incidence of hepatitis expressed as the number of cases per months of treatment, and the 1985 and 1989 classifications are compared (table).

It is noteworthy that: (a) two drugs in groups 1 and 2 in 1985 were withdrawn from the market that year: oxyphenbutazone because of haematological toxicity and isoxicam because of skin toxicity; (b) pirprofen, which was eventually withdrawn (in 1990) because of hepatic toxicity with, according to the manufacturer,⁶ a frequency of one case per 69 000 months of treatment, was in group 2 in both of our studies; (c) piroxicam and tenoxicam, which were put on the market at different times (1981 and 1988 respectively), were both in group 4 in 1989.

The hepatotoxicity of NSAID has been the subject of reports for some years.⁴ From these reports and our pair of studies emerge a number of broad ideas about NSAID induced hepatotoxicity:

- side effects are non-negligible, with regard to either morbidity or mortality
- different chemical structures can produce similar hepatotoxic responses
- older women greatly predominate among affected patients
- a hepatotoxic response is unpredictable and sometimes is unaccompanied by symptoms
- when a drug is reintroduced, side effect is frequently more sudden and severe, thus the readministration of the same drug must be strictly avoided
- these hepatotoxicities are difficult to inves-

tigate for a number of reasons: blood test findings are extremely variable and may show cytolytic, cholestatic, or mixed pattern effects; the clinical picture may or may not suggest an immunoallergic response; the histology is rarely pathognomonic; and, finally, little is known about the mechanisms that initiate it, and little basic research has been done on the subject.

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