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REPLY

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Letter to the editor by Drs. Gatti and Bertazzoli entitled "Evaluation of isolated case reports on hepatotoxicity"

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The authors appreciate the comments by Drs. Gatti and Bertazzoli concerning our case report on fatal hepatotoxicity secondary to the non-steroidal antiinflammatory drug (NSAID) nimesulide. We have taken up the criticism that our method for calculating the odds ratio for hepatic adverse effects is not applicable since nimesulide and COX-2 selective NSAIDs confer a smaller risk of gastrointestinal side effects, thus rendering the denominator of our odds ratio calculation too variable. We have repeated the odds ratio analysis on unsolicited reports of drug-related side effects registered in the World Health Organization database (online search kindly performed by R. Stoller from the Pharmacovigilance Centre of the "Interkantonale Kontrollstelle für Heilmittel" IKS, Bern, Switzerland). To test the hypothesis of Drs. Gatti and Bertazzoli, we have compared the proportion of hepatic side effects in relation to (i) the total number of reported side effects and (ii) the total number of reported side effects excluding gastrointestinal side effects. As shown in Table 1, exclusion of adverse reports related to the gastrointestinal tract does not change the odds ratio estimate, thereby invalidating this concern. In contrast to nimesulide, which clearly shows the highest odds ratio for hepatic adverse effects of all NSAIDs (Table 1), the odds ratio of the coxib celecoxib is only 0.8 (95% confidence interval 0.6, 1.0) in comparison with ibuprofen.

The second comment of Drs. Gatti and Bertazzoli questions our assumption that the total number of reports approximately reflects the relative prescription frequencies, since not all NSAIDs exhibit similar frequencies in causing hepatic and gastrointestinal ADRs. We entirely agree that calculation of an absolute risk is undoubtedly the best measure of the importance of a drug-side effect association, since it indicates how commonly an ADR is likely to occur in a group of exposed individuals. However, for the calculation of absolute risks it is essential that the primary data sources for the drugs in question are comparable. In the absence of rigorously controlled randomised trials or of comprehensive pharmacoepidemiological databases, the likelihood of confounding biases that compromise the validity of the results is no less than in the observational approach adopted by us. For nimesulide, the absolute risk is calculated from the number of spontaneous reports divided by the sales figures. However, underreporting is a well-established serious problem for spontaneous report systems [1, 2]. Because nimesulide is mainly marketed in countries with a low frequency of ADR reporting in relation to population size, the problem of underreporting is further aggravated. We would like to emphasise that the relative risk or odds ratio is the most frequently reported epidemiological parameter and is well suited for establishing an association between a drug and an ADR in the context of an established causality.

The third concern relates to the increased reporting rate secondary to the sharpened awareness of and sensitisation to a particular side effect of a drug. As shown in Table 2, it is of note that the odds ratio for nimesulide was already significantly elevated (9.6 in comparison with ibuprofen in 1996/1997) before the first report of nimesulide-induced acute liver injury was published in 1998. This excludes the possibility of a reporting bias secondary to publications in the literature and is a further indication that nimesulide indeed causes hepatic ADRs more frequently than other NSAIDs.

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Table 1 Spontaneous reports registered in the World Health Organization database of hepatic side effects related to selected non-steroidal anti-inflammatory drugs (NSAIDS). Influence of the exclusion of gastrointestinal (GI) side effects on odds ratio estimate. The following categories were considered to represent hepatic side effects: ''bilirubinaemia'', ''bilirubinaemia aggravated'', ''coma hepatic'', ''hepatic cirrhosis'', ''hepatic failure'', ''hepatic necrosis'', ''hepatitis'', ''hepatitis cholestatic'', ''hepatorenal syndrome'', ''jaundice''. The odds ratios of hepatic drug-related side effects in comparison with ibuprofen were calculated according to Egberts et al. [3] under the assumption that the total number of reports or the total number of reports without GI side effects approximately reflects the relative prescription frequencies. Reports registered prior to 14 November 2001 were included in the analysis. *CI* confidence interval

	Reported side effects			Odds ratio (95% CI) in comparison with ibuprofen based on	
	Hepatic	Others	Others excluding GI	All other reports	Other reports excluding GI
Nimesulide	103	978	762	9.2 (7.3, 11.6)	8.6 (6.8, 10.8)
Sulindac	482	10,183	7957	4.2 (3.6, 4.8)	3.8 (3.3, 4.4)
Diclofenac	1232	35,567	25,800	3.0 (2.7, 3.4)	3.0 (2.7, 3.4)
Ibuprofen	385	33,771	24,460	1.0	1.0

Table 2 Spontaneous reports registered in the World Health Organization database of hepatic side effects related to nimesulide in comparison with ibuprofen: influence of time on odds ratio estimate. Note that the first publication on nimesulide-associated acute liver injury was published in 1998, whereas the reporting odds ratio for nimesulide-associated hepatic side effects was already clearly elevated during the preceding years. For further details see legend of Table 1. *CI* confidence interval

Years included	Reported side effects for				Odds ratio (95%CI)
	Nimesulide		Ibuprofen		
	Hepatic	Others	Hepatic	Others	
All	103	978	385	33,771	9.2 (7.3, 11.6)
2000/2001	39	176	29	2712	20.7 (12, 34)
1998/1999	36	385	54	6568	11.4 (7.3, 17.6)
1996/1997	22	195	40	3462	9.8 (5.6, 16.8)
1994/1995	5	94	38	3129	4.4 (1.6, 11.4)
1992/1993	1	55	28	2647	1.7 (0.2, 12.9)

References

1. Martin RM, Kapoor KV, Wilton LV, Mann RD (1998) Underreporting of suspected adverse drug reactions to newly marketed (''black triangle'') drugs in general practice: observational study. BMJ 317:119–120
2. Eland IA, Belton KJ, van Grootheest AC, Meiners AP, Rawlins MD, Stricker BHC (1999) Attitudinal survey of voluntary reporting of adverse drug reactions. Br J Clin Pharmacol 48:623–627
3. Egberts AC, Meyboom RH, De Koning FH, Bakker A, Leufkens HG (1997) Non-puerperal lactation associated with antidepressant drug use. Br J Clin Pharmacol 44:277–281