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Letters to the Editor

Increased risk of gastrointestinal adverse effects under SSRI/NSAID combination may be due to pharmacokinetic interactions

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We read with great interest the article by de Jong *et al.* [1] on the combined use of SSRIs and NSAIDs. The report describes that the combination of NSAIDs with SSRI increased the use of peptic ulcer drugs, which were used as proxy for gastrointestinal adverse effects. Tricyclic antidepressants augmented the risk of peptic ulcer drug use less than SSRIs. Furthermore, the authors emphasize that there are until now no reports about adverse effects caused by the combination of Cox-2 inhibitors and SSRIs. As no separate analyses were presented for the different SSRIs and the different NSAIDs, the report suggests a class effect for SSRIs explaining the observations. The results are discussed by the authors as indicating a pharmacodynamic interaction of the two substance classes, since both classes are independently associated with these types of side-effects. They finally identify the impairment of the haemostatic function due to inhibition of serotonin reuptake as a plausible basis of the observed interaction.

These conclusions call for some comments. Firstly, a risk of bleeding disturbances has also been shown for this type of substance, and has been related to alterations of thrombocyte aggregation [2], which weakens the hypothesis of a pharmacodynamic interaction. More importantly, some NSAIDs are substrates of the cytochrome P450 2C9 (e.g. diclofenac, ibuprofen), whereas others in this drug category (e.g. ketoprofen) are not metabolized by this enzyme [3]. Besides, the cox-2-inhibitors celecoxib and rofecoxib are both not significantly metabolized by CYP2C9 [4]. On the other hand, SSRIs differ with regard to their antagonistic properties on this enzyme [5, 6]. Fluvoxamine is, for example, a strong CYP2C9 blocker, which increases its risk for pharmacokinetic interactions with CYP2C9 substrates, whereas the affinity of other SSRIs (e.g. sertraline) for this enzyme is rather weak. The relative risk of interactions may therefore be expected to vary among the class of SSRIs. Furthermore, frequently used tricyclic drugs like amitriptyline or clomipramine are not significant inhibitors of CYP2C9.

In conclusion, it cannot be ruled out, that the observations reported by de Jong *et al.* might be due to pharmacokinetic interactions. The increased risk of gastrointestinal side-effects with NSAID/SSRI combination could be mostly due to increased plasma concentrations of NSAIDs when combined with some particular SSRIs, especially with fluvoxamine. Without analyzing separately the inhibiting and noninhibiting SSRIs on the one hand, and the CYP2C9 substrates on the other, the conclusion that SSRIs as a group may be associated in combination with NSAIDs with such an overproportional risk of gastrointestinal bleeding seems premature.

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Authors' response

Combined use of NSAIDs and SSRIs increases the risk for gastrointestinal adverse effects

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Zullino and Khazaal rightly indicate that NSAIDs and SSRIs both cause alterations of thrombocyte aggregation and consequently increase the risk of gastrointestinal adverse effects. However, they question whether the 10 times higher risk for GI adverse effects during combined use of an NSAID with an SSRI is due to a pharmacodynamic interaction, and whether this higher risk is a class effect of the SSRIs rather than of individual SSRIs.

The NSAIDs in our study group consisted of diclofenac (46%), ibuprofen (31%), naproxen (14%) and small numbers of indomethacin, aceclofenac, piroxicam, meloxicam, rofecoxib and nabumeton. Apart from one patient taking rofecoxib all other NSAIDs are metabolized by CYP2C9 [1]. Measured by proxy, we found for this group a relative risk of 3.3 (95% CI 1.5, 7.1) [unpublished data]. In their case-control study De Abajo *et al.* reported a relative risk for GI adverse effects of 3.7 for unspecified NSAIDs [2].

For the SSRIs we found a relative risk of 1.2. The SSRIs in the study group are fluoxetine (24%), citalopram (7%), paroxetine (60%), sertraline (2%) and fluvoxamine (6%). Of these, only fluvoxamine is a strong CYP2C9 blocker. However, the patients who actually reported GI adverse effects in combination with an NSAID, had the relatively weak blockers fluoxetine and paroxetine. Therefore, the 10 times higher risk, reported for the combined use, cannot be explained by a mere additive effect of the increased risks of SSRIs and NSAIDs. Genetic polymorphism of CYP2C9, causing poor metabolism, might be a contributing factor to this increased risk [3].

In conclusion, our data do not support the suggestions of Zullino & Khazaal. We believe that the 10 times higher risk for the combination of NSAIDs and SSRIs as compared with SSRIs alone is not caused by mere pharmacokinetic interaction. Instead, polymorphism of CYP2C9 might be involved. Efforts should be made to avoid the combination.

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