Dear Sir,

The paper by Tan et al. reported on three patients who presented with acute hepatitis after taking nimesulide. I would like to highlight some important elements about the correct use of non-steroidal anti-inflammatory drugs (NSAIDs) and the lessons drawn from spontaneous reporting in relation to population-based epidemiological studies.

In particular, it should be noted that in the analysed cases:
- The treatment was longer than 15 days in patients 1 and 3;
- The concomitant use of other potentially hepatotoxic drugs was confirmed in patient 3 (diclofenac) and possibly in patient 2 (an undefined traditional Chinese medication);
- The drug administration was not readily stopped at the appearance of symptoms (after two weeks in patients 1 and 2).

The authors correctly cautioned against the prolonged use of nimesulide, which should be avoided with all NSAIDs and COX-2 inhibitors. However, as a general warning for use of all NSAIDs, and not only for nimesulide, it should also be highlighted that their concomitant use with other potentially hepatotoxic drugs could increase the risk of liver damage, and that the use of NSAIDs, including aspirin, should be avoided in patients with cirrhosis due to the increased risks of gastric or renal complications.

In my view, another important point is that with every potentially hepatotoxic drug (i.e. almost every drug, not only the NSAIDs), the physician has to alert the patient to pay attention to otherwise unexplained symptoms, even the minor ones (e.g. malaise, anorexia, flu-like symptoms), without waiting for the appearance of jaundice, an ominous sign of a high risk of acute liver failure. This alert is considered an inexpensive and potentially useful way to promptly stop the treatment when needed, and this should be mandated. The usefulness of liver tests for monitoring drug hepatotoxicity is debatable due to the rarity of clinically meaningful toxicity, particularly for short-term use.

The article also did not provide data about nimesulide prescriptions in Singapore, and therefore it is not possible to calculate the reporting rate. In any case, it is to be noted that spontaneous reports of adverse drug events are helpful warning signals of rare toxicities, but do not allow us to determine its incidence or relative risk, and can lead to spurious conclusions. More meaningful data may be obtained from population-based epidemiological studies reporting the incidence or comparative risk of hospitalisation and death.

Based on published population-based epidemiological studies, the risk of serious liver injury due to the use of NSAIDs is quite low, and only a small risk of hospitalisation for acute liver injury (without death or transplantation) was reported in the largest published epidemiological population-based study (almost two million prescriptions) on nimesulide vs. other NSAIDs (Table I). The usefulness of liver tests for monitoring drug hepatotoxicity is debatable due to the rarity of clinically meaningful toxicity, particularly for short-term use.

Table I. Incidence of admission for hepatopathies and liver injury among current users of NSAIDs.

<table>
<thead>
<tr>
<th>NSAID</th>
<th>Patient-year (current use)</th>
<th>All hepatopathies</th>
<th>Liver injury</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Rates per 100,000 patient-years</td>
<td>Events</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>1,022</td>
<td>97.8</td>
<td>1</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>5,992</td>
<td>66.8</td>
<td>2</td>
</tr>
<tr>
<td>Cinnoxicam</td>
<td>1,541</td>
<td>64.9</td>
<td>1</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>4,482</td>
<td>44.6</td>
<td>2</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>35,760</td>
<td>39.2</td>
<td>8</td>
</tr>
<tr>
<td>Nimesulide</td>
<td>48,294</td>
<td>35.2</td>
<td>16</td>
</tr>
<tr>
<td>Naproxen</td>
<td>7,833</td>
<td>25.5</td>
<td>1</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>19,848</td>
<td>25.2</td>
<td>4</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>4,232</td>
<td>23.6</td>
<td>-</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>22,051</td>
<td>22.7</td>
<td>4</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>6,619</td>
<td>15.1</td>
<td>1</td>
</tr>
<tr>
<td>Past use</td>
<td>378,433</td>
<td>18.2</td>
<td>56</td>
</tr>
</tbody>
</table>
Although NSAIDs are cited as a common cause of liver damage, the apparently high incidence of NSAID-induced liver injury, like with antibiotics, reflect a frequent use in the general population.\(^{(6)}\) Very few fatal cases were reported, suggesting that the mortality rate is likely to be lower than 1/100,000 patient-years.\(^{(5)}\) It is to be noted that NSAIDs’ potential hepatotoxicity is considerably lower than the expected upper GI toxicity, which confer an excess risk of 1,000–1,500/100,000 patient-years of exposure for upper GI complications,\(^{(2,10)}\) and that nimesulide has been reported on the low-mid level of upper GI risk.\(^{(11,12)}\)

Finally, I would like to highlight that the authors’ statement, “nimesulide has never been approved for use in countries like USA, Canada, Australia and New Zealand in view of concern over its safety profile” is not correct, as the registration of nimesulide was never requested in the US and Canada. In Australia and New Zealand, the marketing authorisation was submitted in 1999 and 2000, respectively, but due to the request of extensive and long-lasting efficacy trials on musculoskeletal diseases by the local authorities, the investment was judged commercially uninteresting and the registration application was voluntarily withdrawn by the company (information disclosed by Helsinn Healthcare SA).

Yours sincerely,

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Conflict of interest statement: Dr Franco Bissoli is a clinical consultant of Helsinn Healthcare SA, Lugano, Switzerland, for drug safety.

REFERENCES