Limitations of Postmarketing Surveillance in the Analysis of Risk of Pregnancy Loss Associated With Maternal Mefloquine Exposure

To The Editor—I read with great interest the recent study by Schlagenhauf and colleagues [1] that provides an analysis of pregnancy and fetal outcomes based on reports of predominantly maternal mefloquine exposures derived from more than 24 years of accumulated postmarketing surveillance data. Their study is highly comparable in methodology to that of an earlier study by Vanhauwere and colleagues [2], who analyzed data collected during the first 10 years following the drug’s European licensure (through 1996). Owing to similarities in methodology, the potential limitations of the study by Schlagenhauf et al in informing updated recommendations on the use of mefloquine should be considered with reference to the historical context of the earlier study.

Around the time of publication of Vanhauwere et al’s study [2], the widespread use of the drug during pregnancy was discontinued [7] based on findings from epidemiological studies of increased risk of stillbirth [3, 4] and spontaneous abortion [5, 6] associated with maternal periconceptional mefloquine exposure. In addition, the manufacturer’s original recommendations that women avoid mefloquine in pregnancy were reinforced [4]. In the developing world, the use of mefloquine during pregnancy was, in most instances, replaced by use of the better-tolerated [8] drug combination sulfadoxine-pyrimethamine (SP), and formal recommendations excluding mefloquine for this indication [9] remain unchanged.

Notwithstanding the earlier publication by Vanhauwere and colleagues, in the intervening 14 years few additional epidemiological data have become available to rationally inform a change in these recommendations, and the updated surveillance data presented by Schlagenhauf et al adds comparably little to further inform such a change. A comparison of the cumulative prospective maternal exposures reported by Schlagenhauf and by Vanhauwere (Table 1) demonstrates a 65% decline in the incremental rate of reporting during the intervening 14 years. Fewer than half the original number of prospective reports of maternal exposure were received during this period, corresponding to only slightly more than 4 per month. To put this figure in further context, during much of the period covered by the Vanhauwere study, monthly prophylactic exposures exceeded 100 000 per month [2]. Furthermore, in both studies, fewer than 5% of exposures were prospectively reported by patients themselves [1, 2].

Although the postmarketing surveillance data presented by Schlagenhauf and colleagues have utility, it is not clear what new conclusions regarding risk of

<table>
<thead>
<tr>
<th>Postmarketing Surveillance Study Author (Publication Year)</th>
<th>Cutoff date for inclusion of exposure reports</th>
<th>Cumulative (incremental) months of postmarketing surveillance</th>
<th>Cumulative (incremental) prospective maternal exposure reports</th>
<th>Mean cumulative (incremental) prospective maternal exposure reports per month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schlagenhauf (2012) [1]</td>
<td>26 October 2010</td>
<td>296.9</td>
<td>2246</td>
<td>8.3</td>
</tr>
<tr>
<td>Incremental Period</td>
<td></td>
<td>169.6</td>
<td>720</td>
<td>4.2</td>
</tr>
</tbody>
</table>

* Assumes inclusion of reports received since 31 January 1986, as per the methodology of Schlagenhauf et al [1]. Mefloquine was first licensed in Europe in 1985 [2].

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pregnancy loss may be meaningfully drawn from such a small and potentially biased sample. Epidemiological data from early cohort studies clearly linked periconceptional mefloquine exposure to a risk of pregnancy loss [3–6], and recent data fail to compellingly challenge these observations.

Given mounting evidence of a plausible biological mechanism by which mefloquine may adversely affect the viability of the implanting embryo and of the developing placenta [10], the apparent reluctance of Schlagenhauf et al to attribute causality to this epidemiological association may benefit from reconsideration. Pending further experimental study [10], caution should be exercised in recommending the broader use of mefloquine during the periconceptional period solely on the basis of limited postmarketing surveillance data.

Notes
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References