Hydroxychloroquine and hearing loss

Introduction
Hydroxychloroquine (Plaquenil®) is an antimalarial agent which is approved for rheumatoid arthritis, systemic lupus erythematos, discoid lupus erythematos, prophylaxis and treatment of acute malaria, and photodermatosis [1]. In the Netherlands it has been approved since 1966. Hydroxychloroquine is chemically closely related to chloroquine (Nivaquine®). Hearing loss or ototoxicity are not mentioned in the SPC of hydroxychloroquine [2]. The SPC of chloroquine states both hearing loss and deafness as possible ADRs.

Reports
Until May 31, 2005 Lareb received three reports of hearing loss associated with the use of hydroxychloroquine. No cases have been reported in association with the use of chloroquine. Report A concerns a female aged 69, who experienced hearing loss (especially low tones) and tinnitus several months after starting hydroxychloroquine for indication lupus erythematos. The hearing loss was confirmed with an audiologic examination. Five years after discontinuation of the hydroxychloroquine, functioning of her right ear is still impaired.

Case B was reported by the MAH and concerns a female aged 57, who experienced deafness and tinnitus 4 years after starting hydroxychloroquine. Hydroxychloroquine was withdrawn and one year later the patient had not recovered.

Recently we received a third report of hearing loss (C). It concerns a female aged 51, who experienced hearing loss 7 months after starting hydroxychloroquine for the indication scleroderma. An audiogram showed a bilateral perception hearing reduction of 30 to 50 dB for high frequencies. The hydroxychloroquine has been withdrawn, 2.5 months later patient has not recovered.

Table 1. reports of hearing loss associated with the use of hydroxychloroquine.

<table>
<thead>
<tr>
<th>Patient, Sex, age Source</th>
<th>Dose</th>
<th>Concomitant medication</th>
<th>Adverse drug reaction</th>
<th>Time to onset, remarks, outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>A F, 69 (pharmacist)</td>
<td>1 dd 400 mg</td>
<td>propranolol verapamil oxazepam nasal fluticasone</td>
<td>tinnitus hearing decreased</td>
<td>several months, not recovered for right ear 5 years after discontinuation</td>
</tr>
<tr>
<td>B F, 57 (MAH)</td>
<td>1 dd 200 mg</td>
<td>not specified</td>
<td>deafness tinnitus nausea dizziness ataxia</td>
<td>4 years, not recovered 1 year after discontinuation</td>
</tr>
<tr>
<td>C F, 51 (dermatologist)</td>
<td>2 dd 200 mg</td>
<td>insulin simvastatin</td>
<td>hearing decreased</td>
<td>7 months, not recovered 2.5 months after discontinuation</td>
</tr>
</tbody>
</table>
Other sources of information

Literature
Ototoxicity has been described for both hydroxychloroquine and chloroquine. A literature search reveals three publications of reversible and irreversible hearing loss in association with the use of hydroxychloroquine [3-5], and 9 publications in association with chloroquine.

Databases
The database of the Upsala Monitoring Centre of the WHO contains 28 reports of deafness and 23 reports of decreased hearing in combination with the use of hydroxychloroquine. For chloroquine 29 cases of deafness and 27 cases of decreased hearing were reported. All associations are disproportionally present in the WHO database.

Mechanism
The mechanism of hydroxychloroquine induced hearing loss is unknown. There may be a relationship with cinchonism, a range of symptoms including otoxic reactions, associated with the use of quinidine-derivates. Because there also is a chemical relationship between (hydroxy)chloroquine and (hydroxy)quinine, typical quinine ADRs like cinchonism and ototoxicity could be expected.

Prescription data
Table 2. Total number of prescriptions of chloroquine, hydroxychloroquine, and primaquine per year since 2000 (Source: GIP College voor Zorgverzekeringen, Diemen).

<table>
<thead>
<tr>
<th></th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>P01BA01 Chloroquine (Nivaquine ®)</td>
<td>3.500</td>
<td>3.202</td>
<td>2.410</td>
<td>1.384</td>
<td>.</td>
</tr>
<tr>
<td>P01BA02 Hydroxychloroquine (Plaquinil ®)</td>
<td>63.441</td>
<td>62.156</td>
<td>66.054</td>
<td>70.702</td>
<td>74.138</td>
</tr>
<tr>
<td>P01BA03 Primaquine</td>
<td>64</td>
<td>44</td>
<td>39</td>
<td>38</td>
<td>53</td>
</tr>
</tbody>
</table>

Conclusion
Lareb has received three reports of hearing loss in patients using hydroxychloroquine, in all cases the hearing loss was persistent or irreversible. Hearing loss and deafness are disproportionally present in the WHO database for both chloroquine and hydroxychloroquine. Hydroxychloroquine is chemically related to quinine and hydroxyquinine, which are well known for their ototoxic potential. In the literature several cases of irreversible deafness have been described with the use of hydroxychloroquine. Therefore, irreversible hearing loss should be listed in the SPC of hydroxychloroquine.

References