Blindness and Neuropathy From Diiodohydroxyquin-Like Drugs

Committee on Drugs

The halogenated hydroxyquinolines—iodochlorhydroxyquin, diiodohydroxyquin, broxyquinoline, and chloroquinaldol (Table I)—were long thought to have little toxicity, but it is now clear that these compounds can cause serious and irreversible damage to the nervous system. Toxicity is a function of dose and duration of therapy. Single, large doses cause cerebral dysfunctions, characterized by disorientation and retrograde amnesia. Optic atrophy and peripheral neuropathy can occur when moderate doses are used for more than three weeks.

Neuropathy has been reported in 12 children and we know of three others who had taken halogenated hydroxyquinolines in high doses (at least adult doses) and/or for more than three weeks. Fourteen of the 15 had loss of visual acuity; 13 had permanent optic atrophy. Dysesthesia, weakness and other manifestations of peripheral neuropathy, reported so commonly in adults, were noted in less than half. Perhaps the reporting was uncommon because the majority of cases were treated before the age of 4 when it is difficult to diagnose such findings. Broxyquinoline was the drug in two cases; the remaining patients had taken either iodochlorhydroxyquin or diiodohydroxyquin. Although the reason for therapy in the earlier cases was acrodermatitis enteropathica, a rare disease, the more recent cases reported from the United States have included children treated for a more common problem, chronic nonspecific diarrhea. Because of concern that the few cases of this serious adverse effect of which we are aware may represent only the “tip of the iceberg,” it seemed appropriate to call attention to the toxicity of these drugs and to make recommendations for their use in hopes of preventing new cases.

These drugs have been recommended and widely used for the treatment of chronic nonspecific diarrhea, even though efficacy has not been fully established. Any value that they may have in the treatment of this heterogeneous group of diseases is outweighed by the serious and often irreversible damage that can insidiously occur with chronic treatment of a child.

Villarejos et al. studied the long-term use of iodochlorhydroxyquin (10 mg/kg/day, six days a week for 16 weeks) in children from an area of Honduras where there was a high endemic level of diarrhea. Treated children had lower rates of diarrhea than placebo or nonplacebo controls. No neuropathy was noted even though the home of each study subject was visited six days a week by nurse’s aides. Because infantile diarrhea is a major problem in many countries, the results of this study could lead to widespread, chronic use of halogenated hydroxyquinolines. We would be concerned that in such a less-controlled clinical situation increases of dose and/or length of therapy would occur and cause a large number of cases of permanent neuropathy. Such a change, from an apparently safe dose of diiodohydroxyquin used to treat cases of nonspecific diarrhea in a formal clinical trial to a larger, toxic dose in the day-to-day practice situation, has been responsible for neuropathy. We believe that the risk of neuropathy offsets possible benefits from the chronic use of these drugs as a chemoprophylactic agent against diarrhea.

Although the halogenated hydroxyquinolines have been used in an attempt to prevent and to cure “traveler’s diarrhea,” they have not been shown to be effective. Children should not be given halogenated hydroxyquinolines for the prevention or treatment of this symptom complex. Readers should know that these drugs are sold under many trade names (Table I) around the world and are often available over-the-counter.

Diiodohydroxyquin (Diodoquin) is approved (package labeling in the United States) only for the treatment of intestinal amebiasis (30 mg/kg/day for 20 days). It is recommended by some authorities only for the treatment of the asymptomatic passers of the cyst form of E. histolytica in
nonendemic areas. No neuropathy has been reported when diiodohydroxyquin is used in this dosage schedule. Metronidazole is an alternate drug available for amebiasis that is unassociated with such serious neuropathy.

Acrodermatitis enteropathica is a serious, rare disorder. There are anecdotal reports that these halogenated hydroxyquinolines in high, chronic dosages are effective in the treatment of this disorder. There are also treatment failures. No appropriately controlled trial has been done to evaluate effectiveness. Until such a study is done, the physician caring for such children will have to decide for or against treatment based on his clinical judgment. Should he decide to treat, he should use as low a dose and as short a course as possible. It seems unlikely that courses of therapy less than three weeks will cause neuropathy provided the doses do not exceed 10 mg/kg/day for broxyquinoline and iodochlorhydroxyquin, 30 mg/kg/day for diiodohydroxyquin, and 3 mg/kg/day for chlorquinanold. Most of these estimates of safe dosage and length of therapy are based on inferences and not on observational data and should only be considered as guidelines subject to change. Any physician using these drugs must, with the help of parents and child, diligently search for signs or symptoms suggesting a loss of visual acuity or other neurologic abnormality.

CONCLUSIONS

The halogenated hydroxyquinolines can cause serious, permanent neuropathy. Optic atrophy, causing permanent blindness, is the most commonly reported neuropathy in children. In young children, the onset of neuropathy is insidious and hard to diagnose. We, therefore, recommend that these drugs not be used in children, with two possible exceptions: the treatment of the asymptomatic cyst passer of *E. histolytica* in a person not living in an endemic area and the treatment of acrodermatitis enteropathica. If used, parents should be informed of the possible toxicity. Parents, child, and physician should diligently search for the first indication of neuropathy. These drugs are contraindicated in the treatment of nonspecific, chronic diarrhea, and “traveler’s diarrhea.”

**Committee on Drugs**

Sumner J. Yaffe, M.D., Chairman
C. Warren Bierman, M.D.
Howard M. Cann, M.D.
Sanford Cohen, M.D.
John Freeman, M.D.
Sydney Segal, M.D.
Lester F. Soyka, M.D.
Charles F. Weiss, M.D.
Godfrey P. Oakley, Jr., M.D., Consultant

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**TABLE I**

**Proprietary Names* of Four Halogenated Hydroxyquinolines**

<table>
<thead>
<tr>
<th>Halogenated Hydroxyquinoline</th>
<th>Proprietary Names</th>
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<tr>
<td>Iodochlrohydroxyquin: Alchoquin, Amebnil, Amoenoil, Bactol, Barquinol, Budoformin, Chinoform, Clioquinol, Cliquinol, Eczecidin, Enteroinol, Enterozo, Entoro-Septol, Entero-Vioform, Entrotikin, Hi-Entorol, Idoenterol, Nioform, Quinambicide, Rometin, Vioform</td>
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<tr>
<td>Diiodohydroxyquin: Dinoleine, Diodoquin, Diodoxylin, Dirextiole, Diioquin, Di-Quinol, Dyodin, Entequin, Enterosept, Floraxquin, Ioquin, Moebiquin, Quinadome, Rafamebin, Searlequin, SS 578, Stanaquinate, Yoshixin, Zoquaquin</td>
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</tr>
<tr>
<td>Broxyquinoline (5, 7-dibromo-8-quinolino): Broxykinolin, Colepur, Colipar, Fenilor, Intestopan, Paramide</td>
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<tr>
<td>Chlorquinanold (5, 7-dichloro-2-methyl-8-quinolino): Gyntothex, Gynt-Sterosan, Saprosan, Siogeno, Sioteran, Sioteran, Sterosan, Steroxin</td>
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**REFERENCES**

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