Use of astemizole in a large group practice

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Astemizole was released in 1988. In late 1992, a new warning label was added in response to reports of syncope and death from arrhythmia. Records of patients given new prescriptions for astemizole were reviewed to assess compliance with the warnings in a large multispecialty practice. The indication was appropriate in 89% of cases. Excessive doses were used in 4% of cases. Two percent of prescriptions were given to patients with contraindications. Only two complications were documented. Despite carrying a drug warning, astemizole continues to be used inappropriately and is a medicolegal concern. Education and drug evaluations can be used to enhance compliance and decrease the risk associated with the use of astemizole.

(Key words: Astemizole, antihistamine, adverse effects, toxicity, quality assurance)

Astemizole was first introduced into the US market in 1988. It was the second of a new generation of antihistamines, the nonsedating antihistamines. The first of this class was terfenadine. More recently, loratadine has become available. The safety profile of loratadine appears to be improved over the other nonsedating antihistamines, but is more expensive. The nonsedating antihistamines are preferred over the sedating antihistamines in that their adverse effect profile is more acceptable to patients.

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Shortly after the release of astemizole and terfenadine, it became evident that both were associated with prolonged QT intervals and arrhythmias, mainly torsades de pointes. Because of this association, the Food and Drug Administration (FDA) and the manufacturers provided a warning letter to physicians in 1992.[1] For astemizole, the warning stated: (1) That arrhythmias have usually occurred when the dose of 10 mg/d (the recommended dose) was exceeded. Exceeding this dose and the use of loading doses should be avoided. (2) Serum levels of astemizole may be elevated by ketoconazole, erythromycin;, and itraconazole. These drugs should not be used together. (3) Presyncope and syncope may precede fatal arrhythmias and calls for discontinuing astemizole. (4) The drug should be avoided in patients with significant liver disease. When astemizole is used as directed, with the preceding precautions kept in mind, it is considered a safe and effective nonsedating antihistamine.

The intent of our study was to evaluate the compliance of the "new warnings" in a large multispecialty group practice. Frequently, a particular medication is selected for a formulary based on price without consideration of the drug's adverse profile. In our group practice, the only nonsedating antihistamine available was astemizole. If the drug was frequently misused, it would suggest that the cost-savings may be outweighed by the risks. In this case, the use of alternate agents may avoid unnecessary medicolegal concerns.

Methods

Outpatient records were reviewed monthly on all patients with new prescriptions for astemizole without regard to the patient's age, sex, or previous health. The information was collected during the year 1993. The reviewers included four physicians from the Pharmacy and Therapeutics Committee. The group practice that was reviewed contained approximately 70 physicians of the surgical, medical, family practice, and pediatric specialties. The physicians reviewed the records by following a checklist, noting the following for each record:

Table
Data on Use of Astemizole in a Large Group Practice*

Study period	No. of charts	Proper indication, %	Proper dose, %	Warnings present, %	Compli-cations, %	Steroids used, %
First 6 months	194	89	96	2	1	37
Second 6 months	58	89	100	6	0	48
Total	**252**	**89**	**98**	**3**	**0**	**39**

*Percentages rounded to whole numbers

- ☐ indication,
- ☐ dosage,
- ☐ concurrent medications, and
- ☐ medical illnesses, including hepatic or cardiac disease, presyncope, and syncope.

They recorded adverse effects to astemizole. All patients who received astemizole were older than 12 years. Further demographics were not assessed.

An electrocardiogram (ECG) was not required to be available or obtained before patients started taking astemizole. If an ECG was in the record, it was evaluated for a prolonged QT interval, arrhythmias, or conduction abnormalities, all of which may complicate therapy with astemizole.

Feedback was given monthly to physicians prescribing the drug inappropriately in order to enhance compliance. This interaction was not punitive, but simply a brief reeducation of the proper use of astemizole. The combined use of nasal steroids and astemizole was assessed. This assessment was deemed important because of the increasing use of nasal steroids and the belief by some that nasal steroids are the preferred mode of therapy for allergic rhinitis.

The data were descriptive only; thus, statistics were not indicated.

Results

A total of 252 records were reviewed. The data are compiled in the *Table*. The indication was appropriate in 89% of the cases. Inappropriate use included nonallergic rhinitis and single-dose therapy for acute allergic diseases, such as urticaria. The dose was appropriate in 98% of cases. During the first 6 months of the study, five (4%) of the patients received inappropriate doses. Four patients (1.6%) received a loading dose, while one patient (0.4%) received twice the recommended dosage. All doses were appropriate during the second 6 months of the study.

Eight (3%) of the patients receiving prescriptions for astemizole had relative contraindications: 3 patients (1.2%) had prolonged QT intervals, 2 patients (0.8%) were receiving erythromycin, 1 patient (0.4%) had a significant conduction abnormality, and 2 patients (0.8%) had documented arrhythmias. Complications were rare. Only 2 (0.8%) of the 252 patients had adverse effects, which included an arrhythmia (type undocumented) and an episode of syncope. Nasal steroids were used in 39% of the patients. The effectiveness of astemizole was not assessed.

Discussion

Despite a drug warning by the FDA and the manufacturer, astemizole continues to be used in inappropriate doses and in patients with relative contraindications. The concern is that physician education may not be up to date and that quality assurance programs may be necessary to improve compliance to the "standard of care." In large group practices, proper use of medications is most easily accomplished by drug utilization reviews. Drugs with high usage, high price, or potentially fatal adverse effects are the most appropriate to study. If selection of a medication is based on price and alternate agents are available, drug reviews should be done to ensure that savings are not outweighed by risk. Additionally, the data collected should become available to individual physicians to enhance effective drug usage. During this drug utilization review, feedback was provided to physicians prescribing the drug inappropriately. During the first 6 month's of the study, 4% of patients received excessive doses, whereas during the last 6 months, all doses were within guidelines. This compliance was attributed to the ongoing monthly feedback given to physicians during the study.

Arrhythmias complicating therapy with astemizole have been documented. The frequency of arrhythmia, however, is extremely rare. Between 1988 and 1992, there were 44 serious cardiovascular events associated with astemizole. These events included 23 cases of torsades de pointes, 10 cases of ventricular tachycardia, 9 cardiac arrests, and 5 cardiovascular deaths.[2] Almost all events were associated with overdose. Our data are consistent with this experience, in that adverse effects were infrequent and could not be directly attributed to astemizole.

Both astemizole and terfenadine are metabolized by cytochrome p450. Erythromycin[3] and ketocona-

zole[4] are metabolized by the same enzyme and inhibit the metabolism of astemizole, increasing serum levels and the potential for toxicity. Because of the similarity of fluconazole, metronidazole, itraconazole, and miconazole to ketoconazole, these drugs should also be avoided until data are available suggesting their combined safety. The macrolides troleandomycin and clarithromycin are metabolized similarly to erythromycin and should be avoided when using astemizole.

Prolongation of the QT interval has been documented with pentamidine isethionate, cisapride, amiodarone, probucol, tricyclic antidepressants, phenothiazines, terfenadine, bepridil hydrochloride, and the antiarrhythmics quinidine, disopyramide phosphate, and procainamide hydrochloride. Combining these medications with astemizole may increase the potential for prolongation of the QT interval and torsades de pointes. Diuretics can cause hypomagnesemia and hypokalemia, both of which predispose to prolonged QT interval and arrhythmias. This may increase the risk for arrhythmias and adverse effects from astemizole. Our data suggest that erythromycin still poses the greatest risk for drug interactions. This drug interaction is assumed to be secondary to the frequent use of erythromycin and that both drugs are used in a similar patient population.

Our study did not require that an ECG be available before prescribing astemizole. If a record contained an ECG, the ECG was reviewed for preexisting abnormalities that could predispose to adverse effects from astemizole. Electrocardiographic abnormalities that contraindicate the use of astemizole were infrequently found. The most common abnormality was prolonged QT interval. An ECG does not appear to be indicated before starting astemizole therapy, except inpatients who have a history of, or are high risk for, arrhythmias.

Only two adverse effects occurred. One patient had syncope, and another had an arrhythmia (unspecified). Neither adverse effect could be directly attributed to astemizole but, because of the possibility, the medication was discontinued. This experience coincides with past studies demonstrating that arrhythmias are rare with the use of astemizole.[2]

The most common indication for astemizole was allergic rhinitis. Nasal congestion is often the most troublesome symptom for the patient with allergic rhinitis. Antihistamines provide little or no benefit in decreasing nasal congestion. The regular use of nasal steroids decreases congestion and is effective in greater than 90% of patients with allergic rhinitis.[5] It is surprising that nasal steroids were used in only 39% of the study population.

Inappropriate indications for astemizole included: (1) nonallergic rhinitis (for which antihistamines have minimal effect; (2) as a single dose on an as-needed basis; and (3) for acute transient rashes. The last two indications are ineffective uses of astemizole because of the drug's prolonged half-life and delayed effect.[4] The long half-life also accounts for astemizole's prolonged effect in suppression of skin tests. This inhibition may persist for weeks, making astemizole a poor choice to start before skin testing.[6]

Comment

Our study reconfirms that drug utilization reviews are an effective means of tracking physician's prescribing practices and education of physicians. Although risk exists with use of astemizole, if the drug is appropriately used, it appears to be safe and have little potential for adverse outcomes.[7]

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