Tocainide

Tocainide was recently approved for the treatment of ventricular arrhythmia. It is an oral congener of lidocaine and has similar electrophysiologic effects. The drug is available only for oral use, and the dosage is 400 to 800 mg three times daily titrated to its effect on arrhythmia and the occurrence of toxic effects. The half-life of the drug is approximately 11 hours, and the reported therapeutic blood levels are 4 μg/ml to 10 μg/ml. The drug is metabolized by the liver to inactive metabolites, but approximately 35 percent may be excreted unchanged by the kidney. Therefore, adjustment of dosage is necessary when administering this agent to patients with significant renal insufficiency.

Similar to lidocaine, tocainide does not affect the electrocardiogram, and there are no changes in the P-R, QRS or Q-T intervals. When blood levels are very high, QRS prolongation may occur.

Oral tocainide has no effect on left ventricular function, although there may be transient depression in contractility when the drug is used in high doses in patients with an acute myocardial infarction.

Side Effects

Tocainide causes side effects similar to those of lidocaine. The most common adverse effects are those involving the gastrointestinal tract and central nervous system. Gastrointestinal side effects include nausea, vomiting, abdominal discomfort, and anorexia. Most of these are due to a direct effect of the drug on the stomach and can be treated by its administration with food or antacids. Side effects on the central nervous system are of two types. Most common are those that are related to dosage and blood level of the drug, including tremors, paresthesias, dizziness and light-headedness, ataxia, slurred speech, and lethargy. Other side effects which may not be dose-related include change in mood and mentation, alteration in personality including psychosis, seizures, insomnia, thought disorders, and hallucinations. Since these side effects are similar to those produced by lidocaine, caution is necessary when administering this drug to a patient receiving tocainide. Other side effects include rash, pneumonitis, lupus-like syndrome, pericarditis, and hepatitis. As with other drugs, congestive heart failure or aggravation of arrhythmia may occur.

Clinical Indications

Tocainide is only effective for the treatment of ventricular arrhythmia, and it is not useful for supraventricular arrhythmias. It suppresses ventricular premature beats, including complex forms, which occur in a variety of clinical situations. Tocainide is safe and effective when used in patients with serious arrhythmias associated with an acute myocardial infarction. In patients with a history of malignant sustained tachyarrhythmias, tocainide prevents a recurrence. Response to lidocaine predicts the response to tocainide in 76 percent of patients and is a helpful guide.

Mexiletine

Mexiletine is an oral congener of lidocaine, and these two agents have many properties in common. Mexiletine can be administered either orally or intravenously. The intravenous dosage is 10 mg/min to a loading dose of 400 mg. A continuous infusion of 600 to 900 mg/day is used for maintenance therapy. The oral dose of drug is 200 to 400 mg three times per day. Therapeutic blood levels ranges from 0.7 μg/ml to 1.6 μg/ml, and the average half-life is 11.5 hours. Approximately 85 percent of mexiletine is metabolized by the liver to inactive metabolites, while the remaining drug is renally excreted unchanged. Alkalization of the urine decreases the renal clearance of the drug and can elevate blood levels. It is usually unnecessary to alter the dosage of mexiletine in patients with congestive heart failure or mild renal or hepatic insufficiency.
Oral mexiletine does not generally affect the P-R, QRS or Q-T intervals, but there have been reports of atrioventricular block occurring in patients receiving the drug intravenously. Similar to lidocaine, mexiletine does not depress left ventricular function, even in patients with underlying left ventricular dysfunction.

**Side Effects**

The most frequent side effects caused by mexiletine are related to the gastrointestinal and central nervous systems. Most common are nausea and vomiting, which can often be prevented by coadministration of the drug with food. Side effects on the central nervous system include dizziness, tremor, blurred vision, light-headedness, ataxia, slurred speech, memory impairment, thought disorders, insomnia, changes in personality, and, rarely, seizures. As with tocainide, some of these side effects are related to the blood level. Other side effects include development of an asymptomatic antinuclear antibody titer, cutaneous rash, LFT abnormalities, congestive heart failure, and exacerbation of arrhythmia.

**Clinical Indications**

Mexiteline is indicated for ventricular arrhythmias and has no role for supraventricular arrhythmias. It is effective for the suppression of ventricular premature beats, including complex forms. In patients with life-threatening refractory tachyarrhythmias, mexiletine will prevent a recurrence. There have been several reports of enhanced antiarrhythmic efficacy when the drug is combined with other membrane-active drugs or β-adrenergic blocking agents. Similar to trials with other antiarrhythmic agents, mexiletine has not decreased the incidence of sudden death in patients after myocardial infarction, however, as with other such studies, the drug was randomly administered regardless of the occurrence of arrhythmia or the effect of the drug.

**Encaïnide**

Encaïnide exerts potent effects on the myocardium, significantly slowing impulse conduction. Encaïnide is orally administered, and the usual dosage is 25 to 50 mg three or four times daily, up to a maximum dosage of 200 mg/day. The drug is rapidly absorbed from the gastrointestinal tract and has a half-life of 1.6 to 2.6 hours. It is metabolized by the liver to several metabolites, two of which (OD-methyl encaïnide and methoxy-OD-methyl encaïnide) have antiarrhythmic effects. Several days of dosing are required before steady-state levels of encaïnide and its metabolites are achieved, and antiarrhythmic effects may continue for several days after discontinuation of the drug.

As predicted by encaïnide's electrophysiologic effects, there is an increase in P-R and QRS intervals related to blood level. It has been reported that lengthening of the QRS interval may be a guide to dosing, but this is not reliable. The Q-T interval generally is not altered.

In studies in animals, encaïnide does not depress left ventricular function, and clinical studies have confirmed that it is devoid of significant negatively inotropic activity, although studies in patients with left ventricular dysfunction are lacking. In our experience, encaïnide rarely exacerbates congestive heart failure, even in patients with a reduced ejection fraction.

**Side Effects**

Side effects caused by encaïnide are mild and include nausea, dizziness, fatigue, and paresthesias. In our experience, aggravation of arrhythmia occurs in 23 percent of patients. This is a complication associated with all antiarrhythmic drugs, but the incidence is higher with encaïnide. Aggravation of arrhythmia is not predicted by electrocardiographic changes, drug level, or dosage administered. We observed a higher incidence among patients with a history of congestive heart failure and an intraventricular conduction delay on the electrocardiogram.

**Clinical Use**

Encaïnide is an effective drug for suppressing ventricular premature beats, including complex forms; however, most reported studies involved patients without a history of malignant ventricular arrhythmia. We have reported that encaïnide is effective in patients with refractory and symptomatic ventricular tachyarrhythmias, but its role in such patients has yet to be defined.

Encaïnide prevents the recurrence of certain supraventricular tachycardias, especially those associated with preexcitation syndromes, predicted by the significant effects of the drug on accessory pathway tissue. It appears to be less effective for the prevention of atrial fibrillation or flutter.

**Ethmozine**

Ethmozine, developed in the Soviet Union, is a phenothiazine derivative but is devoid of the side effects usually ascribed to this class of drugs. Although ethmozine exerts mild membrane-stabilizing activity, it is possible that some of its antiarrhythmic activity is related to effects on the central nervous system. Ethmozine is available only for oral use. Although the dosage has not been well defined, up to 15 mg/kg/day or 600 to 1,200 mg daily in three divided doses has been administered. The therapeutic blood level remains uncertain. The drug is metabolized by the liver to metabolites that are as yet undefined.
Ethmozine generally does not affect the electrocardiogram, although slight prolongation of P-R and QRS intervals may occur. The Q-T interval is not altered.

Ethmozine is devoid of negatively inotropic effects in animals. In our experience using radionuclide ventriculography, ethmozine does not change left ventricular ejection fraction; however, approximately 3 percent of patients have developed clinical congestive heart failure while receiving ethmozine.

**Side Effects**

Ethmozine has a low incidence of adverse reactions, occurring in approximately 20 percent of patients.\(^{67,68}\) Side effects are usually mild and include nausea, vomiting, rash, dizziness, tremor, and urinary retention. As with other antiarrhythmic drugs, congestive heart failure and aggravation of arrhythmia have been observed.

**Clinical Use**

The major role of ethmozine is in the treatment of ventricular arrhythmia. It has been reported to be effective for suppressing ventricular premature beats, including complex forms, but its role for therapy in patients with serious ventricular arrhythmia is as yet uncertain.\(^{67,68}\) We have reported ethmozine to be effective in approximately 55 percent of such patients, although long-term results with the drug are lacking.\(^{60}\)

Preliminary data suggest that ethmozine may be effective for certain supraventricular arrhythmias, especially those associated with the Wolff-Parkinson-White syndrome; however, data are as yet incomplete.

**Flecainide**

Flecainide has effects on the electrophysiologic properties of the myocardium\(^{79}\) which are similar to encainide.\(^{79}\) The drug is orally administered, with the usual dosage being 100 to 200 mg twice per day. In patients with serious arrhythmia and left ventricular dysfunction, the initial dosage is 100 mg twice daily and should be slowly increased every four days. The average half-life is 13 hours but may be as long as 20 hours during long-term administration.\(^{71}\) Several days are necessary before steady-state levels are achieved. The recommended therapeutic blood level is less than 1μg/ml. Approximately 75 percent of flecainide is metabolized by the liver to inactive metabolites, while 25 percent is excreted unchanged in the urine.\(^{71}\) Reduction of dosage is necessary in patients with renal impairment.

Flecainide may prolong the P-R and QRS intervals, and it has been suggested that lengthening of the QRS interval is a guide to dosing, but this remains uncertain.\(^{79}\) Q-T prolongation generally does not occur.

Flecainide is negatively inotropic, and in both animal and clinical studies, it depresses left ventricular function.\(^{73}\) Exacerbation of congestive heart failure in patients with underlying left ventricular dysfunction has been observed.

**Side Effects**

Side effects have been reported in up to 30 percent of patients and include dizziness, visual disturbance, headache, nausea, tremor, and diarrhea.\(^{74}\) Adverse effects on the cardiovascular system include conduction abnormalities, exacerbation of congestive heart failure, and aggravation of arrhythmia.

**Clinical Studies**

Similar to encainide, flecainide has been reported to significantly suppress ventricular premature beats, including complex forms;\(^{75,76}\) however, these reports involve patients without a history of malignant ventricular arrhythmia. Its role in those who have experienced more serious ventricular tachyarrhythmia is unclear. It has been reported to be effective in such patients during long-term therapy, although a recurrence of incessant ventricular tachycardia difficult to terminate has been observed.\(^{76}\) Flecainide may have a role in preventing certain supraventricular tachycardias, especially those associated with the Wolff-Parkinson-White syndrome, but more studies are necessary to define its role.

**Lorcainide**

Lorcainide is a membrane-active drug which is available for intravenous and oral use.\(^{77}\) The intravenous loading dose is 200 mg infused at a rate of 20 mg/min, followed by a maintenance dose of 400 mg over 24 hours. The oral dosage is 100 to 200 mg twice or three times daily. Therapeutic blood levels are reported to be 0.15μg/ml to 0.4μg/ml. The drug is metabolized by the liver, with an elimination half-life of 7.6 hours.\(^{78}\) One metabolite, norlorcainide, has antiarrhythmic effects.

Lorcainide may prolong the P-R and QRS intervals. This may be related to blood levels. Generally, Q-T interval prolongation does not occur.

When administered intravenously, there may be a transient and mild depression of left ventricular contractility and a slight reduction in cardiac output. During oral therapy with the drug, congestive heart failure has not been observed.\(^{78}\)

**Side Effects**

Lorcainide causes frequent side effects, reported by up to 55 percent of patients.\(^{79}\) The most common side effects are sleep disturbances, including insomnia and nightmares.\(^{80}\) Although it is reported that these problems can be prevented by concomitant therapy with a benzodiazepine drug, this does not occur in all patients.\(^{80}\) Occasionally, these side effects abate after a
week of therapy. Other adverse effects include rash, nausea, conduction abnormalities, and arrhythmia aggravation.

Clinical Effects

Lorcainide is useful only for ventricular arrhythmia, and it has no role for atrial arrhythmias. Like other agents, it suppresses all forms of ventricular premature beats.77,80 In patients with refractory sustained ventricular tachyarrrhythmia, lorcainide has been effective in about 38 percent, but studies involving long-term therapy with this drug are as yet lacking.79

Propafenone

Propafenone is a membrane-active drug that has electrophysiologic effects on all cardiac tissue.81 There are preliminary data that it also exerts mild calcium-blocking and β-adrenergic blocking activity. Propafenone is administered by the oral route, and the dosage is 150 to 300 mg three times daily. Therapeutic plasma levels range from 0.5 μg/ml to 3 μg/ml. Propafenone has first-pass effect, with more than 99 percent of the drug being metabolized by the liver.82 The half-life is approximately six hours but may be prolonged at higher dosages, resulting from a saturation of metabolic sites.

As predicted by its electrophysiologic effects, propafenone prolongs P-R, QRS, and Q-T intervals. It has been reported that prolongation of the P-R interval may correlate with blood level and antiarrhythmic efficacy, but this relationship is uncertain.83 Propafenone is negatively inotropic, and in animal studies, it causes a dose-related decrease in left ventricular contractility and cardiac output. In clinical trials, propafenone reduces left ventricular function in some patients with underlying dysfunction.84

Side Effects

Side effects occur in 30 percent of patients, and the most common are gastrointestinal, including nausea, vomiting, and alteration in taste.84,85 The most serious toxic effects involve the cardiovascular system. There are reports of conduction abnormalities, including atrioventricular block and sinus arrest, exacerbation of congestive heart failure, and aggravation of arrhythmia.

Clinical Use

Propafenone is an effective agent for suppression of ventricular arrhythmia in patients with frequent ventricular premature beats and will prevent recurrent sustained tachyarrrhythmias in patients with a history of malignant arrhythmia.86 Preliminary data suggest that propafenone is an effective agent for terminating and preventing supraventricular tachycardia associated with the Wolff-Parkinson-White syndrome.86

Amiodarone

Amiodarone is a unique antiarrhythmic drug which exerts several pharmacologic effects on the myocardium.87 Its direct electrophysiologic effect is a prolongation of the action potential duration and refractory periods. The drug has noncompetitive β-adrenergic blocking and α-adrenergic blocking activity and produces blockade of the calcium channel. Lastly, amiodarone contains substantial amounts of iodine and interferes with thyroxine metabolism. It is possible that some of amiodarone’s antiarrhythmic activity is related to its interaction with thyroxine.

Amiodarone has been administered by the intravenous and oral routes. When given intravenously, the dosage is 5 to 10 mg/kg. The primary electrophysiologic effect of the intravenous drug is on the atrioventricular node, causing a reduction in conduction and prolongation of the refractory period.88 The drug is rapidly distributed to peripheral stores within adipose tissue. Since the volume of distribution is enormous, weeks or months of loading are required before stores are saturated and a steady-state blood level is achieved.89 The oral dosage of amiodarone depends upon the nature of the arrhythmia. We usually administer 600 mg daily for one to two weeks when treating supraventricular tachyarrrhythmias, continuing 400 mg daily for two to four weeks, and 200 to 400 mg daily thereafter. The dosage is 1,200 to 1,500 mg daily for one week in patients with ventricular tachycardia or ventricular fibrillation. A daily dosage of 600 mg is continued for an additional one to two months, with a dosage of 200 to 600 mg daily thereafter. Frequently, another partially effective antiarrhythmic agent is concomitantly administered, since the onset of amiodarone’s activity is delayed. As a result of the large adipose stores, the half-life of amiodarone is 40 to 60 days or longer, and antiarrhythmic activity and side effects may persist for several months after discontinuation of the drug.88 Metabolism of amiodarone involves deiodination, as well as hepatic transformation to desethylamiodarone which has antiarrhythmic activity.

Amiodarone produces significant changes on the electrocardiogram, including P-R and Q-T prolongation and the development of a prominent U wave. Sinus bradycardia is common and usually is without symptoms.

As a result of its pharmacologic effects, amiodarone causes smooth muscle relaxation and is a peripheral and coronary arterial vasodilator. The drug does have a direct depressant effect on left ventricular contractility, but the reduction in afterload counterbalances this, and in general, cardiac output is maintained. The development of congestive heart failure during long-term therapy is unusual.87,89
Side Effects

Side effects occur frequently, in as many as 70 percent of patients, although the majority are mild, well tolerated, and do not require discontinuation of the drug. Serious side effects have occurred in 18 percent, and in our experience, drug discontinuation is necessary in 8 percent of patients. Most common are corneal microdeposits due to lacrimal gland secretion of the drug. These are usually asymptomatic, although minor visual disturbances including blurred vision and halos have been reported. We have had several patients develop macular degeneration and decreased visual acuity while receiving amiodarone. Although the relationship to the drug is uncertain, the retinal changes stabilized or reversed when amiodarone was discontinued. Dermatologic side effects include solar sensitivity, the development of purpuric discoloration on the hands and feet, and, rarely, a blue-gray cutaneous rash which primarily affects sun-exposed areas. Constipation and headache occur commonly during the loading period but may continue even with a reduction of dosage. Asymptomatic abnormalities of LFTs are common, and only rarely has hepatitis been reported. Thyroid abnormalities are common, and symptomatic hyperthyroidism and hypothyroidism each occur in approximately 5 percent of patients. Ataxia is frequent, especially in older patients receiving a higher dosage. Cardiac toxic effects include sinus node depression, conduction abnormalities, and aggravation of arrhythmia. Among the most serious side effects are pulmonary toxic effects, which occur in approximately 5 percent of patients and consist of pulmonary infiltrates or fibrosis. The onset may be insidious, beginning with nonspecific complaints of cough, fatigue, and shortness of breath. Respiratory failure and death have been reported. It has been our practice to obtain routine chemistries, thyroid function tests, and chest x-ray films every six months during long-term therapy.

Drug interactions are common with amiodarone. Most frequent are interactions with warfarin, resulting in a potentiation of anticoagulative effect, and with digoxin, leading to an increase in digoxin levels. Interactions have also been reported with other membrane-active antiarrhythmic agents, β-adrenergic blockers, and anesthetic drugs.

Clinical Use

Amiodarone is very effective for a wide range of arrhythmias. In our experience, it prevents recurrent paroxysmal atrial fibrillation or flutter in over 80 percent of patients in whom other agents were ineffective. Amiodarone will not revert sustained atrial fibrillation or flutter but will prevent their recurrence after chemical or electrical cardioversion. The drug is very effective for preventing supraventricular tachycardia, especially when associated with the Wolff-Parkinson-White syndrome.

Amiodarone has been reported by many investigators to be highly effective for preventing recurrent ventricular tachycardia and ventricular fibrillation, however, there has been no uniformity of patient populations, methods for evaluation of therapy, or use of other antiarrhythmic agents.

Aggravation of Arrhythmia

Although each of the antiarrhythmic drugs has its own profile of side effects, the ability to aggravate arrhythmia is a potential complication which can occur with any of these agents, as shown by the following tabulation listing the incidence (percent) of aggravation of arrhythmia for various drugs:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-adrenergic blocker</td>
<td>7-15</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>6</td>
</tr>
<tr>
<td>Encaainide</td>
<td>23</td>
</tr>
<tr>
<td>Ethmozine</td>
<td>5</td>
</tr>
<tr>
<td>Flecaainide</td>
<td>13</td>
</tr>
<tr>
<td>Lorcaainide</td>
<td>8</td>
</tr>
<tr>
<td>Mexiletine</td>
<td>8</td>
</tr>
<tr>
<td>Procainamide</td>
<td>9</td>
</tr>
<tr>
<td>Propafenone</td>
<td>10</td>
</tr>
<tr>
<td>Quinidine</td>
<td>15</td>
</tr>
<tr>
<td>Tocainide</td>
<td>10</td>
</tr>
</tbody>
</table>

Although aggravation of arrhythmia appears to be more frequent in patients with underlying cardiac disease who have had malignant arrhythmias, its occurrence is unpredictable. When aggravation occurs, blood levels are not toxic, and there are no specific electrocardiographic changes associated with this complication. Aggravation of arrhythmia represents an idiosyncratic reaction to this class of drugs.

Conclusion

The antiarrhythmic drugs represent a diverse group of agents. Although some of the drugs have similar electrophysiologic effects, each agent is unique. The pharmacology, antiarrhythmic effects, and toxic effects differ among the many drugs, requiring knowledge about each one.

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