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PROCAINAMIDE HYDROCHLORIDE Injection, USP

PRODUCT DESCRIPTION	DELIVERY SYSTEM	UNIT SIZE	UNITS / BOX	NDC#
Procainamide HCl Inj., USP (100 mg/mL)	Luer-Jet™ Prefilled Syringe	1000 mg / 10 mL	5	76329-3399-5

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Please see reverse for important safety information, including **boxed warning**, and indications and usage, for Procainamide Hydrochloride Injection, USP.

Rx Only
12/16
01-023-01

PROCAINAMIDE HCl
INJECTION, USP

WARNING: The prolonged administration of procainamide often leads to the development of a positive anti-nuclear antibody (ANA) test, with or without symptoms of a lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefits versus risks of continued procainamide therapy should be assessed.

DESCRIPTION:

Procainamide Hydrochloride Injection, USP, is a sterile, nonpyrogenic solution of procainamide hydrochloride in Water for Injection. It is available in 100 mg per mL concentration. The 100 mg per mL potency contains 0.9% w/v benzyl alcohol and 0.09% sodium bisulfite as preservatives. The solution may contain hydrochloric acid and/or sodium hydroxide for pH adjustment. pH 5.0. Procainamide hydrochloride, a Group 1A cardiac antiarrhythmic drug, is p-amino-N-[2-(diethylamino) ethyl] benzamide mono-hydrochloride. It differs from procaine which is the p-aminobenzoyl ester of 2-(diethylamino)-ethanol. Procainamide as the free base has a pK_a of 9.23; the monohydrochloride is very soluble in water.

INDICATIONS AND USAGE:

Procainamide hydrochloride injection is indicated for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia, that, in the judgement of the physician, are life-threatening. Because of the proarrhythmic effects of procainamide, its use with lesser arrhythmias is generally not recommended. Treatment of patients with asymptomatic ventricular premature contractions should be avoided.

Initiation of procainamide treatment, as with other antiarrhythmic agents used to treat life-threatening arrhythmias, should be carried out in the hospital.

Antiarrhythmic drugs have not been shown to enhance survival in patients with ventricular arrhythmias.

Because procainamide has the potential to produce serious hematological disorders (0.5 percent) particularly leukopenia or agranulocytosis (sometimes fatal), its use should be reserved for patients in whom, in the opinion of the physician, the benefits of treatment clearly outweigh the risks. (see ***WARNINGS*** and Boxed Warning.)

CONTRAINDICATIONS:

Complete Heart Block: Procainamide should not be administered to patients with complete heart block because of its effects in suppressing nodal or ventricular pacemakers and the hazard of asystole. It may be difficult to recognize complete heart block in patients with ventricular tachycardia, but if significant slowing of ventricular rate occurs during PA treatment without evidence of A-V conduction appearing, PA should be stopped. In cases of second degree A-V block or various types of hemiblock, PA should be avoided or discontinued because of the possibility of increased severity of block, unless the ventricular rate is controlled by an electrical pacemaker.

Idiosyncratic Hypersensitivity: In patients sensitive to procaine or other ester-type local anesthetics, cross sensitivity to PA is unlikely. However, it should be borne in mind, and PA should not be used if it produces acute allergic dermatitis, asthma, or anaphylactic symptoms.

Lupus Erythematosus: An established diagnosis of systemic lupus erythematosus is a contraindication to PA therapy, since aggravation of symptoms is highly likely.

Torsades de Pointes: In the unusual ventricular arrhythmia called "les torsades de pointes" (twistings of the points), characterized by alternation of one or more ventricular premature beats in the directions of the QRS complexes on ECG in persons with prolonged Q-T and often enhanced U waves, Group 1A antiarrhythmic drugs are contraindicated. Administration of PA in such cases may aggravate this special type of ventricular extrasystole or tachycardia instead of suppressing it.

WARNINGS:

Mortality:

In the National Heart, Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multicentered, randomized, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmias who had a myocardial infarction more than six days but less than two years previously, an excessive mortality or non-fatal cardiac arrest rate (7.7%) was seen in patients treated with encainide or flecainide compared with that seen in patients assigned to matched placebo-treated group (3.0%). The average duration of treatment with encainide or flecainide in this study was ten months.

The applicability of the CAST results to other populations (e.g., those without recent myocardial infarctions) is uncertain. Considering the known proarrhythmic properties of procainamide and the lack of evidence of improved survival for any antiarrhythmic drug in patients without life-threatening arrhythmias, the use of procainamide as well as other antiarrhythmic agents should be reserved for patients with life-threatening ventricular arrhythmias.

Blood Dyscrasias: Agranulocytosis, bone marrow depression, neutropenia, hypoplastic anemia and thrombocytopenia in patients receiving procainamide hydrochloride have been reported at a rate of approximately 0.5%. Most of these patients received procainamide within the recommended dosage range. Fatalities have occurred (with approximately 20–25 percent mortality in reported cases of agranulocytosis). Complete blood counts should be performed promptly if the patient develops any signs of infection (such as fever, chills, sore throat or stomatitis), bruising or bleeding. If any of these hematologic disorders are identified, procainamide therapy should be discontinued. Blood counts usually return to normal within one month of discontinuation. Caution should be used in patients with pre-existing marrow failure or cytopenia of any type. (See ***ADVERSE REACTIONS***).

Digitalis Intoxication

Caution should be exercised in the use of procainamide in arrhythmias associated with digitalis intoxication. Procainamide can suppress digitalis-induced arrhythmias; however, if there is concomitant marked disturbance of atrioventricular conduction, additional depression of conduction and ventricular asystole or fibrillation may result. Therefore, use of procainamide should be considered only if discontinuation of digitalis, and therapy with potassium, lidocaine, or phenytoin are ineffective.

First Degree Heart Block

Caution should be exercised also if the patient exhibits or develops first degree heart block while taking PA, and dosage reduction is advised in such cases. If the block persists despite dosage reduction, continuation of PA administration must be evaluated on the basis of current benefit versus risk of increased heart block.

Predigitalization for Atrial Flutter or Fibrillation

Patients with atrial flutter or fibrillation should be cardioverted or digitalized prior to PA administration to avoid enhancement of A-V conduction which may result in ventricular rate acceleration beyond tolerable limits. Adequate digitalization reduces but does not eliminate the possibility of sudden increase in ventricular rate as the atrial rate is slowed by PA in these arrhythmias.

Congestive Heart Failure

For patients in congestive heart failure, and those with acute ischemic heart disease or cardiomyopathy, caution should be used in PA therapy, since even slight depression of myocardial contractility may further reduce cardiac output of the damaged heart.

Concurrent Other Antiarrhythmic Agents

Concurrent use of PA with other Group 1A antiarrhythmic agents such as quinidine or disopyramide may produce enhanced prolongation of conduction or depression of contractility and hypotension, especially in patients with cardiac decompensation. Such use should be reserved for patients with serious arrhythmias unresponsive to a single drug and employed only if close observation is possible.

Renal Insufficiency

Renal insufficiency may lead to accumulation of high plasma levels from conventional doses of PA, with effects similar to those of overdosage (see ***OVERDOSAGE***), unless dosage is adjusted for the individual patient.

Myasthenia Gravis

Patients with myasthenia gravis may show worsening of symptoms from PA due to its procaine-like effect on diminishing acetylcholine release at skeletal muscle motor nerve endings, so that PA administration may be hazardous without optimal adjustment of anticholinesterase medications and other precautions.

Sulfite Sensitivity

Procainamide Hydrochloride Injection contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

PRECAUTIONS

Blood-Pressure and ECG Monitoring

Blood pressure should be monitored with the patient supine during parenteral, especially intravenous, administration of PA. There is a possibility that relatively high although transient plasma levels of PA may be attained and cause hypotension before the PA can be distributed from the plasma volume to its full apparent volume of distribution which is approximately 50 times greater. Therefore, caution should be exercised to avoid overly rapid administration of PA. If the blood pressure falls 15 mm Hg or more, PA administration should be temporarily discontinued.

Electrocardiographic (ECG) monitoring is advisable as well, both for observation of the progress and response of the arrhythmia under treatment, and for early detection of any tendency to excessive widening of the QRS complex, prolongation of the P-R interval, or any signs of heart block (see ***OVERDOSAGE***). Parenteral therapy with PA should be limited to use in hospitals in which monitoring and intensive supportive care are available, or to emergency situations in which equivalent observation and treatment can be provided.

General

Immediately after initiation of PA therapy, patients should be closely observed for possible hypersensitivity reactions. In conversion of atrial fibrillation to normal sinus rhythm by any means, dislodgement of mural thrombi may lead to embolization, which should be kept in mind.

After achieving and maintaining therapeutic plasma concentrations and satisfactory electrocardiographic and clinical responses, continued frequent periodic monitoring of vital signs and electrocardiograms is advised. If evidence of QRS widening of more than 25 percent or marked prolongation of the Q-T interval occurs, concern for overdosage is appropriate, and interruption of the PA infusion is advisable if a 50 percent increase occurs. Elevated serum creatinine or urea nitrogen, reduced creatinine clearance or history of renal insufficiency, as well as use in older patients (over age 50), provide grounds to anticipate that less than the usual dosage or infusion rate may suffice, since the urinary elimination of PA and NAPA may be reduced, leading to gradual accumulation beyond normally-predicted amounts. If facilities are available for measurement of plasma PA and NAPA, or acetylation capability, individual dose adjustment for optimal therapeutic levels may be easier, but close observation of clinical effectiveness is the most important criterion.

Information for Patients

The patient should be encouraged to disclose any past history of drug sensitivity, especially to procaine or other local anesthetic agents, or aspirin, and to report any history of kidney disease, congestive heart failure, myasthenia gravis, liver disease, or lupus erythematosus.

The patient should be counseled to report any symptoms of arthralgia, myalgia, fever, chills, skin rash, easy bruising, sore throat or sore mouth, infections, dark urine or icterus, wheezing, muscular weakness, chest or abdominal pain, palpitations, nausea, vomiting, anorexia, diarrhea, hallucinations, dizziness, or depression.

Laboratory Tests

Laboratory tests such as complete blood count (CBC), electrocardiogram and serum creatinine or urea nitrogen may be indicated depending on the clinical situation, and periodic rechecking of the CBC and ANA may be helpful in early detection of untoward reactions.

Drug Interactions

If other antiarrhythmic drugs are being used, additive effects on the heart may occur with PA administration, and dosage reduction may be necessary (see ***WARNINGS***).

Anticholinergic drugs administered concurrently with PA may produce additive antivagal effects on A-V nodal conduction, although this is not as well documented for PA as for quinidine.

Patients taking PA who require neuromuscular blocking agents such as succinylcholine may require less than usual doses of the latter, due to PA effects on reducing acetylcholine release.

Drug/Laboratory Test Interactions

Supraphar macologic concentrations of lidocaine and meprobamate may inhibit fluorescence of PA and NAPA, and propranolol shows a native fluorescence close to the PA/NAPA peak wavelengths, so that tests which depend on fluorescence measurement may be affected.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed.

Teratogenic Effects: Pregnancy Category C

Animal reproduction studies have not been conducted with PA. It also is not known whether PA can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. PA should be given to a pregnant woman only if clearly needed.

Nursing Mothers

Both PA and NAPA are excreted in human milk, absorbed by the nursing infant. Because of the potential for serious adverse reactions in nursing infants, a decision to discontinue nursing or the drug should be made, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Cardiovascular System: Hypotension and serious disturbances of cardiorhythm such as ventricular asystole or fibrillation are more common with intravenous administration of PA than with intramuscular administration. Because PA is a peripheral vasodilator in concentrations higher than the usual therapeutic range, transient high plasma levels which may occur especially during intravenous administration may produce temporary but at times severe lowering of blood pressure (see ***OVERDOSAGE*** and ***PRECAUTIONS***).

Multisystem: A lupus erythematosus-like syndrome of arthralgia, pleural or abdominal pain, and sometimes arthritis, pleural effusion, pericarditis, fever, chills, myalgia, and possibly related hematologic or skin lesions (see below) is fairly common after prolonged PA administration, perhaps more often in patients who are slow acetylators (See Boxed Warning and ***PRECAUTIONS***). While some series have reported less than 1 in 500, others have reported the syndrome in up to 30 percent of patients on long term oral PA therapy. If discontinuation of PA does not reverse the lupoid symptoms, corticosteroid treatment may be effective.

Hematologic: Neutropenia, thrombocytopenia, or hemolytic anemia may rarely be encountered. Agranulocytosis has occurred after repeated use of PA, and deaths have been reported. (See Boxed Warning, ***WARNINGS*** section.)

Skin: Angioneurotic edema, urticaria, pruritus, flushing, and maculopapular rash have also occurred.

Gastrointestinal System: Anorexia, nausea, vomiting, abdominal pain, diarrhea or bitter taste may occur in 3 to 4 percent of patients taking oral procainamide.

Nervous System: Dizziness or giddiness, weakness, mental depression and psychosis with hallucinations have been reported.

Elevated Liver Enzymes: Elevations of transaminase with and without elevations of alkaline phosphatase and bilirubin have been reported. Some patients have had clinical symptoms (e.g., malaise, right upper quadrant pain). Deaths from liver failure have been reported.

OVERDOSAGE

Progressive widening of the QRS complex, prolonged Q-T and P-R intervals, lowering of the R and T waves, as well as increasing A-V block, may be seen with doses which are excessive for a given patient. Increased ventricular extrasystoles, or even ventricular tachycardia or fibrillation may occur. After intravenous administration but seldom after oral therapy, transient high plasma levels of PA may induce hypotension, affecting systolic more than diastolic pressures, especially in hypertensive patients. Such high levels may also produce central nervous depression, tremor, and even respiratory depression.

Plasma levels above 10 mcg/mL are increasingly associated with toxic findings, which are seen occasionally in the 10 to 12 mcg/mL range, more often in the 12 to 15 mcg/mL range, and commonly in patients with plasma levels greater than 15 mcg/mL.

Treatment of overdosage or toxic manifestations includes general supportive measures, close observation, monitoring of vital signs and possibly intravenous pressor agents and mechanical cardiorespiratory support. If available, PA and NAPA plasma levels may be helpful in assessing the potential degree of toxicity and response to therapy. Both PA and NAPA are removed from the circulation by hemodialysis but not peritoneal dialysis. No specific antidote for PA is known.