

Teaching CPR: Someone's life depends on it

In 1966, a National Academy of Sciences–National Research Council (NAS–NRC) Conference on Cardiopulmonary Resuscitation (CPR) recommended the training of medical, allied health, and other professional personnel in the external chest compression technique as established by the standards of the American Heart Association (AHA).^{1,2} In 1973, a second national conference on CPR and Emergency Cardiac Care, cosponsored by the AHA and the NAS–NRC, recommended that CPR training programs be extended to the general public.³ Since then, multiple studies have indicated that bystander-initiated CPR improves survival rates of patients who have cardiac arrest in a nonhospital environment.^{4,5}

A recent study by Gallagher and colleagues⁶ provides further evidence of the value of bystander-initiated CPR. The authors gathered data from 2071 out-of-hospital resuscitations performed during a 6-month period in New York City. They sought to determine how much the “quality” of bystander-initiated CPR influenced survival. Effective bystander-initiated CPR was associated with a 4.6% survival rate. Effective CPR was defined as ventilation producing visible chest compression plus chest compression producing palpable carotid or femoral pulse. Victims of cardiac arrest in the study were characterized as “survivors” if they were discharged from the hospital to home. Overall, survival in this study was 2.9% among the 662 victims who received bystander-initiated CPR and 0.8% among the 1409 victims who received no bystander-initiated CPR.

These results contrast those findings from a 1982 Seattle study by Cobb and Hallstrom.⁷ The researchers noted that the survival rate was the same in victims whether they received CPR by highly trained rescuers or lay rescuers. Both of these studies support CPR as the initial component to any successful resuscitation from cardiac arrest.

With this in mind, the American Osteopathic Association (AOA) in its position paper on CPR training strongly supports the instruction of CPR techniques to the general public. It also “encourages member physicians to qualify as instructors in

basic life support so as to enable them to teach cardiopulmonary resuscitation courses in schools, churches, and other organizations on a voluntary basis.”⁸ The osteopathic medical profession rests on the tenet of health promotion/disease prevention. The rest of the healthcare profession seems to have adopted a preventive approach as well, and the AHA has developed a 4-hour basic life support module that includes information for the lay public on cardiac risk factors and prudent heart living. The prevention of cardiac disease constitutes part of this approach to living. Strong disease prevention messages delivered during CPR training may have as great an impact on cardiovascular mortality and morbidity as the teaching of emergency measures themselves. Through community education and involvement, CPR may serve as a means of controlling coronary artery disease through prevention.

In accordance with a mandate in the Osteopathic Medicine Oath, “I will be ever vigilant in aiding in the general welfare of the community...,” osteopathic physicians should teach the community to function as the ultimate coronary care unit. This concept assumes a lay public able to recognize the symptoms of a possible myocardial infarction and educated enough to seek prompt entry of the victim into the emergency medical services system. Citizens must be trained to support the life of the cardiac arrest victim until advanced cardiac life support resources become available. The entire community must be trained in recognition and reduction of reversible risk factors among the population with known coronary artery disease, and they must eagerly support an effective emergency medical services system.

Many colleges and state societies afford practicing physicians opportunities to continually renew their CPR certification and to become instructors in these life-saving techniques. Some osteopathic physicians do use the opportunities associated with CPR training to teach their patients and the general public the importance of healthy lifestyles to prevent cardiovascular disease in the first place. But all DOs

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PROPULSID®

cisapride 1 mg/mL suspension

Before prescribing, please consult complete prescribing information of which the following is a brief summary.

Warning: Serious cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, torsades de pointes, and QT prolongation have been reported in patients taking PROPULSID® with other drugs that inhibit cytochrome P450 3A4, such as ketoconazole, itraconazole, miconazole, triazolanolone, erythromycin, fluconazole, and clarithromycin. Some of these events have been fatal. PROPULSID® is contraindicated in patients taking any of these drugs. (See CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and DRUG INTERACTIONS).

INDICATIONS: PROPULSID® (cisapride) is indicated for the symptomatic treatment of patients with nocturnal heartburn due to gastroesophageal reflux disease.

CONTRAINDICATIONS: Concomitant administration of NIZORAL® (ketoconazole) tablets, SPORANOX® (itraconazole) capsules, MONISTAT (v.) (miconazole), fluconazole, erythromycin, clarithromycin, or 1A0® (triazolanolone) capsules with PROPULSID® is contraindicated. (See WARNINGS AND PRECAUTIONS: Drug Interactions).

PROPULSID® (cisapride) should not be used in patients in whom an increase in gastrointestinal motility could be harmful, e.g., in the presence of gastrointestinal hemorrhage, mechanical obstruction, or perforation. PROPULSID® is contraindicated in patients with known sensitivity or intolerance to the drug.

WARNINGS: PROPULSID® undergoes metabolism mainly by the hepatic cytochrome P450 3A4 isoenzyme. Drugs which inhibit this enzyme such as ketoconazole, itraconazole, miconazole, clarithromycin, erythromycin, fluconazole, or triazolanolone can lead to elevated cisapride blood levels.

Rare cases of serious cardiac arrhythmias, including ventricular arrhythmias and torsades de pointes associated with QT prolongation, have been reported in patients taking cisapride with ketoconazole, itraconazole, miconazole, erythromycin, clarithromycin, or fluconazole. Some of these patients did not have known cardiac histories; however, most had been receiving multiple other medications and had pre-existing cardiac disease or risk factors for arrhythmias. Some of these cases have been fatal.

PRECAUTIONS: General: Potential benefits should be weighed against risks prior to administration of cisapride to patients with conditions associated with QT prolongation, such as congenital prolonged QT syndrome, uncorrected electrolyte disturbances or in patients who are taking other medications known to prolong QT interval.

Information for Patients: Patients should be warned against concomitant use of oral ketoconazole, itraconazole, miconazole, erythromycin, clarithromycin, fluconazole, or triazolanolone with PROPULSID®.

Although PROPULSID® (cisapride) does not affect psychomotor function nor does it induce sedation or drowsiness when used alone, patients should be advised that the sedative effects of benzodiazepines and of alcohol may be accentuated by PROPULSID®.

Drug Interactions: Cisapride is metabolized mainly via the cytochrome P450 3A4 enzyme.

Human pharmacokinetic data indicate that oral ketoconazole potentially inhibits the metabolism of cisapride, resulting in a mean eightfold increase in AUC of cisapride. A study in 14 normal male and female volunteers suggest that coadministration of PROPULSID® and ketoconazole can result in prolongation of the QT interval on the ECG.

In vitro data indicate that itraconazole, miconazole, fluconazole, erythromycin, clarithromycin, and triazolanolone also markedly inhibit cytochrome P450 3A4 mainly responsible for the metabolism of cisapride.

In some cases where serious ventricular arrhythmias, QT prolongation, and torsades de pointes have occurred when cisapride was taken in conjunction with one of the cytochrome P450 3A4 inhibitors, elevated blood cisapride levels were noted at the time of the QT prolongation. Normalization of the QT interval after cisapride was discontinued has been observed.

Concomitant administration of anticholinergic compounds would be expected to compromise the beneficial effects of PROPULSID®.

The acceleration of gastric emptying by PROPULSID® could affect the rate of absorption of other drugs. Patients receiving narrow therapeutic ratio drugs or other drugs that require careful titration should be followed closely, if plasma levels are being monitored, they should be reassessed.

In patients receiving and anticoagulants, the coagulation times were increased in some cases. It is advisable to check coagulation time within the first few days after the start and discontinuation of PROPULSID® therapy, with an appropriate adjustment of the anticoagulant dose, if necessary.

Cimetidine coadministration leads to an increased peak plasma concentration and AUC of PROPULSID®; there is no effect on PROPULSID® absorption when it is coadministered with ranitidine. The gastrointestinal absorption of cimetidine and ranitidine is accelerated when they are coadministered with PROPULSID®.

Carcinogenesis, mutagenesis, impairment of fertility: In a twenty-five month and carcinogenicity study in rats, cisapride at daily doses up to 80 mg/kg was not tumorigenic. For a 50 kg person of average height (1.46 m body surface area), this dose represents 50 times the maximum recommended human dose (1.6 mg/kg/day) on a mg/kg basis and 7 times the maximum recommended human dose (54.4 mg/m²) on a body surface area basis. In a nineteen month and carcinogenicity study in mice, cisapride at daily doses up to 80 mg/kg was not tumorigenic. This dose represents 50 times the maximum recommended human dose on a mg/kg basis and about 4 times the maximum recommended human dose on a body surface area basis.

Cisapride was not mutagenic in the *in vitro* Ames test, human lymphocyte chromosomal aberration test, mouse lymphoma cell forward mutation test, and rat hepatocyte UDS test and *in vivo* rat micronucleus test, male and female mouse dominant lethal mutations tests, and sex linked recessive lethal test in male *Drosophila melanogaster*.

Fertility and reproductive performance studies were conducted in male and female rats. Cisapride was found to have no effect on fertility and reproductive performance of male rats at oral doses up to 160 mg/kg/day (100 times the maximum recommended human dose on a mg/kg basis and 14 times the maximum recommended human dose on a mg/m² basis). In the female rats, cisapride at oral doses of 40 mg/kg/day and higher prolonged the breeding interval required for implantation. Similar effects were also observed at maturity in the female offspring (F₁) of the female rats (F₂) treated with oral doses of cisapride at 10 mg/kg/day or higher. Cisapride at an oral dose of 160 mg/kg/day also exerted contragestational/pregnancy disrupting effects in female rats (F₂).

Pregnancy: Teratogenic effects: Pregnancy category C: Oral teratology studies have been conducted in rats (doses up to 160 mg/kg/day) and rabbits (doses up to 40 mg/kg/day). There was no evidence of a teratogenic potential of cisapride in rats or rabbits. Cisapride was embryotoxic and fetotoxic in rats at a dose of 160 mg/kg/day (100 times the maximum recommended human dose on a mg/kg basis and 14 times the maximum recommended human dose on a mg/m² basis) and in rabbits at a dose of 20 mg/kg/day (approximately 12 times the maximum recommended human dose on a mg/kg basis) or higher. It also produced reduced birth weights of pups in rats at 40 and 160 mg/kg/day and adversely affected the pup survival. There are no adequate and well-controlled studies in pregnant women. Cisapride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Cisapride is excreted in human milk at concentrations approximately one twentieth of those observed in plasma. Caution should be exercised when PROPULSID® is administered to a nursing woman, and particular care must be taken if the nursing infant or the mother is taking a drug that might alter PROPULSID®'s metabolism. (See CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, DRUG INTERACTIONS).

Pediatric Use: Safety and effectiveness in children have not been established.

Geriatric Use: Steady-state plasma levels are generally higher in older than in younger patients, due to a moderate prolongation of the elimination half-life. Therapeutic doses, however, are similar to those used in younger adults.

The rate of adverse experiences in patients greater than 65 years of age was similar to that in younger adults.

ADVERSE REACTIONS: In the U.S. clinical trial population of 1728 patients (comprising 506 with gastroesophageal reflux disorders, and the remainder with other motility disorders) the following adverse experiences were reported in more than 1% of patients treated with PROPULSID® (cisapride) and at least as often on placebo. The percent of patients who discontinued treatment is displayed in parentheses.

Central & Peripheral Nervous Systems: Headache 19.3% (1.1%), 17.1% (0.4%) Gastrointestinal: Diarrhea 14.2 (0.7), 10.3 (0.1) Abdominal pain 10.2 (1.2), 7.7 (0.9) Nausea 7.6 (1.0), 7.6 (0.3) Constipation 6.7 (0.1), 3.4 (0.0) Flatulence 3.5 (0.4), 3.1 (0.4) Dyspepsia 2.7 (0.1), 1.0 (0.0) Respiratory System: Rhinitis 7.3 (0.1), 5.7 (0.1) Sinusitis 3.6 (0.0), 3.5 (0.0) Coughing 1.5 (0.2), 1.2 (0.0) Resistance Mechanism: Viral infection 3.6 (0.2), 3.2 (0.0) Upper respiratory tract infection 3.1 (0.0), 2.8 (0.0) Body as a Whole: Pain 3.4 (0.0), 2.3 (0.0) Fever 2.2 (0.1), 1.5 (0.0) Urinary System: Urinary tract infection 2.4 (0.0), 1.9 (0.0) Micturition frequency 1.2 (0.1), 0.6 (0.0) Psychiatric: Insomnia 1.9 (0.3), 1.3 (0.4) Anxiety 1.4 (0.1), 1.0 (0.1) Nervousness 1.4 (0.2), 0.7 (0.0) Skin & Appendages: Rash 1.6 (0.0), 1.6 (0.3) Pruritus 1.2 (0.1), 1.0 (0.0) Musculoskeletal System: Arthralgia 1.4 (0.1), 1.2 (0.0) Vision: Abnormal vision 1.4 (0.2), 0.3 (0.0) Reproductive, Female: Vaginitis 1.2 (0.0), 0.9 (0.0)

The following adverse events also reported in more than 1% of PROPULSID® patients were more frequently reported on placebo: dizziness, vomiting, pharyngitis, chest pain, fatigue, back pain, depression, dehydration, and myalgia.

Diarrhea, abdominal pain, constipation, flatulence, and rhinitis all occurred more frequently in patients using 20 mg of PROPULSID® than in patients using 10 mg.

Additional adverse experiences reported to occur in 1% or less of patients in the U.S. clinical studies are: dry mouth, somnolence, palpitation, migraine, tremor, and edema.

In other U.S. and international trials and in foreign marketing experience, there have been rare reports of seizures and extrapyramidal effects, tachycardia, elevated liver enzymes, hepatitis, thrombocytopenia, leukopenia, aplastic anemia, pancytopenia, and granulocytopenia. The relationship of PROPULSID® to the event was not clear in these cases.

There have been rare cases of sinus tachycardia reported. Rechallenge precipitated relapse in some of those patients.

Rare cases of cardiac arrhythmias, including ventricular arrhythmias, torsades de pointes and QT prolongation, in some cases resulting in death, have been reported. Most of these patients had been receiving multiple other medications and had pre-existing cardiac disease or risk factors for arrhythmias. A causal relationship to PROPULSID® has not been established.

OVERDOSEAGE: Reports of overdose with PROPULSID® (cisapride) include an adult who took 540 mg and for 2 hours experienced retching, borborygmi, flatulence, stool frequency and urinary frequency.

A one-month-old male infant received 2 mg/kg of cisapride, 10 times the prescribed dose, four times per day for 5 days. The patient developed third degree heart block and subsequently died of right ventricular perforation caused by pacemaker wire insertion.

Treatment should include gastric lavage and/or activated charcoal, close observation and general supportive measures.

In instances of overdose, patients should be evaluated for possible QT prolongation and for factors that can predispose to the occurrence of ventricular arrhythmias, including torsades de pointes. Single and doses of cisapride at 4000 mg/kg, 160 mg/kg, 1280 mg/kg and 640 mg/kg were lethal in adult rats, neonatal rats, mice, and dogs, respectively. Symptoms of acute toxicity were prostr, tremors, convulsions, dyspnea, loss of righting reflex, cataplexy, catatonias, hypotonia and diarrhea.

DOSEAGE AND ADMINISTRATION: 5 mL (1 teaspoon) suspension = 5 mg.

Adults: Initiate therapy with one 10 mg tablet of PROPULSID® (cisapride) or 10 mL of the suspension 4 times daily at least 15 minutes before meals and at bedtime. In some patients the dosage will need to be increased to 20 mg, given as above, to obtain a satisfactory result.

In elderly patients, steady-state plasma levels are generally higher due to a moderate prolongation of the elimination half-life. Therapeutic doses, however, are similar to those used in younger adults.

HOW SUPPLIED: PROPULSID® Tablets are provided as scored white tablets debossed "Janssen" and P/70 containing the equivalent of 10 mg of cisapride in blister packages of 100 (NDC 50458-430-01) and in bottles of 100 (NDC 50458-430-10) and 500 (NDC 50458-430-50). PROPULSID® is also provided as blue tablets, debossed "Janssen" and P/70, containing the equivalent of 20 mg cisapride in bottles of 100 (NDC 50458-440-10).

PROPULSID® Suspension is provided as a bright pink homogeneous suspension containing 1 mg/mL of cisapride in 16 oz. bottles containing 450 mL (NDC 50458-450-45).

Store at room temperature (59°-86°F/15°-30°C). Protect the tablets from moisture. The 20 mg tablets should also be protected from light.

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innovators in GI therapy

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editorials

(continued)

should accept the responsibility to educate the public in the prevention of heart disease and in the proper techniques of CPR. Neglecting this responsibility could very well cost someone's life. ♦

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