Table 14–3. SELECTED CARDIOTOXIC AGENTS*

AGENTS (CHEMICAL CLASS OR USE CATEGORY)	CARDIAC EFFECT AND/OR PRIMARY SITE	ASSOCIATED DISEASE STATE AND/OR MECHANISM
Substituted Aliphatic Hydrocarbons		
A. Haloalkanes	Negative chronotropic, inotropic, and dromotropic effects that depress heart rate, contractility, and conduction	Cardiotoxicity exceeds that of similar chain length unsubstituted hydrocarbons; maximum toxicity at 4 Cl atoms
1. Chloroform	Arrhythmias	Sensitizes the heart to endogenous catecholamines
2. Cyclopropane and diethylether[a,b]	Arrhythmias	Sensitize the heart to catecholamines
3. Freons (fluorocarbons)[c]	Reduces cardiac output and coronary flow	Reflex increases in sympathetic and parasympathetic impulses to heart via respiratory tract mucosa irritation
4. Haloanesthetics (halothane, methoxyflurane and enflurane)	Negative chronotropic, inotropic, and dromotropic effects; possible cardiac arrest	Myocardial depression
5. Substituted ethanes	Negative inotropism	
B. Alcohols and aldehydes		
1. Acetaldehyde	Negative inotropic effects (after moderate ethanol intake)	Release of catecholamines and resulting sympathetic effects (at higher doses); toxicity diminishes with increasing aldehyde chain length
2. Ethanol	Decreases cardiac contraction; causes arrhythmias and ventricular fibrillation with sudden death (after chronic exposure); cardiomegaly (found upon autopsy)	Pulmonary congestion; congestive heart failure; leakage of myocardial cells; depression of oxidative phosphorylation in heart mitochondria; interstitial fibrosis and increased lipid in muscle cells[d]
3. PEG 500[e]	Enhancement of the pressor effects of epinephrine	
4. Propylene glycol[e]	Enhancement of arrhythmogenic effects of digitalis	
Heavy Metals[f,g]		
1. Barium	Potent arrhythmogen; production of ventricular tachycardia	Greatly prolongs action potentials
2. Cadmium		Antagonism of Ca^{2+} ion; shortens action potential
Acute	Prolongation of PR interval; heart failure in diastole	
Chronic	Cardiac hypertrophy and vacuolation in the Purkinje cells	
3. Cobalt	Cardiac lesions, heart failure	Antagonism of endogenous Ca^{2+}, complexes of cobalt with macromolecules
4. Lanthanum	Effects upon sarcolemmal ion channels	Blocks Ca^{2+} channels
5. Lead		
Prenatal[h]	Postnatal sensitization to the arrhythmogenic effects of norepinephrine	
Adult[i]	Negative inotropism; ECG abnormalities and rhythm changes; deformation of T wave; prolongation of PR interval	Displacement of Ca^{2+}; interference with Ca availability; interference with energy metabolism and ATP synthesis in heart

Table 14–3. (*Continued*)

AGENTS (CHEMICAL CLASS OR USE CATEGORY)	CARDIAC EFFECT AND/OR PRIMARY SITE	ASSOCIATED DISEASE STATE AND/OR MECHANISM
6. Manganese	Effects upon sarcolemmal ion channels	Blocks Ca^{2+} channels
7. Nickel	Effects upon sarcolemmal ion channels	Blocks Ca^{2+} channels
8. Vanadium	Both positive and negative inotropic effects *in vitro* depending upon species; decrease of left ventricular contraction and negative chronotropic effects in intact animal	Inotropic changes related to alteration in available surface Ca^{2+}; effects upon phosphorylation reactions; inhibition of Na^+K^+ATPase
Gases		
1. Carbon disulfide	Angina pectoris	Formation of thiocarbamates; inhibition of dopamine hydroxylase; disruption of lipid and thyroxine metabolism; development of coronary heart disease
2. Carbon monoxide (acute)	Tachycardia, bradycardia, extrasystoles; increased demand for oxygen by the heart; production of angina pectoris; myocardial infarction	Interference with myocardial energy metabolism
Drugs		
A. Cardioactive drugs		
1. Antiarrhythmics	Decreased conductivity and automaticity of the myocardium	
a. Quinidine and procainamide	Prolongation of QRS and QT intervals; ventricular fibrillation after i.v. injection; extrasystoles, low doses accelerate while large doses prolong AV conduction; cardiac arrest	
b. Lidocaine	Sinus bradycardia; depressed automaticity of Purkinje fibers and myocardial cells; depressed myocardial contractility	Shortened action potentials of Purkinje fibers and myocardial cells
c. Phenytoin	Suppression of automaticity; cardiac arrest	
2. Adrenergic agonists		
a. Epinephrine and[j] isoproterenol	Positive inotropic and chronotropic effects; ST segment deviation, ectopic beats, and subendocardial necrosis	Myocardial hypoxia; cellular Ca^{2+} overload
b. Isoproterenol[j] (only)	Hypercontraction of myofibrills in apical subendocardium; appearance of donut-shaped granules in mitochondria, myocytolysis	Excessive Ca^{2+} influx
3. Adrenergic antagonists as well as reserpine and guanethidine	Deceased cardiac contractility; production of AV block; heart failure (effects of overdose); angina and possible myocardial infarction (effects of withdrawal)	Receptor supersensitivity; excess numbers of receptors
4. Glycosides of digitalis,[k,l] strophanthin, and oleandrin	Increase in cardiac contractility, irritability, and arrhythmias	Inhibit the sarcolemmal Na^+ pump (Na^+K^+ATPase) with elevation of intracellular Ca^{2+} via Na^+/Ca^{2+} exchange
	Premature ventricular contractions	Ventricular fibrillation
	Prolonged PR interval	Complete heart block

5. Nicotine	Arrhythmias	Suppresses K^+ conductance
6. Vasodilators and antihypertensives (hydralazine, diazoxide, minoxidil)	Similar effects to epinephrine, via reflex tachycardia during hypotension	
B. Ca^{2+} antagonists[g]		
1. Bepridil	Negative chronotropic and ionotropic effects	Blocks slow Ca^{2+} channels; depressed Ca^{2+} release from the SR
2. Papaverine	Negative chronotropic and ionotropic effects	Blocks slow channels; inhibits phosphodiesterase and elevates cAMP
3. Verapamil and nifedipine	Negative chronotropic and ionotropic effects	Excitation contraction uncoupling; block both slow Ca^{2+} and Na^+ channels; depress or block Ca^{2+} influx into myocardial cells
C. CNS active drugs[m]		
1. Amphetamine and cocaine[m]	Increased heart rate; blood pressure increase causing great risk when there is preexisting angina, hypertension, and atherosclerosis	Increased work load on the heart
2. Imipramine and amitryptyline	Low doses enhance cardiac contractility, whereas high doses depress it as well as coronary flow and heart rate; quinidinelike effects on the heart; prolongation of the PR, QRS, and QT interval; bundle branch block; supraventricular and ventricular arrhythmias	Cardiac arrest; catecholamine reuptake inhibition; anticholinergic effects
3. Lithium (long-term) (toxic dose)	Ventricular arrhythmias and in rare instances, myocardial lesions	
4. MAO inhibitors	Palpitation	Exaggerated sympathomimetic effects
5. Marijuana	Positive inotropic and chronotropic effects; premature ventricular contractions; enhanced ventricular automaticity	Facilitation of SA and AV nodal conduction; increased work load on heart
6. Methyldopa[d]	Focal or diffuse interstitial infiltration with eosinophils, lymphocytes, and plasma cells	Hypersensitivity myocarditis
7. Methysergide	Endomyocardial fibrosis; valvular defects	
8. Neuroleptics[n] (phenothiazines and butyrophenones)	Tachyarrhythmias, hypotension, ventricular tachycardia, and fibrillation (rare), conduction defects; prolongation of QT interval; abnormalities in T wave sinus tachycardia, widening of QRS complex	Quinidine-type toxicity; peripheral α receptor blockade; central and peripheral anticholinergic actions
9. Barbiturates	Depression of myocardial contactility	Inserts in lipid bilayer of membrane; stabilizes membranes
D. Chemotherapeutic agents		
1. Antimicrobial antibiotics a. Antimicrobial antibiotics b. Some macrolides and chloramphenicol	Weak negative inotropic effects	Depressed Ca^{2+} uptake
2. Antineoplastic antibiotics a. Anthracylines[o,p] (doxorubicin and daunorubicin)	Arrhythmias (acute) Congestive cardiomyopathy (after chronic use); cardiac dilation, atrophy and degeneration of the myocytes, and interstitial edema and fibrosis (seen at autopsy)	Possibly due to histamine release; generation of reactive oxygen; peroxidation of membrane lipids and consequent changes in permeability and in cellular homeostasis

Table 14–3. *(Continued)*

AGENTS (CHEMICAL CLASS OR USE CATEGORY)	CARDIAC EFFECT AND/OR PRIMARY SITE	ASSOCIATED DISEASE STATE AND/OR MECHANISM
b. 5-Fluorouracil	Myocardial ischemia; cardiac arrest	
c. Cyclophosphamide (large doses)	Myocardial capillary microthrombosis; pericarditis	Cardiac failure
3. Emetine	Sinus tachycardia dose-related arrhythmias and myocardial necrosis, ventricular fibrillation	Conduction disturbances; effects upon K^+ ion movements
4. Monensin and lasalocid[f]	Positive inotropic effect; increased cardiac output; occasional increase in heart rate and automaticity; increased coronary blood flow	Increased excitation-contraction coupling; enhanced metabolism of cardiac cells; increased sarcolemmal cationic trap for Na^+, and lasalocid a cationic trap for K^+
5. Penicillin and sulfonamide[d]	Focal or diffuse interstitial infiltration with eosinophils, lymphocytes and plasma cells	Hypersensitivity myocarditis
E. Carcinogenic agents[d]		
1,3-Butadiene and nitrosamines	Sarcoma formation within heart	Induction of chemical carcinogenesis
F. Agents and drugs producing cardiovascular teratogenesis[q]		
1. Bis(dichloroacetyl) diamine	Ventricular septal defects; dextrocardia; ectopia; tetralogy of Fallot; pulmonic stenosis	
2. Caffeine	Ventricular septal defects	
3. Cortisone		
4. Dextroamphetamine	Ventricular and atrial septal defects	
5. Ethanol	Ventricular septal defects	
6. Phenobarbital		
7. Salicylate and indomethacin	Ventricular septal defects	Systemic hypertension
Toxins[g]		
1. Batrochotoxin	Ventricular arrhythmia, fibrillation, positive inotropic effects	Increase in resting Na^+ permeability; actions upon protein constituents of Na^+ channel
2. Cobra venom cardiotoxin	Systolic arrest; disruption of myocardial cell membranes and myofibrils	Depression of Ca^{2+} accumulation in SR; inhibition of Ca-ATPase; SR membranes become more leaky; depression of Ca^{2+} accumulation in mitochondria; ultimate Ca^{2+} overload
3. Endotoxin	Reduced coronary perfusion; depression of contractility; negative inotropic and chronotropic responses to NE and histamine	Depression of Ca-ATPase activity, depression of Ca^{2+} uptake, reduced Ca^{2+} release by action potentials
4. Grayanotoxins	Positive inotropic action	Increases Na^+ permeability; opens voltage-dependent Na^+ channels
5. Sea anenome toxins (ATX-II and CTX)	Conduction defects; negative chronotropic effect; positive inotropic effects	Greatly slows inactivation of Na^+ channels