

Cardiac Toxicities of Antibiotics

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Isolated heart muscle preparations are useful in the study of cardiac toxicities of drugs and environmental chemicals: such tissues allow assessment of chemical effects on heart muscle that is free from indirect *in vivo* influences that can mask or even accentuate cardiac responses measured in the intact animal. In the present study, left atria of guinea pigs were used to demonstrate a direct cardiac depressant effect of greater-than-therapeutic concentrations of several aminoglycoside antibiotics. The toxic effect of these antibiotics seems to be a calcium-dependent event, and may prove useful to characterize contractile responses of the heart. Other antibiotic agents can also depress cardiovascular function, as summarized in this report, but mechanisms of action have not been clearly defined.

Introduction

A variety of pharmacologic and environmental chemicals can influence cardiovascular function; however, such effects are not always easily detectable before serious damage to the heart or blood vessels has occurred. The heart is particularly susceptible to the actions of exogenous chemicals due, in no small part, to the functional dependence of this organ on dynamic and discrete ionic balances at the myocardial cell level (1). Not only can drugs directly affect myocardial integrity, but they may also modify cardiac performance by decreasing the ability of the heart to compensate when affected by disease. In recognition of such problems and the resulting need for experimental means of identifying cardiovascular effects of chemicals, "model" cardiac systems have been developed to characterize normal heart function and to predict the responsiveness of this organ to chemical challenge. Although limitations are routinely encountered when effects of drugs in isolated tissue models are extrapolated directly to human populations, heart muscle preparations have generally proven to be useful in the study of cardiac toxicities of chemicals.

Recently, we became interested in cardiac muscle and vascular smooth muscle models and have found certain *in vitro* preparations to provide predictive

information relative to *in vivo* cardiovascular manifestations of drug toxicities (2-4). In addition, a particular group of clinically used agents was identified to also have potential application for probing cardiovascular function. These drugs, the aminoglycoside antibiotics (i.e., neomycin-streptomycin group), were found to depress arterial muscle function in rather specific manners that could best be explained by an inhibitory effect on a portion of cellular calcium ion (Ca^{2+}) bound to superficial membrane sites (2, 5, 6). Due to the contractile dependence of heart muscle on adequate cellular stores of Ca^{2+} (1, 7), it also seemed that the cardiac depressant effects of these agents could involve Ca^{2+} . Studies with atrial muscle of rats supported this contention (3) but provided little information relative to the influence of these agents on the contractile reactivity of heart muscle to inotropic interventions. The present report describes preliminary studies of the effects of selected aminoglycoside antibiotics on contractile function of isolated heart muscle of the guinea pig and also summarizes various aspects of the general subject of cardiac toxicities of antibiotic agents.

Materials and Methods

Male albino guinea pigs weighing between 150 and 250 g were decapitated with a guillotine; the hearts were rapidly excised and immediately placed in a Krebs—bicarbonate buffered solution (compo-

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sition given below) aerated with 95% O₂-5% CO₂. The tension developed by atria was recorded in a similar way to that previously reported (8). The left atrial appendage was carefully dissected from the heart, mounted between two miniature clamps and suspended vertically in a 15 ml tissue bath. The upper clamp was connected by silk suture to a pre-calibrated force-displacement transducer (Grass Ft .03) for measuring isometric contractions on a multichannel recorder (Grass model 7B). The lower clamp was connected directly to a stationary rod in the bottom of the tissue bath. Muscle length was adjusted by raising or lowering the force-displacement transducer mounting unit with an integral micromanipulator. Initially, length-tension relationships were tested with each muscle and 1 g of diastolic tension was found consistently to yield maximum or near maximum contractile tension. Thereafter, 1 g of diastolic tension was placed on each muscle. The maximum rate of tension development (dT/dt), a more sensitive inotropic index than tension alone, was measured in some preparations by electrically differentiating contractile tension by use of a Grass 7P20 differentiator.

Electrical stimulation was accomplished with single square wave impulses of greater-than-threshold voltage and 2 msec pulse duration, delivered at designated frequencies (1.0 Hz unless stated otherwise) from a Grass S44 stimulator.

Contractile tension and dT/dt were measured and expressed as grams of developed tension (or force) and grams per second, respectively, or values obtained in the presence of a drug were expressed as a percentage of predrug (control) values obtained in that muscle. All measurements are expressed as the mean \pm 1 standard error of the mean ($\bar{X} \pm$ SE) and the difference between two means was evaluated statistically by Student's *t* test.

The Krebs-bicarbonate solution was identical with that employed previously in heart muscle studies (8) and contained (millimolar concentration): NaCl, 118; KCl, 4.7; NaHCO₃, 24; KH₂PO₄, 1.2; MgSO₄, 1.2; CaCl₂, 2.5; and glucose 11. Ethylenediaminetetraacetic acid (EDTA, $3.3 \times 10^{-5}M$) was added to prevent oxidation of catecholamines. Solutions were prepared with demineralized water, adjusted to pH 7.4, continuously aerated with 95% O₂-5% CO₂ and maintained at $34 \pm 0.5^\circ C$.

The drugs used were 1-isoproterenol hydrochloride (Sigma Chemical Company, St. Louis, Mo.), digoxin (The Vitarine Co., Inc., New York) and the sulfate salts of gentamicin (Schering Corp., New Jersey), kanamycin (Sigma), amikacin (BB-K8; Bristol Laboratories, New York) and sisomicin (Schering). All concentrations refer to the base. Effects of drugs on heart muscle were exam-

ined by additions of small aliquots of concentrated stock solutions directly to the bathing medium of the tissue bath. After a drug response was obtained for the designated time interval, the bathing solution was changed several times and replaced with fresh medium. If the muscle was to be reexamined for paired responses, time was allowed for contraction to return to control values and to stabilize before proceeding with an experiment. With all preparations, the muscle was allowed to stabilize for at least 45 min after contraction had been initiated before an experiment was started, and bathing solution was routinely replaced every 15-20 min.

Results

Initial studies evaluated the effects of gentamicin (2.0, 4.0mM) on contractile responses to Ca²⁺. Cumulative concentration-response curves to Ca²⁺ (2.5-14.0mM) were first determined in atria not treated with gentamicin and then (after appropriate rinsings and restabilization) redetermined after the negative inotropic effects of gentamicin reached a steady-state value (about 15 min). As shown in Figure 1, 2 and 4mM gentamicin reduced contractile force (tension) by about 60 and 90%, respectively, in the control medium containing 2.5mM Ca²⁺. However, despite the pronounced depressant ef-

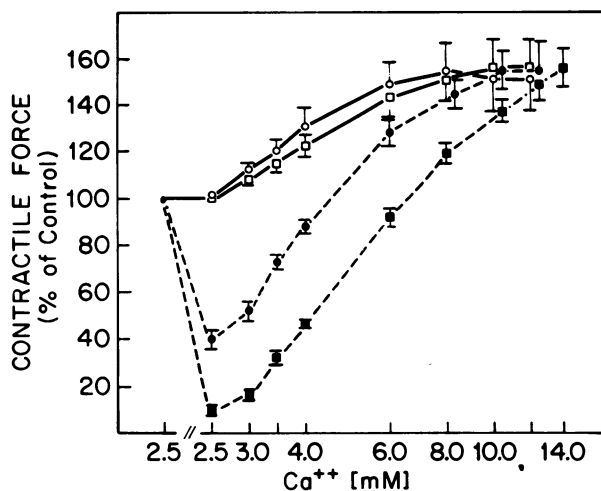


FIGURE 1. Effects of gentamicin (Gent) on the positive inotropic response to Ca²⁺ in electrically driven left atria of guinea pigs: (○) prior to exposure to Gent; (●), 10 min after exposure to 2mM Gent; (■) 10 min after exposure to 5mM Gent; (□) after recovery from Gent. Each point represents the mean \pm S.E. of 6 atria. Contractile force is expressed as a percentage of predrug control values. Values in initial 2.5mM Ca²⁺ represent contractile values prior to addition of Gent; values in second 2.5mM Ca²⁺ indicate contractile tension observed after 10 min exposure to the designated concentration of Gent.

fects of gentamicin, the antibiotic-treated heart muscle preparations responded to the positive inotropic effects of Ca^{2+} . In fact, when the larger concentrations of Ca^{2+} ($> 8mM$) were tested, the contractile responses of gentamicin-treated atria were similar to control Ca^{2+} responses (Fig. 1). Thus, the cardiac depressant activities of even large concentrations of gentamicin could be overcome by increasing Ca^{2+} availability.

If the Ca^{2+} -gentamicin interaction represented a simple physiologic antagonism, then positive inotropic agents other than Ca^{2+} should also be expected to overcome the depressant action of the antibiotic. This possibility was examined by comparing the contractile effects of different interventions (i.e., isoproterenol, digoxin and increased frequency of stimulation) in control atria and in atria treated with large concentrations of gentamicin.

Responses to cumulative increases in the concentration of isoproterenol (1×10^{-10} to $3 \times 10^{-7}M$) were determined in eight control atria and in eight other atria treated either with $2mM$ ($n = 4$) or $4mM$ ($n = 4$) gentamicin. As shown in Figure 2, isoproterenol produced a characteristic increase in contractile tension and dT/dt in both control and gentamicin-treated tissues. However, contractile responses to isoproterenol were reduced in gentamicin-treated atria, and even large amounts of isoproterenol ($> 1 \times 10^{-8}M$) could not increase contractility of gentamicin-treated atria to the magnitude seen in control atria (Fig. 2).

Contractile responses to digoxin (1 to $4 \mu M$) in control atria ($n = 12$) and in atria exposed to 1 ($n = 5$), 2 ($n = 4$), or $4mM$ ($n = 3$) gentamicin are summarized in Figure 3. Although gentamicin-treated muscles

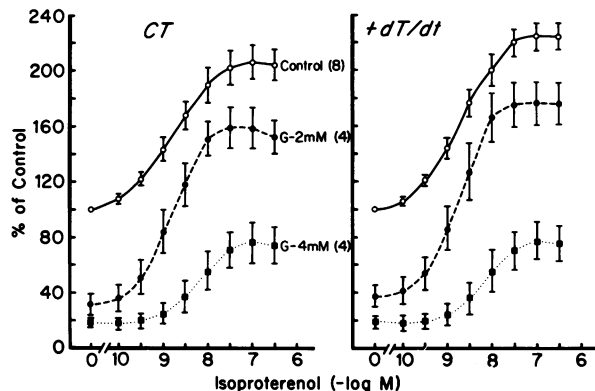


FIGURE 2. Effects of gentamicin (G) on the positive inotropic response to isoproterenol in guinea pig left atria: (○) control ($n = 8$) atria; (●) atria treated with $2.0mM$ gentamicin ($n = 4$); (■) atria treated with $4.0mM$ gentamicin ($n = 4$). Contractile tension (CT) and dT/dt are shown as percent of pre-isoproterenol control values. Each point represents the mean \pm S. E.

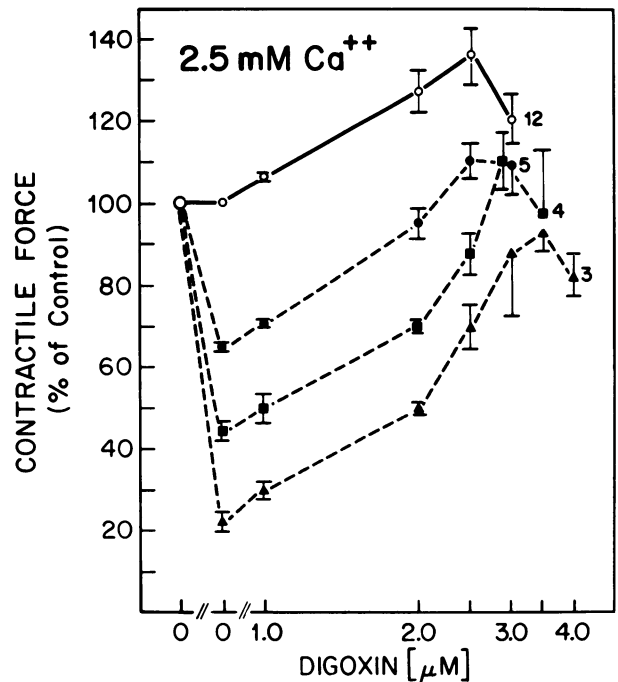


FIGURE 3. Effects of gentamicin (Gent) on the inotropic effects of digoxin: (○) atria not treated with Gent ($n = 12$); (●) atria treated with $1.0mM$ ($n = 5$) (■) $2.0mM$ ($n = 4$), or (▲) $4.0mM$ ($n = 3$) Gent. Values shown at the first 0.0 concentration of digoxin represent contractile force prior to exposure to either drug. Values at the second 0.0 digoxin concentration represent contractile force 10 min after the addition of designated Gent concentrations. All values are expressed as percent of predrug control. Each point represents the mean \pm S.E.

demonstrated inotropic responsiveness to digoxin, contractile force of these tissues did not reach the level observed in control atria (Fig. 3). Data in Figure 3 also demonstrate that the effects of gentamicin in control atria (i.e., not exposed to any drug) are concentration-dependent since 1, 2, and $4mM$ reduced contractile strength by about 35, 55, and 80%, respectively, prior to exposure to digoxin. Similar concentration-dependent effects of gentamicin were observed over a wide range of concentrations (0.1– $4mM$) of the antibiotic (data not shown).

Frequency-tension relationships were determined in atria before treatment with gentamicin and again after the negative inotropic effect of gentamicin reached steady state. As shown in Figure 4 with typical myograms and as summarized in Figure 5, contractility of gentamicin-treated atria increased as stimulation frequency was increased from 0.1 to 2.0 Hz. However, contractile tension and dT/dt responses of these atria did not reach the values obtained by control atria (Figs. 4 and 5). The reversibility of the gentamicin effect is also demonstrated

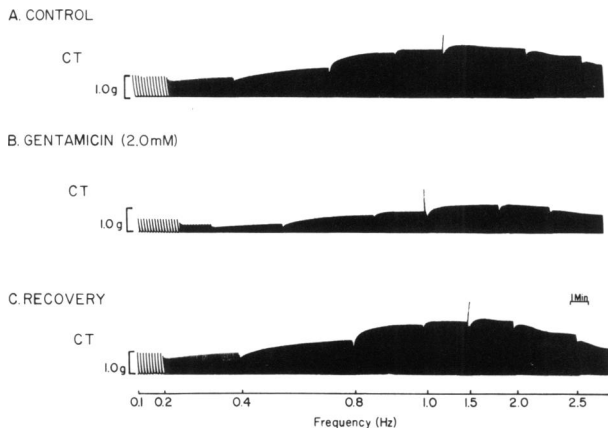


FIGURE 4. Left atrial myograms showing the response of contractile tension (CT) to frequency variation: (A) in control; (B) after treatment with 2.0mM gentamicin; (C) followed by recovery after removal of the drug. Tracings are typical of those summarized in Fig. 5.

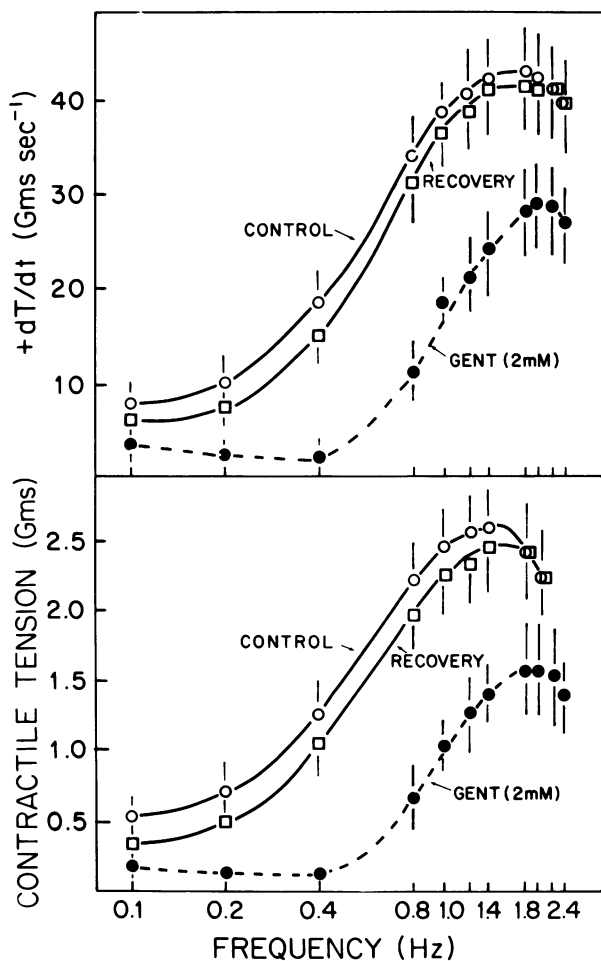


FIGURE 5. Effects of gentamicin (Gent) on the frequency-force relationship. Absolute values of contractile tension (g) and $+dT/dt$ (g/sec) are shown at different frequencies in atria (○) prior to exposure to Gent, (●) following exposure to Gent for 10 min, and (□) after recovery from Gent. Each point represents the mean \pm S.E. from 6 atria.

in Figures 4 and 5, since responses of the atria after gentamicin was removed from the tissue bath (recovery data) were similar to control data obtained in the pre-gentamicin period.

Although present studies utilized gentamicin as a representative aminoglycoside agent, several test experiments were conducted with sisomicin, amikacin and kanamycin. As was seen with gentamicin, large concentrations ($> 2mM$) of these agents were required to appreciably reduce contractile force. Absolute values of contractile tension of atria exposed to a selected concentration of each of these antibiotics are summarized in Table 1.

Discussion

Metabolic byproducts of various microorganisms have been utilized for different biomedical purposes, in addition to their most useful application as antibacterial drugs. In this respect, antibiotics could be considered as fortuitous and natural "contaminants" of the environment. The aminoglycoside group of antibiotics, for example, have greatly enhanced the treatment of a wide range of infections caused by gram-negative organisms. Although the bactericidal effects of these drugs differ as to specific spectrum of activity, these agents produce similar adverse side effects, including toxicities of the auditory-vestibular apparatus and the kidney (9), neuromuscular blockade (10) and, in some incidences, cardiovascular depression (Table 2). In the present study, cardiotoxicity of selected aminoglycoside antibiotics was demonstrated and furthermore, evaluated to include potential interrelationships with other inotropic interventions.

Large concentrations of gentamicin, kanamycin, amikacin, and sisomicin reduced isometric contractile tension of electrically driven left atria of guinea pigs. This tissue preparation has the advantage of allowing assessment of drug effects on heart muscle that is free from indirect *in vivo* influences which can mask or even accentuate cardiac responses measured in the whole animal. Using gentamicin as a representative agent, we found that this drug not only produced a negative inotropic effect in isolated heart muscle, but also decreased contractile responses to several positive inotropic interventions, i.e., isoproterenol, Ca^{2+} , digoxin, and increased frequency of stimulation. However, gentamicin interacted with Ca^{2+} responses differently than it affected responses to the other agents. Depression of cardiac function by gentamicin could be completely antagonized by increased concentrations of Ca^{2+} , but only partially by the positive contractile effects of increased stimulation frequency or supramaximal concentrations of isoproterenol or digoxin. This difference suggests that the cardiac depressant ef-

Table 1. Myocardial depressant effect of antibiotics in isolated electrically-driven left atria of guinea pigs.

Antibiotic	n value ^a	Contractile tension, g ± SE			Significance ^c
		Control	Response ^b	% of Control	
Kanamycin (3.8mM)	10	2.19 ± 0.12	1.54 ± 0.13	70.1 ± 4.9	p < 0.01
Amikacin (4mM)	6	1.99 ± 0.19	1.33 ± 0.15	66.8 ± 3.4	p < 0.001
Sisomicin (2mM)	9	1.92 ± 0.25	1.13 ± 0.19	56.3 ± 4.5	p < 0.001

^a n value = number of atria.

^b Response measured after 10 min exposure to antibiotic.

^c Paired *t*-test.

Table 2. Cardiovascular effects of antibiotics.

Antibiotic	Species	Preparation	Effect	Comments	Reference
Streptomycin	Dog	<i>In vivo</i>	Cardiovascular depression	During anesthesia	(17)
	Cat, rabbit	<i>In vitro</i> (Langendorf)	Contractile depression		(17, 18)
	Dog	<i>In vitro</i> (heart-lung)	Cardiovascular depression		(16)
	Dog, cat rhesus monkey	<i>In vivo</i>	Hypotension		(21, 25)
	Rat	<i>In vitro</i> (papillary muscle)	Contractile depression	Additive w/ halothane	(24)
	Human		Persistent Hypotension	Postoperative cardiac surgery	(17)
Dihydrostreptomycin	Rabbit	<i>In vitro</i> (Langendorf)	Contractile depression		(18)
	Dog	<i>In vitro</i> (heart-lung)	Contractile depression		(16)
Kanamycin	Human		Cardiac arrest	Overdose	(26)
	Rabbit	<i>In vitro</i> (Langendorf)	Contractile depression		(27)
	Dog	<i>In vivo</i>	Cardiovascular depression	During anesthesia	(17)
	Rat	<i>In vitro</i> (papillary muscle)	Contractile depression	Additive w/ halothane	(24)
Neomycin	Human		Cardiovascular depression	Review of case reports	(10)
	Rhesus monkey, baboons	<i>In vivo</i>	Cardiovascular depression	During anesthesia	(4, 21)
Gentamicin	Rat	<i>In vitro</i> (atria)	Contractile depression		(3)
	Rhesus monkey	<i>In vivo</i>	Cardiovascular depression	During anesthesia	(4)
Tetracyclines	Dog	<i>In vitro</i> (heart-lung)	Contractile depression		(16)
	Dog	<i>In vivo</i>	Cardiovascular depression	During anesthesia	(17)
	Cat, rabbit	<i>In vitro</i> (Langendorf)	Contractile depression		(17, 18)
Chloramphenicol	Rabbit, cat	<i>In vitro</i> (Langendorf)	Contractile depression		(17, 18)

Table 2 continued

Antibiotic	Species	Preparation	Effect	Comments	Reference
Erythromycin	Dog	<i>In vivo</i>	Cardiovascular depression	During anesthesia	(17)
	Dog	<i>In vitro</i> (heart-lung)	Contractile depression		(16)
	Toad	<i>In vitro</i>	Contractile depression		(22)
	Chick	<i>In vitro</i>	Decreased pulsatile rate	Embryonic chick heart	(23)
	Rat	<i>In vitro</i> (papillary muscle)	Contractile depression	Additive w/ halothane	(24)
	Cat	<i>In vitro</i> (Langendorf)	Contractile depression		(17)
	Dog	<i>In vivo</i>	Cardiovascular depression	During anesthesia	(17, 19)
	Dog	<i>In vivo</i>	Ventricular arrhythmias	After digitalis or ischemia	(20)
Lincomycin	Human		Cardiac arrest	Overdose	(15)
Oleandomycin	Rabbit	<i>In vitro</i> (Langendorf)	Contractile depression		(18)
	Dog	<i>In vivo</i>	Cardiovascular depression	During anesthesia	(19)
Colymycin	Dog	<i>In vivo</i>	Cardiovascular depression	During anesthesia	(17)
	Cat	<i>In vitro</i> (Langendorf)	Contractile depression		(17)

fect of aminoglycosides is a Ca^{2+} -dependent phenomenon that can be antagonized by increased concentrations of Ca^{2+} in the interstitium, but only partially antagonized by procedures that mobilize available Ca^{2+} (e.g., isoproterenol, digoxin, and increased frequency of stimulation) (1, 7).

The dependence of myocardial contraction on an increase in the intracellular concentration of free Ca^{2+} is now unequivocal, and an influx of Ca^{2+} into the myofiber directly activates actin-myosin elements and/or causes additional release of Ca^{2+} from cellular sequestration sites (1, 7). The precise molecular mechanisms and cellular loci involved in myocardial Ca^{2+} fluxes have not been precisely identified and are under intensive investigation in many laboratories. In view of the effects of gentamicin on myocardial contractile function, this antibiotic may prove useful as a pharmacologic tool to probe Ca^{2+} -dependent inotropic events in heart muscle. The antagonistic interaction of aminoglycosides and Ca^{2+} has been recognized in a variety of mammalian tissues (5, 6, 12-14), and present findings provide a basis for more detailed investigation of the influence of these agents on Ca^{2+} -dependent processes in contracting myocardium.

Although the present study focused on the

aminoglycosides, the potential cardiovascular toxicities of other antibiotics should not be disregarded. For example, large doses of lincomycin have been reported to disrupt impulse conductance through the excitable tissues of the myocardium, resulting in arrhythmias, cardiac standstill and, in some cases, ventricular fibrillation (15). Also it seems that the arrhythmogenic effects of digitalis can be affected by lincomycin (15). Hypotensive episodes have occurred during administration of chloramphenicol, and studies with perfused heart preparations revealed a myocardial depressant effect of this antibiotic (16). Studies with anesthetized dogs showed that tetracycline, vancomycin, erythromycin, and colymycin decreased cardiac output, systemic blood pressure and myocardial contractile force (17). Tetracyclines, erythromycin, oleandomycin, chloramphenicol, and colymycin have all been reported to decrease contractile force of isolated cardiac preparations (16-18). Table 2 summarizes several reports describing *in vivo* and *in vitro* cardiovascular effects of various antibiotics, including the aminoglycosides. Since many of these reports involve experimental studies with greater-than-therapeutic doses of the antibiotics, these agents should not be indiscriminately categorized as

“cardiovascular depressants.” Nevertheless, in view of the now rather lengthy list of antibiotics that have been reported to affect hemodynamics, the potential for cardiovascular toxicity with these agents should be considered when untoward circulatory changes are detected in patients undergoing antibacterial therapy.

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