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CARDIOVASCULAR DEPRESSANT EFFECTS OF NEOMYCIN AND GENTAMICIN IN RHESUS MONKEYS

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1 The acute cardiovascular effects of neomycin and gentamicin, representative aminoglycoside antibiotics, were examined in surgically-prepared anaesthetized rhesus monkeys.

2 Intravenous administration of 14, 28, and 56 mg/kg of neomycin consistently induced a dose-dependent depression of systemic blood pressure, cardiac output, left ventricular contractile force, maximum dF/dt of left ventricular contraction, and heart rate. Neomycin produced similar cardiovascular depressant effects when heart rate was maintained constant by electrical pacing.

3 Maximum depression of haemodynamic values usually occurred within 2 to 5 min after injection of neomycin; values then gradually returned to control levels within 20 to 30 (14 mg/kg) or 60 to 80 (56 mg/kg) minutes.

4 Injection of $CaCl_2$ (1.35 mEq Ca^{2+}/kg, i.v.) during the peak depressant effect of neomycin produced a rapid and maintained restoration of cardiovascular function to control levels; conversely, noradrenaline (2 μg, i.v.) or isoprenaline (0.5 μg, i.v.) produced only transient reversal of the neomycin effects.

5 Similar evidence of cardiovascular dysfunction was observed with gentamicin.

6 These findings demonstrate the direct cardiovascular depressant effects of aminoglycoside antibiotics in a higher primate species, and suggest that this adverse response is related to an alteration of calcium ion function.

Introduction

Although cardiovascular depression is infrequently recognized as an untoward side effect of the aminoglycoside antibiotics, several instances of adverse circulatory changes have been observed during therapy with representatives of this group of agents. Hypotensive episodes, for example, have occurred during treatment with gentamicin (Warner & Sanders, 1971; Hall, McGibbon, Evans & Meadows, 1972), streptomycin (Fisk, 1961; see Pittinger, Eryasa & Adamson, 1970), kanamycin (Ream, 1963), and neomycin (Pittinger, Long & Miller, 1958). Cardiovascular collapse has also been observed subsequent to exposure to aminoglycoside antibiotics (Ream, 1963; see Pittinger *et al.*, 1970). However, these adverse haemodynamic responses were not attributed to direct cardiovascular depressant effects of the antibiotics involved. Instead, cardiovascular changes have been unexplained or ascribed as secondary to bacteraemia (Hall *et al.*, 1972) or to the well-known respiratory depressant effects of these agents (Ream, 1963; Pittinger *et al.*, 1970).

It seems, therefore, that cardiovascular dysfunction may be an adverse side effect of the aminoglycoside antibiotics, but the potential for this activity is usually overlooked. Furthermore, few experimental studies have examined the direct haemodynamic effects of this extensively used group of drugs, and apparently no attempts have been made to investigate the mechanism of the cardiovascular effects of an aminoglycoside antibiotic. Present studies were undertaken in rhesus monkeys in order to examine *in vivo* the acute cardiovascular effects of typical aminoglycoside antibiotics, neomycin and gentamicin, in a higher primate species, and to determine the influence of Ca^{2+} and other inotropic agents on these responses.

Methods

The primates used in this study were young male rhesus monkeys (*Macaca mulatta*) weighing 4.0 to 6.0 kg. Monkeys were procured from a primate importer after a minimum 30-day post-capture holding period. After arrival at our facilities, the monkeys were placed on a minimum 60-day

health-conditioning programme to assure that only monkeys in good health were used in an experiment. During this period, tuberculosis testing and deworming were carried out; however, care was taken to assure that monkeys were not exposed to drugs or environmental chemicals for at least 20 days before their use in an experiment.

Food was withheld for 14 to 16 h, and a monkey was then anaesthetized with pentobarbitone, 28 to 35 mg/kg administered intraperitoneally. During an experiment, supplementary doses of pentobarbitone were administered periodically in order to maintain a relatively constant depth of anaesthesia. The trachea was cannulated and positive pressure ventilation was maintained with a Harvard small-animal respirator. The right femoral artery was catheterized for monitoring of systemic blood pressure with a Statham P23DC transducer, and the ipsilateral femoral vein was catheterized to facilitate injection of drugs. The thoracic cavity was entered at the left 4th intercostal space, the lung was retracted dorsally with a moistened gauze sponge, and the pericardium was incised longitudinally.

The ascending aorta was carefully isolated and a Narco Bio-Systems, Inc., precalibrated electromagnetic flow probe (6-8 mm internal diameter) was placed around the aortic root. This flow probe was connected to a Narco Bio-Systems, Inc., electromagnetic flow meter that converted velocity of aortic blood flow to volume flow which was expressed as cardiac output (minus coronary flow) in ml/minute. Left ventricular contractile force was monitored by use of a Walton-Brodie strain gauge arch sutured to the left ventricular free wall, and contractile force was assessed in mm deflection of the recording instrument. The contractile signal was differentiated electronically (Grass 7P20) to obtain the first derivative of left ventricular contraction (maximum dF/dt), and this value was also assessed in mm deflection of the recording device. Heart rate was measured with a Grass 7P4D cardiotachometer that was triggered by either the electrocardiogram or the ventricular strain gauge deflection. Where indicated, heart rate was maintained constant by electrically pacing the heart with a Grass S-44 stimulator via needle electrodes placed in the left auricle. All parameters were recorded on a Grass 7B polygraph multichannel recorder. After the surgical procedures were completed, a 20 to 30 min stabilization period was allowed before the injection of any drug.

The sulphate salts of gentamicin (Gentamicin Reagent Solution, Schering Corp.) and neomycin (Sigma Chemical Co.) were used; dosages refer to the active antibiotic base. The gentamicin was a commercial reagent solution with no designated additives. Neomycin was dissolved in 0.9% w/v NaCl solution (saline); injections of equal volumes of saline produced no discernible effects on measured cardiovascular functions.

Initially, neomycin was injected intravenously in order to determine a dose-response relationship to the maximum cardiovascular effects produced by 14, 28, and 56 mg/kg of the antibiotic. Injections were usually made at 45 to 80 min intervals, but time was allowed in each case for measured parameters to return to control ± 10% of control levels and to stabilize before another injection was made. In three other monkeys, the effects of neomycin were determined both when heart rate was maintained constant by electrical stimulation and when heart rate was not paced. If the same dose of neomycin was administered to an individual monkey more than once, the response of that monkey to the dose was calculated as the average value.

In experiments that were designed to examine reversal of the neomycin effects, responses to the maximum dose of the antibiotic (56 mg/kg) were measured over a 1 h post-injection period. Reversal of cardiovascular depressant effects of neomycin by Ca^{2+} ($CaCl_2$, 10 mg/kg; 1.35 mEq Ca^{2+}/kg), noradrenaline (2 μg, total dosage), or isoprenaline (0.5 μg, total dosage) was determined by injection of one of these agents intravenously 2 to 3 min (2.5 ± 0.5) after the administration of 56 mg/kg of neomycin. The temporal relationship of recovery from cardiovascular depression seen after intervention with Ca^{++}, noradrenaline, or isoprenaline was compared to recovery seen after the administration of only 56 mg/kg of neomycin. Experiments were also conducted to examine the influence of Ca^{2+} on gentamicin-induced cardiovascular depression.

In several monkeys, control haemodynamic responses to Ca^{2+} ($CaCl_2.2H_2O$, 10% solution in distilled water), noradrenaline ((−)-noradrenaline hydrochloride), and isoprenaline ((−)-isoprenaline hydrochloride) were obtained before the administration of an antibiotic.

All values are expressed as the mean ± one standard error of the mean and the difference between two means was examined statistically by use of Student's t-test.

Results

Intravenous administration of neomycin consistently produced a dose-related depression of systemic blood pressure, heart rate, cardiac output, left ventricular contractile force, and dF/dt in open-chest rhesus monkeys. Typical

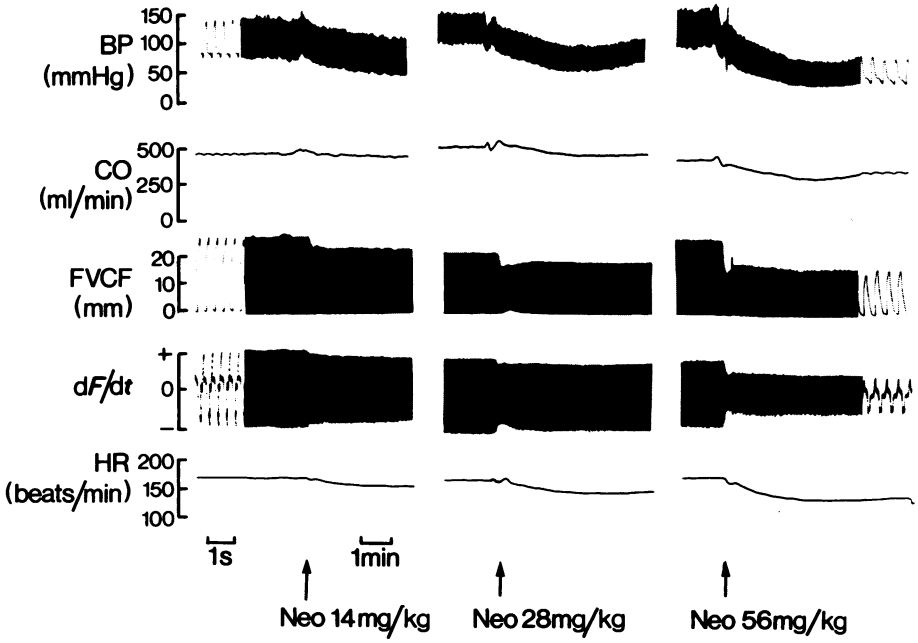

Figure 1 Cardiovascular depressant effects of 14, 28, and 56 mg/kg of neomycin intravenously in open-chest rhesus monkeys. BP = blood pressure; CO = cardiac output; LVCF = left ventricular contractile force; d*F*/d*t* = differentiated LVCF; HR = heart rate; Neo = neomycin.

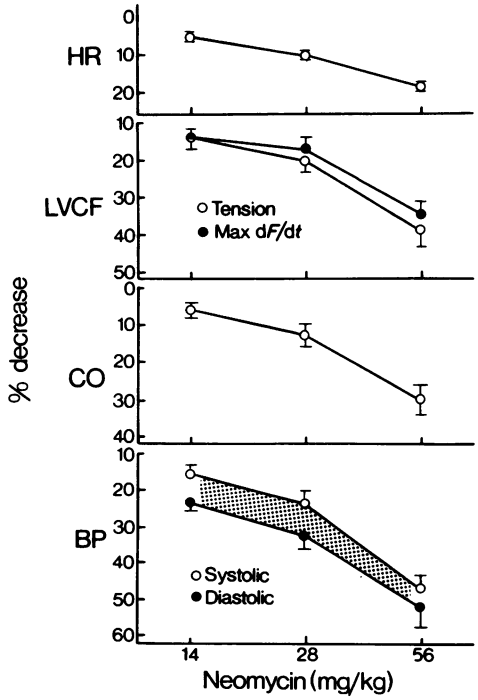

Figure 2 Dose-related cardiovascular depressant effects of intravenously administered neomycin in open-chest rhesus monkeys. Each value is the mean ± s.e. of 7 to 11 responses obtained from 7 to 9 monkeys, except cardiac output where $n = 6$. If an individual monkey was given the same dose of neomycin more than once, the average response was determined and used in calculating the mean response of the population to that dosage. BP = blood pressure; CO = cardiac output; HR = heart rate; LVCF = left ventricular contractile force.

responses of the cardiovascular system to the three doses of neomycin studied, 14, 28, and 56 mg/kg, are shown in Figure 1; absolute values of measured cardiovascular parameters are presented in Table 1; and Figure 2 displays the average percent depression of cardiovascular function produced by neomycin. With each dose of neomycin, maximum depression of the measured parameters usually occurred within 2 to 5 min after injection. Cardiovascular function then gradually returned to control or near control levels within 20 to 30 min after the lowest dose of neomycin (14 mg/kg) and usually within 60 to 80 min following injection of the largest dose (56 mg/kg) of the antibiotic.

Although the negative inotropic effects produced by each dose of neomycin appeared to be more pronounced than corresponding negative chronotropic responses (Figure 2), the possibility existed that tension changes in the myocardium

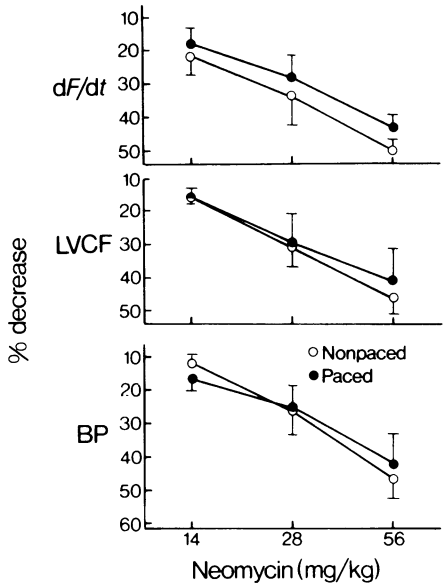

Figure 3 Effects of neomycin on blood pressure, left ventricular contractile force, and maximum d*F*/d*t* of left ventricular contraction in rhesus monkeys during paced and nonpaced heart rate conditions. Neomycin was injected in the same monkeys on a random schedule during electrical pacing of heart rate (●) and when heart rate was not paced (○). Effects of neomycin 14 and 56 mg/kg were examined in 3 monkeys; 28 mg/kg was examined in 2 of the monkeys. BP = systolic blood pressure; d*F*/d*t* = maximum d*F*/d*t* of LVCF; LVCF = left ventricular contractile force.

were secondarily influenced by the neomycin-induced relative bradycardia. This aspect was examined in three additional monkeys by determining the effects of neomycin both when heart rate was maintained constant and when the heart was not paced. Under these conditions, blood pressure and generated tension in the myocardium seemed to be variably less affected by neomycin when the heart was paced; and maximum d*F*/d*t* of left ventricular contraction was slightly less depressed by all three doses of neomycin when heart rate was maintained constant (Figure 3). Although the small number of paced-nonpaced experiments preclude valid statistical evaluation, these examples illustrate that there seem to be minimal differences in the cardiovascular effects of neomycin during paced and nonpaced heart rate conditions.

The extent of cardiovascular depression produced by 56 mg/kg of neomycin was measured at various time intervals for 60 min after injection.

Table 1 Cardiovascular effects of neomycin in rhesus monkeys

Neomycin	*Function*	*Pre-neomycin*	*Post-neomycin*	*Difference*	P*
14 mg/kg	Systolic BP (mmHg)	127.7 ± 8.4	108.1 ± 8.6	19.7 ± 2.9	<0.005
	Diastolic BP (mmHg)	74.5 ± 6.7	57.3 ± 5.9	17.2 ± 2.5	<0.005
	LVCF	23.5 ± 1.3	20.3 ± 1.4	3.1 ± 0.4	<0.005
	d*F*/d*t*	11.0 ± 0.9	9.9 ± 0.9	1.5 ± 0.2	<0.05
	CO (ml/min)	493.3 ± 26.9	463.3 ± 29.0	30.4 ± 6.9	<0.05
	HR (beats/min)	163.0 ± 9.7	153.6 ± 9.4	9.4 ± 1.7	<0.01
28 mg/kg	Systolic BP (mmHg)	118.8 ± 8.4	90.2 ± 9.0	28.6 ± 4.1	<0.001
	Diastolic BP (mmHg)	67.4 ± 4.8	45.2 ± 4.3	22.2 ± 3.1	<0.001
	LVCF	24.1 ± 1.8	19.7 ± 1.4	4.5 ± 1.0	<0.01
	d*F*/d*t*	10.2 ± 0.9	8.6 ± 0.9	1.9 ± 0.3	<0.05
	CO (ml/min)	536.0 ± 22.3	471.0 ± 15.4	65.0 ± 15.8	<0.01
	HR (beats/min)	163.5 ± 11.1	146.7 ± 11.6	16.8 ± 2.0	<0.005
56 mg/kg	Systolic BP (mmHg)	127.7 ± 9.9	69.3 ± 10.4	58.4 ± 4.8	<0.001
	Diastolic BP (mmHg)	74.7 ± 7.2	36.2 ± 6.7	38.5 ± 5.3	<0.001
	LVCF	25.2 ± 1.0	15.3 ± 1.2	9.9 ± 1.2	<0.001
	d*F*/d*t*	10.8 ± 1.1	6.9 ± 0.8	3.6 ± 0.6	<0.005
	CO (ml/min)	545.6 ± 37.3	398.8 ± 46.6	146.9 ± 17.1	<0.001
	HR (beats/min)	160.5 ± 8.1	130.6 ± 6.9	29.9 ± 2.4	<0.001

Each value is the mean ± s.e of 6-9 responses.
* Paired *t*-test for the neomycin response and corresponding control value. LVCF = left ventricular contractile force; d*F*/d*t* = differentiated LVCF; CO = cardiac output; HR = heart rate; for additional information, see legends for Figure 2 and 4.

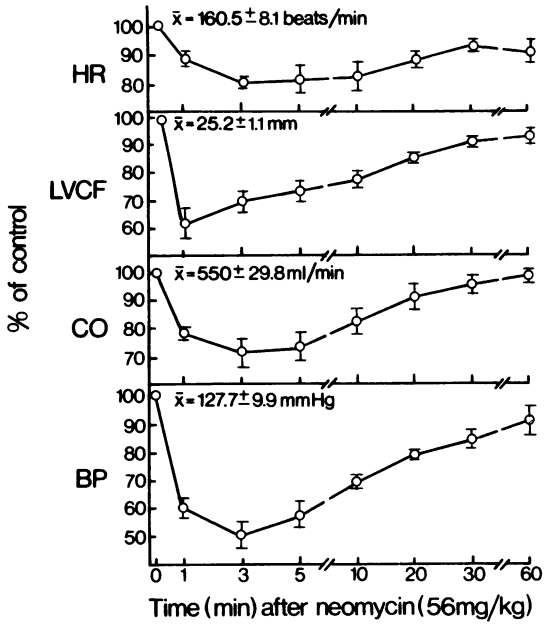

Figure 4 Recovery from the cardiovascular depressant effects of 56 mg/kg of neomycin in open-chest rhesus monkeys. Each value is the mean ± s.e. of 7 to 11 responses obtained from 7 to 9 monkeys, except cardiac output where $n = 6$. If an individual monkey was given the same dose of neomycin more than once, the average response was determined and used in calculating the mean response of the population to that dosage. BP = systolic blood pressure; CO = cardiac output; HR = heart rate; LVCF = left ventricular contractile force.

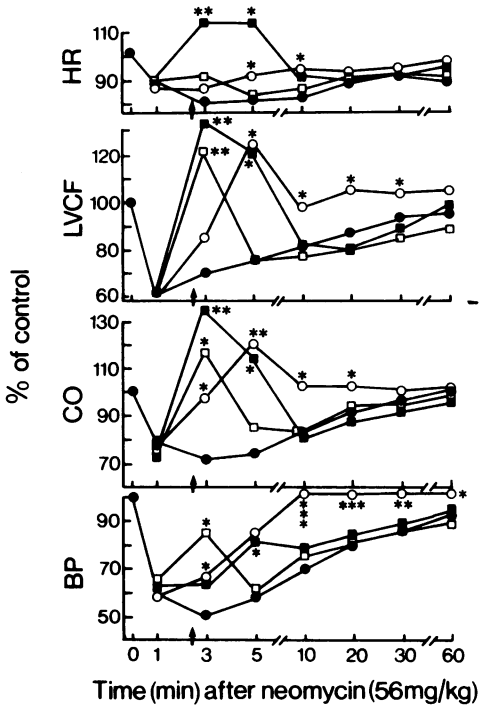

Figure 5 Antagonism of the cardiovascular depressant effects of neomycin (56 mg/kg) by calcium chloride, noradrenaline, or isoprenaline in rhesus monkeys. BP = systolic blood pressure; CO = cardiac output; HR = heart rate; LVCF = left ventricular contractile force (●) neomycin 56 mg/kg; (○) neomycin + $CaCl_2$ 10 mg/kg (1.35 mEq/kg Ca^{2+}); (■) neomycin + isoprenaline 0.5 μg; (□) neomycin + noradrenaline 2μg. Ca^{2+} ($n = 4$-5), noradrenaline ($n = 3$-4), or isoprenaline ($n = 4$-5) was injected intravenously at arrow. Control neomycin curve ($n = 7$-9) was obtained from Figure 4.

* $P < 0.05$; ** $P < 0.005$; *** $P < 0.0005$; values are significantly greater than corresponding neomycin control values.

Values are shown in Figure 4, and they indicate the gradual recovery of haemodynamic parameters during the period. These curves of mean values will be displayed as control curves in several subsequent tracings to facilitate comparison of the antagonism of the effects of neomycin by noradrenaline, isoprenaline, and Ca^{2+}.

The administration of $CaCl_2$ 10 mg/kg (1.35 mEq Ca^{2+}/kg) during the peak depressant effects produced by 56 mg/kg of neomycin rapidly restored physiological values to control or near control levels (Figure 5). Within 2 to 7 min after administration of Ca^{2+}, systemic blood pressure, left ventricular contractile force, and cardiac output were similar to values seen prior to the administration of the antibiotic. Antagonism by Ca^{2+} was a maintained effect since cardiovascular function remained near control levels following the administration of this cation. Antagonism by Ca^{2+} of the depressant effects of neomycin on myocardial contraction, cardiac output, and blood pressure was statistically significant ($P < 0.05$ to $P < 0.0005$) at virtually all time intervals examined (Figure 5); antagonism of the negative chronotropic effects of neomycin by Ca^{2+} was less reliable (Figure 5).

In contrast to the effects seen with Ca^{2+}, noradrenaline and isoprenaline did not produce sustained antagonism of the neomycin effects (Figure 5). Both of these agents rapidly restored left ventricular contractile force and cardiac output to control or greater-than-control levels; however, this antagonism was of short duration and these parameters returned to depressed levels within a few minutes (Figure 5). Noradrenaline

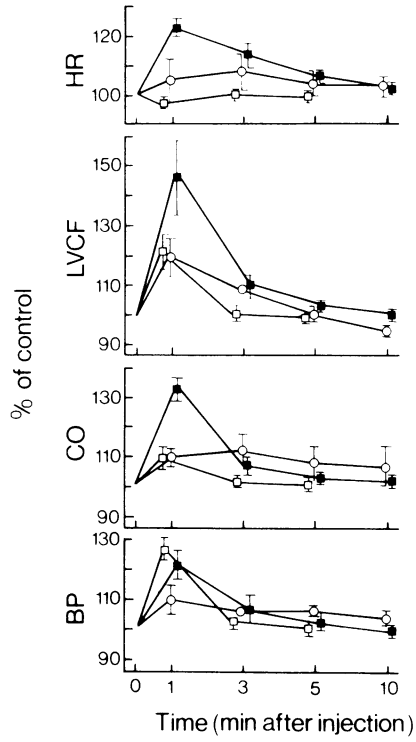

Figure 6 Cardiovascular effects of intravenously administered $CaCl_2$ (1.35 mEq Ca^{2+}/kg) (○), noradrenaline (2 μg) (□), and isoprenaline (0.5 μg) (■) in open-chest rhesus monkeys. Each value is the mean ± s.e. of 3 to 5 responses obtained from 3 or 4 monkeys. For abbreviations, see Figures 1-3.

and isoprenaline each produced a transient partial reversal of neomycin-induced hypotension. Isoprenaline produced a pronounced increase in heart rate whereas noradrenaline had minimal effect on heart rate in the presence of neomycin. The effects of noradrenaline and isoprenaline on measured parameters were not reliably different ($P > 0.05$ to $P > 0.6$, Figure 5) from control values seen with neomycin at 10, 20, 30 and 60 min after injection of the antibiotic.

Noradrenaline, isoprenaline and Ca^{2+} produced pronounced increases in blood pressure, cardiac output, and left ventricular contractile force in control monkeys that had not received an antibiotic (Figure 6). Isoprenaline and Ca^{2+}, but not noradrenaline, also increased heart rate (Figure 6). Physiological values returned to control levels within 10 min after injection of these inotropic agents (Figure 6).

In additional experiments, gentamicin produced cardiovascular depressant effects similar to that seen with neomycin. For example, intravenous administration of 30 to 40 mg/kg of gentamicin (37.5 ± 2.5 mg/kg; $n = 4$) produced a reduction of: systolic blood pressure from 136.0 ± 3.6 to 93.0 ± 7.5 mmHg (31.8 ± 4.0% decrease); diastolic blood pressure from 76.0 ± 1.0 to 47.0 ± 2.5 mmHg (38.1 ± 3.3% decrease); left ventricular contractile force from 25.2 ± 1.9 to 12.0 ± 1.8 mm (53.1 ± 3.9% decrease); dF/dt from 11.0 ± 0.6 to 5.8 ± 0.8 mm (48.3 ± 4.4% decrease); cardiac output from 452.5 ± 11.8 to 335.0 ± 20.2 ml/min (25.4 ± 6.2% decrease); and heart rate from 196.2 ± 2.4 to 173.0 ± 6.4 beats

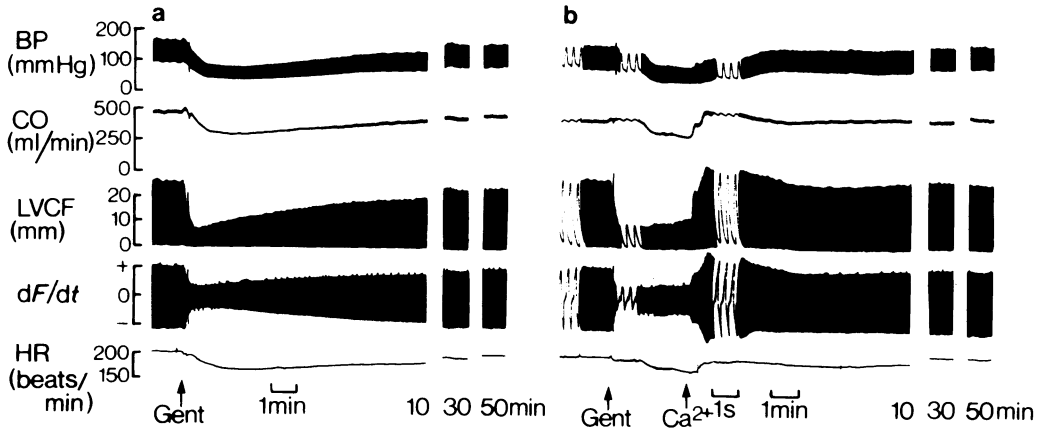

Figure 7 Cardiovascular depressant effects of gentamicin and reversal of gentamicin effects by calcium chloride in a rhesus monkey. (a) Typical responses to i.v. gentamicin (Gent, 40 mg/kg); (b) reversal of gentamicin (40 mg/kg) effects by intravenous $CaCl_2$ (1.35 mEq Ca^{2+}/kg). Agents were injected at arrows; 10, 30, and 50 min refer to time after injection of gentamicin. For abbreviations, see Figures 1-3.

per minute (11.8 ± 3.1% decrease). Ca^{2+} administration rapidly antagonized the depressant effects of gentamicin in rhesus monkeys and produced a maintained restoration of cardiovascular function to control values (Figure 7).

Discussion

Intravenous antibiotic therapy is often a routine procedure for prophylaxis or treatment of bacterial infections that may occur secondary to cardiovascular dysfunction (Rosenblum & Frieden, 1972). However, potential haemodynamic changes that may be elicited by antibiotics themselves are rarely considered when adverse cardiovascular experiences are examined for aetiological factors. For example, hypotensive episodes (Warner & Sanders, 1971; Hall *et al.*, 1972), transient cardiac arrest (Ream, 1963), and even cardiovascular collapse resulting in death (see Pittinger *et al.*, 1970) have occurred subsequent to the administration of aminoglycoside antibiotics; yet, direct cause-effect relationships were not suggested. Usually, cardiovascular changes observed under such circumstances are attributed to respiratory depression, bacteraemia, or underlying pathological conditions. In the present study, clinically normal rhesus monkeys were used to examine the myocardial and haemodynamic effects of representative aminoglycoside antibiotics in a controlled manner, and in the absence of influence by pre-existing disease. These observations establish the direct relationship of gentamicin and neomycin with suppression of cardiovascular activity in a higher primate species.

Intravenous administration of gentamicin or neomycin consistently produced a negative inotropic effect on the myocardium of healthy, surgically-prepared rhesus monkeys. Adverse cardiac contractile changes elicited by neomycin or gentamicin were invariably accompanied by a relative bradycardia and substantial decreases in systemic blood pressure and cardiac output. Similar evidence of myocardial contractile dysfunction was observed when heart rate was maintained constant by electrical pacing; therefore, tension changes produced in the heart by neomycin do not depend upon a negative chronotropic effect of this antibiotic. However, the possibility cannot be excluded that neomycin and gentamicin directly affected the vasculature causing a decrease in peripheral vascular resistance and venous return and, in this manner, contributed further to the depression of myocardial contractile strength. This possibility does not seem unlikely in view of recent evidence that aminoglycoside antibiotics inhibit vascular smooth muscle contractile function (Adams, Goodman & Weiss, 1974), and apparently have more pronounced effects on resistance arteries than on larger conduit vessels (Adams & Goodman, 1975). However, Cohen, Wechsler, Mitchell & Glick (1970) have examined the cardiac effects of streptomycin in dogs using an experimental preparation (Wildenthal, Mierzwiak, Myers & Mitchell, 1968) that maintained heart rate, aortic pressure, and cardiac output at constant levels. Under these circumstances, which circumvent chronotropic, blood pressure, and peripheral vascular influences, streptomycin produced a direct and dose-dependent suppression of myocardial contractility (Cohen *et al.*, 1970).

The mechanism of the *in vivo* negative inotropic activity of an aminoglycoside antibiotic on heart muscle was not investigated by Cohen *et al.* (1970) and, apparently, has not been examined before. Present experiments, however, provide evidence that the myocardial depressant effects of this group of agents may be associated with a modification of Ca^{2+} function. Cardiovascular parameters that had been depressed by neomycin or gentamicin in rhesus monkeys were rapidly restored to control or near control levels by Ca^{2+} administration; physiological values remained near control levels after intervention with this cation. Since Ca^{++} injection in control monkeys did not produce a sustained elevation of haemodynamic values, it seems that Ca^{2+} not only exerted a positive inotropic response in the presence of neomycin or gentamicin depression, but that this cation also completely antagonized the adverse effects of these antibiotics.

Conversely, two other positive inotropic agents, noradrenaline and isoprenaline, did not produce a sustained antagonism of the neomycin effects. These sympathomimetic amines produced rapid elevations in myocardial function in neomycin-treated monkeys. However, these positive changes were not maintained inasmuch as myocardial contractile force, dF/dt, and cardiac output returned to depressed levels within a few minutes and then gradually returned to control levels indistinguishable from the recovery values seen with neomycin alone. In control monkeys that had not been exposed to an antibiotic, however, the duration of the cardiovascular effects of noradrenaline and isoprenaline were similar to that seen with Ca^{2+}. Thus, present findings in nonhuman primates suggest that the myocardial depressant effects of aminoglycoside antibiotics may be associated with a reversible alteration of Ca^{2+} function.

Contraction of a heart cell is believed to be dependent upon the intracellular concentration of available Ca^{2+} in the vicinity of the contractile

apparatus (Nayler, 1973b; Katz & Repke, 1973). Extracellular Ca^{2+} and/or Ca^{2+} that is bound to superficial areas of the sarcolemma is considered to be essential for coupling membrane excitation with intracellular events that culminate in tension changes in the myocardial cell fibre (Langer & Frank, 1972; Nayler, 1973a). Recently, the negative inotropic activity of gentamicin in isolated cardiac muscle was found to be Ca^{2+}-dependent. In electrically-driven left atria of rats, the myocardial depressant effects of gentamicin were competitively reversed by Ca^{2+}, whereas noradrenaline acted as a partial antagonist to gentamicin (Adams, 1975). These data suggested that gentamicin altered the activity of contractile-Ca^{2+} in isolated myocardium. The present *in vivo* findings may be interpreted as support for the contention that aminoglycoside antibiotics alter the activity of contractile-Ca^{2+} in the heart in some manner.

Although experimental data that directly examine the effect of an aminoglycoside antibiotic on Ca^{2+} movements in the myocardium are not available, a recent investigation has clearly shown a specific alteration of Ca^{2+} fluxes by aminoglycoside antibiotics in vascular smooth muscle. In rabbit aortic smooth muscle, gentamicin, kanamycin, streptomycin, and neomycin inhibit the uptake of radiolabelled Ca^{2+} at superficial binding sites (Adams, Goodman, Lupean & Weiss, 1973; Adams *et al.*, 1974; Goodman, Weiss & Adams, 1974). By affecting a Ca^{2+} fraction located at superficial sites, aminoglycoside antibiotics inhibit the ability of arterial muscle to respond to vasoconstrictor agents that normally use this and other interrelated Ca^{2+} pools to generate tension changes in the vessel wall (Adams *et al.*, 1974; Adams & Goodman, 1975). Aminoglycoside antibiotics may also interfere in a reversible manner with the function of Ca^{2+} in the heart cell, as they do in vascular smooth muscle. This mechanism may well explain the acute myocardial depression produced by neomycin and gentamicin in the present study and the rapidity and thoroughness of antagonism by Ca^{2+}.

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