CARDIOVASCULAR ACTIONS OF PANAX GINSENG IN DOGS*

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Among Oriental peoples the panaccan use of *Panax ginseng* persists today as it has for centuries. Physicians in some areas of the Near East dispense this substance in powder, pill and tincture form and adhere to beliefs in its curative and "tonic" properties [Schultz (1)]. This widespread popularity and use have prompted a number of studies to determine possible pharmacological foundations for its continued employment.

Evidence has been advanced to indicate that ginseng stimulates the central nervous system and respiration [Petkov (2)], stimulates gastric and intestinal motility [Yoon (3)], corrects nutritional disorders [Myerhoff (4)], and blocks the hyperglycemic response to adrenaline [Kondo (5)]. Regarding the actions of ginseng on mean arterial blood pressure, the reports of Kim (6), Petkov (2), Hwang (7) and Park (8) indicate that the primary effect of ginseng is depressor followed by pressor in a variety of intact animals. Since the physiological basis of this response is uncertain, we have attempted, with modern instrumentation, to determine the extent of cardiac and/or vascular participation in the blood pressure response to ginseng administration.

METHODS

Thirty-five mongrel dogs (11-20 kg) under sodium pentobarbital anesthesia (30 mg/kg) were used in this study. Systolic, diastolic and mean carotid blood pressures were measured with Statham pressure transducers and a model 5c Grass polygraph. Cardiac contractile force was determined *in situ* by means of a Walton-Brodie strain gauge arch sutured directly to the right ventricle of the open-chest dog. Artificial respiration in open-chest preparations was maintained with a Starling respirator adjusted until just adequate to eliminate spontaneous breathing movements. In order to study more directly the effects of ginseng on the myocardium, contractile force measurements were also obtained from isolated trabecular strips from the right ventricles of five dogs. These thin strips, maintained at 37°C in a liberally oxygenated Krebs-Henseleit solution, were stimulated by means of adjacent electrodes which delivered a square-wave stimulus at the rate of one per second and a duration of five milliseconds. The intensity of the

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stimulus was adjusted to twice the threshold voltage necessary to induce contraction. Femoral blood flow measurements were ascertained in some of these animals by the use of a Carolina Medical Electronics square-wave electromagnetic flowmeter; in others, a Shipley-Wilson rotameter was employed for this purpose.

The root portion of *Panax ginseng* (C. A. Mey from Keumsan, Korea) was ground and extracted with 95% ethanol as described by Park (8) and Hwang (7). The resultant extract was subsequently evaporated to a dry residue. Preceding each experiment a ginseng solution was freshly prepared by dissolving a portion of the dry residue in warm 0.9% saline. Any insoluble fraction was removed by fine filtration. This filtrate comprised the injection solution of ginseng employed in this study.

Unless otherwise specified, all intravenous and intra-arterial injections were given into the femoral vein and femoral artery, respectively. Epinephrine and histamine doses are expressed as the base drug.

RESULTS

General Character of the Blood Pressure Response to Ginseng

The mean arterial blood pressure of the dog showed a characteristic biphasic response to intravenous injections of ginseng (10 and 20 mg/kg) as shown in Fig. 1. Following

FIG. 1. Typical blood pressure response to an intravenous injection of ginseng (20 mg/kg). Dog, male, 14 kg.

MBP : mean arterial blood pressure.

S/D : systolic/diastolic arterial blood pressure.

G : *Panax ginseng* (20 mg/kg) injection into femoral vein.

an intravenous injection of ginseng, there occurred a transitory hypotension which was promptly succeeded by a more prolonged hypertension. In ten dogs given 10 mg/kg intravenous doses of ginseng, the mean arterial hypotensive response averaged 25 mm Hg in amplitude, with a range of magnitude between 15 and 50 mm Hg. This hypotensive phase generally lasted about twenty seconds. The ginseng-induced hypertensive phase, in these animals, usually fell short of the hypotensive phase in amplitude, but exceeded it in duration. This hypertensive component averaged a 17 mm Hg rise in mean arterial pressure with variations in amplitude ranging between 0 and 40 mm Hg.

The duration of the hypertensive component was quite variable, generally persisting from 2 to 4 times as long as the hypotensive component. The arterial diastolic pressure typically fell more than did the systolic pressure with a consequent slight increase in pulse pressure during the hypotensive phase. At the peak of the hypertensive phase, pulse pressure did not differ appreciably from the preinjection control level.

When a 20 mg/kg intravenous injection of ginseng was given, the average amplitude of the hypotensive component was increased about 50 per cent. The hypertensive component was also appreciably increased but to a lesser extent. The basic character of the total blood pressure response remained unchanged.

The Effect of Ginseng on Ventricular Contractile Force

Ginseng produced highly variable effects on ventricular contractile force as measured *in situ* in thirteen dogs. When a 10 mg/kg intravenous injection of ginseng was employed, eight cardiac positive inotropic and five cardiac negative inotropic responses occurred. Neither the positive nor negative inotropic responses were pronounced. However, when a 20 mg/kg intravenous injection of ginseng was given to the same animals the inotropic responses were predominantly negative (e.g., Figs. 4 and 5) in eleven of the thirteen dogs. In the remaining two animals, a weak positive inotropic response was elicited. Fig. 2 illustrates an instance in which ginseng induced a weak positive inotropic effect.

FIG. 2. A comparison of epinephrine and ginseng effects on blood pressure, blood flow and myocardial contractile force. Dog, female, 16 kg. Artificial respiration.

MBP : mean arterial blood pressure.

S/D : systolic/diastolic arterial blood pressure.

BF : femoral artery blood flow.

CF : myocardial contractile force.

E : *l*-epinephrine (1 mcg/kg i.v.).

G : 1st G = Panax ginseng (20 mg/kg i.v.)

2nd G = Panax ginseng (10 mg/kg i.v.)

Note the relative impotence of ginseng as a cardiac stimulant.

The relative impotence of ginseng as a cardiac stimulant is emphasized by a comparison with the epinephrine response on the same record.

In the studies on isolated trabecular strips, the addition of ginseng in concentrations up to 1 mg/ml of the bath produced no perceptible change in contractile force. This concentration is approximately ten thousand fold that of epinephrine necessary to elicit

a perceptible positive inotropic response in such preparations. Parenthetically, higher concentrations of ginseng will cause considerable foaming when the required oxygen is bubbled through the tissue bath. Presumably this is due to the presence of saponins in ginseng (9). Moreover, in two large, open-chest dogs the very slow infusion, over a 5-minute period, of up to 50 mg of ginseng (0.5 ml volume) directly into the right main coronary artery did not produce a significant alteration in cardiac contractile force as measured by the Walton-Brodie strain gauge arch.

Effect of Ginseng on Heart Rate and EKG

A very slight bradycardia could be detected in association with the hypotensive phase of the blood pressure response to ginseng. Also perceptible was a slight tachycardia concurrent with the subsequent hypertensive phase. Both the bradycardia and tachycardia were transitory and were best discerned during the descending and ascending phases of the hypotensive and hypertensive responses, respectively.

Intravenously administered ginseng (10 and 20 mg/kg) did not evoke significant alterations in the electrocardiograms (lead II) of two dogs. A normal sinus rhythm was maintained throughout the period of the blood pressure responses and there was no detectable evidence of altered cardiac conduction (Fig. 3).

FIG. 3. Electrocardiogram taken during blood pressure response to an intravenous injection of *Panax ginseng* (20 mg/kg). Dog, female, 12 kg.

EKG : electrocardiogram (lead II).

MBP : mean arterial blood pressure.

A : control EKG before ginseng.

B : EKG during hypotensive phase of ginseng response.

C : EKG during hypertensive phase of ginseng response.

Note the absence of a perceptible EKG effect by ginseng.

Effect of Intravenous Ginseng on Femoral Artery Blood Flow

Intravenous ginseng injections invariably produced transitory increases in femoral artery blood flow (Figs. 2 and 4). In seven dogs, the average increase in femoral flow was 23 ml/min for an intravenous dose of 10 mg/kg of ginseng. The limits of this increase ranged between 11 and 34 ml/min and varied in duration from thirty to ninety seconds. A 20 mg/kg intravenous dose of ginseng elevated femoral flow an average of 35 ml/min in the same animals. These increases ranged between 18 and 57 ml/min and lasted from forty to one hundred seconds.

Effect of Intra-Arterial Ginseng on Femoral Artery Blood Flow

Since the possibility existed that the changes in the blood flow evoked by intravenous ginseng might be secondary to systemic blood pressure changes, small amounts of ginseng were injected into the femoral artery in order to observe the direct effects on the vascular bed of the leg. Injection of 0.1 ml ginseng containing from 0.5 mg to 2.0 mg were made with a 27 gauge needle directly into the femoral artery just distal to the point of flow measurement. In nine dogs, these small intra-arterial injections invariably elicited marked increases in femoral artery blood flow (Fig. 4), but were inadequate to evoke alterations in systemic pressure, cardiac contractile force or heart rate. By this procedure femoral artery blood flow was raised 70 ml/min in one animal.

FIG. 4. A comparison of cardiovascular responses to intravenous and intra-arterial injections of Panax ginseng. Dog, male, 18 kg. Artificial respiration.

MBP: mean arterial blood pressure.

S/D: systolic/diastolic blood pressure.

CF: myocardial contractile force.

BF: femoral artery blood flow.

A: ginseng (G) 20 mg/kg intravenously.

B: ginseng (G) 1 mg intra-arterially.

C: ginseng (G) 0.1 mg intra-arterially and physiological saline (S), same volume as previous ginseng injection, given intra-arterially.

Note intra-arterial injections of ginseng evoked pronounced blood flow increases in the absence of systemic blood pressure changes.

Effect of Bilateral Vagotomy on Cardiovascular Responses to Ginseng

Bilateral vagotomy in three dogs did not significantly alter the character of the blood pressure response to intravenous doses of 10 and 20 mg/kg of ginseng. Likewise, femoral blood flow, heart rate and cardiac contractile force responses to ginseng were little affected by vagotomy.

Effect of Atropine on Ginseng Responses

In contrast to the results obtained after vagotomy, the intravenous administration of atropine sulfate (1 mg/kg) to ten dogs consistently eliminated the primary hypoten-

sive phase of the blood pressure response to ginseng. The hypertensive phase, if changed at all by this procedure, was generally slightly potentiated.

The magnitude of the increase in femoral blood flow elicited by intravenous ginseng was usually markedly reduced by atropine. An even greater reduction by atropine in the increased flow response to small intra-arterial injections of ginseng generally occurred. In several experiments the rise in femoral flow evoked by intravenous (10 and 20 mg/kg) and intra-arterial injections of ginseng (0.5–2 mg) was abolished by pretreatment with atropine. Fig. 5 graphically illustrates these actions of atropine.

FIG. 5. Effects of atropine on cardiovascular responses to *Panax ginseng*. Dog, male, 16 kg. Pretreated with reserpine (1 mg/kg subcutaneously) 20 hours prior to administration of ginseng. Artificial respiration. (See Fig. 4 for explanation of abbreviations in right margin).
 A : control response to intravenous ginseng (G) 20 mg/kg.
 B : histamine (H) 2.5 mcg intra-arterially for comparison with ginseng responses.
 C : control response to intra-arterial ginseng (G) (1 mg).
 Between C and D atropine sulfate (1 mg/kg i.v.) was administered.
 D : response to intravenous ginseng (G) (20 mg/kg) after atropine.
 E : Response to intra-arterial ginseng (G) (1 mg) after atropine.
 Note disappearance of both the hypotensive and increased blood flow responses to ginseng after atropine.

Effects of Adrenergic Blocking Agents on Ginseng Responses

The intravenous administration of 15 mg/kg of phenoxybenzamine (3 dogs) or 7 mg/kg of phentolamine (2 dogs) did not materially alter the characteristic blood pressure response to intravenous ginseng (10 and 20 mg/kg) provided the systemic pressure was not markedly reduced by too rapid an administration of the adrenergic blocker.

For example, a pronounced depression of arterial blood pressure prior to the intravenous injection of ginseng reduced proportionately the amplitude of the hypotensive response to this drug. If this depression was sufficiently severe, the hypotensive component of the blood pressure response to ginseng was virtually eliminated. The hypertensive component of the ginseng response was not significantly affected by previous administration of these adrenergic blockers.

The slight positive or negative cardiac inotropic responses, resulting from intravenous administration of ginseng, were also unchanged by these adrenergic blocking agents. Moreover, the increases in femoral blood flow elicited by either intravenous or intra-arterial injections of ginseng were not appreciably altered by these adrenergic blocking agents if excessive hypotension was avoided by slow administration of the blocking agents.

It is of further interest to note that the blood pressure and femoral blood flow responses to ginseng were unaffected by the previous intravenous administration of 10 mg/kg of dichloroisoproterenol (DCI) to three dogs. In one of these, however, ginseng (20 mg/kg) evoked a slight cardiac positive inotropic response which could not be re-evoked after DCI. In the other two dogs, the 20 mg/kg control dose of ginseng elicited a slight negative inotropic effect which was unaffected by the administration of DCI.

Effects of Ganglionic Blockade on Cardiovascular Actions of Ginseng

In three dogs, the intravenous administration of tetraethylammonium chloride (20 mg/kg) did not materially alter the primary hypotensive phase of the ginseng response provided an excessive reduction of the control blood pressure was avoided during pretreatment with the ganglionic blocking agent. The hypertensive phase of the ginseng response, likewise, was relatively unchanged by ganglionic blockade. Similarly, the cardiac inotropic and femoral hyperemic responses to ginseng were not appreciably modified by ganglionic blockade in these animals.

Effects of Antihistaminics on Ginseng Responses

Intravenous tripeleminamine (10 mg/kg) in three dogs and diphenhydramine hydrochloride (10 mg/kg) in two dogs did not significantly modify the characteristic biphasic character of the blood pressure responses to intravenous ginseng. The amplitude of the hypotensive component of this response was reduced slightly in some cases presumably by the antihistaminics but this effect was not constant. The hypertensive phase of the ginseng response remained unaltered. Similarly, cardiac inotropic responses to intravenous ginseng were not materially changed as a result of antihistamine pretreatment.

On the other hand, ginseng-induced increases in femoral blood flow were somewhat reduced by these antihistamines. This reduction, again, was inconstant and seemed more pronounced in the case of intra-arterial than intravenous injections of ginseng.

Effects of Reserpine on Ginseng Responses

Pretreatment with subcutaneous reserpine (1 mg/kg) twenty hours prior to the administration of ginseng was performed in three dogs. These animals showed some

modification in the typical blood pressure response to ginseng. In Fig. 5, following reserpine pretreatment, the hypotensive phase of the response to intravenous ginseng was reduced appreciably in amplitude whereas the subsequent hypertensive phase was slightly potentiated both in duration and magnitude. Catecholamine depletion was presumably high in these dogs since strong electrical stimulation (5 V, 5 msec, 20/sec) of the intact vagosympathetic trunk while evoking cardiac arrest did not elicit pupillary dilatation.

Effect of Altering the pH of the Ginseng Solution

Since the pH of the ginseng solution used for intravenous injections was found to be around 4, it seemed important to ascertain the cardiovascular effects of intravenous and intra-arterial injections of isotonic saline made equally acidic with HCl. These injections, equal in volume and acidity to those of ginseng-produced responses similar to, but weaker than, the ones elicited by the ginseng solution. Weak hypotensive and cardiac negative inotropic responses, as well as slight increases in femoral blood flow, could be evoked by rapid intravenous injections of acidified saline. However, no secondary hypertensive response similar to that associated with ginseng injections could be elicited

FIG. 6. Effect of altering pH of intra-arterially injected ginseng solution.

Dog, female, 17 kg. Artificial respiration.

(See Fig. 4 for explanation of abbreviations in right margin).

Left tracing: ginseng (G) (1 mg) administered intra-arterially at its normal pH of about 4.

Right tracing: ginseng (G) (1 mg) administered intra-arterially after its pH had been neutralized to 7.

Note that the increased blood flow response to ginseng can still be evoked at a pH of 7.

with the acidified saline. Furthermore, it is noteworthy that the characteristic cardiovascular actions of ginseng could still be evoked by intravenous injections of this substance after its pH had been adjusted to 7. Fig. 6 illustrates this finding.

DISCUSSION

A crude extract of this type probably contains many bioactive principles and therefore, does not lend itself well to precise cardiovascular evaluation. Moreover, evidence of tachyphylaxis to intravenous ginseng previously reported by others (10) was occasionally observed in this study and this further complicates interpretation of the data. Nonetheless, certain inferences can be drawn from these experiments.

A few points seem clear regarding the initial hypotensive phase of the ginseng-induced response. The immediacy of this response and the inability of antihistaminics to suppress it suggest that the hypotension is not primarily the result of endogenous histamine release. This finding is concordant with that of Hwang (7) who administered ginseng to cats and rabbits. Lee *et al.* (10), however, postulated that the ginseng-induced hypotension in dogs was caused by a release of endogenous histamine.

The failure of dichloroisoproterenol (DCI) to modify this fall in blood pressure apparently excludes the possibility of *beta* vascular receptor participation in the hypotensive response to ginseng. Furthermore, the inability of tetraethylammonium chloride, in the presence of a reasonable blood pressure, to prevent this depressor response indicates that the initial hypotensive phase is not attributable to vasodilatation caused by transitory ganglionic blockade. Hwang (7) similarly reported that hexamethonium does not modify this initial hypotensive response in cats and rabbits. In perfusion studies on the hind legs of frogs, Kondo (11) suggested that ginseng produced vasodilatation through an inhibition of peripheral sympathetic nerves. Hwang (7), on the basis of blood pressure studies in the cat and rabbit also hypothesized that the ginseng-induced hypotension was caused by an inhibition of sympathetic vasoconstrictor tone. The fact that ganglionic blockade, in our experiments, did not appreciably modify the initial hypotensive response to ginseng indicates that sympathetic inhibition at the ganglia is not the primary causal mechanism in the dog.

Finally, the ginseng-induced hypotension is not dependent upon a negative cardiac inotropic effect, as the former can occur even in the presence of a positive inotropic response (Fig. 2).

In our experiments, the elimination of the initial hypotensive response by atropine suggests that a cholinergic mechanism is predominantly involved in this response. Moreover, the persistence of this hypotensive response to ginseng after bilateral vagotomy indicates a peripheral, rather than central, site of action. In this regard, Petkov (2) stated that the abrupt, transitory hypotensive response to ginseng was little influenced by vagotomy. He also reported that atropine completely antagonizes ginseng-induced contractions of the isolated rabbit bowel (12). Atropine can also block the augmentation of gastric motility induced in cats by ginseng (3). Kim (6) reported that vagotomy

eliminated ginseng-induced hypotension in rabbits. Hwang (7), on the other hand, concluded from studies on cats and rabbits that neither vagotomy nor atropine could abolish the initial hypotensive response to ginseng. Park (8) likewise reported that neither vagotomy nor atropine affected this initial hypotensive response in cats, rabbits or dogs. In the rat, however, he reported an elimination of the hypotensive phase by vagotomy in 3 out of 9 animals. In this species, he also reported that atropine often reversed the ginseng-induced hypotensive phase to one of hypertension.

Regardless of such conflicting pharmacological findings, it appears from the physiological data presented herein that peripheral vasodilatation produced by ginseng accounts for most of the hypotensive response. Although the observation that the increased blood flow and hypotension caused by ginseng are concurrently antagonized by atropine indicates a cholinergic mechanism is involved in this phenomenon, further studies are needed to explain conflicting reports in the literature.

The cause of the hypertensive component of the ginseng response remains enigmatic. It is not reflexly induced by the preceding hypotensive component because it persists, and is sometimes enhanced, following elimination of the hypotensive component by atropine. Moreover, ganglionic blockade little affects the hypertensive component of the ginseng response. These observations suggest that ginseng causes little or no central sympathetic stimulation in anesthetized dogs. The failure of phentolamine and phenoxybenzamine to alter the character of this ginseng response suggests further that the pressor component is not due to a direct or indirect peripheral stimulation of adrenergic *alpha* receptors by ginseng. In short, the pressor component does not appear to be primarily sympathetically mediated. Park (8) also found that phenoxybenzamine did not block the hypertensive component of the ginseng response in rats, cats, rabbits or dogs. In contrast, Hwang (7) reported that the pressor response to ginseng was eliminated in the spinal cat by phenoxybenzamine and, paradoxically, that this drug markedly potentiated the pressor component of the ginseng response in intact cats. Both Hwang and Park suggest the possibility that the blood pressure responses to ginseng may be due to a release of endogenous serotonin since antiserotonin agents inhibited the hypertensive effect. Regardless of mechanism, the data presented herein indicates that the pressor effect of ginseng is mediated at vascular, rather than cardiac or central sites.

The aforementioned investigators and the present authors are cognizant of the numerous conflicting hypotheses regarding the mechanism of ginseng's actions. The use of different species of experimental animals, different sources and varieties of ginseng and different doses of this substance have undoubtedly contributed to the existence of much conflicting data. Moreover, tachyphylactic phenomena may also contribute to the diversity of responses reported.

It is clear from our studies, and previous ones, that ginseng can induce an appreciable vasodilatation followed by a more prolonged pressor action. Our data further indicate that these actions are produced at the vascular level. All reports agree that these effects are of short duration. Whether blood levels of ginseng following inges-

tion of various ginseng preparations are adequate to produce such effects in humans is questionable.

SUMMARY

1. Ginseng administered intravenously (10–20 mg/kg) to anesthetized dogs produces, characteristically, a transitory depressor followed by a slightly longer pressor response.

2. Direct measurements of cardiac contractile force indicate ginseng produces variable and insignificant cardiac actions. Moreover, recordings of heart rate, together with denervation studies, indicate that ginseng affects blood pressure in anesthetized dogs principally at the vascular level.

3. Intravenous and intra-arterial injections of ginseng produced significant, but transient, vasodilatation in the femoral bed as demonstrated by blood flow measurements. Such vasodilatation apparently accounts for the depressor action of ginseng. Atropine consistently reduced or abolished the vasodilatation and depressor actions of ginseng.

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