Acute and Chronic Toxicity of Caffeine: A Review

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Caffeine is a plant alkaloid found in as many as 63 species of plants growing throughout the world (1), and is probably the most widely used and socially acceptable drug ranking next to alcohol and tobacco. The alkaloid principally present in coffee, tea and cocoa plants is consumed in huge quantities as a constitutent of nonalcoholic beverages such as coffee, tea and cola-type drinks. Caffeine still enjoys the status of a GRAS (Generally Recognized As Safe) substance since there is no scientific evidence to prove that caffeine at levels added to cola-type beverages poses a hazard to the public (2). Nevertheless, recent evidence suggesting that chronic intake of caffeine contributes to various health effects including myocardial infarction, arrhythmias, hypertension, peptic ulcer, fibrocystic breast disease, birth defects and pancreatic cancer, has renewed public concern about exposure to caffeine (1,3).

The immense popularity of caffeine-containing beverages and chocolates is exemplified by the fact that 2-3 billion pounds of coffee is consumed annually in the United States alone (1,4). Approximately 100-150 mg of caffeine is found in an average cup of brewed coffee and 30-50 mg in a similar cup of tea, while the amount of the alkaloid in a 12-oz bottle of a cola-type drink varies from 35 to 55 mg (1,4). On the other hand, a small chocolate bar contains approximately 25 mg of caffeine (5). In addition to the consumption of caffeine in popular beverages and chocolate products, many prescription as well as over-the-counter drugs contain varying amounts of caffeine as a drug for use as a CNS stimulant, an analgesic and a diuretic. Although most of the consumption of caffeine is through the intake of popular beverages, drug preparations (6) and diet pills (7), it has also been used in naturopathic therapies as caffeine enemas which have been linked at least to two human deaths (8). Even though caffeine is a safe drug and its acute toxicity is low, in some instances it is possible that caffeine can cause acute or chronic poisoning in animals (9) and people (4,10,11). For example, people/patients interested in weight control often consume large amounts of caffeine in the form of diet pills, diuretics and diet beverages. According to a published case report (7), a 16-year-old anorexic patient drank as many as 24 cans of a caffeine-containing diet beverage every day leading to a syndrome of chronic caffeinism. Similary, we recently observed an acute fatal caffeine poisoning in a dog which ate 100 tablets of caffeine accidentally (9). And yet, according to recent evidence chronic intake of caffeine may cause a variety of health effects (1,3). The chronic problem is especially serious with young animals and children who seem to be at high risk. A child who daily consumes five servings of a cola-type drink and three small chocolate bars ingests as much of the stimulant as a caffeine-dependent adult gets from eight cups of coffee (5). Thus it may become a powerful habit-forming stimulant that acts on CNS, producing a condition of wakefulness and increased mental activity.

It is now apparent that caffeine is becoming widely available in high concentrations and large quantities. The reason for its increasing popularity is not clear, but most likely includes the use of caffeine on the street as a substitute for the more tightly restricted and less readily available amphetamines. The current popularity and familiarity of the public with stimulant drugs in general, most notably cocaine, may have a role. Therefore, it is likely that increased availability of caffeine may well lead to increased occurrence of poisoning in both humans and domestic animals. The purpose of this review is to renew and emphasize awareness about toxicity of caffeine in children, adults and also in domesticated animals.

ABSORPTION AND DISTRIBUTION

Caffeine is readily and rapidly absorbed from the gastrointestinal tract and the peak plasma concentrations of caffeine after a single oral dose (6-9 mg/kg) in a healthy person are achieved within 30-60 min after its administration (1,4,12). Its rectal and subcutaneous absorption is equally rapid. It is freely and equally distributed throughout the total body water with its average plasma half-life in therapeutic doses being 3-6 hr in healthy adults (10,13-15). However, half-life of an overdose of caffeine is expected to be several-fold longer than that of a therapeutic dose. For instance, the estimated half-life of caffeine in an overdosed patient (4.8 g) has been reported to be 9 hr (7). Absorption of caffeine is not influenced by whether caffeine is dissolved in pure water or present in coffee (16). Interestingly, presence of food does not influence absorption of caffeine in coffee from the stomach as no significant difference in time required for reaching peak plasma concentrations of caffeine has been observed with or without food (17). However, other

factors such as the extent and duration of caffeine consumption, liver function and smoking are, of course, known to alter the half-life of caffeine in body. As mentioned above, half-life of an overdose of caffeine is quite long whereas it is shorter in coffee drinkers due to microsmal enzyme induction and subsequent faster elimination. On the other hand, liver dysfuntion is expected to prolong the half-life of caffeine due to its decreased metabolism and elimination (18). Smoking in humans reduces the mean plasma half-life due to its concomitantly increased elimination through demethylation and oxidation (19) whereas pregnancy has been reported to prolong the mean plasma half-life of caffeine (20). In newborn and premature infants, the half-life of caffeine ranges from 1.5 to 6 days (21). This is apparently due to the fact that hepatic drug-metabolizing enzyme system in the newborn is not fully developed for biotransformation of the drug. As has been reported in the literature, the half-life of caffeine in infants is greatly prolonged, but it gradually approaches that for the adult by 6 months of age (6).

As for the animals such as mice, the plasma half-life of caffeine at doses up to 100 mg/kg is about 1.5 hr whereas in rats, at doses less than 10 mg/kg, it is about 1.5 to 2 hr (22). However, at higher doses such as 100 mg/kg, plasma disappearance of caffeine in these animals is delayed.

METABOLISM AND DISPOSITION

Caffeine is primarily metabolized in the liver by the microsomal drug metabolizing enzymes although it is distributed throughout all tissues and organ systems. In adults, it is biotransformed through N-demethylation and oxidation to 1-methyluric acid and 1-methyxanthine (2,12). These metabolites are then excreted by kidney in the urine. An additional urinary metabolite that has been recently detected is 5-acetylamino-6-amino-3-methyluracil (23). It is speculated that this metabolite is an acetylated product of 1-methylxanthine. In contrast, liver detoxification of caffeine in the newborn through the aforementioned pathways is almost absent, obviously, due to undeveloped drug-metabolizing enzyme system, and consequently the drug is excreted by the kidney as the unchanged parent compound (24-25).

Animal species such as rat and mouse metabolize caffeine through N-demethylation and oxidation to a number of xanthines and uric acid derivatives (26-27). Additionally, hydrolytic ring-splitting of caffeine occurs in rats resulting in the diaminouracil derivatives (26). Thus, the formation of the diaminouracil derivatives and 1,3,7-trimethyluric acid differs appreciably from man. Metabolites of caffeine in primates include a mixture of xanthines, uric acid derivatives and some unknown compounds (2). Although uric acid derivatives are principal urinary metabolites of caffeine in animals and humans, there is no evidence that the ingestion of caffeine aggravates gout.

Since most of the absorbed caffeine is metabolized by the hepatic microsomal enzymes, factors affecting the enzyme system will have profound influence on the metabolism and toxicity of caffeine. For instance, agents such as phenobarbital and polycyclic aromatic hydrocarbons that increase the capacity of drug-metabolizing enzymes have been shown to markedly stimulate the liver metabolism of caffeine in rat and dog (28). For similar reasons, metabolism and disposition of caffeine appear to be enhanced in smoking. In contrast, agents inhibiting the liver microsomal enzymes such as certain macrolide antibiotics are expected to block caffeine metabolism and delay its disposition (29). Similarly, in patients such as alcoholics with hepatic cirrhosis the rate of metabolsim of caffeine is decreased and toxicity increased. As is true for many drugs, liver metabolism of caffeine can be modified by other conditions including age, diseases, undernutrition and several others that will affect the function of liver and kidney.

TOXICOLOGY OF CAFFEINE

Acute Toxicity

Fatal poisoning in animals and humans by caffeine appears to be rare probably because caffeine is not a very toxic compound, has emetic properties, and is also believed to have a wider therapeutic index than theophylline, resulting in a lower incidence of toxicity (30). A fatal intoxication by caffeine has been reported in a human patient after intravenous administration of some 3.2 g of caffeine or a dosage of about 57 mg/kg (31). This dose is apparently lower than the intravenous LD50's of 101 mg/kg and 105 mg/kg for mice and rats, respectively, and the minimum lethal intravenous dose of 80-100 mg/kg for cats (32). On the other hand, a comparison of toxicity of caffeine given orally indicates that there is not appreciable species-difference in oral caffeine toxicity (Table 1). This may be attributed to the rapid absorption of caffeine from gastrointestinal tract of those species. It is also apparent from Table 1 that a fatal oral dose of caffeine in people is about 10 g, although oral doses in reported fatalites range from 5 to 50 g. According to Elkins and Spoerke, an average total dose of 480 mg of caffeine results in clinical signs of caffeine tox-

Table 1. Comparison of minimum oral toxic doses of caffeine in various species (32)

Species	Dose (mg/kg)
Man	150-200 (lethal)
Dog	140-150 (")
Cat	100-150 (")
Rat	174-210 (LD50)

Table 2. Tissue concentrations of caffeine in people fatally poisoned with the alkaloid

Patient (age in yrs)	Total oral dose (g)	Specimen	Tissue level caffeine (mg/100 ml or 100 g)	Ref
Female(34)	-	Blood	10.6	10
		Liver	11.6	
Female(27)	6.5-12	Blood	-	4
		Liver	32.9	
Female(45)	50	Blood	7.9	34
		Liver	21.4	
Female(42)	-	Blood	11.4	35
		Liver	-	
Female(19)	18	Blood	18.1	36
		Liver	-	
Male(1,8)	18	Serum	71.0	37
		Liver	43.0	
Female(5)	5.3	Serum	15.9	38
		Liver	19.8	

icity (33). A review of literature yields few cases of human poisoning from caffeine, most of which were the result of doses erroneously administered by hospital personnel or of accidental caffeine ingestion (Table 2). For example, in one case of caffeine poisoning, a woman was mistakenly given 50 g of caffeine instead of 50 g of glucose (34). That caffeine is becoming one of the potential suicidal substances readily available to the general public is exemplified by a fatal case of caffeine poisoning reported by Alstott et al (4). In this case, a woman ingested possibly 6-12 g of caffeine and died 7 hr later. Another case of suicide with caffeine has been recently reported by Bryant (35), in which a woman was a victim of caffeine poisoning. A case report given by McGee (36) concerns a fatality in a 19-year-old woman caused by ingestion of a caffeine-containing over-the-counter appetite suppressant, which raises serious questions regarding possible risk associated with such preparations. Occasionally, it is not surprising to see caffeine poisoning in children. For example, a 15-month-old child died of caffeine poisoning after receiving 90 ml of 20% caffeine sodium benzoate (total dose 18 g) instead of 90 ml of 2% caffeine sodium benzoate solution (37) whereas another 5-year-old child ingested about 53 tablets of an over-the-counter diuretic preparation containing caffeine (total dose 5 g) and died in about 6 hr postingestion (38). Further review of literature reveals a few similar cases of caffeine poisoning in dogs, all of which died following consumption of a large number of tablets containing caffeine (39-42).

The concentrations of caffeine in liver and blood samples from reported cases of fatally poisoned humans are summarized in Table 2. While the concentration of caffeine in blood from those individuals range from about 80 ug/ml to about 700 ug/ml, the concentrations in liver varied from 116 ppm to 430 ppm. Toxic reactions in adults may be observed following the ingestion of 1 g (15 mg/kg) or more of caffeine leading to plasma concentrations above 30 ug/ml (6,21). Clinical signs of toxicosis are mainly referable to the central nervous and circulatory systems. By contrast, approximately 1-3 mg/kg dose of caffeine is typically required to produce expected pharmacological actions (43).

Although not always found, emesis and convulsions, among other clinical signs, are usually prominent consequences of acute caffeine poisoning. Convulsions seen in caffeine poisoning due to a fatal dose are usually attributed to its central stimulating effect (21). According to Rall (21), early in the poisoning convulsions are epileptiform in nature and later become similar to those caused by strychnine followed by death due to respiratory failure. In low doses, caffeine affects cardiac function indirectly by increasing vagal tone and directly by increasing heart rate via its effect on the myocardium. However, in high doses, the direct effect on the myocardium is the dominant change that leads to an increase in heart rate. Although the effect of caffeine on systemic blood pressure is unpredictable (21) the coronary arteries and the pulmonary and general systemic vessels become dialated following caffeine ingestion (43). Severe pulmonary edema also appears to be a consistent feature of acute caffeine poisoning. According to Boyd (44), in experimental rats poisoned with caffeine, capillaries and veins of the lamina propria were found to be dilated and engorged with blood in all areas of the gastroinestinal tract resulting in congestion and hemorrhage.

There is no specific antidote for the treatment of acute caffeine poisoning. The treatment is symptomatic and fluid therapy has been recommended as one of the important measures. Emergency measures for treating oral caffeine poisoning (45) include initiation of emesis unless the patient is comatose, convulsing, or has lost the gag reflex. If any of these contraindications are present, endotracheal intubation should precede gastric lavage. Administration of activated charcoal to prevent further absorption of caffeine is also recommended. Next, a cathartic such as magnesium sulfate has been suggested for the expulsion of caffeine present in the intestines. In addition to these standard emergency measures, seizures should be treated with an appropriate dose of diazepam (45) or with sodium pentobarbital (46) given to effect. These anticonvulsant drugs are known to counteract CNS stimulating effect of caffeine and may help the poisoned patient to relax but may not alleviate the toxic effects of caffeine on the heart. Administration of an appropriate pharmacologic agent (eg, lidocaine, phenytoin) is recommended for the treatment of cardiac arrhythmias. According to Sullivan (46), insulin, which has been shown to be antagonistic to caffeine, may aid in the recovery of the caffeine poisoned subject. Monitoring fluid and electrolyte balance, and administration of antacids to neutralize gastrointestinal irritation are other symptomatic measures which are equally

important in the management of caffeine poisoning.

Chronic Toxicity

The therapeutic dose of caffeine required for induction of expected pharmacological actions ranges from 50 to 200 mg, depending on whether it is used as a simple stimulant, analgesic, diuretic or for treatment of neonatal apnea (43). Since caffeine is widely available in a number of popular beverages and medications, it is possible that an individual in everyday life can ingest doses much higher than the typical short-term pharmacologic doses, often without being aware of it. It has been reported that eight out of ten adults in US drink coffee and the average coffee drinker consumes three and one-half cups (400-500 mg of caffeine) per day (1). Furthermore, according to a conservative estimate at least 20% of adult North Americans consume 500-600 mg of caffeine daily (5). Among heavy coffee or tea drinkers, it is very likely that doses may exceed this value by large amounts. Today's American children are consuming a substantial amount of cola and chocolate products, thus ingesting amounts of caffeine daily that are much higher than the pharmacological levels and this may be a cause for concern. Little research has been done on the amounts and possible effects of caffeine in beverages and chocolates and how it is absorbed, metabolized and excreted in coffee and cola drinkers.

Caffeine is a xenobiotic which can have effects on many body systems when taken even at pharmacological doses over a period of time. Pharmacologic effects of caffeine on metabolism, and on the central nervous, cardiovascular, respiratory, renal and gastrointestinal systems are well-established (21). However, what is confusing and controversial is that the effects of caffeine in habitual and naive users are not clearly defined (47) and the consequent variability in response to caffeine which is observed within the population. When used as a drug in naive patients, caffeine stimulates CNS (47), increases heart and respiratory rate, systolic blood pressure, plasma renin activity and plasma epinephrine and norepinephrine (48), produces a mild increase in urinary output and sodium excretion (48). However, it should be noted that habitual coffee users become tolerant to the cardiovascular effects of caffeine (49). Similarly, with long-term administration, subjects become tolerant to the diuresis induced by caffeine (47).

Caffeine has been shown to stimulate gastric acid and pepsin secretion (21), however, recent studies have suggested that something other than caffeine in coffee, which contains as many as 300 compounds, may be responsible for increased gastric acid and pepsin secretion (47). In addition to these effects, low doses of caffeine have been shown to increase metabolic activity with increase in concentrations of free fatty acids, blood glucose and serum cholesterol (47). Thus, caffeine has important effects on many body systems. However, further research in coffee and cola drinkers, and especially children, is necessary to help clarify some of the recent conflicting data linking coffee to many health effects. For example, caffeine has been implicated as a cause of many adverse health effects, including heartburn (50), myocardial infarction (51-52), fibrocystic breast disease (53), peptic ulcer (50), renal cancer (47) and pancreatic cancer (3). Whether these chronic effects of caffeine can really be attributed to coffee drinking remains to be defined (1) and further investigations need to be done.

Behavioral Effects

Caffeine is a pharmacologically powerful but relatively safe CNS stimulant. Indeed, the popularity of caffeinated beverages may be attributed to these properties. It is claimed that coffee and tea promote rapid and clear thinking, improved intellectual efforts and enhance mental activity as a result of caffeine-induced stimulation of all parts of the brain (43). Considering these effects, it is not surprising why it has become a habit-forming stimulant. Taken together, the ingestion and consequent actions of high doses of caffeine--whether from coffee, tea, cola drinks, over-the-counter substances, or prescription medications--are all described as caffeinism by some behavioral scientist. Thus caffeinism is characterized by nervousness, irritability, agitation, headache, tachypnea, tremulousness, reflex hyperexcitability and occasional muscle twitchings, hyperesthesia, ringing in the ears, visual flashes of light and insomnia (21,43). These symptoms are overcome when caffeine is eliminated from the diet. Similar clinical complaints can result from a characteristic caffeine withdrawal syndrome, which include headache, irritability, inability to work effectively, nervousness, lethargy and restlessness (1,5). The throbbing headache of caffeine withdrawal that begins a day after high consumers forgo their daily intake, is relieved by more caffeine.

Mutagenic Effects

Caffeine has been reported to cause chromosomal abnormalities in mammaliam cells in culture while in microorganisms it has proved to be a potent mutagen (54). These effects which seem to be associated with inhibition of DNA-repair processes, are observed only with concentrations of caffeine that are much higher than those found in beverages. In addition, available data suggest that caffeine is not mutagenic in mammals when given alone or in combination with known mutagens.

Teratogenic Effects

Caffeine is a week teratogen in some laboratory animal species (55). For example, it produces fetal abnormalities in mice at doses at least 50 times higher than those taken by people (56). On the other hand, a study in which coffee was added to the drinking water of rats at levels resulting in daily intakes of caffeine approximately 9, 19 and 38 mg/kg for 5 weeks prior to

mating and through gestation produced no teratogenic effects (57). Another recent study in rats with brewed and instant coffee in the drinking water at levels resulting in caffeine intakes of approximately 20, 40 or 80 mg/kg/day for 30 weeks through two pregnancies showed no embryotoxicity or teratogenicity at any dose although there was evidence of delayed calcification at the two highest doses (58). Thus, at high doses, caffeine appears to have some teratogenic activity in mammals. On the other hand, in people, a retrospective study indicated that pregnant women who ingested more than 600 mg of caffeine in beverages daily may have had an increased incidence of spontaneous abortion, stillbirth or premature delivery (59). Because of the findings that coffee drinking during pregnancy was associated with low birthweight infants and a high incidence of complicated delivery, the FDA issued a warning in 1980 advising pregnant women to avoid or limit caffeine intake (60). However, subsequently published reports indicate that the low birth weights were associated with factors such as smoking and demographics rather than caffeine use (61) and that there was no excess incidence of malformations in infants whose mothers were heavy drinkers of caffeine-containing beverages (62). Thus these conflicting data warrant further investigation on the potential developmental toxicity of caffeine on the human fetus and neonate.

Toxicologic Analysis of Caffeine

Caffeine in biologic tissues is quantitatively determined spectrophotometrically (14). First, the specimen is extracted with chloroform under alkaline conditions and caffeine from the resultant chloroform solution is then recovered by extracting with .5 N sulfuric acid. Caffeine in sulfuric acid is quantitated by subjecting the solution to UV spectrophotometry at 272 nm.

Confirmation of caffeine can be made using thin-layer or gas chromatography. Thin-layer chromatography involves use of silica gel plates with fluorescent indicator and the development of the plate spotted with sample and standard in a solvent system of acetone:benzene:chloroform (25:40:40). Spraying of the plate with acidic (10% HCl) iodoplatinate reagent (9 g KI + 300 ml H_2O + 10 ml chloroform), a gray color spot for caffeine is obtained (10). Caffeine gives an absolute R_f value of 0.13 in this system.

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STRETCH YOUR MEETING INTO SHAPE

Starting with the head and shoulders and working down to the feet, this simple series of exercises sets the blood flowing, loosens up stiff muscles, and clears the mind. They're especially beneficial for anyone who spends long periods of time sitting--like meeting attendees. Most of the exercises can be done in a chair, and the entire series should take only a few minutes to get through. Any stretching should be static: that is, stretch slowly and hold the stretch without bouncing. Hold it there for three to five seconds, then release and relax. Maintain regular breathing throughout. Add music (marching, disco, or anything with a good steady beat) and give your meeting a fresh shot of energy.

WARM-UP

Stand up and walk around the room for 30 seconds as a mini-warm-up. Take a few deep breaths. And smile--grin until your cheeks ache--to relieve tension in your facial muscles. Then take your seat again to begin the exercises.

HEAD AND NECK

1. Slowly drop your chin to your chest and roll your head in full circles--first clockwise, then counterclockwise. Keep your shoulders dropped and relaxed throughout.
2. Do nods--slow, exaggerated "yeses," forward and back five times; then "nos," side to side five times.
3. Try to put your ear to your right shoulder, without hunching. Go only as far as you can without pain. Hold for five counts. Then repeat to the left.

ARMS AND SHOULDERS

1. Start with shrugs, both shoulders, up and down, five times. Then shrug alternately, one shoulder up, one down, then switching. Repeat three times.
2. Bring shoulders forward, then roll them up and back, then up and forward. Repeat, back and forth, five times.
3. Circle shoulders forward five times, then backward five times. Now bring one shoulder forward at a time, alternating left and right. Do five sets.
4. Give yourself a hug, wrapping your arms around yourself. Then fling your bent elbows out and back at shoulder height. Repeat hugging and flinging eight times.
5. Point one elbow over your head toward the ceiling, reaching down your back as far as you can. Press gently on the elbow with the free hand to get maximum stretch. Repeat, alternating arms, three times each.
6. With fingers interlaced behind your head, hold elbows out to the side and keep your upper body straight. Pull your shoulder blades together--hold, then relax. Repeat three times.
7. Finally, keeping fingers interlaced, straighten your arms out in front with palms facing out. Raise your arms over your head, lift, and feel the stretch!

FINGERS AND WRISTS

1. With arms extended above head, open your hands wide. Separate and extend fingers, then make tight fists. Repeat five times.
2. Keeping arms and hands overhead, rotate wrists in a circular motion, first to the right five times, then to the left.
3. Flap your wrists up and down in a waving motion for a count of eight.
4. Shake your fingers and wrists out vigorously.

TRUNK AND LEGS

1. With fingers interlaced behind your head, bend far to one side. Be sure to keep your upper body facing forward. Hold. Repeat to the other side.
2. Lean forward in your chair and touch your toes. Put your head to your knees and stay relaxed in this position for a few seconds.
3. Sit erect in your chair and pull one knee towards your chest, grasping the knee with both arms. Hold for a few seconds, then repeat with the opposite leg.
4. While holding the sides of the chair, lift both legs out in front of you. Try to straighten them so the legs are level with the seat. Hold this position, then relax.
5. With the right leg extended out straight, touch the right ankle or toe with your left hand. Hold five counts. Switch legs and repeat.
6. Scratch your back with the back of your chair, twisting from side to side.

FEET AND ANKLES (It's best to do these with your shoes off!)

1. Sitting erect with your feet flat on the floor, push both heels into floor while lifting toes. Then raise feet up on toes. Repeat, heels then toes, three times.
2. Alternate, pressing one heel up, one down. Switch and repeat eight times.
3. Go into a vigorous march in place, lifting feet 2 to 4 inches off the floor. Continue for eight beats.
4. Jump in place, lifting both feet at once. Remember to sit firmly against the back of your chair.
5. Rotate the ankles in complete circles, six counts to the right, then six counts to the left.
6. Wiggle your toes and vigorously shake out the feet.

COOL-DOWN

Take a nice easy walk around the room. Get a drink of water. Bring your breathing to normal before sitting again.

GENERAL OFFICE EXERCISES (Standing)

Back-To-The-Wall--Stand one to two feet away from a wall, with your back to the wall. Slowly twist and touch the wall behind you with open palms at shoulder height. Now twist and touch to the other side. Repeat four or five times.

Elbow-To-Knee--Interlace fingers behind head. Touch right elbow to left knee and bending at the waist. Then touch left elbow to right knee. Repeat three or four times.

Fingers-To-Toes--Stand with knees slightly bent. Bend at the waist and try to touch your toes with your fingertips. Hold for a few seconds, then slowly roll up straight, until you are reaching up overhead. Repeat.

Shadow Boxing--Show some fancy footwork as you move around--sliding,dodging, jabbing, hooking, and punching. Be creative with this one but stay loose.