

GINSENG USE AMONG TWO GROUPS IN THE UNITED STATES

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Abstract

Two groups of subjects were studied before, during, and after long-term use of commercial *Panax ginseng* preparations. Group A ($n = 10$) consisted of users who also used other psychomotor stimulants including caffeine, while subjects in Group B ($n = 8$) used no drugs other than ginseng. During 12 weeks of regular ginseng use, users in Group A showed signs of central nervous system stimulation and reported feelings of well-being. Two subjects manifested possible allergic reactions while one developed a ginseng abuse syndrome marked by hypertension, nervousness, sleeplessness, skin eruptions, edema, and morning diarrhea. This syndrome was associated with excessive dosages, concomitant intake of caffeine, and possible allergic reactions. Subjects in Group B reported stimulation and feelings of well-being while showing some signs of nervousness. One subject developed a possible contact urticarial reaction to a ginseng cosmetic. All adverse reactions were transient and disappeared when ginseng use was discontinued. It is suggested that adverse reactions can be prevented by moderate use of standardized ginseng preparations while restricting use of other psychomotor stimulants.

Introduction

The therapeutic use of ginseng has been documented in both clinical and experimental medicine. When used according to traditional practices, adverse reactions are extremely rare. Nonetheless, there are a number of general symptoms that contraindicate use of ginseng because of possible side effects (Lu, 1976; Dukes, 1979). In addition, use of large doses of ginseng has results in signs of excessive stimulation (Lu, 1976), insomnia, depression, and nervous disorder (Keys, 1976).

Recently, Siegel (1979) has noted that long-term use of commercial ginseng preparations resulted in a 10% incidence of a ginseng abuse syndrome (GAS) among a group of American users. The syndrome was defined as hypertension together with nervousness, sleeplessness, skin eruption, and morning diarrhea. While these effects mimic those of corticosteroid poisoning and are consistent with preclinical findings (Fulder, 1978), the users developing GAS employed a variety of uncontrolled commercial ginseng products as well as caffeine preparations. It is interesting to note that caffeine itself is contraindicated in traditional Chinese ginseng treatment (Keys, 1976). In an effort to monitor these effects more closely and

control for potential synergistic effects with caffeine, the following study was conducted.

Method

A total of 18 subjects, 21–35 years old, who expressed an intention to begin using *Panax ginseng* were recruited for study. All subjects denied previous use of ginseng preparations. A total of 10 subjects with present histories of psychoactive drug use were designated Group A. Most of these subjects used a variety of stimulants for nonmedical purposes and these drugs included nicotine and cocaine. All subjects in Group A used caffeine daily in the form of tea, coffee, cola beverages, and chocolate. The remaining 8 subjects denied any present history of nonmedical drug use, including caffeine, and these were designated Group B.

After an initial interview and drug-history questionnaire, subjects were given physical and psychological examinations. Then they started their own programs of ginseng use. They were instructed to purchase their ginseng from commercial sources and use only ginseng labeled *Panax ginseng*. They were allowed to use teas, capsules, extracts, and roots and were instructed to follow package directions. All subjects kept daily records of all ginseng used as well as other drugs taken. Examinations were repeated at weekly intervals. After 12 weeks, subjects were asked to discontinue ginseng use for 2 weeks while additional examinations and tests were conducted.

Results

Pre-Ginseng Observations

Initial examinations indicated that all subjects were in good physical health with no detectable psychopathology. Prior to the start of ginseng use, all subjects had blood pressures and body weights within normal ranges. Blood analysis and urine chemistry were also normal.

Preparations and Patterns of Use

Subjects used a wide variety of commercial

Panax ginseng (labeled) products available in the United States including teas, capsules, extracts, and roots. All preparations were used orally. One subject in Group B also used a topical ginseng cosmetic. While all subjects were motivated to use ginseng because of a desire to experience the anticipated effects of stimulation, increased energy, and good health, each group of subjects appeared to develop distinct patterns of use.

Subjects in Group A tended to use ginseng an average of 3 days per week (range, 1 to 7). However, this use consisted primarily of large individual dosages repeated several times on each day of use as subjects reported they were trying to achieve a psychoactive stimulant effect. In addition, some subjects in this group attempted to counteract the sedation of alcohol or marijuana intoxications with ginseng. These subjects in Group A primarily used a total of 3 to 6 grams of ginseng root on each day of use. Total daily dosages varied when other preparations were used (in order of preference): capsules, 24 to 30 grains; or extracts, 2.5 ml to 10 ml. Ginseng teas were rarely used by subjects in Group A.

Conversely subjects in Group B used ginseng an average of 5 days per week (range, 2 to 7) and ingested small amounts on each occasion. They reported use was motivated by a desire to experience tonic rather than short-term effects. Unlike users in Group A who were seeking psychoactive stimulant effects, subjects in Group B reported using ginseng as a nutritional supplement to their diet. The most common dosage form was capsules and consisted of a total daily intake of 8 to 20 grains on each day of use. When other preparations were employed, the most common total daily dosage units were (in order of preference): teas, 1 to 2 cups; extracts, 2.5 ml to 5.0 ml; or roots, 0.5 to 3.0 grams).

Effects

The physiological and psychological effects reported by users in Group A did not differ substantially from those described in an earlier study (Siegel, 1979). Briefly, subjects reported stimulation, feelings of well-being, and increased motor

and cognitive efficiency following ginseng use. During the first week of ginseng use, two subjects experienced skin eruptions and edema. The dermatologic findings indicated purpura and some mechanical denudation of the skin. One subject exhibited edema of the mucosa of the mouth and pharynx. Such reactions strongly suggest an internal allergic reaction similar to that seen with herbs such as chamomile and other Compositae (Mitchell & Dupuis, 1971; Benner & Howard, 1973). Both these subjects withdrew from the study at this time. By the end of the third week of ginseng use, five subjects reported episodic morning diarrhea. By the end of the 12 weeks, a single subject in this group had developed hypertension together with minor skin eruptions, restlessness, insomnia, and morning diarrhea (GAS). This subject reported mixing ginseng preparations in his morning coffee prior to the physical examinations. The magnitude of his hypertension, as well as other reported adverse reactions, appeared to be associated with dosages of ginseng and caffeine taken each day. Throughout the 12 weeks of ginseng use, transient, albeit insignificant, elevations in blood pressures were recorded for 4 subjects in Group A. Only the GAS subject developed significant hypertension together with GAS symptoms. It is interesting to note that while he became restless following large doses of ginseng and caffeine, he also reported feelings of euphoria and pleasure.

In Group B, subjects reported stimulation, feelings of well-being, and some minor increased psychomotor efficiency following ginseng ingestions. There was no detectable hypertension in Group B subjects at any time during ginseng use. However, subjects would sometimes report nervousness during the first week of ginseng use. During that first week, two subjects in Group B reported skin eruptions but this could only be confirmed in one subject who had eczematoid eruptions suggesting the possibility of an allergic contact urticarial reaction to a topical ginseng cosmetic (Fisher, 1975).

Blood chemistry, urine analysis, and endocrine function tests were unremarkable for all subjects in Groups A and B.

Post-Ginseng Observations

No unusual physical or psychological findings were detected in examinations conducted in the two weeks following cessation of ginseng use. All blood pressures, body weights, urine analyses, and blood chemistry values were within normal ranges. During this period, subjects no longer reported morning diarrhea, stimulation, or increased psychomotor functioning. Several subjects in each group expressed the intention to resume ginseng use after the study.

Comment

The major observations of this study indicate that subjects who ingest large amounts of ginseng together with other psychomotor stimulants may experience transient adverse reactions. Subjects who do not use other stimulant drugs with ginseng appear less likely to encounter these side effects. The major positive effects likely to be reported by all subjects include stimulation and feelings of well-being. Rare transient allergic reactions may be experienced.

Psychological reactions to ginseng use differed for subjects in Group A and Group B. Users in Group A admitted to seeking psychoactive stimulation, used large dosages to achieve these effects, but also reported a number of untoward side effects including morning diarrhea, and minor elevations in blood pressure. The single subject in this Group who developed GAS appeared to regularly ingest large amounts of ginseng over a long period of time. His motivation to achieve a psychoactive intoxication and his continued pursuit of that intoxication despite side effects would seem to constitute a clear case of abuse. Conversely, subjects in Group B appeared to take ginseng more as a nutritional supplement than a psychoactive drug, ingested smaller amounts, and reported less dramatic subjective and physical effects.

An important variable uncontrolled in this study is dose and quality of ginseng. Users here employed the wide variety of ginseng preparations commercially available in the United States, and

these products vary widely in pharmacological activity (Liverti & Marderosian, 1978) as well as directions for recommended dose regimes. The wide variety of effects observed here, also seen in a larger population of ginseng users (Siegel, 1979) may have resulted from uncontrolled use of an uncontrolled product. It may be speculated that adverse reactions may not have occurred if users employed a standardized ginseng preparation together with a moderate dose regime. However, these results do reflect problems associated with ginseng as it is currently available and used in the United States. When such use involves the type of side effects seen here, however transient and rare, both the user and the therapeutic potential of *Panax ginseng* are abused.

Chairman: Now the time is open to discussion.

Rückert: Dr. Siegel, in your very interesting observations, I would like to have two questions. First of all, I am convinced as you mention at the end that the side effects of ginseng products would not have happened if there would have been used standardized products according to the recommended dosage because many clinical and pharmacological tests done with standardized ginseng show that there are no side effects if you have good standardized products. Now do you have records about the products used for these tests?

Siegel: Yes, we do.

Rückert: Yes, because we have just now a collection of products in the United States market in the laboratory in Switzerland. Although the investigation of the products has not yet been finished, some of the results show very large differences in contents of the products and not all ginseng products are pure ginseng products. Sometimes they are mixed with some other ingredients which are not stated on the labels. In my presentation I will show a certain list which shows difference of products in the American and European markets. This goes as far as that we found in California a product which was labeled true *Panax ginseng* but we

didn't find even any milligram of ginsenoside in this product. Let's say it was not ginseng and we are just now trying to find out what it is. It has a bit of taste contained in the ginseng capsule but there is no ginseng in this product. This shows the problem of such studies, because when the consumers are buying now ginseng products, they don't know even what's in there and they might buy even something else than ginseng and, therefore, there is such results you have got with over dosage of ginseng products. Should I think not appear to the high class standardized ginseng products taking in the regular recommended dosage. Would you agree with this?

Siegel: Thank you for your comments. I would agree that this study only reflects commercial ginseng as it is commonly sold and used in the United States. There is a variety of commercial products varying widely in the contents as you point out. In fact we have identified that some of the ginseng preparations contained vitamin C, caffeine, and others but there is no labeling to indicate the other additives that is put on. So, our interest is really just looking at any public health problems that develop with users using labeled ginseng products. This is not mean to comment on the use of standardized preparations or pure ginsenoside that would be given a clinical study. This is a clinical out-patient study of street drug users if I can use the vernacular expression. And the major point that I wish to underline is that there are two different groups of users that we have been able to identify in the United States. That differ probably from the Oriental users or perhaps even Western European users. One is the type who seeks a psychoactive effects when they are confronted with capsules, or ampules of extracts. They attempt to take them until they can feel differently, subjectively feel a stimulation. By that point I may have taken too much. We saw three cases in the years 1975 to 1976. They came into the emergency room in UCLA hospital with a shock after injecting the contents of ginseng ampules. Now I think

they stand for all our use. So we have a user in the United States who is prone to abuse, prone to seek the psychoactive effects and I dare say we will continue to do so despite actual labeling. But the other group of users, group B, who are using ginseng as a nutritional supplement, were not really having any problems. The minor skin problem we saw were very transient and certainly do not alarm us at all.

Chairman: Another question, please.

Lee: First of all I'd like to comment that your follow-up from the original paper indicating so-called ginseng abuse symptom with more careful study has been quite commendable. There are some reservations to be made with your findings. First of all I agree with you with the respect that with the ginseng used for legitimate purpose there is no any so-called ginseng abuse symptoms. That I must agree with you. Another thing, the reservations concerning with your so-called ginseng abuse symptoms to be made with this study is this. First, there is no quality or quantity control of this as you mentioned and the characteristics of the ginseng pharmacology is the chronic nature of this preparation. Drug effect is rather chronic one and acute effect is not too much prominent with this ginseng preparation and the people who are belonging to Group A who are seeking for the acute psychosomatic effect is probably using a very unusual amount of large ginseng preparation; otherwise, they wouldn't be expected to have this sort of acute effects. So another condition, whatever response you may get among this patient group of patients whether it could be legitimate to the ginseng effect or something coming with ginseng preparation, it's not clear yet. Secondly, you have one case out of whole Group A patients a clear-cut case of this so-called ginseng abuse symptom. And under the condition you mentioned I wonder whether it is right scientifically speaking to attribute this person's response as the ginseng abuse symptom; because, if you use this sort of term, it is very misleading. It's rather individual variation which we expect among this many patients

because one, it's not even two, a single case of such a symptom can be attributed to this use is very misleading, to say the last. You also mentioned initially those people who are belonging to Group A have been using cocaine or some other psychosomatic drugs. I wonder whether this particular person who showed so-called ginseng abuse symptom have previous use of this cocaine application. Would you comment on that?

Siegel: Yes, thank you for your comments. The single case, there were ten people in this group, initially two of them dropped out after the first week when they have skin problem leaving 8 people and it was one out of the 8 that a ginseng abuse syndrome developed by hypertensive condition which went away when ginseng use was stopped. This is comparable to the other study where we were looking at 130 people over 2 years and approximately 10% of that group of 14 individuals also developed the same exact condition. It is one case but we studied a lot more closely in terms of daily blood pressures in the other 14 cases. As far as that individual's use of cocaine, individual had admitted to use of cocaine in the past was not currently using that in the period of study here. But was currently using much caffeine and occasionally marijuana.

Lee: Well, the comparison of the 10% incidence in two groups of previous study and in this group is rather coincident, as far as I am concerned, because it's one single case out of ten and if you figure out that there is a 10% of population, I think it's a little far-fetched from your conclusion. I rather agree with your conclusion that in most cases, ginseng as far as toxic side symptom is concerned it's rather inert. And this your previous Group A people who has previous history of use of cocaine such preparation, I wonder the trustworthiness of their testimony in your experiment because you know very well that his statement by those patients are not really taken literally as they say. They are screened for narcotics and cocaine on a regular basis every week. However, every week's

regular basis would not be enough to test the use of their cocaine part of things as you well know. I think that an in-patient study would be the only answer to those kind of control.

Siegel: That's right. That was what I was coming to. This kind of study should be done with more careful analysis in in-patients and this sort of ambulant patients who are free is not ideal at large. I think this sort of conclusion, especially, I am very hesitate to use the term ginseng abuse symptom because that already prejudice the readers with certain concept. We should define more carefully these words which is being used in the literature. Don't you agree with that?

Lee: No, I don't. I think that this individual also that he was abusing ginseng, that he was not using properly, he was only interested in seeking a psychoactive effect used large doses, couple of the dose with caffeine would achieve that effect. That was a clear case of abuse not only abuse of recommended traditional medicine practices with ginseng, it was an abuse of the recommended package directions. And it was also an abuse in the sense that he was experienced in average reactions and still continue to do it. He was only seeking one effect and I think that he would also agree that this kind of dosage is a clear case of abuse. It's not the proper use. Well, you are taking their words all right. Assuming that is the case, still abuse syndrome and this person is abusing ginseng I quite agree. If any person taking sodium chloride saline injection and he keeps giving that one in large quantity, to the body undoubtedly this person will have a symptom which is coming from inert rather medicinal drug abuse. So in that sense, when you use the term abuse, I totally agree with you but you are using abuse symptom in a way that absent syndrome, I think this is where some confusion rises.

Siegel: I agree, I understand what you say, but when you say abuse symptom you can take any sodium chloride solution or any other glucose solution, any injection which is perfectly legitimate can be abused and be said and published as abused symptom if you use that term in that

sense.

Okuda: I have some comment on this problem.

We examined the clinical effect of Korean red ginseng powder on diabetes and hyperlipidemia. Red ginseng powder was orally administered 3 to 5 grams per day for three to four years to a about three to four hundred patients but I never experienced such side effects as hypertension and skin eruption. This is our experience in Japan.

Siegel: Thank you for your comments.

Staba: Dr. Siegel, I enjoyed your presentations, but using your definition of ginseng abuse syndrome, did your experimental design permit any of these observations in the monkeys?

Siegel: Yes, I didn't read the full paper which I did hand out you to all the speakers. We had video-monitoring of the animals and audio-monitoring and double-blind observers scored the behaviour for the frequency of the occurrence of a variety of different ethnological postures that the monkeys engaged in and for the duration of the time they spend in engaging those postures. To summarise that all I can say is that they show typical stimulation effects. There was no indications that those monkeys took an excess amount to cause abnormal behaviours. In fact, they were free access for 23 hours a day and their intake was only 10 grams per monkey per day, which indicated that they were getting some kind of optimal dose and they wanted no more and we saw some minor weight losses in every animal. It was not significant. And hyper activity throughout the 20 days of that study there was no indication like with cocaine, if you did this with cocaine monkeys would continue to take cocaine to the exclusion of all the food and water, and it eventually overdose or suffer some abnormal behavioral problem such as extreme aggressiveness selfmutilation. That might cost you some kind of abuses in monkey we saw no evidence of that with ginseng at all. Monkeys readily took the put them in the mouth as they would with ginseng root itself they wetted it with saliva put it in their pouches and soften it chew it, take it out occasionally and rechew it

and put it back until eventually the whole thing was swallowed. They readily continued to do that, and they seemed to enjoy the experience. They certainly made a lot of hood barks which are noises that they make in anticipation of pleasant food. I didn't see any evidence of abuse, therefore, in the monkeys at all.

Yamamoto: I myself prescribed ginseng powder and ginseng saponin fractions from ginseng. We always use ginseng or ginseng saponin fractions from Korean or Japanese ginseng. We, I think, used over 100 patients received ginseng or ginseng saponins but I never encountered side effects such as hypertension or skin rashes, and by the way, could you tell me how much the extent of weight loss in monkey as you described in the former abstract.

Siegel: Yes, I will give you the copy of the paper. The weight loss is not in there but I will send you the data. It's insignificant.

Lee: Do you classify the hypertension as an eminent characteristic of the ginseng abuse symptom?

Siegel: Yes.

Lee: Well, then I must mention this. You know that blood pressure is very much notorious and this is well known among medical people. It depends on when you take under what condition. Same person shows all different blood pressures. Therefore, we should be careful to standardize when you take the blood pressure. Now this one subject among ten, in other words about 10% according to your terms, did develop hypertension. I am very doubtful whether we wouldn't get the same result if you take a completely normal person and administer him a ginseng extract preparation or whatever you call it, these ginseng preparation over twelve weeks of time and then measure blood pressure I have reasonable doubt any occurrence of single person of hypertension can be attributed to a solely due to that administration of that drug. Probably there are it's more likely that the general population there will be incidence of this one case even without the use of this ginseng extract. We have been working on hypertension

as well as many other vascular system and this one single incidence of this to be named as ginseng abuse symptom I think this is going a little too far.

Siegel: The hypertension was observed in 5 subjects. In these subject, it was recorded every day. Secondly, that is not what I call ginseng abuse syndrome. What I define as the ginseng abuse syndrome is that we have seen among the users we are studying is hypertension coupled with the occurrence of several the other findings such as nervousness, sleeplessness, skin problems and morning diarrhea. These are identical to what we see with critical stir like poisoning and we have to see all of them together in one individual before would label the syndrome. That is what we saw in one individual while other individual showed one or two of the other symptoms non of them had them all except him.

Lee: I noticed in your previous publication that there is similarity in the structure between this and did you tell us preparation, did you tell us to be sure it's still with the compounds? And also you mentioned the corticosterone but they are widely different substances and has entirely different pharmacological action and to put them dump them together and mentioned some steroid structure similarity I think it's again going a little too much of imagination. And four transient cases of hypertension occasionally observed, I wouldn't count on that, because that sort of transient blood pressure fluctuation is common even in normal population and I wouldn't call it hypertension.

Siegel: It's more than just elevated. It was elevated above the hypertensive limits.

Lee: You said transitory when you presented your paper. What was the range of this transient.

Siegel: They were published in the literature in Germany. I have a copy, I will give you.

Kim: I rather have a sort of pretty fundamental question about the design of your experiment. When you conduct this kind of experiment, we should concern very carefully couple of things. One is how you get the samples. Second, dosage.

When I hear about your presentation, the first question about the samples seems to me that your samples doesn't represent healthy persons. Even though you mentioned the person you tested responded like a regular person but you mentioned that the persons are drug users and they are pretty healthy physically but I have a question whether they are mentally healthy or not. This is the first question.

Siegel: May I answer the first question?

Kim: Sure.

Siegel: Thank you for your comment. These people, whether they are mentally healthy or not, are very typical of the type of drug users we have in the United States. We have 40 million marijuana users in the United States. We have 15 million cocaine users. We have a lot of multiple polydrug users as you refers now. And it is estimated that well over 50% of the population of the U.S. engaged in non-medical psychomotor stimulating use every day, 90% of the American males use caffeine everyday. These are the kinds of users there. Those are the ones we are looking at. I think they are representative. They may not be representative cross country comparisons, but they are representative within our country.

Kim: O. K. I like to go to the second question about the dosage. You stressed a couple of times about abuse syndrome or overdose syndrome. If I were you, I would give the amount of ginseng in the gradual increase for a certain time for a long period so that we make the result from this person about overusing syndrome, I would get a certain amount for certain period for a long time. It seems to me you draw out your result from the person who takes ginseng or ginseng product from your country as much as they can until they get the psychomotive stimulant or this kind of syndrome and then you discussed the result out of this people about their physical result or syndrome. It seems to me the fundamental design of your experiment was not very carefully designed, if I say very strictly.

Would you like to comment about that?

Siegel: Yes, it was an experiment. It was simply an outpatient study, a ginseng users using commercial product in the U.S. It was not an experimental manipulation. And I agree with you. The types of questions that you all are asking need to be answered in carefully controlled double-blind in patients studies within entire diet and intake of the individual is held under control. That is what is necessary. Our interest is only to try to understand why people were coming into our emergency rooms with problems. And what kind of problems they encounter in their normal use. Not our controlled use but their uncontrolled use of uncontrolled products. The problem is their's. I don't think it's ginseng's problem at all. Thank you.

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