

NEMZETI KÖZSZOLGÁLATI EGYETEM

Doktori és Habilitációs Tanács

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**A kábítószer fogyasztás vizsgálata a Magyar Honvédség állományánál
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Analysis of drug abuse in the Regular Hungarian Army with a special emphasis on opiates.

1. Introduction

Drug abuse is a world-wide problem in our modern world. Drugs are an international health problem which causes mental and physical addiction. In addition, the addict in search of “a fix” is liable to do anything to satisfy the habit. Drug production, trafficking and consumption are a major economic factor that affects both politics and the society. Anti-drug programs are very expensive to implement and maintain, not to mention the enormous effort spent by the staff in order to keep them running. In addition, drug consumption is accompanied by a myriad of other medical problems. To make matters even more difficult, most drugs are relatively easy to manufacture with laboratory equipment, although there is no checks of their sterility nor of their purity. This all adds up to a product that is not sterile, and can contain dangerous, toxic by-products. In fact, the literature cites some cases of drug- ingestion that caused death due to the toxic pollutants (2, 3). In another word, what you are paying for on the street does not always contain what you think. The problem is not only confined to the civilian population, but also spills over into the world’s military services (of which the Hungarian Army is part of). This area especially interest us, so there is a continuous effort to halt it while it still is in its infancy, and so maintain the army’s drug-free state.

2. Research objectives

In the first part of my thesis, I evaluated the results the drug control programs of the Hungarian Army (begun in 1996). I will first try to analyze the changes we observed over time. In the second part, I will address the large number of positive results we found on preliminary drug screening, and I will look at the impact of poppy-seed ingestion upon this result, and will try to see if there is a realistic way to distinguish the poppy-seed ingestion from illicit drug abuse from the laboratory point of view. This is especially important in our culture, where it is customary to use poppy-seed for dietary supplements. It is also known, however, that drug users ingest poppy-seeds. Finally, it is important to keep in mind that many of the accepted medicines commonly used contain opiate alkaloids as an active ingredient.

3. The reason this subject was chosen.

Drug consumption in Hungary began about thirty years after it appeared in the west. However, the drug culture in Hungary is rapidly closing the gap. In the mid- 1990s, it became apparent that it was becoming a big problem, and an effective strategy to combat it needed to be established.

In the Hungarian Defense Forces (HDF), it was essential to set up a legal framework to begin the screening, develop an effective drug screening apparatus, and set up an accredited laboratory which in turn would measure the effectiveness, and set up new policies for effective drug control. In the beginning, the large amount of positive results on preliminary screening made it imperative to find something that would be able to distinguish between illicit drug consumption and the legitimate ingestion of poppy-seed for dietary purposes.

4. Exploration of the Hypothesis

The drug use in the Hungarian Army is similar to the general population; however, the proportion of the venerable population is much higher. This fact, combined with the fact that many of the recruits bring different habits from home, the enforced discipline, short breaks, the unpredictable future, the exposure to fatalities, cause many recruits to desire to escape from reality, in the form of mind-altering drug consumption. The old drug of choice, ethyl alcohol, has now been replaced by newer, more modern drugs.

Faced with this situation, it is important to develop a drug prevention strategy as well as to regularly screen for drug usage to be assured of the effectiveness of our programs. Since this is an ongoing process, it should be able to amend the programs to compensate for the changing habits. In our particular case, it is essential to be able to exclude people who are not abusing the drugs, but in fact legally ingesting poppy-seed as a food supplement.

5. Basis of my research

An important part of my research was scientific integrity, a systematic approach and the conclusions I drew from the results. For my research, I also regularly looked through the international and national articles that had been published. I also published articles regularly and gave talks about the subject. I was in constant contact with the specialists in this field, and I used their valuable information to expand upon my own theories as well as strengthen them.

Part of my paper will be to introduce and try to answer two diverging questions.

1. From the first group of questions, the use of Drugs in the Hungarian Army. This was based on the results of the Department of Toxicological Research during the last 15 years, and for it, I looked at the results of their testing and the statistical analysis. I will review these things in the first part of my thesis.
2. The role of Poppy seed ingestion in the primary drug screen for opiates.

I will try to answer these questions through the help of literature research and local toxicology experts. The information gleaned will then try to answer an increasing number of questions that arise in the areas of physiology, experimental medicine, psychology, and genetics.

These questions pose an important part in the quality assurance of a drug-enforcement program, since with its help; law enforcement individuals might be able to eradicate drug abuse.

I originally began my research by interpreting the observed phenomena, then I used the collected data along with the statistical analysis of it to build up a hypothesis, which was finally built into a conclusion, from which I am able to advance some recommendations on how to solve the problems.

6. The Hungarian army system of drug screening

From the period of 1996 to 2000

The development of the system began originally by randomly collecting urine specimens and testing them along with the results of anonymous questionnaires. In the beginning, the amount of positives were between 10 and 30%. It became obvious we had to educate the people unambiguously about the problems of drug abuse, to develop new laws to combat this problem, and bring into being a rigorously controlled program for testing for drug abuse. The basis of this system was showing how prevention was the best pathway, and raising the awareness of the consequences of drug abuse.

From the period of 2000 to 2005

We started regular, random drug checks in the barracks, and with the danger of being caught, the amount positive drug screens dropped to between 5 and 10%. It was interesting that there were statistic differences in the regions of Hungary as for the amount as well as the type of drug. We found that in the area of Budapest, there was a higher incidence of positivity. In the western part of the country, especially the western and southern border regions, there was also a higher rate of positivity. In the eastern part of the country, there was a higher rate of positivity especially for opiates. The Hungarian army decided to try to try to further decrease the rate of drug abuse by a

two-pronged approach, first by rigorously screening the incoming recruits, the other was to perform a screening test during each annual physical.

The new system we established, the more stringent application of the existing laws, and a “Zero tolerance “ principal as well as the discontinuation of the mandatory military service in 2004 produced truly remarkable results.

We developed a method to check for drug abuse, which was a three-tiered system, in which each level had different sensitivity, and each based on a different way to check for the compounds:

- Immunochromatographic rapid tests, which test for a sensitive group of compounds, suitable for qualitative detection of one or multiple drugs. This is the first stage of screening.
- Immunochemical measurement system, which is semi-quantitative confirmation, compound class-specific, where the clinical laboratory measurement methods include instruments.
- Chemical instrumental test, where the test compound is which is determined qualitatively and quantitatively. We use the Mass-spectrometer-gas chromatograph (GC-MS).

From the period of 2005 and 2011

In this period, 85 to 90% of the samples collected were suitable for testing. Due to the Command system in the Hungarian army, along with the precise instructions that were given to the soldiers and current regulations, the amount of positives among the troops dropped below 1%. In addition, there were also the factors of motivation among the soldiers, the fear of losing their career, and above all, the constant fear of random drug screening.

In 2012, Designer drugs made their appearance in the world market, and the law enforcement agencies reported that drug market increased at least 50%. In the face of this new treat, we have to develop new screening and testing methods in order to maintain our drug-free state. The new testing methods will need new procedures, new tests, new chemicals, and new machines.

In order to introduce an accredited laboratory to test for these new drugs, an appropriate professional and legal framework has to be established in order to ensure international standards are met. The laboratory will have to have their results be accepted as an expert opinion by the Hungarian and international courts. In order to do this, our Toxicological Research Department's instrumentation and testing procedures had to be to upgrade to the same level as the EU-NATO Drug testing laboratories. Our goal in our laboratory is to **establish the fact of drug use**, using the most suitable model for the examination of urine samples. We accepted the NIDA (National Institute of Drug Administration) cut-off limits, since it is the one most often accepted by the national and international practice, as well as in the literature.

We selected the most modern methodology and technique to perform the screening drug tests. The pre-screening FPIA (fluorescence polarization immunoassay) technique with the Abbott AxSYM meter and Thermo CEDIA enzyme immunoassay method was performed. The samples that tested positive were tested further in the gas and liquid chromatographer (HPLC and GC) and gas chromatography in combination with mass spectrometry (GC-MS) technique.

7. Scientific issues regarding the ingestion of Poppy-seed:

My research - along with others - has extended to the poppy plant. In the opinion of some of the researchers, poppy seeds do not contain opiate alkaloids. However, after ingestion of dishes of food that contains poppy seed, the methods used for pre-screening of urine opiate give a positive result. If the poppy-seed does not contain opiate alkaloids, where did the positive result come from? This apparent contradiction has to be investigated in any case.

In Hungary, the most common type of poppy contains alkaloid, the content of which varies

depending on the type of poppy. A few types of poppy contain a concentration of morphine that is well above the EU legal limit. The pod of the poppy contains the largest quantities of alkaloids. If one collects the raw poppy-seed from the pod, one can extract opium. The composition varies greatly depending on the place of cultivation and the processing mode of the poppy. The manufacture of pharmaceutical opiates is from the pod, after removing the fiber. Even today in Hungary, the pharmaceutical industry supplies the world with morphine utilizing this method. In fact, the industrial extraction of morphine was developed by a Hungarian Pharmacist, János Kabay. There are more than 64 opium alkaloids, all of which have a different structure. The major groups are as follows:

- Phenanthrene alkaloids: morphine (5-15%), codeine (0.5%), thebaine (0.2%);
- [Benzyloisoquinoline](#) derivatives: papaverine (0.5-1%), narceine (0.3%);
- Phthalideisoquinoline derivatives: narcotin (5-7%).

Opiate receptors

The major types of receptor for opiates are the μ and κ and δ and the subtypes thereof: $\mu 1$, $\mu 2$ and $\kappa 1$, $\kappa 2$, $\kappa 3$, and $\delta 1$, $\delta 2$. Their impact on the different receptors depends on the structure, because each has a different affinity for binding different receptors. The alkaloids of opium poppy have a higher affinity for the morphine analgesic activity.

8. Morphine pharmacokinetics and pharmacodynamics

From the pharmacokinetic point of view it is important to remember that the effect of the small intestine on the poppy-seed morphine absorption is in the "first-pass" metabolism of C3 and C6 glucuronization in the liver. These are glucuronized in different ratios, that vary from individual to individual, but generally 9:1, morphine-3-glucuronide predominates. The major metabolite, morphine-6-glucuronide molecule exerts a very strong analgesic effect. The C3 morphine glucuronide (M-3-G) is practically an inactive C6 morphine glucuronide (M-6-G), but it is more active than free morphine. The glucuronidation of morphine by oral administration is low. Morphine metabolites in plasma have a half-life of 1.5-4 hours. The conjugated metabolites and small amounts of free morphine are mainly excreted in the urine. The morphine-6-glucuronide excretion in patients with impaired renal excretion is slowed, therefore administration of morphine in these patients is not recommended.

The morphine 3 - and 6-glucuronides that are excreted in the bile then passes on to the intestine where they are hydrolyzed and re-absorbed back into the portal circulation, then on to the liver. This is called the Enterohepatic circulation.

Morphine, due to its high lipid solubility, can be used in preparations of morphine for percutaneous absorption. This can work well, for the morphine molecules bypass the liver and reach the blood-brain barrier rapidly, and passes through to exert their central effects.

Pharmacodynamics and pharmacokinetics of codeine

The derivative of morphine, namely codeine, has a lot less effects on the body than morphine does. It reduces the cough and respiratory center excitability. You can find them present in an amount between 0.3-3% in the unripe pods of the poppy. This opium is considered the second most important alkaloid of the opium family. Codeine is a natural opiate alkaloid.

9. A STUDY OF THE EFFECTS POPPY-SEED INGESTION

The problem of poppy-seed ingestion has ramifications into the theoretical sphere and also into every-day practice. I developed a research project to examine the answers to the following questions about dietary poppy-seed ingestion:

1. After the meal, would one test positive on a drug-screening test?

To what is the extent would the urine test positive for the opiate?

How long would the urine test positive?

2. How much morphine and its metabolites (and which metabolites?) can be measured in the blood?
3. Can laboratory methods distinguish poppy-seed ingestion from other narcotic opiate preparations?
4. Do dietary Poppy-seeds have a measurable effect of mind-altering effects in some individuals, and what are they?
5. How does the influence of individual genetic characteristics UGT2B7, CYP3A4, CYP2C8, UGT1A1, and/or CYP2D6 have on the enzyme system functioning in the case of poppy-seed ingestion, and how does it induce physiological changes?

10. The Experiment

Volunteers agreed to have laboratory and psychological tests performed on them. The major part of the study lasted from 24 to 48-hours. A laboratory analysis was also performed on the poppy-seed that was fed to the volunteers.

In our original protocol, only participants were allowed to participate in the study that did not consumed poppy seeds at least one week before the study.

At “0” time, the volunteers emptied their bladders completely. A Psychological test was performed. After that, a blood and urine specimen were taken and run to see the biological background, and to rule out interference.

At this time, a pastry (strudel) was consumed, which contained between 150 and 180 grams poppy-seed (depending on the volunteer’s weight), accompanied by 300 cc water.

From the starting point of “0”, we took blood samples at 60minutes, 120 minutes, 180 minutes, 240 minutes, 300 minutes, and 360 minutes. Afterward, urine specimens were obtained every 2 hours until 12 hours, when we obtained a urine sample only every 6 hours. We allowed the volunteers to drink only after 120 minutes after the ingestion of the poppy-seed.

Throughout the 48 hours of the testing, we kept exact records of the liquid intake and the urine output. The volunteers had to drink at least 2 liters within the first 24 hours. Every voiding of the bladder had to be recorded at what time it occurred. If at all possible, when the time of the exam came up, a 50 ml sample of urine was obtained, sealed in a plastic tube and stored.

The urine samples were examined with an immunochemical test (FPIA, Abbott AxSYM) (drug screening), afterward they were examined again with gas chromatography coupled with mass spectrometer (GC / MS) to study the emergence of opiate metabolites.

The blood samples were taken at 0 '-60'-120'-180'-240'. They were examined initially with the GC-MS and LC / MS, and the second time around with the LC / MS / MS to determine the blood levels of morphine and codeine.

Psychological studies

We focused on attention span, perseverance, short-term memory tests. Since the study group was of diverse backgrounds, we tried to steer away from tests that would depend upon either educational level or intelligence. The measurements were carried out, and the subject themselves acted as their control, i.e. before and after consumption of poppy seed cake (between 60-120 minutes after ingestion), the volunteers completed two tests. Since these tests were made in quick succession, it was mandatory that the tests would not depend on a learning process to resolve them. A control group was also tested, and these volunteers did not ingest poppy-seed, but had a pastry filled with nuts instead. They took the same tests as the poppy-seed group did, and the tests were repeated between 60 and 120 minutes later. These studies were performed on both groups to exclude the possibility of fatigue and the daily monitoring of the meal-induced satiety-induced changes in performance and the learning process.

We expected that ingestion of poppy-seed would cause a change in concentration, and associative capabilities

Finally, we tested the poppy seeds using the HP-LC method.

11. RESULTS

1. The urine samples collected at specified times were examined with the immunofluorescence technique (Abbott AxSYM) to check the changes in the opiate concentrations. Of course, before the ingestion of the poppy-seed, the concentrations of the opiate in the urine samples were always zero. The results of the following urine specimens proved my hypothesis, for they showed that after the second hour (although they varied in each individual), in each case, the concentration of the opiates were well above the cut-off value, and even in the third to sixth hour period, concentrations above 1500-2000ng/ml were recorded. The following morning (24 hours), samples taken showed that the levels were one third less than the cut-off, but there were still measurable amounts of opiates in the urine.
2. The same samples were then tested by GC-MS analysis, whereby the concentration of morphine and codeine of the sample was determined by solid-phase extraction (SPE) and, after derivatization SIM mode, utilizing the internal standard method. The result here was similar to the drug-screening tests. The samples contained concentrations of opiate; 1000-2000 ng / ml of morphine were found, while the codeine concentration was over 50-250 ng / ml.
3. In the blood samples taken from the first four hours, we determined the levels of free morphine and morphine-3 and -6 glucuronides. The CNS activity of morphine depends on the availability of morphine and morphine-6-glucuronide for they are responsible for changes as they pass through the blood-brain barrier and bind to the μ 1 receptors. The various methods of measurements have shown that the blood concentrations of free morphine did not exceed 5 ng / ml. This value is below the therapeutic concentration (10 ng / ml). But non-the-less, there is a mind-altering effect that were proven by the results of the psychological tests.
4. The psychological test results were analyzed by statistical methods. Among the psychological tests run, there was a noticeable difference in the two groups (namely the Poppy-seed group and the control group). The Digital tachitoscope tests 1 and 5 showed that the average performance improved in the control group. In the Mawi straight and reverse

tests, the performance did not deteriorated in the poppy-seed group, while in the second round of tests, the control group scored worse than they did in the original test. In the Revesz-Nagy test, the control group scored better in the second round, while in the Poppy-seed group, the average of the tests remained unchanged. The Conflict management task showed that the effect of the opiates in the poppy-seed group caused them to become more patient than the control group.

In the group there were three subjects who complained of drowsiness, and whose results could be seen, but overall, the poppy-seed group demonstrated a decrease in concentration and performance.

5. There was a paradoxical effect in the subjects who had a CYP enzyme system, (dependent upon heredity), so the rules only apply to the general population.
6. The tests on the morphine content of poppy-seed by the HP-LC system revealed that they contained 90.1 mg / g. The poppy was washed with water at different temperatures, and the concentration of morphine was measured in the washing liquid and in the remaining poppy. It was shown that by raising the temperature of the washing liquid, the active ingredient in the fluid is proportionately increased. This fact suggests that the morphine in the poppy seeds is on the surface and can be easily removed. This assumption is proved by photos.

12. CONCLUSIONS

1. Over the past decade and a half, drug screening programs have continuously evolved. This is to ensure that the most effective procedures are in place for enforcing the compliance to the laws, ensure the most effective procedures are in place for the enforcing compliance, and engage in drug prevention in collaboration at all times. The armed forces can not function without workplace drug purity, so the "zero-tolerance" principle needs to be enforced even if you have to make financial sacrifices to do so.
2. Consumption of drugs is a fact of contemporary life, and according to the international standards, the easiest way of proving this is by testing the urine. However, when the subject is "under the influence of drugs", the blood has to be tested within a few hours.
3. While we are discussing the opiates, it is worthwhile to keep in mind that in the case of poppy-seed ingestion, where the free morphine is measured, the concentration will be 5 ng / ml or less, and in this case the hair will not contain detectable amounts of the compound.
4. I recommend that we should run specific tests to try to distinguish the results of illegal opiate ingestion from the poppy-seed ingestion. I would like to propose an extension in the testing procedures with a new procedure that I have introduced, which can be accredited in the future. The applied methodology should be applied in the first stage of the screening tests when the initial result is positive. (The poppy seed that matures in the pod produces the largest quantities of opiates. The poppy seeds seem to fall outside this process. The opium in the inner surface of the particles can stick to the poppy-seeds. Depending on the type of poppy and amounts of these particles, different alkaloid concentrations can be found. The Industrial processes use these characteristics for purifying opiates. However, the poppy-seeds which are used for dietary purposes are not subjected to this type of analysis, which often cause unforeseen problems.)

5. I've created an algorithm which helps to distinguish the poppy-seed ingestion from illegal drug consumption and the use of opiate-containing medications.
6. My research has showed that correct procedures are in place that can easily solve the problem of poppy-food use.

13. New Scientific Results

1. I developed a new for a drug testing system, which will prevent the abuse of drugs in the armed forces.
2. I have tried to show that the effect of the intoxicating poppy opiate poppy-seed is caused by the adhering particles, illustrated with photographs and paintings as well further shown with measuring the poppy opiate washing.
3. I developed a methodology for the determination of codeine and morphine in poppy seeds, as well for the GC-MS measurement of urine morphine and codeine, as well as a methodology of determination of the blood morphine and codeine with the GC-MS and LC-MSMS .
4. Examination of the results of the psychological tests proved that poppy-seed ingestion has a clearly measurable effect in the change in performance of people (of course in varying degrees).
5. I tried to demonstrate that the cut-off levels of the Screening tests should be raised from 300 ng / mL to 1000 ng / ml. In this range namely the drug abuse can be clearly differentiated from the poppy seed consumption, so that a significant amount of redundant work saves the test system.

RECOMMENDATIONS FOR PRACTICE

1. Research has clearly demonstrated that only the persistent fear of getting caught by random drug tests force vulnerable persons to withhold drug consumption. The drug screening system should be maintained in order to preserve the purity of the Hungarian Army!
2. The checks specified in the system should be carried out continuously, depending on the actual needs of the developed control system!
3. NAT control laboratory accredited by updating shall be operated continuously, improving the equipment, laboratory procedures, and to expand the scope of the test compounds and the matrix as well as the needs increasing the qualifications of the people working in the laboratory!
4. I recommend that the procedures I introduced should be performed in the differential diagnosis of all persons who test positive for opiates, in order to elicit the cause of the positive test result.
5. On the basis of my research, I recommend that poppy-seed foods be excluded from the menu in troops before a mission! This clearly can prevent problems in persons with

increased susceptibility to the development of the paradoxical effect, and even in the suspicion of drug abuse.

6. It has been shown that the opiate molecules are stuck to the outside of the poppy seeds, and this causes the typical effects of opium ingestion. Plain hot water can remove the opium material by washing the grains, and this can prevent morphine-induced paradoxical reactions.
7. The overall success of all drug testing and drug prevention specialists depends upon the proposed continuous cooperation with each other to prevent the Hungarian Army from showing any symptoms of drug use.