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Review Article

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Vietnamese herbal opioid addiction treatment medication Heantos-4

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ABSTRACT

Heantos-4 is a non-toxic, non-addictive herbal detoxification medicine for opioid addiction. It was initially invented in Vietnam in the 1980s and tested and developed further in Vietnam in the early 1990s. Since 1995 it has been studied in international cooperation, standardized first into earlier versions and finally to the current version Heantos-4. The various versions have been utilized at Vietnamese inpatient rehabilitation clinics since 1991. During detoxification, it has a predominantly sedative effect. It likely acts as a dopaminergic stabilizer, counteracting both hyperdopaminergic and hypodopaminergic states. Up to 2008, an estimated 9000 patients had been treated. An uncontrolled phase III clinical trial carried out in Vietnam in 2008 indicated an approximately 90% success rate during an initial seven-day inpatient detoxification treatment. This formally unpublished trial is briefly reviewed in this article. In 2012, Heantos-4 was licensed for over-the-counter outpatient use in Vietnam. The Heantos-4 formulation consists of extracts of twelve plants commonly used in Traditional Chinese Medicine (TCM). In addition, animal-based gelatin is utilized as a binding agent. The product has been said to conform to Good Manufacturing Practices (GMP) standards. The patent of the product belongs to the National Institute of Chemistry of the Vietnam Academy of Science and Technology (VAST). An initial hindrance to clinical trials and international adoption was a lack of necessary polypharmacokinetic methods for determining the constituent molecules and the active agents of the complex mixture. In 2020 a key active agent l-tetrahydropalmatine (l-THP) was identified. Due to synergistic effects between components Heantos-4 likely provides better tolerability and a greater therapeutic efficacy in comparison to l-THP alone. The article also briefly describes the approximately 40-year history of the development of Heantos, partly based on unpublished internal documents of the United Nations Development Programme (UNDP). In the 2000s, a severe opioid epidemic emerged in the United States. More than ever an effective method for resolving opioid addiction is needed. As of yet only uncontrolled clinical trials of Heantos have been carried out. There is thus an urgent need for randomized controlled clinical trials.

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INTRODUCTION

The following section presents background information on the development of Heantos. The details are largely based on an unpublished internal document 'United Nations Development Programme: International Development of the Anti-Drug Medication HEA(N)TOS. Project background and preliminary results of safety and efficacy tests conducted in Vietnam. March 1999' (UNDP, 1999). The report comprises a collection of various documents: project background, a description of development of Heantos since 1995, documents from the Hanoi Institute of Chemistry, agreements between the United Nations Development Programme (UNDP), the United Nations Office for Project Services (UNOPS) and the Vietnamese government, a statement from Dr. Donald Jasinski of the Johns Hopkins School of Medicine, descriptions of patient cases, a report of an initial pharmacological standardization process, results of initial safety and toxicity tests, a report of an initial trial of 110 patients as well as project budgeting information.

One of the documents included in the report was a 'Brief of new and important information on Heantos medicine (VIE/96/003) project' by the Institute of Chemistry of the Vietnam Academy of Science and Technology (VAST) (VAST, 1998). Another was a letter from the Institute of Orthopaedics Science and Rehabilitation for Wounded Veterans and Invalids which had performed the initial uncontrolled 110-patient clinical trial (Anh, 1996).

Colonial Health Policies and their Reversal in Vietnam

Vietnam's history includes the French colonial era (1858-1945). It was followed by the warring era (1945-76) which included the Vietnam War (1954-75). After the 1976 reunification of North and South Vietnam, Vietnam became

a socialist republic (1976-1991) and subsequently a 'socialist-oriented market economy'.

The opium problem in Vietnam was initiated by British opium flooding from China to Burma (Myanmar) and North Vietnam along with migratory Chinese (Nguyen & Scannapieco, 2008). Opium was swiftly outlawed but after the beginning of the colonial rule the French established an opium franchise to finance its expenses which led to opium use spreading to lowland provinces. By the early 1940s, it was estimated that 2% of the population and 20% of the elite were addicts.

A central feature of health policy of the French colonial era was the marginalization of traditional medicine in relation to modern biomedicine: a 'general, though not overall, rejection of traditional medicine's public health value' (Wahlberg, 2006). This created a situation in which a large part of the population lacked access to the preferred form of healthcare. The marginalization led to decreased economic opportunities and social capital for practitioners of traditional medicine. In turn, there were fewer practitioners and apprentices, which resulted in a decline in the professional skill level of new generations of practitioners.

In 1954, after the end of the colonial rule, strict drug policies were introduced that resulted in a drop in opium consumption (Nguyen & Scannapieco, 2008). Yet efforts to eradicate localized opium production in North Vietnam remained unsuccessful until the 1990s.

A reversal of the colonial era policies regarding traditional medicine was declared in President Ho Chi Minh's 1955 speech which endorsed China's Chairman Mao's policy of integrating traditional medicine and biomedicine (Wahlberg, 2006). The approach of including the traditional practitioners in the official healthcare system and then devising quality control and continuous education systems for them aimed at efficient utilization of existing human and pharmacological resources. The objective was to enable local and individual self-sufficiency in healthcare instead of building dependencies on expensive synthetic pharmaceuticals, out-of-reach treatment facilities and the few biomedicine experts available.

In 1965, the health minister clarified that the prejudice of practitioners of biomedicine against ethnopharmacology 'derives from an erroneous conception of science and a profound ignorance of results obtained by traditional medicine' (Wahlberg, 2006). He added that due to the extreme variety of compounds available in medicinal plants, random experimentation with them is infeasible and knowledge must be derived from existing practices. He also noted that unless collected and preserved, the knowledge would disappear in one generation.

A massive project of collecting, organizing, selecting, analyzing and regulating herbal medicines and treatment practices was initiated in 1957 (Wahlberg, 2006). In the following decades, a Vietnamese ethnopharmacology industry was established. The industry adopted relatively strict organizational and regulatory practices similar to those applied in biomedicine.

Early Development of Heantos

The development of Heantos was initiated in the 1980s by a traditional Vietnamese herbalist Tran Khuong Dan. Dan's father and brother were traditional herbalists who were both addicted to opium. His brother eventually died as a result of the addiction, leaving Dan wondering why his brother had been unable to heal himself (Larimer, 1997). Dan initiated a search for traditional cures in which he traveled to rural areas, and interviewed opium producers, who were known to have developed their own methods of withdrawal for after the harvest season. He persuaded the opium producers to reveal their secret recipes, in the end collecting 115 different formulas for managing withdrawal symptoms during periods of no harvest. However, he was disappointed to find that most formulas contained small amounts of opium while others were not sufficiently effective (Wahlberg, 2006).

As Dan had been the taught principles of traditional medicine by his father, he formulated a theory of the mechanism of addiction and proceeded to find herbal components to match the requirements of his theory (Wahlberg, 2006). In the tradition of self-experimentation, he deliberately made himself addicted to opium and tested various mixtures until he found one that successfully assisted in recovery (Larimer, 1997; Sung *et al.*, 2003; Aldhous, 2005). After that he addicted himself to heroin and successfully retested his cure. The self-funded process was said to have taken 10 years and cost 100,000 US dollars (Swan, 1997).

In September 1990, Dan presented local health authorities his water extract syrup of thirteen components (Wahlberg, 2006). A few months later the information had reached the prime minister and the Ministry of Health granted a license to proceed with trials. Initially named TKD, the name of the product was changed to Heantos, meaning 'the heat of the sun' (Leibniz Institute of Plant Biochemistry, 2006).

According to a report from a Vietnamese rehabilitation institute for war veterans, the institute's attempts to detoxify seriously injured and severely opioid-addicted war veterans of the US-Vietnam war of 1955-1975 had so far been unsuccessful, and as a result the veterans had been eligible to sustaining doses of morphine at no cost (Anh, 1996). Between 1991 and 1995, 110 addicts were enrolled in an initial trial with the original liquid-form Heantos. They had been addicted for 5-20 years and were primarily using the free morphine but some were supplementing it with other opiates. 70% were paralyzed and in wheelchairs.

The one-week inpatient treatment consisted of a 72-hour detoxification period followed by three to four days to 'restore the health condition of the detoxed addict' (Wahlberg, 2006). This initial trial resulted in 109 successful cases and one unsuccessful case (Anh, 1996). After one year 30% of the patients had needed a second treatment period; later, 5% had needed a third treatment period. The wording of the report appears to suggest a 100% followup, likely because these veterans were permanently hospitalized at the institute. Thus, according

to the report, during the approximately five year period the success rate had been 99.1%. A later report stated that until the end of 1998, none of patients had relapsed (VAST, 1998).

Between 1991-1995 about 4000 patients were treated in a number of treatment centers, proving successful 'in practically all cases' but 'documentation did not comply with internationally recognized standards' (Wahlberg, 2006). Due to a lack of resources, thorough follow-ups could not be organized. Heantos was not licensed for outpatient use and could thus not be self-administered for relapse prevention. The overall relapse rate was estimated to be about 20% (Leibniz Institute of Plant Biochemistry, 2006). The full cost of treatment was estimated to range from 70 to 300 US dollars per patient (Leibniz Institute of Plant Biochemistry, 2006).

In 1995, Tran Khuong Dan begun cooperating with the Institute of Chemistry under the auspices of the Vietnam Academy of Science and Technology (VAST) (Wahlberg, 2006; Sung *et al.*, 2015). On December 22, 1995, the National Centre for Natural Sciences and Technology of Hanoi requested assistance in the further development of Heantos from the United Nations Development Program (UNDP) (UNDP, 1999). The results of the initial 110-patient trial drew the interest of UNDP. The United Nations Office for Project Services (UNOPS) was chosen to act as an executing agency for the project (UNDP, 1999).

The Johns Hopkins School of Medicine Chemical Dependence Unit engaged in discussions with Vietnamese scientists, subsequently confirming that Heantos contained no addictive substances (despite an earlier conjecture by UN International Drug Control Programme and other Western parties) (Wahlberg, 2006). These developments resulted in an initiation of concerted research efforts aimed at international adoption of Heantos.

Initially, opiate addictions had mainly been a problem in rural highlands among ethnic minorities with a tradition of opium poppy cultivation (Suh & Stier, 1997; Nguyen & Scannapieco, 2008). In other areas the issue had been confined to the marginalized and unemployed, including the injured war veterans. By 1997, however, it had begun spreading to cities. An investigation into reasons behind a sudden increase in traffic accidents found out that more than half of the taxi drivers in one company used heroin. Primary school children and 15-25 year olds in well-off districts and even nine-year olds were found smoking heroin. 22 people, including several from the police and the Interior Ministry, were sentenced for trafficking over 800 kg of heroin between 1992 and 1995. The average official incomes of the sentenced were 100 US dollars a month while the street price of heroin was around 50000 US dollars a kilogram.

In 1997, one American multi-drug addict with a history of five-year daily intravenous heroin use was successfully treated in Vietnam (UNDP, 1999). The patient mostly slept and denied experiencing any withdrawal symptoms. In one-month surveillance the patient was taking Heantos-3, his physical health had improved and drug screens were negative.

In 1997 and 1998 six more patients from the United States, Europe and Africa were treated in Vietnam (VAST, 1998). After 3-12 months there had been no relapses. In addition, 30 patients in China were treated with 14 patients not relapsing after 7 months (VAST, 1998). Six had relapsed after 4 months; for the rest there were apparently no data.

Between 1995 and 1997 the original liquid form had been developed into capsules of three types: Heantos-1 for 'disinfection and withdrawal of cravings', Heantos-2 for adjustment of sleep during the first 5 days of treatment, and Heantos-3 for prevention of relapse, to be taken for 1-6 months after the initial treatment period (VAST, 1998). The length of the detoxification period (the first phase of the one-week treatment period) had been shortened from 72 hours to 36 hours.

Animal testing was performed to determine toxicity. High doses (half of LD) were initially observed to cause convulsions but the issue was resolved by adjusting component ratios (VAST, 1998). According to a 1998 report by the Vietnamese Institute of Drug Quality Control, Heantos versions 1-3 did not contain insecticides, addictive substances or toxic alkaloids (UNDP, 1999). On mice, all versions of Heantos had a sedative effect. With Heantos 1, the lowest lethal dose was 10 g/kg. With Heantos-2, the lowest lethal dose was 740 mg/kg and LD 2650 mg/kg. With Heantos-3, the lowest lethal dose was 5 g/kg. A one-month long controlled test on rabbits revealed no differences between groups in any of the common serological parameters tested.

A trial with 200 patients was carried out to determine a standard dose to avoid the convulsion side-effect (VAST, 1998). Dosing for Heantos-1 for the whole 36-hour detoxification period was 25 x 500 mg, dosing of Heantos-2 for the five-day post-detoxification period was 5 x 250 mg, and dosing of Heantos-3 for the 3-month period after treatment was 100 x 250 mg. The method was deemed 'very effective and completely safe'.

A report by UNOPS stated that 'these results and hundreds of clinical reports in Vietnam, indicating the short-term effectiveness, are only considered so far as anecdotal evidence in the Western world, and therefore, cannot substitute the scientific scrutiny, which is rigorously imposed by Western regulatory systems to verify claims for new medications' (UNDP, 1999). The rationale for initiating international scientific co-operation was to fulfill the regulatory requirements of the United States Food and Drug Administration agency (FDA). A 1997 letter from Dr. Jasinski states that Vietnamese results cannot be dismissed because the methods did not meet American standards, and that an international research project was in the public interest (UNDP, 1999). Dr. Jasinski also stated that the aim of the project was to test the efficacy of Heantos not only for opiate addiction but also for cocaine addiction.

As Heantos is a herbal product with no toxic or intoxicating properties, technically fulfilling regulatory requirements for new medicines would have been unnecessary, as the product could simply have been introduced as an over-the-counter herbal

product. Regardless, at the beginning of 1997 the UNOPS coordinator estimated the process to take 3-4 years, i.e. to finish around 2000. The aim was to establish a foundation for later research of similar herbal products in the Western societies.

In 1998, a clinic associated with Tran Khuong Dan was accused of covering up the death of at least one patient in his care (Boggan, 1998). The UNDP and UN International Drug Control Programme (UNDCP) were said to be in conflict, with the UNDCP saying they 'are hearing' that there 'might have been as many as six deaths'. In addition, the UNDCP suspected that Heantos would contain kratom (*Mitragyna speciosa*): 'if that is the case, then this isn't a cure, it's a substitute and it would be no better than the methadone we give people now'. UNDCP also required proof that the treated addicts 'are still off the drugs'. A later 2005 article mentioned a statement by Wahlberg that 'rumors circulated that some patients had died following adverse reactions but subsequent safety evaluations by the Vietnamese authorities have given Heantos a clean bill of health' (Aldhous, 2005).

By 1998, three competing herbal opiate detoxification products with different constituents, Vinantidic-TKC, HuFuSa and Cedemex, had been invented (Mathes, 1998; Ghodse *et al.*, 2007). Despite the co-operation between the UNDP and the government of Vietnam, by 1999 Heantos still had not been licensed for outpatient use (VAST, 1998). HuFuSa, produced by a pharmaceutical factory under the Ministry of Defense was the only one licensed for sale as an over-the-counter medication and effectively had a monopoly on the outpatient detoxification product market. The inventor of Cedemex accused officials of discrimination to protect the monopoly of HuFuSa (Mathes, 1998).

In early 1999, a Finnish medical doctor imported a small amount of HuFuSa to Finland and distributed it to seven buprenorphine addicts for six-day unsupervised outpatient detoxifications to be performed at home (Turkia, 1998, 2016). The product was in a capsule form. Patient experience was positive: HuFuSa was observed to inhibit most of the physical cravings. Physically the patients described the effect as 'the body being heated up from the inside'. Side-effects included sleepiness, dry mouth, feeling hot, and disturbances of near vision. According to retrospective self-reports, four of the seven patients initially reduced their buprenorphine doses (6 mg on average) to zero, one patient from 6 mg to 0.2 mg, and one from 2.5 mg to 1 mg. One patient failed due to misunderstanding the length of the detoxification period to be six months instead of six days. The physician was however soon forced to stop treating opiate addicts and the experiments and follow-up were halted. In the end, assumedly 2-3 patients withdrew permanently from buprenorphine. All in all the results were considered good. With regard to later developments concerning HuFusa, in 2002 the inventor of HuFuSa was accused of bypassing regulatory requirements, failing to properly disclose the ingredients of the product, forging documents, and multiplying the price of the product 27-fold in order to acquire personal financial gain (Phuong & Hung, 2002). Currently HuFuSa is no longer used in Vietnam.

In 1999, five clinicians from the United States, Denmark, Sweden and Norway visited a Heantos clinic in Hanoi for 10 days, observing a detoxification process of 9 Vietnamese and 5 international patients. The group concluded that Heantos appeared superior to Western standard methods and it seemed to suppress all withdrawal symptoms with few complaints from patients (Wahlberg, 2006).

According to a testimonial of one European multi-drug addict with a history of drug use of approximately 15 years, Heantos treatment 'took away all the physical pain from the first day. It also got me rid of all the mental desire. I no longer want to take drugs. I did not do anything special for this to happen … I do understand that after reading my words you must be thinking that I am still on drugs or completely off my trolley' (Jacque, 2000).

Years 2000-2020

The UN International Drug Control Programme persisted with a skeptical attitude expressed in their 2001 statement that 'there is insufficient information available … and that there does not appear to be any evidence that Heantos is more effective than any other products available for a similar "treatment"' (Wahlberg, 2006).

In February 2002 a patent 2569 on Heantos was granted to the VAST Institute of Chemistry (Sung, 2005). Despite that, a 2006 report by a group of international experts on herbal medicine in the treatment of substance abuse mentions that after the initial phase, the government of Vietnam 'appears to have lost interest' in Heantos (Ghodse *et al.*, 2007). The report also complains that the Vietnamese expert present at the meeting did not provide further information.

On project organization, the report describes that 'From the late 1990s, toxicity studies and clinical trials have been agreed and started in the United States (Johns Hopkins University, National Institute on Drug Abuse), in Germany (since 2001 in Essen) and Denmark and funded from various bilateral and multilateral sources (e.g. UNDP and UNOPS, UNESCO; while WHO and the UN drug control bodies did not join)' (Ghodse *et al.*, 2007). Studies were said to be ongoing in Germany and Denmark 'as late as 2002'. On effects, the report mentions that Heantos-1 was 'said to have a deliberately negative side effect: should a patient slip back into drug use, he will suffer painful, convulsive fits'.

The report also states that 'given that Heantos is such a complex mixture, satisfying the demands of regulatory authorities has been a persistent problem, even a 2004 European Union (EU) directive, designed to lower the hurdles for certain herbal remedies, doesn't provide much assistance. Non-disclosure of the constituents of the composition will remain an obstacle for the evaluation of the safety, efficacy and usefulness of any composite herbal medicine' (Ghodse *et al.*, 2007).

An important phytochemical study of Heantos by the Leibniz Institute of Plant Biochemistry in Germany confirmed the

initial Vietnamese results of non-toxicity, and identified 194 constituents from 12 plants but could not determine which of these were the active ones or what was the exact mechanism of action (Wahlberg, 2008). A report lists seven German and one Vietnamese external collaborators in the project (Leibniz Institute of Plant Biochemistry, 2006). Apparently, a standardization protocol was established which allowed a phase II clinical study to be performed in 2003-2005 at the University of Essen, Germany (Sung *et al.*, 2015). The study was said to have been 'the first one applied to such a complex traditional Asian medicine' (Leibniz Institute of Plant Biochemistry, 2006). The VAST Institute of Chemistry noted that the aim of the research was never isolation and synthesis of a single active agent but optimization of efficacy and standardization of the product (Wahlberg, 2006). The result of this work was the Heantos-4 capsule which combined the previous three separate capsules into one.

Up to 2005 funding was said to have primarily originated from the UNDP and the Norwegian government, with additional support from UNESCO (Aldhous, 2005). Randomized controlled patient trials were initially going to be carried out by Johns Hopkins School of Medicine but it failed to secure funding. In 2001 the regional government of Nord-Rhein Westfalen agreed to fund a trial in Germany (Aldhous, 2005; Wahlberg, 2006). In 2005 a randomized controlled trial with 60 patients was being planned in Essen, Germany (Aldhous, 2005). The trial was apparently never carried out.

In 2006, Wahlberg stated that 'since the involvement of Johns Hopkins researchers in early 1995, the ongoing quest to validate the efficacy of Heantos in the treatment of addiction has pretty much read like concerted efforts to gradually notch up `levels of evidence' as endorsed by the WHO, albeit not without numerous complications and contestations' (Wahlberg, 2006).

In keeping with the strategy to slowly accumulate further clinical data, by 2008, an estimated 9000 patients had been treated with Heantos in Vietnam (Wahlberg, 2008). Phase I, II and III clinical studies were carried out in Vietnam and successfully finalized in 2011 (NAMED, 2011; Sung *et al.*, 2015). The Vietnamese Drug Administration licensed production and clinical use of Heantos-4 in 2012. It was said to be effective and cheap with no observed side effects and also deemed suitable for outpatient use. Subsequently, it was adopted by most of the Vietnamese addiction treatment centers. A follow-up study in one treatment center indicated a 5-10% relapse rate three months after treatment (Sung *et al.*, 2015). A description of an uncontrolled phase III clinical study on the manufacturer's website indicates an approximately 90% success rate (NAMED, 2011). Up to the end of 2020, clinical trials had still not been carried out outside Vietnam.

According to the manufacturer's instructions, the detoxification period was to be initiated at least 24 hours from the last use of drugs but not before the onset of withdrawal symptoms (NAMED, 2015). On the first day, depending on body weight and severity of addiction, the dosage of Heantos-4 was 5-6 capsules (500 mg each) twice with 6-7 hours in between the doses. On the second and third days the dosage was 5-6 capsules after meals, four times a day. On days four to seven, the dosage was 5-6 capsules once in the evening before sleep. If needed, the treatment could be prolonged up to 10 days.

Due to lack of suitable analytic methods, polypharmacokinetics, i.e. determination of pharmacokinetics of multicomponent herbal medicines such as Heantos, had been considered 'beyond the scope of traditional research' (Lan *et al.*, 2013). It is unclear why the UNDP and the universities were determined to pursue this route regardless: due to lack of knowledge of the lack of necessary analytical methods, unfounded optimism (assuming the methods could be invented on the fly) or something else. A method based on metabolomics coupled with multivariate statistical tools that focus on the comprehensive analysis of small molecules in biofluids was proposed in 2013 (Lan *et al.*, 2013).

A strong sedative effect had been observed with high doses. A 2016 study examined effects on burst-firing of thalamic neurons due to the involvement of thalamus in non-REM sleep and control of arousal (Cain *et al.*, 2016). Heantos-4 was observed to inhibit some and potentiate some types of neuronal calcium currents and to exacerbate absence seizure activity in a strain of mice highly susceptible to such seizures. Accordingly, caution may be warranted with seizure-prone individuals. It is unclear whether this feature is related to the previously mentioned 'deliberately negative side effect' of 'painful, convulsive fits'.

The first preclinical study on the mechanism of action of Heantos-4 was undertaken at the University of British Columbia (UBC), Vancouver, Canada, under the guidance of Anthony Phillips and Michael Krausz (Sung *et al.*, 2015). Further studies are still ongoing (Cain *et al.*, 2016; Dias *et al.*, 2016; Ahn *et al.*, 2020). In 2016, the first preclinical assessment of the effects of Heantos-4 on opiate withdrawal and the rewarding properties of morphine was published (Dias *et al.*, 2016). The study suggested Heantos-4 acts as a dopaminergic stabilizer, counteracting both hyperdopaminergic and hypodopaminergic states. No intrinsic reinforcing properties were observed which indicated low potential addictive liability. The study also listed 12 constituent herbs and one binding agent of Heantos-4 as well as the main phytochemical compounds isolated from it. Tetrahydroprotoberberines l-THP and l-SPD were said to be of principal interest, given the evidence already linking them to models of addiction (Nesbit & Phillips, 2020).

In the 2010s there were attempts for international distribution of Heantos-4 as a dietary supplement but these seem to have stalled due to either inadequate supply of the product from Vietnam or difficulties in acquiring international import certificates (Heantos.com, 2020). A further attempt to distribute an alternative herbal opiate detoxification product in the United States was blocked by the FDA due to unsubstantiated advertising (US FDA, 2018).

In 2020, almost three decades since the initial official Vietnamese results about the 110 war veterans treated with liquid-form Heantos, an article about neural bases for

attenuation of morphine withdrawal by Heantos-4 capsules was published (Ahn *et al.*, 2020). A persistent dysfunction of the mesolimbic dopamine system, with the nucleus accumbens being a key but not the only affected region, had already been recognized as a key pathological feature of chronic exposure to opioids. Due to this acquired dysfunction, discontinuation of opioids results in a hypodopaminergic state.

Out of the 194 identified compounds in Heantos-4, the rat model study identified l-tetrahydropalmatine (l-THP) as a key active ingredient of Heantos-4, with a central dopaminergic mechanism of action (Ahn *et al.*, 2020). Heantos-4 and its constituent l-THP alone were observed to possess comparable potency in reversing the hypodopaminergic state in the nucleus accumbens and observed somatic features of withdrawal after their onset. A single treatment was notably effective and the effect was nearly immediate, observable in a few minutes after administration. The precise quantity of l-THP for inducing side-effects remains undetermined but the dosing used in the study was well-tolerated.

The authors noted that the use of combined botanical extracts may account for the clinical success of Heantos-4 (Ahn *et al.*, 2020). The component interactions may cause synergistic effects that further attenuate the withdrawal symptoms. Dias *et al.* (2016) note that 'the literature on herbal medicines contains many examples of beneficial synergistic effects of the combination of different herbs when compared to an individual active ingredient' (Dias *et al.*, 2016).

L-tetrahydropalmatine has also been explored as a treatment option for cocaine-use disorders (Ahn *et al.*, 2020). Anecdotal data indicates that Heantos has been used for detoxification from crack cocaine in Brazil (Grupo Vida Sorocaba, 2016).

REVIEW

This section begins with a brief description of the plants included in Heantos-4 and reviews the existing uncontrolled phase III trial.

Some properties of the constituent components of Heantos-4

A list of twelve plant-based constituent components and one binding agent has been provided in Dias *et al.* (2016). The list includes extracts of seven types of roots, a tuber, a rhizome, a branch, a fruit, and a seed. An analysis of Heantos-4 product has been carried out in Vietnam, the results of which were published in 2013 in four separate articles in the Vietnam Journal of Chemistry, volume 51. These analyses indicate which compounds from the constituent plant materials have been extracted into the final product but the articles were not available online. The following summaries briefly describe the key properties of the individual plant components.

- Crude polysaccharides of *Codonopsis javanica* (*Radix Campanumoeae*) displayed nerve growth factor-like neurotrophic activity, have a protective effect on cerebral ischemia-reperfusion injury, facilitate improvement of learning and memory function in mice, and may be a new type of immunomodulator (Wu *et al.*, 2020).
- *Ophiopogon joponicus* root (*Radix Ophiopogonis japonici*) has traditionally been used in Vietnam for antitussive, expectorant and tonic purposes (Chen *et al.*, 2016).
- Astragalus membranaceus root (*Radix Astragali membranacei*) compounds have anti-oxidant, anti-aging, cardioprotective, immune-enhancing, memory and learning enhancing, and hematopoietic effects (Liu *et al.*, 2019). They can protect the mitochondria by scavenging reactive oxygen species, inhibiting mitochondrial permeability transition, and increasing antioxidant enzyme activity to improve aging in mice.
- Licorice root (*Radix Glycyrrhizae*) contains glycyrrhizin which exhibited in vitro antiviral efficacy against hepatitis A virus, human immunodeficiency virus type 1 and various other viruses, reduced hepatocellular damage in chronic hepatitis B and C, reduced risk of hepatocellular carcinoma in hepatitis C virus-induced cirrhosis (Lim, 2016). Licorice root has also exhibited neuroprotective, anti-cholinergic, anti-inflammatory, adaptogenic (anti-stress), estrogenic, pulmonoprotective, antithrombotic, antiangiogenic, anti-tyrosinase, wound-healing, antitussive, renoprotective, antiosteoporotic, radioprotective, cytoprotective, choleretic, anticolvulsant, vasorelaxant and antiparasitic activities.
- Angelica sinensis root (*Radix Angelicae sinensis*) compounds have antioxidative, anti-inflammatory, anti-aging, hematopoietic and neuroprotective effects (Chen *et al.*, 2013; Liu *et al.*, 2019). In combination with Astragalus membranaceus it has traditionally been used to treat diabetes mellitus and this combination has been observed to ameliorate vascular endothelial cell dysfunction induced by excessive oxidative stress (Yin *et al.*, 2020).
- Rehmannia glutinosa root (*Radix Rehmanniae glutinosae*) contains catalpol which has been observed to elevate serotonin and brain-derived neurotrophic factor, protecting against depression and neurodegeneration (Bhattamisra *et al.*, 2019). It has also demonstrated an increased mitochondrial biogenesis and activation of PI3K/Akt pathway for insulin sensitizing effect. In addition, catalpol exerted analgesic, sedative, hepatoprotective, purgative, anti-inflammatory, antimicrobial, antitumor, and antiapoptosis actions.
- *Polygala tenuifolia* root (*Radix Polygalae*) has been used for improving cognitive function and for treatment of insomnia, forgetfulness, depression, cough and palpitation (Zhao *et al.*, 2020). Its extracts possess neuroprotective, cognitive-enhancing, antidepressant, hypnotic-sedative, anti-inflammatory, antiviral, antitumor, antioxidant, antiaging, and antiarrhythmic effects.
- Tuber of *Stephania glabra* (*Tuber Stephaniae glabrae*) has traditionally been used to treat asthma, tuberculosis, dysentery, hyperglycemia, cancer, fever, intestinal complaints, sleep disturbances and inflammation (Semwal & Semwal, 2014). Its components have been shown to possess anti-anxiety, neuroprotective, anti-hypertensive, muscle-relaxant, antimicrobial, antihelminthic, anti-diabetic, anti-allergic, anti-inflammatory and antitumor effects. It is a source

of tetrahydropalmatine. It is endangered in many areas; bioreactor cultivation techniques have been experimented with.
- Ginger rhizome (*Rhizoma Zingiberis*) exerts in vitro anti-inflammatory, anti-oxidative, antimicrobial and antiviral effects; in vivo, it exerted antipyretic, analgesic, antimicrobial and androgenic effects (Chrubasik *et al.*, 2005). Some ginger constituent chemicals were more potent than aspirin in a cyclooxygenase-1 (COX-1) inhibitor assay and also potent inhibitors of cyclooxygenase-2 (COX-2). Ginger has traditionally been used as a broad-spectrum antiemetic but definitive studies are lacking.
- Cinnamon branch (*Ramulus Cinnamomi*) compounds exert anti-inflammatory, analgesic and neuroprotective effects, among others (Zhang *et al.*, 2019).
- Chinese date fruit (*Fructus Ziziphi jujubae*) exerts hepatoprotective, antioxidant and anti-inflammatory effects (Villanueva & Villanueva, 2017). It is traditionally used prophylactically for liver diseases and management of hepatitis. A clinical trial about the alleviation of idiopathic chronic constipation indicated some effect.
- Seeds of a *Ziziphus mauritiana* tree (*Semen Ziziphi mauritianae*) contain cyclopeptide alkaloids including sanjoinines (Zhang *et al.*, 2016). Sanjoinines exert sedative activity, and Ziziphus species have traditionally been used as a treatment for insomnia (Morel *et al.*, 2009).

Donkey-hide gelatin (*Colla Corii asini*), gelatin obtained from the skin of the donkey (*Equus asinus*), is utilized as a binding agent (Dias *et al.*, 2016). It exerts anti-anemia, anti-inflammatory, anti-tumor, anti-fatigue, bone-repair and positive immunomodulatory activity in vivo (Wang *et al.*, 2014). Currently, its production appears unsustainable (Murray, 2019).

In summary, in addition to the previously mentioned dopaminergic mechanism of action, Heantos-4 likely exerts sedative, neuroprotective, anti-inflammatory and analgesic effects that are relevant for opiate detoxification.

The Heantos-4 clinical trial of 2008-2009

An uncontrolled multi-center phase III clinical trial (n=255) with Heantos-4 was carried out in Hanoi, Vietnam between November 2008 and December 2009. The results appear to have been published only on the manufacturer's website and not published in a peer-reviewed journal (NAMED, 2011).

Patients had to fulfill ICD-10 criteria for opioid use disorder (F11.23). Exclusion criteria included lack of withdrawal symptoms on admission, acute or chronic brain, liver, kidney or heart dysfunctions (e.g. epilepsy), severe mental illness (e.g. schizophrenia), and human immunodeficiency virus infection.

The mean age was 33 years with 2.4% of patients being female. The level of education was relatively low with 65.4% being unemployed. 4.3% had been addicted for less than a year, 42.7% for 1-5 years, 34.9% for 6-10 years, and 18.0% for more than 10 years. 92.5% used only heroin, 7.8% used heroin and other opiates or opioids, and one person used heroin and methamphetamine. 31.7% smoked heroin, 49.4% injected it, with the rest both smoking and injecting.

4.3% used drugs once a day, 25.1% twice a day, 43.5% three times a day, 18.8% four times a day, and 8.2% at least five times a day. 0.8% was estimated to have a mild addiction, 25.1% a moderate addiction, and 74.1% a severe addiction. 14.1% had not attempted withdrawal before. 14.5% had attempted withdrawal once, 22.4% twice, 12.2% three times, and 36.9% at least four times; it was not stated which methods had been used in these attempts. In summary, the demographics indicated a representative patient sample.

Successful treatment was defined as following through the full treatment regime, a remission of withdrawal symptoms, and a negative opioid screen result at the end of the period. Unsuccessful treatment was defined as any of the following: the patient not following through the whole treatment regime, a need to administer medicines other than Heantos-4, a non-remission of withdrawal symptoms, or a positive opioid screen result at the end of the period. In addition, treatment results were divided into four categories according to the time to remission (2-3 days, 4-5 days, 6-7 days, >7 days), reduction in withdrawal symptoms, and opioid screen test result.

The treatment period was seven days. Withdrawal symptoms were assessed with both self-reporting and observation five times during the period, scoring each symptom on a three-grade scale. Adverse effects were graded on a four-grade scale. The treatment regime used doses of 3.5 g (seven Heantos-4 capsules) except for three patients who received 3 g doses. On the first day, the first dose was administered at least 24 hours after the last use of drugs but not until the appearance of withdrawal symptoms, and a second dose after 6-8 hours later (however, approximately a quarter of patients received only one dose on the first day). On the second and third days, one dose was administered after a meal in the morning and in the evening. From the fourth to the seventh day, one dose was administered in the evening before sleep.

Urine test opioid screens were administered four times, electrocardiogram test twice, and psychological assessment twice during the period. Standard serological and urine tests were performed twice, before and after the treatment period.

Of the 255 patients, 230 were classified as successful (90.2%) and as 25 unsuccessful (9.8%), respectively. 19 of the 25 underwent full treatment; also they were considered 'a moderate success' due to leaving the hospital with a negative opioid screen and a remission of withdrawal symptoms. Six of the 25 (2.4% of patients, 24% of unsuccessful) discontinued the treatment period early, two of which (0.8%) were opioid screen positive when leaving the treatment early due to family emergencies (one death and one hospitalization of a family member). The rest (n=253) were opioid screen negative. One patient left on day four for a wedding and another on day five for a job interview. Additional two patients left on day five, believing they had already succeeded.

The successful and unsuccessful cases differed with respect to the severity of addiction, with only the severely addicted classified as unsuccessful (25/164, 15.2% probability). The successful cases experienced only mild withdrawal symptoms whereas the unsuccessful cases experienced moderate symptoms. The successful cases also required a shorter time to remission of withdrawal symptoms.

In an earlier phase II study, treatment results were assessed as very good in 22.6%, good in 67.7%, fair in 9.7% and poor in 0% of cases. In this phase III study, the results were assessed as very good in 31.7%, good in 57.8%, fair in 10.4%, and poor in 0% of cases, respectively.

There appear to have been two overlapping criteria for defining success. On the four-grade scale, no patients obtained a 'poor' result. In addition, all 251 patients who underwent the full treatment period were opioid screen negative and in remission of withdrawal symptoms. It appears that 25 cases were classified as unsuccessful solely due to the administration of diazepam on the second and third days due to the severity of withdrawal symptoms. However, it was concluded that the use of diazepam had enabled retention in the treatment for 19 patients in the 'unsuccessful' group, and the combination of Heantos-4 and diazepam was said to be 'a remarkable success'. The dosing was said to be significantly lower than the standard dosing used in an official national detoxification regime (dosing information was given as number of pills instead of milligrams).

Interpreted in less strict ways, the trial results could thus be stated as 99.2% success (remission of withdrawal symptoms and opiate screen negative, n=253), or 97.6% success (remission of withdrawal symptoms, opiate screen negative, and no interruption of the planned treatment regime, n=249).

The Beck depression inventory (BDI) and Zung Self-Rating Anxiety Scale (SAS) were used to assess psychological status before and after treatment. Changes in BDI scores before and after treatment were statistically significant: the percentage of patients with no depression changed from 3.5% to 27.0%, mild depression from 22.6% to 42.6%, moderate depression from 47.8% to 21.7%, and severe depression from 26.1% to 8.7%. Similarly, changes in SAS scores were statistically significant: the percentage of patients with no anxiety changed from 23.5% to 67.8%.

No adverse effects or fatalities were observed during the trial. On average patients gained some weight. There were no notable changes in somatic markers. There was no mention of a follow-up after leaving the hospital.

DISCUSSION

Comparing the reported success rates of the initial 110-patient and the later 255-patient uncontrolled trials to typical results of opioid detoxification treatments, it may seem feasible to assume the results to be too good to be true. There may also be non-replicable cultural factors for a high success rate. Regardless, the results could also be seen as an indication of a possible huge opportunity for improvement. Also, the anecdotal Finnish experience with a similar product, HuFuSa, indicated a high success rate (57%) in the initial detoxification self-administered unsupervised at home, a rate much better than what had been achieved with any other methods in that patient group. A method for relapse prevention was not available at the time; Heantos-4 is designed to also provide that.

The process of standardization and licensing lasted approximately 15 years in Vietnam, and licensing and adoption are still uninitiated in other countries. During this time, opioid abuse has famously exploded in the United States (Phillips & Krausz, 2018). Assuming that the efficacy of Heantos would be even a fraction of what has been indicated we may ask: has it been a rational decision to distrust the initial Vietnamese research results and delay adoption of Heantos for more than two decades? Are Western societies really able to afford inefficiencies of this magnitude? Why couldn't the standardization proceed in parallel with emergency authorized clinical use, as it did in Vietnam?

The case of Heantos could be seen as an example of the adverse effects of overregulation. Good intentions may have led to the opposite result: an effective, affordable and safe treatment may have been ignored because an incompatible regulatory system was forced on it. The feasibility of regulatory requirements to ensure the pharmacological safety of treatments could have been compared with the realities of addicts' lives to decide which one is the most relevant threat: not knowing the mechanism of action of a substance with which thousands of patients had already been successfully treated, or abusing contaminated, completely unregulated substances. Another consideration is whether, in such a situation, the risk of an affordable experimental treatment possibly being ineffective is at all relevant, or whether almost anything would be worth a try. Also, the well-known societal repercussions including crime and judiciary and health care costs should be taken into consideration.

It remains unclear whether it would still be best to simply introduce Heantos-4 worldwide as a dietary supplement. This would ensure just-in-time availability during the often very short time windows when an addict is both in hopeful enough a mood to initiate a detoxification process and free from external demands to continue drug abuse (e.g. drug debts requiring one to keep selling opioids and remain in the subculture).

However, either production may already have lagged behind demand or there have been organizational issues with respect to obtaining international import certificates. Ensuring production and distribution thus remains an unresolved issue. Assumedly, with effort, most of the herbs can be sustainably cultivated for the purpose. Alternatively, developing similar products may be an option.

CONCLUSIONS

Currently, finding effective means for solving the opioid epidemic seems more important than ever. Based on the

available knowledge, Heantos-4 appears a feasible option for detoxification. It seems highly recommendable to prioritize international clinical trials for it.

A preliminary comparison of l-THP alone versus Heantos suggested that l-THP alone was associated with more adverse effects than Heantos. Multicomponent herbals are occasionally known to possess better tolerability and therapeutic efficacy than isolated agents.

As l-tetrahydropalmatine has also been explored as a treatment option for cocaine-use disorders, in addition to the planned opioid trials, trials could also be initiated on Heantos-4 treatment of addiction to stimulants such as cocaine (as intended already in 1997), crack cocaine, amphetamine and methamphetamine.

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