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## Ascorbic Acid (Vitamin C) Effects on Withdrawal Syndrome of Heroin Abusers

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**Abstract.** Background: Ascorbic acid (vitamin C), administered orally in high doses has been observed to relieve pain and reduce opioid use in cancer patients. In vitro studies have also shown that antioxidants, such as vitamin C, may, at high concentrations, inhibit the endogenous opioid degrading metallo-enzyme and increase endorphin levels. In the present study the effects of oral administration of high doses of vitamin C on withdrawal syndrome of heroin abusers were investigated. Materials and patients: Ascorbic acid at doses of 300 mg/kg b.w/day, supplemented with vitamin E (5 mg/kg b.w/day), was orally administered in two groups of heroin addict subjects consisting of in-patients (Group A, 30 males) and one of out-patients (Group B, 10 males), for a minimum of 4 weeks. The group A in-patients were also administered the conventional (diazepam + analgesic) medication. The results on the intensity of withdrawal syndrome (WS), estimated according to DMS-III criteria, were compared to a third group of heroin addict in-patients (group C, 30 males-control group), treated only by conventional medication. Results: The patients of the vitamin C-treated groups (in-patients and out-patients) experienced mild WS (in 46.6% to 50% of the subjects) in contrast to the control group patients, who experienced mild WS in 6.6% of the cases. The vitamin C-treated subjects expressed major WS ranging from 10% to 16.6%, in contrast to the untreated subjects (control group), who expressed a major WS in 56.6% of the cases. Conclusions: The results indicate that high doses of ascorbic acid administered orally, may ameliorate the withdrawal syndrome of heroin addicts. Further studies are needed in order to estimate the dose- and time-dependent effects of ascorbic acid treatment, and to clarify its mechanisms of action in the withdrawal syndrome.

Withdrawal syndrome (WS) is described as an unbearable experience by drug addicted subjects and represents a major obstacle in their undergo willingness to detoxification. The syndrome begins as a generalized over-stimulation of the autonomous nerve system (ANS) and fever, followed by psychokinetic restlessness and panic behavior. Its gravity ranges according to the abuser's addiction profile and it may prove fatal, without medical care. Detoxification hospital units treat the addicted patients, recruiting a range of drugs that includes benzodiazepines, analgesics,  $\alpha$ -2-adrenergic agonists, opiate receptor antagonists, as well as certain amino-acids, neuropeptides, NO-synthase inhibitors and neutral endopeptidase (NEP)-inhibitors (1-7). In a previous randomized clinical trial we observed substantial pain relief and reduction of dosage or complete cessation of analgesic opioids, in cancer patients treated orally with antioxidants, which included high doses of ascorbic acid (8).

In the present study the effects of large doses of ascorbic acid (vitamin C) orally administered to drug abusers, mainly to heroin addicted subjects, are presented with promising perspectives towards withdrawal syndrome (WS) treatment.

### Patients and Methods

Sixty males, admitted to the DeTox Unit of the Psychiatric Hospital of Thessaloniki, Greece (in-patients) and ten patients who were registered in the Consulting Station for Drugs of Ioannina, Greece (out-patients), aged 22-40 years old, were enrolled in the protocol. Patients with established psychiatric disorders, gastrointestinal disorders and patients who were HIV-positive and hepatitis C-positive were excluded from the study (10 in-patients and 3 out-patients). The medical history, clinical and laboratory examination, were recorded on the Special Treatment Patient's Card. All information relevant to drug-abuse such as the main, secondary and/or other substances of abuse, the method of administration and the recent frequency of drug intake was listed (Table 1) in order to estimate the severity of dependence among the patients of the groups (10). The illegal substance, the age of drug use initiation and duration of use and, in particular the age of heroin use initiation were registered. Furthermore the adoption of high risk behavior in relation to recent use of syringes in common with other addicted persons, was also registered.

Patients of all the groups were heroin addicts, since heroin was

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Table I. Drug Intake Profile. (A patient is registered with his initials and two numbers, e.g. x.x 1.3, where the first number represents the method of administration and the second the frequency of intake).

Method of administration	Listing No	Frequency
Injection	1	0-1/week
Smoking	2	2-6/week
Orally	3	Daily
Inhaling	4	0
Unknown	5	Unknown

Table III. Symptoms and signs evaluating withdrawal syndrome.

Signs
arterial hypertension, diarrhea, fever, hyperventilation, muscle cramps, mydriasis, nausea, paleness, perspiration, piloerection, tachycardia, tremor, vomiting.
Symptoms
agitation, anxiety, depression, pain, panic, psychokinetic restlessness

recorded as the main substance of abuse. The secondary substances used simultaneously were pills or syrups and cannabis derivatives (mainly marijuana). Two individuals from the in-patients group A mentioned methadone as the secondary substance of abuse, while two of the control in-patient group mentioned cocaine and alcohol, respectively.

All the patients declared daily heroin injections and daily, or 2 to 6 times per week, use of the secondary substances of addiction, whereas 3 subjects from each group referred to heroin as the initial substance of use. It was clear from the medical records that pills and cannabis were used from the vulnerable age of adolescence. The mean age, the mean time of drug use initiation, as well as the mean age of heroin use initiation, frequency and duration, showed no statistically significant differences between the three groups (Table II), a result indicating no significant differences of the severity of dependence according to SDS criteria (10).

High dose vitamin treatment included the oral, daily administration of a) ascorbic acid 300 mg/kg b.w (tablets of 1g), divided in 4 daily doses of no more than 5 g of ascorbic acid each, dissolved in 200 ml of tap water, b)  $\alpha$ -tocopherol (vitamin E), 5mg/kg b.w (tablets of 100 mg), divided in 3 daily doses of almost 100 mg each, for four weeks.

The patients were divided into three groups:

- i) The control patients group (C), consisted of 30 male patients, who were treated by the conventional medical therapy, described below. The patients of this group were administered the juice of one fresh orange dissolved in 200 ml tap water, four times daily.
- ii) The in-patients group (A), consisted of 30 male patients, who were treated in addition to conventional medical therapy, with a high vitamin C dose.
- iii) The out-patients group (B), consisted of 10 male patients, treated only with a high vitamin C dose.

The mean age of the patients, their age at heroin use start and the duration of their use are shown in Table II.

Table II. Mean age and heroin use characteristics of patients in all groups.

Group-Number of patients	Mean age (Years)	Mean age of heroin use start (years)	Duration of heroin use (years)
Control-30	29.6 ± 6.2	20.5 ± 4.1	9.1 ± 4.2
C-Inpatients-30	29.7 ± 5.0	20.1 ± 3.7	9.5 ± 4.2
C-Outpatients-10	30.8 ± 4.9	20.1 ± 4.5	10.5 ± 2.3
p	> 0.05	> 0.05	> 0.05

Table IV. Distribution of withdrawal syndrome (WS) intensity (percentage and number of patients) in the study groups.

Group	No. of patients	Intensity of WS					
		Mild		Moderate		Major	
		n	%	n	%	n	%
Control	30	6.6	2	36.6	11	56.6	17
C-inpatients	30	46.6	14	36.6	11	16.6	5
C-outpatients	10	50.0	5	40.0	4	10.0	1

During the first 24 hours of hospitalization of the inpatients groups, subjects were kept without any medication in order to avoid any synergistic implication with unknown drugs, possibly taken prior to admission. The out-patients were also deprived of any medication over the same period. On the second day of admission both groups of in-patients were administered, for five days, the conventional medical treatment consisting of: (6 mg) bromazepam once a day, (30+500 mg), codeine phosphate + paracetamol, respectively, 3 to 5 tablets per day and 2 mg flunitrazepam, once or twice a day, was administered only to patients addicted to these substances.

The in-patients of the De ToxUnit were hospitalized under medical care for 4 weeks, while the Consulting Station out-patient were treated at home under medical supervision. Treatment of the out-patient group started 5 weeks after the inpatients groups. Physical examination and routine blood, biochemical and urine tests were performed on the subjects of all the groups before the initiation of the program and were repeated twice during the 4-weeks/treatment.

Urine specimens of the out-patients and in-patients were tested daily with the Triaze-8 test (Merck NJ, USA), in order to exclude other drugs being used during the treatment period.

All the patients were evaluated for the appearance and intensity of WS by scoring according to DMS-III (9), (Table III).

Evaluation of the WS in the in-patients groups was performed on the various signs and symptoms second and fourth day of the treatment by a member of the medical staff of the Unit, ignoring the classification of the patients according to the various groups (blind study). The same person also evaluated the out-patient group. The WS intensity of each patient was classified as major (Ma), moderate (Mo) mild (Mi), according to the integrated scoring of the above signs and symptoms.

## Results

All the patients from the second day of admission manifested WS of various intensity. The in-patients group A (vitamin C + conventional treatment) manifested a well-tolerated mild WS in 14 out of 30 (46.6%) cases moderate syndrome for 11(36.6%) of them and major syndrome only for 5(16.6%). In the out-patient group B (only vitamin treatment), 5 patients (50.0%) manifested a mild syndrome, 4(40.0%) moderate and only 1(10.0%) a major syndrome.

In contrast, among in-patients of the control group (conventional treatment), only 2 patients (6.6%) manifested a mild syndrome, whereas 11(36.6%) manifested a moderate and 17(56.6%) a major syndrome (Table IV).

Urine detection revealed no use of concomitant drugs during the treatment period. None of the major symptoms and signs of WS syndrome were registered in patients of the groups after the fourth day of the study. During the four weeks of follow-up, the patients of the vitamin C administration groups expressed a vivid feeling of well being and a strong improvement in appetite and psychokinetic behavior, without any signs of depression or insomnia, in contrast to the control group. Side effects and/or blood, urine and biochemical disturbances were not recorded in any patient.

## Discussion

In a previous randomized clinical trial of cancer patients treated orally with antioxidants, amongst which was ascorbic acid (Vitamin C), in large doses (300 mg/kg b.w), we observed substantial pain relief, a reduction of dosage or complete cessation of analgesic opioids and a remarkable feeling of well being (8). The patients in the present study tolerated the orally administered high doses of ascorbic acid (up to 20 g per day), for at least 28 days, without any side effect. Experimental tumor bearing animals and most cancer patients have also tolerated similar or higher daily doses of vitamin C for a substantially longer period of time (up to 3 years) (8,11). Tocopherol (vitamin E), scavenging the ascorbyl radical may prevent the side effects in vitamin treated patients and maintain vitamin C levels in blood by reducing dehydroascorbic to ascorbic acid (11). According to our results, administration of ascorbic acid in high doses to heroin addicted subjects, either supplementary to the ordinary treatment or as monotherapy seems to exert significant effects in ameliorating the withdrawal syndrome. Most of the patients of both groups treated with vitamin C expressed a significantly mild WS (46.6 to 50%) in contrast to untreated subjects, who expressed a major WS (56.6%) (Table IV).

Our results, even though they strongly underline the beneficial effects of oral administration of ascorbic acid in the treatment of WS, do not provide information about the possible mechanisms being involved. The daily doses and duration of administration used in this study, were those that proved effective in relieving pain and reducing opioid

analgesic use in cancer patients. Thus further studies are needed in order to establish the optimum dose of AA and duration of treatment that may also be effective.

Apart from the beneficial effects of vitamin C on WS of hospitalized addicts, our results indicate that vitamin C alone may also be effective in the home treatment of heroin addicted subjects, under medical supervision. There are a number of ascorbic acid effects suggesting some possible explanation of the efficacy of vitamin C, administered in high doses, to ameliorate WS. Vitamins C and E, and other antioxidants prevent the loss of 11- $\beta$ -hydroxylase activity in cultures of fetal human adrenocortical cells, by protecting the interaction of cytochrome P-450 with certain steroids and oxygen and initiation of lipid peroxidation, which results in its own destruction or inactivation (12). Intraperitoneal administration of ascorbic acid may also increase cortisol synthesis in ODS rats (13). Intravascular and oral administration of high doses of ascorbic acid have, in addition, been effective in stimulating the immune system and fortifying the adrenocortical function, by increasing ACTH and cortisol release and elevating their plasma levels in healthy subjects (14-15). Current protocols in our laboratory investigating the possible effects of intravascular and oral administration of ascorbic acid on endorphins, suggest that  $\beta$ -endorphin may be increased along with ACTH in animals and humans, by high concentrations of vitamin C (unpublished data). *In vitro* studies also indicate that ascorbic acid at concentrations of 10 mM, may exert a significant inhibition of the endogenous opioid degrading metalloenzyme, neutral endopeptidase (NEP), probably increasing opioid levels (16-17).

Various hormonal and vitamin disorders have also been found in heroin addicts. Significantly lower ACTH and c-AMP plasma levels have been found in heroin addicts, when compared to normal subjects (18), with impaired circadian rhythmicity to ACTH,  $\beta$ -endorphin and  $\beta$ -lipotropin (19). Chronic opiate abuse leads to hypoadrenalism through impairment of the hypothalamic-pituitary-adrenal axis (20), but abrupt withdrawal of heroin may be followed by hypercortisolism (21). Heroin addicts, without nutritional deficiencies, may have low vitamin C, B6 and albumin levels and suffer various immune disorders. (22). It is thus quite possible that high doses of vitamin C may increase the concentrations of ACTH, cortisol and endorphins in such a way as to improve the metabolic conditions of the brain in heroin abusers, ameliorating the withdrawal syndrome. Vitamin C may also exert other actions on the CNS leading to amelioration of the withdrawal syndrome. Ascorbic acid may scavenge endogenous nitric oxide free radical release in the CNS, which is implicated for the withdrawal syndrome(6). Increased levels of ascorbate (AA) in the extracellular fluid of the brain (23), may also regulate dopaminergic and glutamergic transmission, resulting in an inverse relationship between AA and 3,4-dihydroxy-phenylacetic acid (DOPAC), a major metabolite of dopamine (24). Furthermore there is a glutamate/ascorbic acid heteroexchange process, such that an

increase in glutamate release triggers the reuptake process which operates by releasing ascorbic acid (25).

In conclusion our results strongly indicate that oral administration of high doses of vitamin C may be effective in ameliorating the withdrawal syndrome in opiate abuse in-patients and out-patients, but further and intensive investigation is needed in order to clarify its mechanism of action, the minimum dosage regimen and the duration of administration.

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