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COMPARATIVE PHARMACOKINETICS OF IODIDE ANION AT ADMINISTRATION OF IODINE PREPARATIONS

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Abstract

The purpose of the present research was to comparatively analyze pharmacokinetics and bioavailability of iodide anion of the "Armenicum" (capsules) preparation containing a complex of iodine with dextrins and "Iodoral" tablets at various administration routes.

Twelve healthy volunteers of both sexes were involved in the study. Concentration of iodide anion was determined by Termo 720A MTR, selective electrode W/B ORION IONPLUS IODIDE ELECTRODE (Thermo Fisher Scientific, the USA).

Bioavailability of iodide anion after intake of capsules was 87.5±13%. The bioavailability of capsules was 90.6±15% for men, 86.4±8% for women and statistically did not differ. The comparative analysis of pharmacokinetics of iodide anion after administration of "Iodoral" tablets and "Armenicum" capsules showed that the maximal concentration after administration of "Iodoral" tablets (1.91±0.35 μg/mL) was higher than after administration of "Armenicum" capsules (0.778±0.53 μg/mL) and $AUC_{0-\infty,}$ of iodide anion in blood serum was higher after "Iodoral" single administration. At the same time, the sharpest differences were recorded for value of apparent volume of distribution describing iodide anion penetration degree in organs and body tissues. As obvious from collected data, the volume of iodide anion distribution after administration of "Armenicum" was approximately 3 times higher than after intake of "Iodoral" (16.9L and 5.4L, accordingly).

Thus, proceeding from pharmacokinetic data, it is possible to assume that presence of dextrins in "Armenicum" capsules makes the full delivery of iodine in intracellular space more possible. The latter can provide basis for the assumption that compared to "Iodoral", "Armenicum" can be, apparently, more effective means for treatment of diseases of various organs and body tissues of high affinity to iodine, in particular, thyroid and mammary glands.

Keywords: iodide, iodide anion, pharmacokinetics, "Armenicum".

INTRODUCTION

Since 1940 to 1990 it has been considered that iodine represents certain danger to the organism and it is necessary to strictly limit its consumption. The reasons for it were works published in 1948 by J. Wolff and I. Chaikoff on research of radioactive iodine pharmacokinetics in rats asserting that at receipt of iodine in an organism, when its concentration reaches 0.2 *mg/kg* (10^{-6} *M*) a blocking of thyroid hormones synthesis takes place causing hypothyroidism and many other diseases [*Wolff J., Chaikoff I., 1948; Wolff J., 1969*]. The given phenomenon was named "effect of Wolff-Chaikoff" and for long years there was a basic obstacle to research pharmacodynamics and pharmacokinetics of iodine. Now it is proved that a principal cause of erroneous conclusions of authors was absence of an analytical method for determination of iodide anion in blood; owing to that the researchers had to use radioactive iodine, which under the characteristics, is a very toxic element [*Eskin B. et al., 1967; Bürgi H. et al., 2001; Abraham G. et al., 2006*]. Only in 1999, when G. Abraham's method of iodide anion determination in bio-liquids was developed, an opportunity appeared for research on pharmacokinetics of iodine. The research on pharmacokinetics of preparations, which contain molecular iodine and potassium iodide, convincingly prove that for characterization of their absorption, distribution and elimination it is optimal

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to register iodide anion concentration in bio-liquids [*Abraham G., 2004; Abraham G., Brownstein D., 2005; Abraham G. et al., 2005*] is optimal. During the period from 2000 to 2009 with the help of the given method the pharmacokinetics of "Iodoral" tablets containing iodine and potassium iodide has been investigated [*Abraham G., 2004; Abraham G. et al., 2004; 2005; 2006*; *Abraham G., Brownstein D., 2005*].

During the last 10 years we have also investigated pharmacokinetics of the preparation containing a complex of iodine and potassium iodide with dextrins registered in Armenia and other countries as "Armenicum" [*Panossian A. et al., 2000; Hovhannisyan A., 2007; Abrahamyan H. et al., 2008; Abrahamyan H., Hovhannisyan A., 2009 a, b; Hovhannisyan A., Abrahamyan H., 2009*]. Thus, no doubt, there is an interest in carrying out the comparative analysis on pharmacokinetics of iodide anion after administration of the preparation containing a complex of iodine with dextrins and "Iodoral" tablets

The purpose of the present research was to conduct the comparative analysis on pharmacokinetics and bioavailability of "Iodoral" tablets and iodide anion at various ways of delivering "Armenicum" that contains a complex of iodine with dextrins at its single and multiple administration to the organism.

METHODS

The clinical part of research was carried out on the basis of "Armenicum" Clinical Center. Prior to research each participant was orally and in a written way introduced to the purposes and protocol/design of the research, and a written informed consent was obtained from each subject before the study. The research involved volunteers, whose written informed consent to participate in the study corresponding to inclusion/exclusion criteria described in the Study Protocol was obtained. The Study Protocol was in compliance with the revised declaration of Helsinki and authorized by Ethical Committee, Ministry of Health of the Republic of Armenia (MOH RA) and the Scientific Centre of Drugs and Medical Technologies Expertise of MOH RA (Order No. 12/6-22-6142 of 01.12.08).

Twelve healthy volunteers of both sexes (6 men and 6 women) were involved in this study. Mean age of volunteers was 37.8±11.4 years; height: 172±7.4 *cm*; weight: 71.6±5.9 *kg*, and a body mass index made 24±2 m/kg^2. During research the meals of volunteers were standardized.

In this study we used the following preparations: "Armenicum" (concentrate) for intravenous infusion and capsules manufactured by "Armenicum+" CJSC, which are registered in RA. Contents of 1 bottle of "Armenicum" (concentrate) infusion include: iodine (0.16 *g*), potassium iodide (0.24 *g*), lithium chloride (0.004 *g*), polyvinyl alcohol (0.06 *g*), dextrin (2.0 *g*), sodium chloride (0.114 *g*), water for injections - up to 20 *mL*. One capsule of "Armenicum" contains 0.029 *g* iodine, 0.043 *g* potassium iodide, 0.0007 *g* lithium chloride, 0.011 *g* polyvinyl alcohol, 0.36 *g* dextrin, 0.032 *g* sodium chloride.

At intravenous infusion the dosage of "Armenicum" was 20 *mL* of a concentrate and contained 6 *mg/kg* of total iodine. One capsule of "Armenicum" contains 0.48 *g* dry concentrate and 0.072 *g* total iodine. Intravenous infusion was done within 1 hour with a speed approximately of 3.3 *mL/min*; a capsule was administered with 240 *mL* water.

At the first stage, on day 1 of bioavailability research the volunteers received one intravenous infusion of a concentrate, and after 7 days they took 1 capsule of a preparation.

At multiple combined administrations on days 1, 3 and 5 of research the same volunteers received single intravenous infusion, according to the instruction of a preparation. On days 2, 4, 6 of research volunteers took 3 capsules of a preparation per day (1 capsule every 6 hours). Within the next 7 days volunteers continued to take 3 capsules a day. Blood samples (7 *mL*) were taken in standard test tubes to collect blood serum. The selected samples of blood were centrifuged at 600 *g* during 15 *min*. The obtained serum samples were stored in a refrigerator at -20°C until the moment of analyses.

Preparation of blood samples: Total serum (~5 *mL*) passed through cartridges for solid-phase Strong Anion Exchanger cartridges SAX (Altech, USA). Then, cartridges were washed out with 5 *mL* of 5*M* $NaNO_3$. The eluent containing iodide anion was collected in test tubes, added 10 *mL* water, mixed, and concentration of iodide anion was measured by a potentiometer Termo 720A MTR, selective electrode W/B ORION IONPLUS IODIDE ELECTRODE (Thermo Fisher Scientific, USA) according to G.E. Abraham method [*Abraham G., 2004; Abraham G. et al. 2004*]. Concentration of iodide anion was determined by calibration curve, which kept linearity for solutions of the standard in a range of iodide

anion concentration from 0.006 up to 50 *μg/mL* (r=0.9988). The limit of detection in serum made 0.001 *μg/mL*, a limit of quantitative detection made 0.001 *μg/mL*. Accuracy of the method made 95±2%, selectivity: 99±2%. Specificity, repeatability and reproducibility of the method were characterized by the coefficient of variation (CV) below 5% that corresponds to validation requirements on bioanalytic methods.

The pharmacokinetic parameters were calculated using Kinetica 4.1.1.program (Termo Electron Corporation, 2004).

The following parameters were calculated:

C_{max}: observed maximal concentration after administration (*μg/ml*);

t_{max}: time corresponding to the observed maximal concentration (*h*);

K_a: absorption rate constant (h^{-1});

AUC_{0-t}: area under the plasma concentration-time curve, calculated by means of trapezoidal rule from time zero to the last data point on curve (*μg*ml/h*);

$AUC_{0-\infty}$: area under the plasma concentration-time curve extrapolated from zero to infinity (*ng*ml/h*);

K_{el}: terminal elimination rate constant (h^{-1});

$t_{½}$: elimination half-life time (*h*):

V_{ss}: apparent volume of distribution at steady-state (*L*).

The statistical analysis has been executed by means of computer programs Statistic for Windows, version 6.0 and Microsoft Excel 2003. All results were analyzed by methods of descriptive statistics, with calculation of values of an average, standard deviation, a minimum, and a maximum. To relate average geometrical values of parameters depending on concentration of the confidential interval and factor of variation obtained with the use of logarithmic transformations of AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} values 95% confidence limits. For comparison of pharmacokinetic parameters the parametrical and nonparametric *t*- tests were used.

For the comparative analysis of pharmacokinetics of "Armenicum" and "Iodoral" preparations, data of G.E. Abraham were used [*Abraham G., 2004; Abraham G. et al., 2004*; *2005; 2006*; *Abraham G., Brownstein D., 2005*].

RESULTS

a) *The bioavailability of iodide-dextrin complex capsules after single dose administration:* Research results demonstrated that immediately after the single intravenous infusion of "Armenicum" iodide anion concentration in blood serum was about 4 *μg/mL*. Further it exponentially decreased, however in 1 and 2 hours some increase of concentration was observed. In 6 hours the level of iodide anion decreased to 0.947 *μg/mL*.

At single administration of capsules, upon achievement of a maximum, iodide anion concentration gradually decreased without essential fluctuations and in 8 hours it reduced to 0.056 *μg/mL* that is close to initial endogen level (0.03-0.1 *μg/mL*) of iodide anion in serum (Figure 1).

The results of comparative analysis on pharmacokinetic parameters of iodide anion in blood serum after single administration of one capsule of "Armenicum" and single intravenous infusion are presented in Table 1. After administration of capsules the half-life of iodide anion was 1.9±0.7 *h* that is 40% less than after intravenous infusion (2.6±0.6 *h*) (Table 1). The latter is connected with intensive biotransformation of iodide anion into other forms of iodine in the gastrointestinal tract or in liver before its complete absorption in a systematic blood stream. Bioavailability of iodide anion after intake of capsules was 87.5±13%: 90.6±15% in men, 86.4± 8% in women; there was no significant difference (P>0.05; n =12).

Table 1.

The comparative analysis pharmacokinetic parameters of iodide anion in blood after single intravenous infusion and single oral administration of "Armenicum" preparation.

Parameters	*Infusion, i.v.*	*Capsules, oral*
Dose, *mg/kg*	6	1
C_{max}, *μg/ml*	4.175±1.25	0.778±0.53
t_{max}, *h*	0.375±0.150	2.375±1.109
$AUC_{0-\infty}$, *μg • h/ml*	16.188±6.209	2.652±1.329
$t_{½}$, *h*	2.633±0.571	1.923±0.74
K_a, h^{-1}	-	2.975±0.458
V_{ss}, *L*	5.016±1.646	16.932±3.649
K_{el}, h^{-1}	0.272±0.056	0.401±0.146

Notes: Means ± SD, n=12

It was also established that rates of absorption, distribution and elimination of iodide anion does not depend on age of volunteers and the initial level of endogenous iodide anion in blood serum.

b) *Multiple combined administration:* Research results demonstrated that initial concentration of iodide anion in blood serum of volunteers was in a range of 0.03-0.1 *μg/mL*.

Figure 2 reflects the results of changes in the initial level of iodide anion in blood serum of volunteers collected and analyzed every day during the research.

The analysis on changes of average values of the initial level of iodide anion in blood has shown that at multiple administration of "Armenicum", concentration of iodide anion significantly increases by 36% (*P*=0.0022). In particular, before the treatment course with Iodide-Dextrin complex the endogenous level of iodide anion in serum was 0.125±0.067 *μg/mL*, and in 13 days, before the last administration of a preparation, it increased up to 0.197±0.08 *μg/mL*.

It is possible to assume that changes of iodide anion concentration in blood serum are first of all connected with the changes in character of iodide anion distribution or changes in the extent of its serum protein binding.

At multiple administration of a preparation the change in pharmacokinetic profile of iodide anion was shown. At the end of the treatment course, on the 13th day, the increase of iodide anion absorption rate and t_{max} change from 2.3 *h* till 1 *h* and presence of the second peak in 2 *h* after intake of a preparation were observed. The phase of sharp decrease of concentration in the interval of 1-3 hours, characteristic for an initial stage of treatment course with the preparation has practically disappeared (Figure 3).

Table 2 presents data on pharmacokinetic parameters of iodide anion in volunteers after a single administration at the 5th and 13th days after the start of combined treatment with "Armenicum" preparations. At multiple administration of "Armenicum" the decrease of maximal concentration of iodide anion in blood was observed. So, if at single administration $C_{max,}$ was 0.78 *μg/mL*, in contrast on the 5th day of alternate multiple combined administration capsules and intravenous infusion it reduced up to 0.71 *μg/mL*, and at continuing administration of capsules 3 times per day within 7 days it mades only 0.35 *μg/mL*. Thus, individual variation of t_{max} also decreased. With the increase of a number of capsules administration the $t_{1/2}$ value increased strictly. For example, after day 13 of the combined administration, in comparison with single administration of

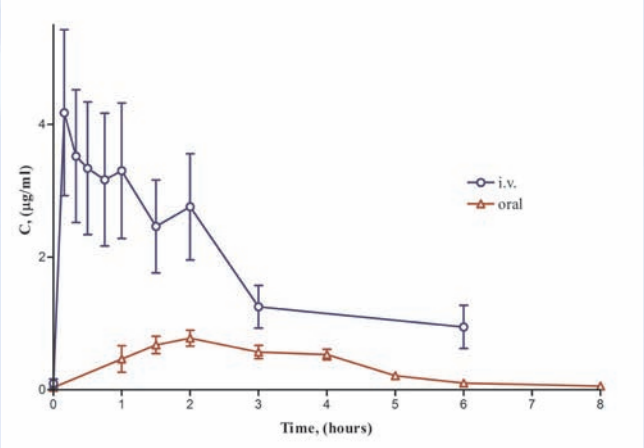

Figure 1. *Changes of iodide anion concentration in blood serum after single intravenous infusion and single oral administration of "Armenicum" preparation. Means ± SD, n=12.*

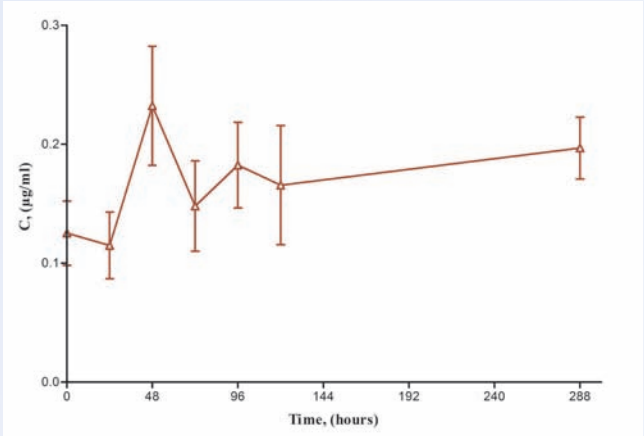

Figure 2. *Changes in endogenous levels of iodide anion in blood serum of volunteers during multiple administration of "Armenicum" preparation. Means ± SD, n=12.*

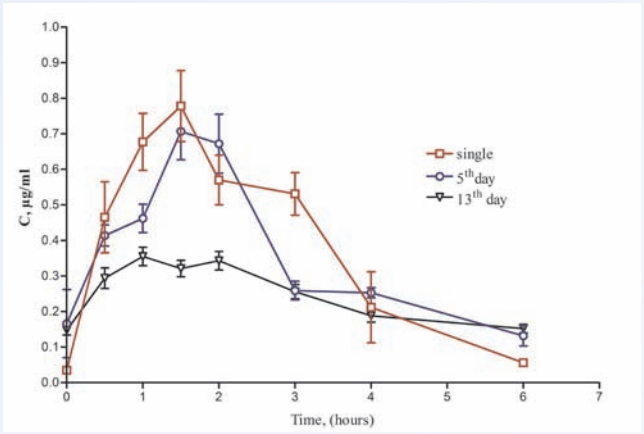

Figure 3. *Change of iodide anion concentration in blood serum after administration of "Armenicum" preparation at single and its multiple combined administrations. Mean ± SD, n=12.*

Table 2.

The comparative analysis of pharmacokinetic parameters of iodide anion after single and multiple administration of "Armenicum" preparation

Parameters	Single dose	5th day	13th day
$C_{max,}$ μg/ml	0,778±0,53	0,707±0,080	0,355±0,026
t_{max}, h	2,375±1,109	1,125±0,479	1,000±0,500
$AUC_{0-\infty,}$ μg • h/ml	2,652±1,329	2,627±2,172	3,177±1,457
$t_{½}$, h	1,923±0,74	2,975±0,458	4,034±1,429
K_a, h^{-1}	2,975±0,458	3,102±3,914	2,902±0,741
V_{ss}, L	16,932±3,649	50,831±16,757	67,312±22,075
$C_{0,}$ μg/ml	0,819±1,021	0,197±0,123	0,121±0,045
$K_{el,}$ h^{-1}	0,401±0,146	0,23±30,046	0,189±0,073

capsules $t_{1/2}$ significantly increased from 1.9±0.7 hours up to 4.0±1.4 hours (P<0.0001).

The sharpest changes were marked for the apparent volume of distribution of iodide anion. Hence, after the treatment course, in comparison with single administration V_{ss} significantly increased from 17 *L* up to 67 *L*, i.e. approximately by 70% (P<0.0001) (Table 2). This increase in volume of iodide anion distribution can be caused by iodide anion accumulation in separate organs and tissues, its capture by erythrocytes or bound by serum proteins [*Abraham G., Brownstein D., 2005*].

Table 3.

The comparative analysis on pharmacokinetic parameters of iodide anion in blood serum after single administration of "Iodoral" tablets and "Armenicum" capsules. Means ± SD, n=12

Parameters	*Iodoral*	*Armenicum*
Dose of total iodide, *mg/kg*	37,5	72
C_{max}, *μg/ml*	1,91±0,35	0,778±0,53
t_{max}, *h*	2,89±0,71	2,375±1,109
$AUC_{0-\infty,}$ *μg • h/ml*	7,347±2,209	2,652±1,329
$t_{½}$, h	2,65±0,91	1,923±0,74
V_{ss}, L	5,376±1,646	16,932±3,649

Notes: Means ± SD, n=12

DISCUSSION

The comparative analysis of pharmacokinetics of iodide anion after administration of "Iodoral" tablets and "Armenicum" capsules has shown that the maximal concentration and $AUC_{0-\infty}$ of iodide anion in blood serum is higher after single administration of "Iodoral" tablets. At the same time, the sharpest differences are marked for value of apparent volume of distribution describing a degree of iodide anion penetration in organs and tissues. As obvious from Table 3, the volume of iodide anion distribution after intake of capsules is approximately 3 times higher than after administration of "Iodoral" (16.9 *L* and 5.4 *L,* accordingly).

The latter can testify that penetration of iodide anion into body tissues and organs is faster and more complete, and probably into intracellular space. The reason for this can be presence of dextrins in "Armenicum" capsules content, which can probably form rather strong complex with the iodine and potassium iodide, capable to easily penetrate through cellular membranes. It might be assumed that penetration of iodide anion into cells and its return to blood has convertible character and achieves steady-state condition approximately in 2 hours after "Armenicum" administration. This can also evidence some increase in concentration of iodide anion in blood serum 1.5-3 hours after administration.

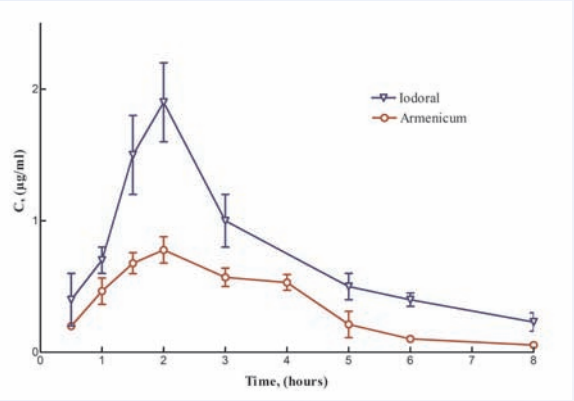

Figure 4. *Changes in concentration of iodide anion in blood serum of volunteers after single oral administration of "Iodoral" (total contents of iodine: 37.5 mg) and "Armenicum" capsules (total contents of iodine: 72 mg).*

The comparative analysis of pharmacokinetic parameters of iodide anion after single administration of "Iodoral" tablets and "Armenicum" capsules has shown that iodide anion after single administration of "Iodoral" tablets is slower absorbed in blood, however statistical difference of t_{max} is not observed ($P > 0.05$) (Figure 4).

Elimination of iodide anion occurs, probably, by biotransformation of iodide anion into other forms of iodine. Thus, the value of its $t_{½}$, statistically did not differ and made 2.65±0.91 and 1.923±0.74 for "Iodoral" tablets and "Armenicum" capsules, accordingly.

Thus, proceeding from the pharmacokinetic data, it is possible to assume that presence of dextrin in "Armenicum" capsules makes the full receipt of iodine in intracellular space more possible. The latter provides basis for the assumption that compared to "Iodoral", "Armenicum" can be, apparently, more effective means for treatment of diseases of various organs described by the high affinity to iodine, in particular, thyroid and mammary glands [*Eskin B. et al., 1967; Eskin B., 1977; 1996; Lacroix D., Wong P., 1980; De Jong P., Burggraaf M., 1983; Ghent W. et al., 1993; Cann S. et al., 1999; Derry D., 2001; Eskin B., Anjum W., 2005*].

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