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Cotinine level as a biomarker of tobacco smoke exposure during pregnancy

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Abstract

Today, smoking today is one of the most common bad habits in the world. Smoking, both active and passive, increases perinatal mortality by 27%, increases the incidence of heart attack and detachment of the placenta, reduces the body weight of the baby, changes the development of coronary artery disease in the newborn, and increases the frequency of spontaneous abortions and stillbirths. Therefore, laboratory studies of nicotine and its catabolic product, cotinine, is an important indicator for monitoring pregnancy.

Key words: pregnancy, cotinine, smoking, newborn.

Котинин – биомаркёр курения табака во время беременности

Курение в современном мире является одной из наиболее распространённых вредных привычек. Курение, как активное, так и пассивное, увеличивает перинатальную смертность на 27%, повышает частоту инфаркта и отслойки плаценты, снижает массу тела новорожденного, изменяет развитие коронарных артерий у новорожденного, увеличивает частоту самопроизвольных абортов и мертворождений. Поэтому, лабораторное исследование содержания никотина и продукта его катаболизма, котинина, является важным показателем мониторинга беременности.

Ключевые слова: беременность, котинин, курение, новорожденные.

Tobacco use is the single most preventable cause of disease, disability, and death in the United States with an estimated 443,000 premature deaths each year, and another 8.6 million people live with serious illness caused by smoking. (CDC. Tobacco Use-Targeting the Nation's Leading Killer, 2011).

In 1984, Attorney General C. Everett Koop presented the first of a series of reports revealing the health consequences of tobacco use including involuntary exposure. While the United States has not overcome the challenges of the "*smoke-free*" society that Koop hoped for by the year 2000, industries across the country now recognize the importance of testing.

For over 20 years a wide range of tobacco (cotinine) testing products for multiple specimen types has been available. ***Cotinine*** is the first-stage metabolite of nicotine. Because the window of detection for nicotine is relatively short (approximately 2 hours), cotinine extends the window of detection for several days and is the preferred method of screening for tobacco use [1].

Levels of cotinine in urine tests are typically much higher than in serum or oral fluid as a result of the higher concentrations of cotinine found in urine [2, 3, 4].

A rapid, one step test for the qualitative detection of Cotinine (nicotine metabolite) in human urine (for determination of Smoking Status Only). The COT One Step Cotinine Test Device (Urine) is a lateral flow chromatographic immunoassay for the detection of Cotinine in human urine at a cut-off

concentration of 200ng/mL. The test device contains mouse monoclonal antibody-coupled particles and Cotinine-protein conjugate. The COT One Step Cotinine Test Device (Urine) provides only a qualitative, preliminary analytical result.

A secondary analytical method must be used to obtain a confirmed result. ***Gas chromatography/mass spectrometry (GC/MS)*** is the preferred confirmatory method [5] (tab. 1).

Table 1

OraSure Test Cutoffs

Biologic fluid	Urine	Blood serum	Oral fluid
Types of Exposure	500 ng/mL	25 ng/mL	10 ng/mL
Second-Hand Smoke	< 100 ng/mL	< 15 ng/mL	< 3 ng/mL
Light Smoking	100-500 ng/mL	15-100 ng/mL	3-33 ng/mL
Regular Smoking	> 500 ng/mL	> 100 ng/mL	> 33 ng/mL

A number of contributing factors influence cotinine testing outcomes such as:

- size of the individual;
- percentage of body fat present;
- rate of metabolism;
- hydration state of the individual;
- type of cigarette/cigar/pipe smoked or tobacco chewed;
- smoking style;
- elapsed time from smoking to testing;
- the pH of the urine (if urine testing is conducted).

The adverse effect of prenatal smoking exposure on human fetal development and growth has been a major public health issue. Active or passive smoking during pregnancy can result in a wide variety of adverse outcomes, including intrauterine growth retardation, premature birth, stillbirth, sudden infant death syndrome, respiratory diseases, and otitis media. Smoking in pregnancy has also been associated with an increased risk of attention deficit disorder and other learning disorders in childhood. Oxidative stress in pregnant women who smoke is assumed to be increased by oxidants and free radicals in tobacco smoke. In pregnancies complicated by cigarette smoking prooxidant-antioxidant imbalance may have a pathomorphological and pathophysiological effect in the fetus.

Maternal smoking during pregnancy greatly increases the rate of perinatal morbidity/mortality and is the major risk factor for Sudden Infant Death Syndrome. Slotkin T. et al. studies in developing rodents indicate that nicotine is a neuronteratogen that targets monoamine pathways involved in the responses to hypoxia [6].

Smoking and severe asthma exacerbations in pregnancy are risk factors for low birth weight babies. During pregnancy, asthma exacerbations are more common and more severe in current smokers than in women nonsmokers. The risk of effects of maternal asthma on the fetus may be greater among smokers [7].

Maternal smoking during pregnancy is known to be associated with not only intrauterine fetal growth retardation and low birth weight, but also with disturbances in postnatal growth and development. Nicotine and its major metabolite cotinine can cross the placental barrier.

The data on smoking which had been obtained from a direct personal interview were verified by determination of serum cotinine concentration. So, more objective investigations of maternal smoking are methods that determine levels of cotinine in the biological liquids of mothers and their newborns.

The findings obtained by Karmowski A. et al. submit new cognitive values to the diagnosis of pathology of pregnancy, i.e. the influence of nicotine on the bodies of mothers and new-born children, estimated by the assay of cotinine**,** the most important metabolite of nicotine. The authors lay a particular stress on the "colostrum-milk way" in the mother-child relationship [8]**.**

The findings presented by Dobek D. and coauthors (1998) contribute to the diagnosis of pathology of pregnancy, i.e. they assess the influence of nicotine on the bodies of mothers and new-born children, estimated by concentration of cotinine. The mean proportional share of cotinine in the fluids and organs in the pregnant women smoking actively was as follows: urine 72.1%, amniotic fluids 14.3%, colostrum 8.9% and placenta 4.7%. The authors pay particular attention to the "colostrum-milk way" in the mother-child relationship.

Women who smoke and breast-feed pose an unknown threat to their infants' health. Stepans M. and Wilkerson N. investigated relationships between ingestion of nicotine in breast milk and physiological effects in the infant. The physiological effects measured in infants were temperature, pulse, respiration, systolic blood pressure, and oxygen saturation. Five smoking and five nonsmoking mother-infant pairs were studied**.** Breast milk was analyzed for nicotine using gas chromatography. Breast milk from smoking mothers contained a mean of 33.1 ng/mL of nicotine while the breast milk from nonsmoking mothers contained a mean of less than 6.45 ng/mL of nicotine. The physiological measurements of the infants were taken before and 20 min after breast-feeding. After breast-feeding, the infants of smoking mothers had a significant change in respiration and oxygen saturation while infants of nonsmoking mothers had a significant change in pulse only. Their results provide a scientific basis for counseling smoking mothers who choose to breast-feed [9].

For the past 40 years, evidence has been accumulating on the effects of passive smoking on the fetus and on children. Over this period, research methods have become more precise and accurate, with confounding factors controlled for and actual exposure to smoke measured and validated by cotinine tests of body fluids. Nearly 200 research papers published worldwide were reviewed by Charlton A. [10]. It is difficult to separate prenatal and postnatal effects with regard to growth, development, and lung function retardation. There is now sufficient evidence that health problems in children are related to maternal and to a lesser degree paternal, smoking during pregnancy, and, after birth, to exposure to environmental tobacco smoke in the home and daycare centers. Exposure to environmental tobacco smoke (ETS) should be noted on pediatric patients' problem lists and addressed at each visit.

The effects of smoke exposure via mothers' milk and/or via passive smoking during the first year of life were investigated by Schulte-Hobein B. et al. in a prospective longitudinal matched-pair study. In order to evaluate the extent of smoke

exposure, cotinine was measured in children's urine and in breast milk once a month throughout the first year of life. Cotinine in the urine was significantly dependent on feeding behaviour: Infants who were breast fed showed concentrations 10-fold higher than those who were bottle fed. Cotinine excretion in the urine of infants from smoking mothers, who were not breast fed (nicotine exposure via only passive smoking) was even higher than that of adult passive smokers. If infants from smoking mothers were breast fed, their urinary cotinine excretion was in the range of adult smokers [11].

In Canada, 8% to 20% of infants are breast-fed by mothers who smoke. To determine whether breast-feeding increases infants' exposure to tobacco smoke byproducts, urinary cotinine excretion was measured by Labrecque M. et al. (1989) in 172 babies, 33 of whom were breast-fed. A milk sample was taken from the mothers who were breast-feeding, and cotinine was measured with gas chromatography. The breast-fed babies had a median cotinine to creatinine ratio of 433 ng/mg, whereas the bottle-fed babies' median was 200 ng/mg. The correlation coefficient between the number of cigarettes smoked by the mother and the breast milk cotinine concentration was significant. Moreover, urine cotinine values from the breast-fed babies increased with higher concentrations of cotinine in the mother's milk.

The extent of smoke exposure via mother's milk and passive smoking was investigated by Schwartz-Bickenbach D. (1987) in a prospective, longitudinal matched-pair study by comparison between children, whose mothers smoked substantially throughout pregnancy and nursing period and children whose mothers did not smoke. The preliminary results show that not only infants of smoking mothers but also those of smoking fathers show a reduction in birth weight. Smoking mothers weaned their babies earlier than non-smokers. Cotinine concentrations in breast milk depended on the number of cigarettes smoked. The highest urinary excretion of cotinine (as expressed by ng cotinine/mg creatinine ratios), were observed in infants fully breast-fed by smoking mothers. Thus it is demonstrated that both nursing and (to a lower degree) passive smoking contribute to the exposure of infants to nicotine and its metabolite cotinine.

An analysis of 44 milk samples from 23 nursing smokers performed by Luck W. and Nau H.(1984) revealed that there was a linear correlation between nicotine concentrations in serum and in milk. The nicotine concentrations in milk were considerably higher than the corresponding serum concentrations. There was also a linear correlation between the cotinine concentrations in serum and in milk. The cotinine concentrations in milk were lower than the corresponding serum concentrations. The half-life of nicotine in milk was determined in four additional smoking mothers. The half-life of nicotine in milk, $T_{50} = 97 \pm 20$ min, slightly exceeded the half-life of nicotine in serum $T_{50} = 81 \pm 9$ min; the difference between these two values was not statistically significant. Cotinine concentrations remained fairly consistent during a 4 hour interval without smoking.

The exposure of infants to nicotine via the breast milk of smoking mothers or via inhaled side-stream smoke ("passive smoking") was evaluated by Luck W. and Nau H. (1985). Newborn infants nursed by smoking mothers and unexposed to passive smoking showed measurable serum concentrations of nicotine (0.2 to 1.6 ng/mL) and its main metabolite, cotinine (5 to 30 ng/mL), and also excreted measurable amounts of nicotine and cotinine in their urine: the ratio of nanograms of nicotine/milligrams of creatinine (N/C ratio) ranged from 5.0 to 110, and the corresponding ratio of nanograms of cotinine/milligrams of creatinine (C/C ratio) from 10 to 555. The significant serum concentrations and urinary excretion rates of nicotine in the breast-fed infants of smoking mothers suggest that nursing contributes to the nicotine exposure of these neonates. In older infants, the wide variation of cotinine excretion values did not allow for separate evaluation of the two exposure routes.

Also, the relationship between nicotine and cotinine concentrations in mother's milk (including 24 h profiles) and the number of cigarettes consumed was studied by Luck W. and Nau H. [12]. A total of 206 milk samples were collected from 34 nursing, smoking mothers. The mothers were distributed into three groups: Group I (1-10 cigarettes/day), group II (11-20 cigarettes/day) and group III (21-40 cigarettes/day). Milk samples from all nursing periods in a 24 h interval were collected. Nicotine and cotinine concentrations were measured by specific gas chromatographic techniques. Over a time interval of 24 h, the nicotine concentrations varied greatly in the milk of smoking mothers, while the cotinine concentrations remained relatively constant. Their results indicate that the exposure of the nursed infant to nicotine and cotinine via milk depends on the daily cigarette consumption but also on individual smoking habits; the time of smoking and smoking frequency prior to nursing, and the time interval between nursing and the last cigarette.

A close correlation was found by Dahlström A. et al. (1990) between nicotine concentrations in the mothers' plasma and milk after smoking, the milk/plasma ratio being 2.9. The amount of nicotine transferred to the infant increased from 0.09 to 1.03 micrograms/kg of the infant body weight when mothers smoked before breast-feeding. The daily dose of nicotine via the mothers' milk was 6 micrograms per kg of the infant body weight. Cotinine, but not nicotine, concentrations in the plasma and milk of the mothers and the urine of the infants reflected the smoking habits of the mothers during pregnancy. There was no correlation between nicotine and cotinine concentrations in the infant's urine and the amount of nicotine given to the infant via the mother's milk.

During Dahlström A.'s study (2004), home visits were conducted, parental smoking habits were recorded, and the times of mothers' last smoke or taking of snuff and breastfeeding were recorded. Breast milk and infant urine samples were collected. Concentrations of nicotine and cotinine were analysed with gas chromatography. The amount of milk ingested during the home visit was calculated by weighing the infants. The concentrations of the metabolite cotinine in infant urine correlated with the dose of nicotine ingested during the home visit. Breastfed infants with a smoking or snuff-taking mother are exposed to nicotine in breast milk.

During home visits, the infant's urine and mothers' milk were sampled and concentrations of nicotine and cotinine

were analyzed by Dahlström A. et al. [13]. The smoking mothers exposed their infants to nicotine in milk with a median nicotine concentration of 47 mcg/L. Analysis of the infants' urine showed that the nonsmoking group had 0.8 and the smoke group 60 mcg cotinine/L. The frequency domain low-to-high frequency (LF/HF) ratio was correlated to milk nicotine concentrations in the milk sample, from smoking mothers.

Serial milk samples were collected by Ilett K.F. (2003) from the women over sequential 24-hour periods when they were smoking and when they were stabilized on the 21-mg/d, 14-mg/d, and 7-mg/d nicotine patches. Nicotine and cotinine in milk were quantified by high-performance liquid chromatographic (HPLC), and the infant dose was calculated. Plasma concentrations of nicotine in the breast-fed infants were assessed, and the infants were also clinically assessed. They concluded that the absolute infant dose of nicotine and its metabolite cotinine decreases by about 70% from when subjects were smoking or using the 21-mg patch to when they were using the 7-mg patch.

The relationship between tobacco smoking in pregnancy and breastfeeding is of public health importance. The Jedrychowski W. et al. birth cohort study provided the opportunity to investigate whether the negative relationship between passive smoking, measured by the cotinine concentrations in maternal blood at delivery and breastfeeding in postpartum, could also be confirmed in nonsmoking mothers [14].

While there are sufficient data regarding the negative effect of exposure to the constituents of tobacco smoke on newborn infants' birth weights, it is still unclear whether this effect may originate in early pregnancy. Ultrasound biometric measurements of fetal bi-parietal diameter (BPD), abdominal circumference (AC) and femur length (FL) were performed by Hanke W. and colab. at the time of enrollment [15]. Serum cotinine concentration was determined at 20-24 weeks of gestation by gas chromatography with mass spectrometry detector (GC/MS) to assess environmental tobacco smoke (ETS) exposure during the previous evening and the morning of the same day. ETS exposure (passive smoking) was assumed to occur when the level of serum cotinine ranged from 2-10 ng/mL. In a multiple regression model for bi-parietal diameter (BPD), after adjustment for pregnancy duration at the time of ultrasound examination, fetal gender, and maternal pre-pregnancy weight, a statistically significant negative association was found between the BPD and serum cotinine concentration. A similar association was identified for subjects with serum cotinine concentrations below 10 ng/mL, corresponding to passive smoking [15].

Leonardi-Bee J. and colab.(2008) wrote that exposure of non-smoking pregnant women to ETS reduces mean birth weight by 33g or more, and increases the risk of birth weight below 2500g by 22%, but has no clear effect on gestation or the risk of being small for gestational age.

The retrospective study by Ward C. and colab. used interview data from parents of 18,297 children born in 2000/2001 and living in the UK 9 months afterwards (the Millennium Cohort Survey) [16]. Comparison of birth weight, sex and gestational age specific (SGA) z score, birth before 37 weeks and birth weight < 2.5Kg (LBW) in infants born to women exposed to: no tobacco smoke, ETS only and maternal smoking whilst pregnant. In the UK, the prevalence of domestic ETS exposure and maternal smoking in pregnancy remains high, and ETS exposure lowers infants' birth weights.

There is growing evidence that ETS exposure may negatively affect birth outcomes, especially birth weight (Pogodina C., 2009). Educational anti-tobacco campaigns and quit smoking initiatives should target both mothers and fathers to ensure smoke-free living conditions and a healthy environment for all family members.

Mennella J.A. (2007) wrote that although there was no significant difference in breast milk intake, despite the taste changes in the milk, infants spent significantly less time sleeping during the hours immediately after their mothers smoked (53.4 minutes), compared with the session when their mothers abstained from smoking (84.5 minutes).

According to Letourneau A.R. data (2007), approximately 40 percent of women smokers will stop smoking cigarettes during pregnancy; however, 70 percent of those who stop will resume smoking by 6 months postpartum. Interventions may be more effective if they include strategies aimed at increasing breastfeeding rates and assisting household members to stop smoking.

The concentration measurements made Milnerowicz H. and Chmarek M. (2005) employed the following methods: total protein by Lowry, albumin by colorimetry, cotinine and lactoferrin by ELISA tests. The assessment of tobacco smoke exposure was based on concentrations of cotinine in breast milk: 197 ± 98 ng/ml in smokers and 23 ± 11 ng/mL in non-smokers; and in serum: 179 ± 87ng/mL and 32 ± 19 ng/mL, respectively.

A high-performance liquid chromatographic (HPLC) assay was used by Page-Sharp M. et al. (2003) for the determination of nicotine and cotinine in human milk. It was developed using an extraction by liquid-liquid partition combined with back extraction into acid, and followed by reverse-phase chromatography with UV detection of analytes. The assay was linear up to 500 microg/L for both nicotine and cotinine. They found that this method was sensitive and reliable in measuring nicotine and cotinine concentrations in milk from a nursing mother who participated in a trial of the nicotine patch for smoking cessation.

Bramer S. L. and Kallungal B. A. (2003) wrote that subjects enrolled in studies are not always screened for routine habits such as smoking. Personal history is not always reliable and therefore an objective biomarker is necessary to screen for smokers. A serum cotinine concentration of 10 ng/mL should be employed as a breakpoint for non-smokers versus smokers; other non-invasive alternatives are collection of urine, saliva, or hair (with suggested breakpoints of 200 ng/mL, 5 ng/mL and 0.3 ng/mg, respectively); screening questions should be accompanied by testing for cotinine; and the inclusion of smokers in studies should be considered once the impact of smoking on the targeted population is understood.

Cotinine levels by radio-immuno-analysis (RIA) were evaluated by Berlanga Mdel R. (2002). Cotinine was 19 times greater in the smoking mothers and six times higher in their infants, as compared to the nonsmoking group.

Also Berlanga Mdel R. (2002) wrote that hair nicotine levels were better able to discriminate the groups of children according to their household's smoking habits at home than urine cotinine. Furthermore, hair nicotine levels were more strongly correlated with number of smokers in the house, and the number of cigarettes smoked by parents and other members of the child's households. Hair nicotine was better related to the questionnaire variables of smoking in a multivariate regression model than urine cotinine.

Biomarkers can provide valid information on ETS exposure, the preferred biomarker being cotinine. However, no reference range of hair cotinine exists to distinguish among active, passive, and unexposed nonsmokers. The Florescu A. and colab. study identifies cutoffs to validate cotinine as a marker for exposure to ETS [17]. Data were obtained from six databases (four in the U.S., one in Canada, and one in France). Active smoking and exposure to ETS were measured in the hair of women of reproductive age, pregnant women, their children, and neonates. Subjects were classified into active smokers, passively exposed to ETS, and unexposed nonsmokers. These new values should facilitate clinical diagnosis of active and passive exposure to tobacco smoke. Such diagnosis is critical in pregnancy and in a large number of tobacco-induced medical conditions.

Cotinine level was analyzed by Polańska K. et al. by means of gas chromatography with mass spectroscopy (GC-MS) [18]. They chose more than 15 ng/mL as serum cotinine level for smokers, 2-15 ng/mL for ETS exposure and less than 2 ng/mL for non-smokers not exposed to ETS. Among non-smoking and not ETS-exposed women, 17% had cotinine level indicating active smoking and 74% ETS exposure. About 4% of the women who indicated ETS exposure during pregnancy had serum cotinine level higher than 15 ng/mL indicating active smoking. The information about active and passive smoking during pregnancy obtained from mothers and based on the questionnaire does not indicate objective maternal exposure to tobacco smoke.

Since the publication of the U.S. Surgeon General Reports in 1996 and 2006 and the report of the California Environmental Protection Agency in 1999, many reports have appeared on the contribution of air and biomarkers to different facets of the secondhand smoke (SHS) issue, which are the targets of this review. The recent studies have allowed earlier epidemiological surveys to be biologically validated, and have their plausibility demonstrated, quantifyingthe levels of exposure to SHS before the bans in various environments showed the deficiencies of mechanical control methods and of partial bans and leading to the frequently correct implementation of the efficient total bans. More stringent regulation remains necessary in the public domain (workplaces, hospitality venues, transport sector, etc.) in many countries. Personal voluntary protection efforts against SHS are also needed in the private domain (homes, private cars). The effects of SHS on the cardiovascular, respiratory and neuropsychic systems, on pregnancy and fertility, on cancers and on SHS genotoxicity are confirmed through experimental human studies and through the relationship between markers and prevalence of disease or of markers of disease risk [19].

Cotinine can be measured in plasma, urine, or saliva, demonstrated by Etzel R.A. (1990). However, distinguishing between active and passive smoking on the basis of a cotinine measurement may be difficult. Passive smokers usually have cotinine concentrations in saliva below 5 ng/mL, but heavy passive exposure can result in levels greater than or equal to 10 ng/mL. Levels between 10 and 100 ng/mL may result from infrequent active smoking or regular active smoking with low nicotine intake. Levels greater than 100 ng/mL are probably the result of regular active smoking. Four categorizations of tobacco smoke exposure are suggested on the basis of saliva cotinine concentrations.

Experience of nausea and vomiting during pregnancy was self-reported for each trimester. Adjustments were made by Boylan S.M. (2012) for confounders, including salivary cotinine as a biomarker of current smoking status. There were no significant associations between fetal growth restriction and nausea and vomiting in pregnancy, even after adjustment for smoking and alcohol intake.

The following study used the Korea National Health and Nutrition Examination Survey IV-2, 3 (2008-2009). A urinary cotinine test was administered to 5485 women of at least 19 years of age. Individuals whose cotinine level was 50 ng/mL were categorized as smokers. A multiple logistic regression analysis was performed to estimate the extent to which body-related variables affect female smoking [20].

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Proprietățile antihipertensive ale benzituronului

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Antihypertensive properties of Benzituron

Benzituron or S-benzylisothiourea chloride is exposed to a new range of hypotensive substances, isothiourea derivatives, it is able to reduce and stabilize the level of the arterial pressure. The benzituron solution, in a dosage of 2 mg/kg, shows a noticeable decrease in hypotension and antihypertension that lasts 4-5 hours. Benzituron can manifest hypotensive action in arterial hypertension. This hypotension is caused by phenylefrine, with increased efficacy when taken with benzituron hypotension, which shows that alpha-adrenoreceptors are not occupied and can react with alpha-adrenomimetic drug. Ephedrine induced hypertension also is decreased by benyituron, even below the initial level. Also, repeated administration of ephedrine doesn't influence vasodilating action of benzituron. Our research showed that one-time administration of angiotensine-II increased BP (blood pressure), while a subsequent injection of benzituron decreased it. Angiotensine-II, when administered 60 min after benzituron, reestablished the level of blood pressure.

Key words: isothiourea derivative, benzituron, blood pressure, antihypertensive effect.

Антигипертензивные свойства бензитурона

Бензитурон или S-бензилизотиуроний хлорид, относится к новому классу гипотензивных средств, производных изотиомочевины, способных снизитъ и стабилизировать уровень артериального давления (АД). Раствор бензитурона в дозе 2 мг/кг вызывает выраженное и медленное гипотензивное и антигипертензивное действия, на длительное время (4-5 часов). Бензитурон может снизить АД, при гипертонии вызванное фенилэфрином, а эффективность фенилэфрина при гипотонии вызванное бензитуроном показывает, что альфа - адренорецепторы свободны и реагируют на администрацию альфа-адреномиметика. Гипертония вызванная эфедрином также понижается бензитуроном, ниже исходных данных, а повторное введение эфедрина не влияет на сосудорасширяющее действие бензитурона. Однократное введение ангиотензина-II вызывает значительное увеличение АД, а последующее инъекция бензитурона сопровождается снижением АД. Уровень АД восстанавливается после повторного введения ангиотензина-II на 60-й минуте действия бензитурона.

Ключевые слова: производные изотиомочевины, бензитурон, артериальное давление, антигипотензивное действие.

Introducere

Maladiile care apar din cauza modificărilor cardiovasculare, constituie o preocupare de bază ale medicinii naţionale şi un obiectiv important al cercetărilor ştiinţifice. Hipertensiunea arterială este unul din factorii de risc în dezvoltarea patologiilor cardiovasculare, care ocupă unul din primele locuri în structura morbidităţii, invalidităţii şi mortalităţii. Conform datelor Ministerului Sănătăţii din Republica Moldova, în anul 2011, în Republica Moldova au fost înregistrate 891 de decese din cauza hipertensiunii arteriale la 100 mii de locuitori, comparativ cu 867 de decese la 100 mii locuitori în anul 2010. Diverse medicamente, aparţinând unor grupe farmacologice variate, sunt capabile să micşoreze presiunea arterială şi sunt destul de active dar, deseori, provoacă reacţii adverse, ceea ce şi limitează utilizarea largă a lor. În acest context, valorificarea unor surse noi de medicamente accesibile, eficace şi inofensive pentru organismul uman constituie o problemă destul de actuală.

Noii derivaţi izotioureici – izoturon, şi alchilizotioureici – difetur (raviten) sunt cunoscuţi ca vasoconstrictori efectivi în hipotensiunea arterială [1, 2], iar substanţa clorură-S-benzilizotiuroniu (benzituron), a demonstrat în urma screeningului (fig.1) a 18 substanţe un efect vasodilatator cu reducerea esenţială a presiunii arteriale pentru timp îndelungat (4-5 ore).

Acest fapt a şi motivat studiul benzituronului, care ar avea avantajul de a optimiza şi extinde posibilităţile de reglare