Dexamethasone - Chemical Structure and Mechanisms of Action in Prophylaxis of Postoperative Side Effects

OANA ROXANA CIOBOTARU[1,7], MARY-NICOLETA LUPU[2,8]*, LAURA REBEGEA[1,9], OCTAVIAN CATALIN CIOBOTARU[2,7], OANA MONICA DUCA[3], ALIN LAURENTIU TATU[4], CARINA DOINA VOINESCU[1,7], GABRIELA STOLERIU[5]*, KAMEL EARAR[6], MAGDALENA MIULESCU[4,8]

[1]Dunarea de Jos University of Galati, Faculty of Medicine and Pharmacy, Clinical Departament, 35 Al. I. Cuza Str.., 800010, Galati, Romania

[2]Dunarea de Jos University of Galati, Faculty of Medicine and Pharmacy, Departament of Surgery, 35 Al. I. Cuza Str., 800010, Galati, Romania

[3]General Hospital Railways, 5-7 Alexandru Moruzzi Str., 800223, Galati, Romania

[4]Dunarea de Jos University of Galati, Faculty of Medicine and Pharmacy, Research Center in the Field of Medical and Pharmaceutical Sciences, Pharmacology Sciences Department, 35 Al. I. Cuza Str., 800010, Galati, Romania

[5]Dunarea de Jos University of Galati, Faculty of Medicine and Pharmacy, Department of Pharmaceutical Sciences, 35 Al. I. Cuza Str., 800010, Galati, Romania

[6]Dunarea de Jos University of Galati, Faculty of Medicine and Pharmacy, Department of Dental Medicine, 35 Al. I. Cuza Str., 800010, Galati, Romania

[7]Research Center in the Health Status of the Population in Correlation with Risk Factors, Faculty of Medicine and Pharmacy, 35 Al. I. Cuza Str., 800010, Galati, Romania

[8]Research Center in the Functional Cardiorespiratory and Neuromotor Exploration, Faculty of Medicine and Pharmacy, 35 Al. I. Cuza Str., 800010, Galati, Romania

[9]Research Center in the minimally invasive surgery, Faculty of Medicine and Pharmacy, 35 Al. I. Cuza Str., 800010, Galati, Romania

Dexamethasone is a synthetic glucocorticoid used for its anti-inflammatory and analgesic effect. In addition to these therapeutic indications, it is also recommended for nausea and vomiting treatment which may occur during the postoperative period, with impact on postoperative evolution, regarding the evolution of wound healing and length of stay (LOS), with a reflection on the costs of hospital admission. Therefore, their prevention is very important for both patients' comfort and a good recovery.

Keywords: synthetic glucocorticoid, disodium salt, nuclear steroid receptors anti-inflammatory, postoperative side effects, prevention

The increased prevalence in nausea and vomiting (PONV) represent a stress factor for the patient who had undergone surgery, and also a negative factor for postoperative recovery process.

In recent years there have been published many studies and articles which attempted to draw out some multimodal strategies in order to prevent PONV, mainly based on risk factors identification, and also an optimal multimodal treatment with antiemetics.[1]

Recently, in 2014 the Society for Ambulatory Anesthesiology published an article which lists the main trigger factors of PONV, including the female gender, non-smokers, patients with antecedents of PONV and the postoperative administration of opioids, and also recommendations regarding their pharmacological management [2].

Antiemetics represent the main method to combat and prevent PONV such as: corticosteroids (Dexamethasone), butyrophenones, serotonergic antagonists, phenothiazines and gastrointestinal prokinetics (Metoclopramide).

Dexamethasone is an adrenocortical steroid which has an anti-inflammatory effect with prophylactic properties, which was highly proven in several publications with a great impact regarding medical statistics. The recommended dose for a prophylactic treatment is an IV dose of 4-5 mg in the immediate postinductionperiod [2].

The chemical formula (fig. 1) of dexamethasone is 9-fluoro-11 β, 17-dihydroxy-16α-methyl-21- (phosphonooxy) pregna-1, 4-diene-3, 20-dione disodium salt [3].

It is a synthetic glucocorticoid which exerts its agonist action by linking itself to specific nuclear steroid receptors.

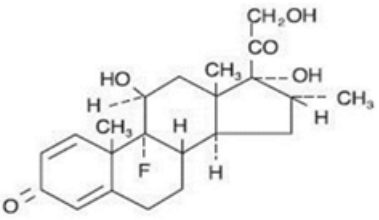

Fig. 1. Chemical formula of dexamethasone [3]

Dexamethasone is a synthetic glucocorticoid, formerly used for its anti-inflammatory and antialgic effect [4].

In 1958, Taub synthetized the *first β-substituted cortical steroid derivatives* and obtained 16β - methylprednisolone acetate, considered to be, at that time, the most potent steroidal anti-inflammatory agents [5,6].

So 16β - methylprednisolone acetate is dehydrated to the 9,11 dehydro – derivative which will be converted in 9α bromo - 11β hydrin derivative, which will determine the epoxide ring closure.

The formation of dexamethasone is made secondary to a *ring-opening reaction with hydrogen fluoride in THF (tetrahydrofuran)* [7] (fig. 2).

Currently, dexamethasone is administered per os, intravenous, intramuscular, ophthalmic substances or dermatological preparations, in shock treatment or anaphylactoid reactions, exacerbations in multiple sclerosis

* email: lupumarynicoleta@yahoo.com; stoleriugabriela@yahoo.com All authors had an equal contribution to this work.

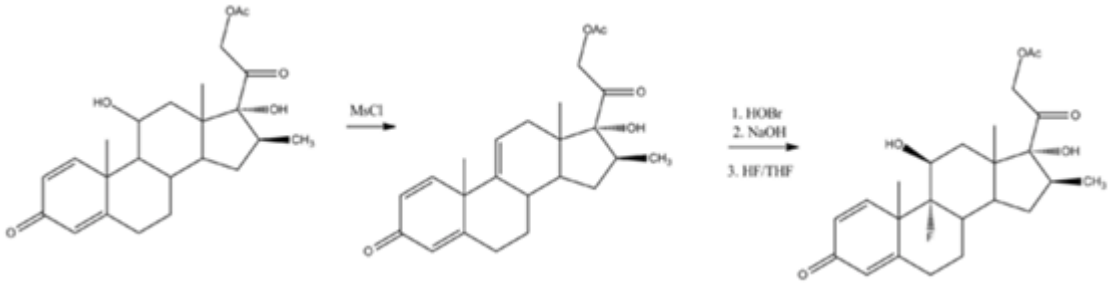

Fig. 2. Synthesis reaction of dexamethasone from 16β - methylprednisolone acetate, to the 9,11 dehydro -derivative, and in the end to dexamethasone [5]

(MSR) or cerebral edema, especially in paraneoplastic type, and also in postoperative nausea and vomiting prevention.

It can also be administered during pregnancy, aiming to increase fetal surfactant production in patients with preterm delivery risk [8].

It has proven effective also in the administration by nebulization in both bronchospasm remission, and prophylactic in pain prevention (sore throat) secondary to extubation - removal of the orotracheal tube (OTT) at the end of the surgical procedure. [9]

The doses used vary depending on the purpose of the administration.

Dexamethasone is metabolized by the cytochrome P450 (CYP) 3A4 within the liver [10,11].

Its elimination occurs via renal excretion. It has a biological half-life of 3 h.

Experimental part

Material and method

We conducted a clinical trial on 1121 patients who underwent traditional or laparoscopic cholecystectomy and all the patients received general anesthesia with orotracheal intubation.

Patients with the following associated pathologies were excluded:

-neoplasia

-segmental intestinal resection

-migraine syndrome

There were two study groups: one consisted of 59.8% of patients medicated with dexamethasoneand a witness group containing patients who did not receive the corticosteroid.The witness group took part in a retrospective cohort study and the study group consisted of patients in whom cholecystectomy was indicated, and who did not match the excluding criteria during 5 months.

Study design

The study fulfils the medical, ethical and deontological criteria, according to the Romanian legislation, and approved by the Faculty of Medicine and Pharmacy Ethic Comissionof Dunarea de Jos University of Galati [12].

Aneshtesia

The induction of anesthesia was made with Fentanyl (1-3µg/kg), Propofol (1-2.5mg/kg) and Atracurium (0.5 mg/kg) and it was maintained with boluses of Fentanyl (2µg/kg) andAtracurium (0.1 mg/kg).

Atropine (0.014mg/kg) and Neostigmine (0.04mg/kg) were used for the reversal of the motor block and awakening.The doses were used according to the indications presented in Morgan and Mikhail's Clinical Anesthesiology [13].

Right before the induction, the study group was medicated with Dexamethasone, a 2 mL ampoule, 4mg/mL (Rompharm, Romania).

Statistical analysis

The statistical analysis was made using the software named IBM SPSS Statistics, version 21 (SPSS Inc. Chicago, IL)

Regarding the analysis for the numeric scalar values, we used the correlation coefficient, also referred to as Pearson's coefficient (r) which shows us that, whether or not there is a relationship between two values, and also a correlation coefficient. If the calculated probability (p-value) is less than the significance level (α=0.05), both values are accepted, as they are correlated. If $p > \alpha = 0.05$,we decide that the two variables are not correlated. The Pearson (r) coefficientcan take a range of valuesbetween +1 and-1. When the coefficient reaches +1 or -1, the correlation coefficient takes a higher value, whether it is in the same direction (+) or in the opposite one (-).The more the coefficient reaches 0, the less the correlation between the two series of variations. If r=0, there is no correlation.

Regarding the analysis of the nominal variables, we calculated the values for the correlation coefficients at a nominal levelö, C and V, and also the probabilities associated with these values. If $p < 0.05$, we can state that there is a correlation betweenthe variables.

We calculated the values for the correlation coefficients τ_b, Kendall's coefficient, γ(Gamma) and Somer's coefficient of correlation (d), for the ordinal variables, and also the probabilities associated to these values. If the associated probabilities of these coefficients arep < 0.05, we must admit that there is a correlation between the variables in the analysis.

The Mann-Whitney Utest is used in order to test the difference between independent groups for which the dependent variable is expressed in ordinal values, or when a parametric statistical test can not be made.

The χ^2 test analyses the association between two variables.

Results and discussions

Among the administrations of dexamethasone, the most interesting one is its usage in postoperative nausea and vomiting prevention, being known that these manifestations are more disturbing for patients undergoing surgical procedures, than postoperative pain itself. Postoperative nausea and vomiting are complications which may occur in 20-40% of patients undergoing surgical procedures [2,14,15]. This type of complications affect postoperative evolution by the risk of dehydration which may occur, bleeding or belated wound healing, all of these determining prolonged hospitalization.

Out of the total number of 1121 patients, 82.2 % were women and 17.8% were men, between 24 and 85 years old. We divided the patients into subgroups, depending on the gender, BMI's value, age, surgical technique, using dexamethasone for prophylaxis of PONVand the PONV's incidence (table 1).

		Frequency	Percent
Gender	Feminine	921	82.2%
	Masculine	200	17.8%
BMI	Normal Weight	198	17.7%
	Obese	303	27.0%
	Severely Obese	146	13.0%
	Morbidly Obese	55	4.9%
	Overweight	419	37.4%
Age	<50	423	37.7%
	>=50	698	62.3%
Cholecystectomy	Classic	159	14.2%
	Laparoscopic	951	84.8%
Dexamethasone	Yes	670	59.8%
	No	451	40.2%
PONV	Yes	188	16.8%
	No	933	83.2%

Table 1
DESCRIPTIVE STATISTICS

**PONV= Postoperatory Nausea and Vomiting; BMI= Body Index Mass;*

The group of patients was analysed taking into account the PONV's incidence, depending on the patients' age and it was noticed that out of the total number of cases which reported PONV, 58,82% were less than 50 years old and for those under or over 50 years old, 41.18%, but this was not statistically relevant ($p = 0.064 > \alpha = 0.05$).

The sex of the patient is one of the risk factors in PONV, proposed by Aphel in creating a risk scale of PONV [16].

Moreover, it was thought that the main reason why the female gender is frequently associated with postoperative nausea and vomiting is the hormonal variation, mostly the estrogen, to which many women are exposed during the immediate postoperative period [17].

Regarding the sex and the incidence of the PONV, among the studied group, it was noticed that all the patients who reported PONV were females.

Statistically, the values of the correlation coefficients for a nominalj level, C and V, and also the probabilities associated to these values were following: $\varphi = -0.209$, C = 0.205 and V = 0.209, $p = 0.035 < \alpha = 0.05$.

By analysing these values, we can conclude that there is a correlation between the postoperative nausea and the patient's sex but the correlation is a weak one.

Many articles share different views regarding the influence of the BMI in PONV, also several research papers suggest that a lower BMI value was associated with a higher incidence in PONV but there are also many clinical trials which disprove this correlation [18].

Regarding the patients distributed depending on the BMI and PONV, there was no significant statistical correlation for our research. By applying the Mann-Whitney and Wilcoxon tests we obtained: $p = 0.586 > \alpha = 0.05$ (the significance level) which means that there is no connection between between the presence of postoperative nausea and BMI.

Due to complex pathogenesis, which represents the main cause of the PONV syndrome, the prophilaxis must be quickly initiated, before the occurrence of PONV.

Considering the presented thesis, in 54.90 % of cases the prophylaxis for PONV was made by intraoperative administration, postinduction of 4-8 mg IV of Dexamethasone. By analyzing this subgroup, we noticed a decrease in the PONV incidence, in comparison with the subgroup where no antiemetic prophylaxis was initiated. Out of the total number of patients who were medicated with Dexamethasone, only 10% reported PONV, by statistically analyzing this statementwe noticed that the value obtained at the χ^2 test was 4.928 and the probability associated to this value is: $p = 0.026 < \alpha = 0.05$, and this result proves that there is a relationship (correlation) between the administration of Dexamethasone and the presence of postoperative nausea.

At a nominal level, the values of the φ correlation coefficients, C and V, and also the probabilities associated to these obtained values are:$\varphi = 0.221$, C = 0.216 si V = 0.221 and the associated probabilities are: $p = < 0.026 < \alpha = 0.05$.

By analyzing these values we can admit that there is a correlation between the administration of dexamethasone and the presence of postoperative nausea and vomiting .

The mechanism of PONV

The mechanism of postanesthetic nausea and vomiting is not completely understood.

The area of the brain involved in this mechanism is located in the solitary nucleus (nucleus tractus solitarius - NTS), receiving information from chemoreceptors via neurons which belong to area postrema. Neurotransmission from NTS *travels* to the hypothalamus, the ventral medulla, and also to a central pattern generator

(CPG), which represents the area where emesis behavior is coordinated [4].

Trigger areas of the chemoreceptors contain many dopaminergic, serotonin 5-hydroxytryptamine type 3 (5-HT3), opioids and neurokinin 1 receptors [19-21].

A great number of neurokinin-1, 5-HT3, acetylcholine, histamine, enkephalin, and glucocorticoids receptors are also found in the NTS, where afferent pathways of the vagus nerve, from the abdominal viscera, are being projected. [22, 23]

The most emetogenic substances used during general anesthesia are volatile anesthetics, nitrous oxide and opioids.

Halogenated inhalational anesthetics have an emetic effect which is directly proportional to the duration of their usage. The stimulation of chemoreceptors depends on the plasmatic concentration of the anesthetics, resulting in stimulation of the NTS and enzyme production [24].

There have been incriminated various mechanisms by which opioids determine the occurrence of PONV:

-paralytic ileus (delayed gastric emptying)

-higher vestibular sensitivity

-direct effect on the trigger area of the chemoreceptors [25].

The action mechanism of dexamethasone in PONV prevention

The action mechanism of dexamethasone aiming to prevent PONV is not completely known.

The antiemetic effect may be the consequence of:

-the anti-inflammatory effect of membrane stabilization [25];

-the inhibition of pro-inflammatory mediators: C-reactive protein, tumor necrosis factor (TNF), interleukins [26];

-the inhibition in production of inflammatory autacoids; autacoids are represented by eicosanoids (derived from membrane lipids, such as PG-type (prostaglandins), prostacyclin, leukotrienes, thromboxane) histamines, somatomedins [27], serotonin-neurotransmitter involved in the occurrence of emesis [28]. Dexamethasone determines tryptophan depletion, which is a precursor for serotonin synthesis. [29] This way, stimulation of serotoninergic receptors decreases;

-inhibition in the release of endomorphins.

Dexamethasone dose usages, according to the studies, in PONV prevention

Literature data report that two preoperative IV doses of dexamethasone were studied in PONV prevention: a low dose (4 - 5 mg) and a high dose (8 - 10 mg).

Several studied have been conducted, taking into consideration multiple factors: The Apfel Score (patient risk factors in the occurrence of PONV), type and duration of the surgical procedure, type of the anesthetics, dexamethasone dosage, dexamethasone efficiency, in single administration or in combination with other antiemetics.

Patient risk factors for PONV (The Apfel Score) [30]:

-female gender

-nonsmoking status

-age < 50 years

-antecedent motion sickness

-postoperative analgesia with opioids.

Therefore, in 2004, Apffel et al. organized six batches of study to which he administered preoperative IV dexamethasone 4 mg, odansetrone 4 mg, droperidol l.25 mg, each of those reported to a batch to which he used the placebo effect. He noticed that all 3 active drugs, in analyzed doses, had similar efficiency in PONV [31].

Buck et al. have proven the efficiency of dexamethasone administration in preoperative IV dose of 8 mg and 10 mg, in plastic surgery, a study published in 2006 [32,33].

Sistla et al. analyze the effect of dexamethasone in preoperative IV dose of 8 mg in patients who underwent laparoscopic cholecystectomy, where they notice reduction in the necessity of postoperative administration of antiemetics (0.56 mg vs. 2.24 mg; P=0.02) [34].

Karanicolas et al., using literature data reported between 1966 and 2007, and 4 bibliographic databases (Web of Science, Embase, Medline, The Cochrane Central Register of Controlled Trials) noticed that the efficiency of the antiemetic effect of dexamethasone gets better by using higher doses (16 mg), compared with its lower doses (2-5 mg) [35].

In 2013, a study conducted by De Oliveira et al, contradicts Karanicolas's study and shows that there were no different results regarding PONV in doses of 4 - 5 mg, compared with the usage of 8 -16 mg [36].

Nevertheless, recent studies evaluated the efficiency of dexamethasone administered in a dose of 8 mg, noticing clear efficiency in PONV prevention, compared with the placebo effect [37,38].

Adverse effects of dexamethasone administration

Due to its anti-inflammatory and immunosuppressant effect, dexamethasone is used in dermatology, oncology, surgery, rheumatology, endocrinology, pneumology, ophthalmology etc. [39-44]. Being a broad-spectrum drug, adverse effects have been known for a long time. They depend on the root of administration, especially on its duration [42, 45, 46].

In PONV prevention, it was pursued the potential occurrence of dizziness and headache.

Studies have shown that dexamethasone administered in PONV prevention did not determine adverse effects, whether higher doses, of 8-10 mg or those of 4-5 mg, were administered [35, 36].

Contraindications of dexamethasone administration

The two most important contraindications of dexamethasone administration are [37]:

-Hypersensitivity to dexamethasone

-Fungal infections

Conclusions

Studies have shown the efficiency of IV dexamethasone in PONV, and the most commonly used dose is 4 mg. However, there were no reports on dexamethasone-related adverse effects, whether higher doses, of 8 - 10 mg or those of 4 - 5 mg, were administered. Even for these doses, and also for single administration, the contraindications for dexamethasone administration shall be maintained.

The analysis of our studies group has proven the fact that the indicence of PONV was frequent in female patients, young patients who were less than 50 years old and also in cases of laparoscopic cholecystectomy.GanMoreover, we noticed a decrease in the PONV frequence for the subgroup in which patients were medicated with Dexamethasone as a prophylactic method for PONV.

Positive statistical correlations were made between the presence of PONV and the female gender, and also between prophylactic administration of Dexamethasone, according to the existing protocols and the incidence of PONV.

References

1.SAEEDA, I., JAIN, P.N., Indian J. Anaesth, **48**, no. 4, 2004, p. 253.
2.GAN, T.J., DIEMUNSCH, P., HABIB, A.S., KOVAC, A., KRANKE, P., MEYER, T.A., Anesth Analg, **118**, no. 1, 2014, p. 85.
3.VENKATA SAIRAM, K., THEJASWINI, J.C., PRUDHVI RAJU, M.V., CHANDAN, R.S., GURUPADAYYA, B.M., MRUTHUNJAYA, K., World Journal of Pharmaceutical Research, **4**, no. 2, 2015, p. 1148.
4.HORNBY, P.J., Am. J. Med., **111,** Suppl.8A, 2001, p. 106S.
5.TAUB, D., HOFFSOMMER, R.D., SLATES, H.L., LWENDLER, N.L., Journal of the American Chemical Society, **80**, no. 16, 1958, p. 4435.
6.TOADER, E., BAHRIN, L.G., JONES, P.G., HOPF, H., SARBU, L.G., STOLERIU, G., REV. CHIM. (Bucharest), **67**, no. 8, 2016, p. 1520.
7.LEDNICER, D. Strategies for organic drug synthesis and design. Steroids; Part 2: Compounds related to progesterone, cortisone and cholesterol, Second Edition Ed A John Wiley& Sons, Inc., 2009, p.179.
8.ELSNOSY, E., SHAABAN, O.M., ABBAS, A.M., GABER, H.H., DARWISH, A., Middle East Fertility Society Journal, **22**, 2017, p. 13.
9.SALAMA, A.K., EL-BADAWY, A.M., Ain-Shams Journal of Anesthesiology, **9**, 2016, p. 104.
10.TEO, Y.L., SAETAEW, M., CHANTHAWONG, S., YAP, Y.S., CHAN, E.C., HO, H.K., CHAN, A., Breast Cancer Res Treat, **133**, no. 2, 2012, p. 703.
11.FILIP-CIUBOTARU, F., MANCIUC, C., STOLERIU, G., FOIA, L., Rev Med Chir Soc Med Nat Iasi, **120**, no. 1, 2016, p. 29.
12.ROGOZEA, L., PURCARU, D., LEASU, F., NEMET, C., Rom J MorpholEmbryol, **55**, no, 2S, 2014, p. 719.
13.BUTTERWORTH, J.F., MACKEY, D.C., WASNICK, J.D., Morgan & Mikhail's Clinical Anesthesiology, Ed McGraw Hill, 2013.
14.HORN, C.C., WALLISCH, W.J., HOMANICS, G.E., WILLIAMS, J.P., Eur J Pharmacol. **722**, no. 1, 2014, p. 55.
15.PHILLIPS, C., BROOKES, C.D., RICH, J., ARBON, J., TURVEY, T.A., Int J Oral Maxillofac Surg, **44**, no. 6, 2015, p. 745.
16.APFEL, C.C., LAARA, E., KOIVURANTA, M., GREIM, C.A., ROEWER, N., Anesthesiology, **91**, no. 3, 1999, p. 693.
17.VAHABI, S., ABASZADEH, A., YARI, F., YOUSEFI, N., Korean J Anesthesiol, **68**, no. 6, 2015, p. 581.
18.CHOI, D.H., SANG K.O., J., AHN, H.J., KIM, J.A., J Korean Med Sci., **20**, no. 5, 2005, p. 811.
19.BRANISTEANU, D.E., IANOSI, S.L., DIMITRIU, A., STOLERIU, G., OANÃ, A., BRANISTEANU, D.C., Experimental and Therapeutic Medicine, **15**, 2018, p. 785.
20.KIZILCIK, N., BILGEN, S., MENDA, F., TURE H., AYDIN B., KASPAR, E.C., KONER, O., Aesth Plast Surg, **41**, 2017, p. 204.
21.NISSAR, A.D., ANDREW, P.R., Chem. Rev., **109**, no. 7, 2009, p. 3158.
22.LESLIE, R.A., SHAH, Y., THEJOMAYEN, M., MURPHY, K.M., ROBERTSON, H.A., Canadian Journal of Physiology and Pharmacology, **68**, no. 2, 1990, p. 279.
23.BALAN, G., PELIN, A.M., MACOVEI, L.A., CONDRATOVICI, A.P., CONDRATOVICI, C.P., BUSILA, C., Rev. Chim. (Bucharest), **68**, no. 3, 2017, p. 603.
24.APFEL, C.C., KRANKE, P., KATZ, M.H., GOEPFERT, C., PAPENFUSS, T., RAUCH, S., HEINECK, R., GREIM, C.A., ROEWER, N., British Journal of Anaesthesia, **88**, no. 5, 2002, p. 659.
25.COLUZZI, F., ROCCO, A., MANDATORI, I., MATTIA, C., Current Pharmaceutical Design, **18**, 2012, p. 6043.
26.TOLVER, M.A., STRANDFELT, P., BRYLD, E.B., ROSENBERG, J., BISGAARD, T., British Journal of Surgery, **99**, 2012, p. 1374.
27.TULBURE, D., DROC, G., Anestezie Terapie Intensiva, Ed Universitara Carol Davila, Bucuresti, 2009, p. 134.
28.CHUA, C.C, HSING, C.H., SHIEH, J.P., CHIEN, C.C., HO, C.M., WANG J.J., European Journal of Pharmacology, **722**, 2014, p. 48.
29.RICHARD, D.M., DAWES, M.A., MATHIAS, C.W., ACHESON, A., KAPTURCZAK, N.H., DOUGHERTY, D.M., Int J Tryptophan Res, **2**, 2009, p. 45.
30.WEILBACH, C., RAHE-MEYER, N., RAYMONDOS, K., WEISSIG, A., SCHEINICHEN, D., PIEPENBROCK, S., Acta Anaesth. Belg, **57**, 2006, p. 361.
31.APFEL, C.C., KORTTILA, K., ABDALLA, M., KERGER, H., TURAN, A., VEDDER, I., ZERNAK, C., DANNER, K., JOKELA, R., POCOCK, S.J., TRENKLER, S., KREDEL, M., BIEDLER, A., SESSLER, D.I., ROEWER, N., N Engl J Med, **350**, no. 24, 2004, p. 2441.
32.BUCK, D.W., MUSTOE, T.A., KIM, J.Y.S., Semin Plast Surg, **20**, no. 4, 2006, p. 249.
33.TATU, A.L., CIOBOTARU, O.R., MIULESCU, M., DUMITRIU BUZIA, O., ELISEI, A.M., MARDARE, N., DIACONU, C., ROBU, S., NWABUDIKE, L.C., Rev. Chim.(Bucharest), **69**, no.8, 2018, p. 2110.
34.SISTLA, S., RAJESH, R., SADASIVAN, J., KUNDRA, P., SISTLA, S., Surg Laparosc Endosc Percutan Tech, **19**, no. 6, 2009, p. 506.
35.KARANICOLAS, P.J., SMITH, S.E., KANBUR, B., DAVIES, E., GUYATT, G.H., Ann Surg, **248**, 2008, p. 751.
36.DE OLIVEIRA, G.S.JR, CASTRO-ALVES, L.J., AHMAD, S., KENDALL, M.C., MCCARTHY, R.J., Anesth Analg, **116**, no. 1, 2013, p. 58.
37.DREAMS Trial Collaborators, BMJ **357**, 2017, j1455.
38.PARTHASARATHY, P., BABU, K., RAGHAVENDRA RAO, R.S., RAGHURAM, S., Anesth Essays Res, **12**, 2018, p. 313.
39.BUMBACEA, R.S., POPA, L.G., ORZAN, O.A., VOICULESCU, V.M., GIURCANEANU, C., Acta Endocrinologica, **X**, no. 4, 2014, p. 595.
40.REBEGEA, L., NECHITA, A., SERBAN, C., DIACONU, C., MACOVEI, L.A., DRAGANESCU, M., FIRESCU, D.,Rev. Chim.(Bucharest), **69**, no. 10, 2018, p. 2833.
41.REBEGEA, L., STEFAN, AM., FIRESCU, D., MIRON, D., ROMILA, A., Acta Medica Mediterranea, **34**, 2018, p. 1265.
42.***Dexamethasone.https://www.drugs.com/pro/dexa-methasone.html.
43.BLOOM, S.L., SHEFFIELD, J.S., MCINTIRE, D.D., LEVENO, K.J., Obstet Gynecol, **97**, no. 4, 2001, p. 485.
44.GRIGOROVICI, A., CHERCIU, M.S., POPESCU, C.M., CIOBANU APOSTOL, D.G., PREDA, C., CÃLIN, A., AELENE, P., Farmacia, **65**, no. 1, 2017, p. 29.
45.TATU, A.L., CLATICI, V., J Am Acad Dermatol, **72**, no. 5, spp. 1, 2015, AB91.
46.TATU, A.L., Acta Endo (Buc), **12**, 2016, p. 232.

Manuscript received: 4.07.2018