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ASSOCIATION OF MEDICAL DOCTORS OF THE REPUBLIC OF SRPSKA,
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Stojiljković. Scr Med 2019;50(4):145-7. DOI:10.5937/scriptamed50-24469

EDITORIAL

On the Occasion of the Fiftieth Volume of the *Scripta Medica* (Banja Luka)

Miloš P Stojiljković[1,2]

ABSTRACT

The article is written by the current Editor-in-Chief of the scientific journal *Scripta Medica* (Banja Luka) on the occasion of publishing the final issue of the fiftieth volume of the journal. Founded in 1966, the *Scripta Medica* (Banja Luka) started as a local journal of the Banja Luka Medical Centre, its General Hospital, later belonging to the Association of Medical Doctors of the Bosnian Krajina region and the Republic of Srpska and the Faculty of Medicine, University of Banja Luka. Its eight editors were: Professor Andrija Mikeš (1966-1968), Dr Dragomir Todorović (1969-1971), Assistant Professor Zvonimir Klepac (1972-1974), Professor Branko Pikula (1975-1990), Professor Bogdan Žigić (1995-2009), Professor Rajko Igić (2010-2013), Professor Predrag Grubor (2014-2018) and Professor Miloš P Stojiljković (since 6 August 2018). It used to appear twice a year or quarterly. The *Scripta Medica* (Banja Luka) has a peer-review process and tends to reach a status of well-established scientific journal.

Key words: medical journal, editors, scientific journal, medicine, dental medicine, pharmacy.

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It is a special occasion for every journal when it reaches the 50th volume. The same applies to the *Scripta Medica* (Banja Luka) that with the issue 4 completes the fiftieth volume. The geographical descriptor "Banja Luka" is added since the journal, started in 1966, had its namesake from Brno, the Czech Republic, published by the Faculty of Medicine, Masaryk University, which was started in 1922 and, regrettably, ended in 2010.

In the tumultuous history of Banja Luka and the whole region, the journal *Scripta Medica* (Banja Luka) had its ups and downs that resulted in certain periods of discontinuity in publication. As a result, in these 54 years since its first appearance in May 1966, there were 50 volumes. The main break was during the latest wars in the Balkans that resulted in the decomposition of Yugoslavia and ensued in the aftermath of this process (1991-1994). As a result of this, the journal had two important dates; one in 2016, when the Editor-in-Chief Professor Predrag Grubor celebrated the 50th anniversary of the foundation of the journal[1] and the current one, when we commemorate the publishing of its 50th volume.

The *Scripta Medica* (Banja Luka) was started in 1966 as the regional professional journal of the medical doctors of the Bosnian Krajina region. This event coincided with the celebration of the 80th anniversary of the General Hospital in Banja Luka[2], whose brief history was outlined by the founding editor Professor Andrija Mikeš.[3] All the editors – eight so far – gave their contribution to the advancement of the journal. Their list and the duration of their stay in office of the Editor-in-Chief, *Scripta Medica* (Banja Luka) is contained in Table 1.

In reality, Professor Bogdan Žigić had effectively served as an editor for "only" 15 years, since the journal temporarily ceased to be published during the four war years (1991-1994). Their photographs are contained in Figure 1.

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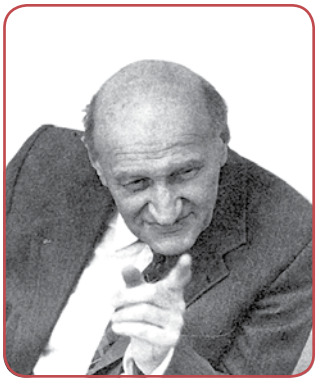
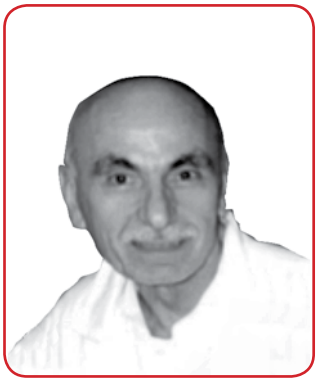


Professor Andrija Mikeš
Editor 1966-1968

Dr Dragomir Todorović
Editor 1969-1971

Assist. Prof. Zvonimir Klepac
Editor 1972-1974

Professor Branko Pikula
Editor 1975-1990



Professor Bogdan Žigić
Editor 1991-2009

Professor Rajko Igić
Editor 2010-2013

Professor Predrag Grubor
Editor 2014-2018

Professor Miloš P Stojiljković
Editor 2018-

Figure 1: Photographs of all editors-in-chief of the *Scripta Medica* (Banja Luka).

A total of 1,223 articles in 85 issues have been published so far (Table 2).

A typical issue of the *Scripta Medica* (Banja Luka) contained 12 articles (range 1-64).

Distribution of various types of articles is contained in Table 3.

The dominant types of articles were original (29%), professional (19%), reviews of important articles published elsewhere (14%) and case reports (12%), with the other categories occurring less frequently.

Table 1: Editors-in-Chief of the *Scripta Medica* (Banja Luka)

Num.	Title, first name and surname	Period in office	Number of years in office
1	Professor Andrija Mikeš	1966-1968	3
2	Dr Dragomir Todorović	1969-1971	3
3	Assist. Prof. Zvonimir Klepac	1972-1974	3
4	Professor Branko Pikula	1975-1990	16
5	Professor Bogdan Žigić	1991-2009	19
6	Professor Rajko Igić	2010-2013	4
7	Professor Predrag Grubor	2014-2018	5
8	Professor Miloš P Stojiljković	2018-	1+

Table 2: Structure of articles per issue

Parameter	Number
No. of available issues	85
No. of articles	1,223
Mean No. per issue	14.39
SD	9.04
Min	1
Max	64
Median	12

Statistical data on the main elements of individual articles are given in Table 4.

Typically, an article published in the journal had two authors (range 1-15), was 4-pages-long (range 1-34) and cited 8 references range 0-238).

What is more important than these impressive numbers, is continuous advancement of the journal that has become increasingly international over the time. It started to publish articles mainly

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Table 3: Types of articles published in *Scripta Medica* (Banja Luka)

Type of article	Number	Percent
Editorial	225	2.04
Original	349	28.54
Professional	235	19.22
Review	43	3.52
History of medicine	4	0.33
Letter to the editor	28	2.29
Current topic	62	5.07
Case report	148	12.10
Special	23	1.88
Book review	81	6.62
Congress review	39	3.19
Article review	174	14.23
In memoriam	12	0.98
Total	**1,223**	**100.00**

Table 4: Characteristics of articles published in *Scripta Medica* (Banja Luka)

Parameter	Pages	Authors	References
Number	5,344	3,092	13,174
Mean	4.38	2.53	10.79
SD	3.01	2.00	13.82
Min	1	1	0
Max	34	15	238
Median	4	2	8

in English since 2010, all in English with abstracts in Serbian since October 2018 and in English only since 2019. The composition of the International Advisory Board of the journal also proves its aspirations towards international recognition. In order to achieve this, the *Scripta Medica* (Banja Luka) adopted a *SCIndeks* editorial platform to assist the communication with the authors and the reviewers.

Out of 49 manuscripts received in the year 2019, a total of 32 articles were published in four issues of volume 50, 2019. With 17 rejected manuscripts, the journal keeps a strict rejection rate of 35%. The composition of articles published in the volume 50 is contained in Table 5.

It is clear that 47% of the published articles belong to the most prestigious category - original articles, followed by case reports (16%) and editorials (13%).

To conclude, 50 volumes of the journal *Scripta Medica* (Banja Luka) give us reason to be proud with what has been achieved so far, but also represent a serious obligation for the current Editorial Board on our way of gaining its full international

Table 5: Structure of articles published in the *Scripta Medica* (Banja Luka), volume 50, 2019

Type of article	Issue No.				Total, volume 50	
	1	2	3	4	Number	Percent
Editorial	1	1	1	1	4	12.50
Original	4	5	3	3	15	46.88
Professional		1	1		2	6.25
Review	1				1	3.13
History of medicine				1	1	3.13
Current topic			2		2	6.25
Case report	1	1	1	2	5	15.63
Special	1			1	2	6.25
Total	**8**	**8**	**8**	**8**	**32**	**100.00**

recognition. Along these lines is our application for the coverage by the Directory of Open Access Journals (DOAJ) earlier this month. There were two attempts to enter the Medline/PubMed coverage so far, in 2011[4] and in 2016,[5] but both of them were unsuccessful. Our intention is to try to achieve this valuable goal by building a truly international Editorial Board, by attracting prestigious authors from abroad to entrust their manuscripts to the *Scripta Medica* (Banja Luka) and through the improvement of the international visibility of the journal.

ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST

None.

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SPECIAL ARTICLE

Reminiscences of Ervin G Erdös

Rajko Igić[1,2,3]

ABSTRACT

This article includes personal reminiscence of the great scientist Ervin G Erdös (1922-2019). Dr Erdös was born in Budapest, where he studied medicine. He finished his medical school in Munich, and obtained MD degree in 1952. There he joined, as a postdoctoral fellow, Professor Eugen Werle who had earlier discovered kallikrein, an enzyme that liberates kinins from kininogen. Dr Erdös continued his work on peptides and peptidases at the universities of Pittsburgh, Oklahoma City, Dallas and Chicago. In his eighties, he retired from the University of Illinois, Chicago. His numerous contributions to science belong to three important areas: 1) enzymes that generate, inactivate, or modulate the activity of kinins and other biologically active peptides, 2) angiotensin-converting enzyme and 3) kinin receptors. These discoveries contributed to our understanding of several bioactive peptide systems. Dr Erdös also found important interactions of the renin-angiotensin and kallikrein-kinin systems.

Key words: renin; ACE, angiotensin; kallikrein; kinin; peptides.

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Ervin G Erdös (1922-2019)

ERVIN G ERDÖS was born in Budapest, in 1922, where he finished Realgymnasium, which is analogous to high school, just at the beginning of World War II. However, since he was Jewish, he could not enter the university. He spent several years working as a steelworker, and later at forced manual labor. Finally, he and his father were deported together to the Sachsenhausen concentration camp in Berlin.[1] At the end of war, he successfully escaped and made his way home. After the war, Ervin entered the medical school in Budapest, but the regime banned him from finishing his final year because he was marked as a dissident. Then he luckily smuggled across the minefields and armed patrols between Hungary and Austria and came to Munich. It took him only one year to learn German and take the final examinations to get his MD degree from the University of Munich in 1950. In 1952 he joined the laboratory of Eugen Werle as a postdoctoral fellow in the Department of surgery where kallikrein, an enzyme that releases kinins from kininogens, was earlier discovered. Research on kinins in Munich inspired his permanent interest in peptides and peptidases (Figure 1).

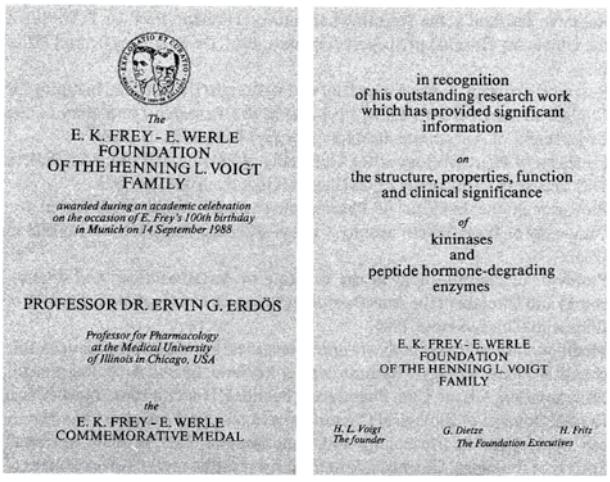

Figure 1: E K Frey – E Werle Commemorative Medal awarded on 14 September 1988 to Professor Ervin G Erdös for his scientific contribution in the research of peptides.

Soon, Dr Erdös emigrated to the USA, where he worked in Pittsburgh, Oklahoma City, Dallas, and Chicago. He retired in his eighties from the University of Illinois at Chicago.

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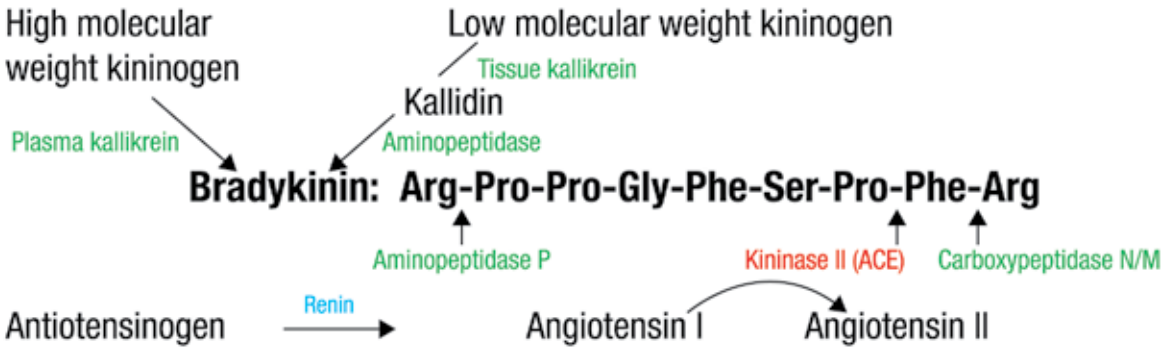

Figure 2: **Peptides and peptidases of the kallikrein-kinin system (KKS) and a portion of the renin-angiotensin system.** The enzymes in the KKS are shown in green, while renin is shown in blue; angiotensin -converting enzyme (ACE), which acts in both systems, is shown in red. Credit *Journal of Biological Chemistry*.[5]

I first met Dr Ervin G Erdös in 1969 at the Fourth International Congress of Pharmacology in Basel, Switzerland while I was working at the experiments for my PhD dissertation. During the dinner that night organized for all participants, I was sitting next to a distinguished gentleman with dark-rimmed glasses. When I introduced myself, he presented his name: "Ervin Erdös from Oklahoma City". We enjoyed an extended conversation that night, and also during a day off for all participants, when we spent together an enjoyable visit to Lake Lucerne that ended with his invitation to me to come to the USA to work with him. In January of the following year I defended my thesis at the University of Sarajevo. I then went to the USA as an exchange scientist for one year to work on the metabolism of vasoactive peptides in Dr Erdös' laboratory.

Dr Erdös discovered aminopeptidase, an enzyme that removes the N-terminal Lys of kallidin to form bradykinin, while a different aminopeptidase (aminopeptidase P) and carboxypeptidase (kininase I) deactivate bradykinin by removing the N-terminal Arg^{1} or the C-terminal Arg^{9}, respectively. He also discovered another enzyme in blood and tissues that removes the C-terminal Phe^{8}-Arg^{9} dipeptide; he named this enzyme kininase II. Later on, he and his co-workers showed that kininase II was identical to angiotensin I-converting enzyme (ACE).[2,3] This discovery connected the kallikrein-kinin system (KKS) with the renin-angiotensin system (RAS; Figure 2). Dr Erdös also discovered prolylcarboxypeptidase, a peptidase that deactivates angiotensin II and other peptides. His numerous contributions to science for more than half of the century span three important areas: 1) enzymes that generate, inactivate, or modulate the activity of kinins and other biologically active peptides, 2) ACE, and 3) kinin receptors. These discoveries contributed to our understanding of several bioactive peptide systems. Dr Erdös also found important interactions of the RAS and KKS. He and his colleagues presented evidence that ACE and the bradykinin B2 receptor physically interact with the cell membrane, and that an ACE inhibitor induces a conformational change that activates the signalling pathway. The ACE inhibitors also bind directly to the B1 kinin receptor to upregulate B1 receptors in the cardiovascular system that are usually expressed in inflammation, injury, or presence of cytokines.[4]

Among his other studies, while in Oklahoma City as a member of the Medical Faculty, Dr Erdös studied the mechanisms of septic and haemorrhagic shock. When the first ACE inhibitor from snake venom (SQ2081, called teprotide) became available, he used it to establish that the endotoxin-induced compensatory rise of blood pressure in shocked dogs was due to the activation of the RAS. It is well known that endotoxin initially causes a sharp drop in the mean systemic arterial pressure, but soon after this decrease, the pressure temporarily rises. Dr Erdös showed that the pressure rise resulted from the release of angiotensin II by ACE.

While Dr Erdös was working at the University of Oklahoma, Dr Edward Frohlich told him that he had difficulties with the cannulation of pulmonary blood vessels for studies of pulmonary circulation in rats. Dr Erdös humorously told him: "I have a man who can cannulate a mosquito." So, Dr Frohlich's technician anaesthetised a rat and invited Ervin and me to come. With the audience of three men, I then successfully cannulated the

pulmonary vessels. This made everyone happy, especially me. Dr Frohlich's technician learned how to do it at the same time; I was glad that my reputation did not suffer, and Dr Erdös was perhaps the happiest of all, because his claim of "mosquito cannulation" became more than simply boasting.

When Dr Erdös moved his laboratory from Oklahoma City to Dallas, Texas, I spent my three vacations, about two months each time, working with him. His laboratory was much better equipped than ours in Sarajevo and Tuzla, so I could continue some work that I began in Sarajevo, namely my studies of the ACE in the retina.[6,7] In the following years many other researchers become interested in ocular ACE; in fact, in 2016 more than 180 publications were retrieved on this subject.[8] Van Haeringen stated in the British Journal of Ophthalmology:[9] "Ophthalmic literature concerning the RAS started in 1977 with a study by Igić and co-workers on the detection of ACE activity in homogenates of the retina." Thanks to Dr Erdös, I was able to discover the presence of this enzyme and other peptidases in the eye, both in animal and human tissues.[10] I was not the only one he helped though. Dr Erdös also helped more than a dozen other young researchers from various countries, including USA, Japan, China, France, Serbia, and Germany. Their names are listed as co-authors on his many published papers.

In addition to the basic scientific research, Dr Erdös made substantial improvements in the methodology required for his studies. One is related to the recording method, the kymograph. This instrument was initially invented by a German physiologist, Carl Ludwig, in the 1840s. In many physiological and pharmacological laboratories around the world, a kymograph was an essential instrument. I also used one in experiments for my PhD thesis to record muscle contractions.[11,12] One piece of thread was attached to a strip of smooth muscle in a tissue bath, and the other was connected by the thread to a lever, which scratches the smoked paper on a slowly rotating drum when the muscle contracts. After each experiment, the record was preserved by fixing the paper with shellac.

To avoid this laborious procedure and the potential loss of data caused by accidental touch by a researcher's hand or elbow, Dr Erdös and two engineers at the Mellon Institute found a replacement. It consisted of a sensitive balance, one arm was connected by a thread to the isolated muscle tissue in the bath and the other to a transformer, while the sensitivity of the device was controlled with a demodulator box. Muscle contractions were then registered on a recorder in ink. To publish this technical innovation, Dr Erdös submitted the manuscript to one of the best journals in pharmacology. However, the editor rejected it because one referee stated that there is absolutely no need for such an instrument.[1] A few months later, in 1962, the paper was published in the *Journal of Applied Physiology* and it was cited in several textbooks.

When I worked with the isolated muscle tissue preparations in Dr Erdös' laboratory in Oklahoma City, I used this original equipment instead of a kymograph, taking advantage of this innovation. After several years, miniaturised electronic transducers for registration of isotonic and isometric contractions became commercially available, and they are still used today in many laboratories.

During his early studies on peptides and peptidases in 1962, Dr Erdös found that bioactive peptides produced by the RAS could never be useful medication, because they were so rapidly inactivated by enzymes; yet the agents that block their effects or inhibit their enzymatic degradation or production could alter their role in certain medical conditions.[13,14] This concept led to the development of the clinically useful ACE inhibitors.

In "A short history of my life and work entwined" written on 145 pages,[1] Dr Erdös describes his school years in Budapest, saying that he was "a remarkably average, uninterested, and generally bored student." For eight years in his middle- and high-school he and his close friend George Weber (who became a Distinguished Professor at the University of Indiana) were preoccupied with playing ball and girl-gazing. Dr Erdös continued, "Had a vote been taken in that school, George and I would certainly have tied for the most unlikely students to become members of the Hungarian National Academy of Science." Indeed, that happened to both of them much later. Today's educators who pressure students to have perfect marks in order to be accepted at the university, might consider that creativity does not depend on grades alone.

Epilogue

On Tuesday, November 12th, Dr Erdös called me. We talked for about ten minutes. He invited me for a visit and at the very end, added: "Rajko, despite my bad condition, on some days, I feel quite well, and I would like to go with you out to a café." I knew that his health was not good enough for that, so I decided to visit him instead. I would make him some Turkish coffee, just like we often did when he visited my lab in Sarajevo as a Fulbright Fellow-Visiting Professor. When I went to visit him that Thursday, I brought with me finely ground coffee, a *džezva* (vessel for extracting the coffee) and small porcelain cups – all the stuff needed to prepare the Turkish coffee.

I waited for Ervin to join me in the salon and reminisced about our long relationship. I could see into his study from where I sat. The things on his desk were unchanged from the times he spent working there. In fact, I had worked with him in that room on a long manuscript that I had written for the *Journal of Biological Chemistry*.[5] Together the salon and study in Dr Erdös' apartment were like a beautiful art gallery with many fine paintings on the walls and large windows open to a magnificent view of Lake Michigan. The lake is about a quarter of a mile away, but on this sunny day, it shone like another piece of the fine art that he cherished.

While I waited for about 10 minutes, many thoughts arose in my mind. When I left my apartment in Tuzla due to the war in Bosnia, I lost all my possessions, including paintings by various important artists. I lost these and other important things, but I saved my life. Now my dear friend and colleague would also lose these valuable art works that he has been collecting for many years and he would also lose his life. The difference between my situation in Tuzla and his in Chicago is that in the former the deep sadness comes a long time later, while in the latter it comes beforehand. In Ervin's case the loss would not be a loss of material possessions, but the loss of relationships with family, friends, and the many colleagues he helped during his long scientific career.

My thoughts were interrupted when Ervin appeared in his wheelchair. He was delighted in showing me of his art collection, including Hungarian-made vases and paintings from around the world. He talked slowly, and sometimes could not finish his thought, but when he showed me a painting by an artist from Sombor, he remarked that it was a pity that Yugoslavia, a beautiful country, had disintegrated into pieces. I prepared the Turkish coffee, and together with Ervin's wife, Sara, we had a long, friendly conversation around the kitchen table. Ervin asked about my wife and sons and said he would like to see my recently published book on geriatrics that I had brought to show him. The book is printed in Serbian, but it had many words in Latin and English and several illustrations. Ervin examined the book for about twenty minutes, only occasionally asking me the meaning of some words.

The next day Ervin went to the hospital for a scheduled appointment, but unfortunately, he did not return home. His condition suddenly worsened, and he died two days later, on Sunday, 17 November 2019. He was 97 years old.

ACKNOWLEDGEMENTS

None.

CONFLICT OF INTEREST

None.

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Bubić Pajić et al. Scr Med 2019;50(4):153-60. DOI:10.5937/scriptamed50-23360

ORIGINAL ARTICLE

Whole vs. Half-Tablets – a Case of Diazepam

Nataša Bubić Pajić[1], Anđelka Račić[1], Biljana Gatarić[1]

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ABSTRACT

Background: Tablet splitting is commonly used in clinical practice as a way to attain a desired drug dose and/or reduce its side effects, particularly among paediatricians and psychiatrists. However, uneven tablet scoring can lead to significant fluctuations of the administered doses, where subpotency or superpotency of drugs might harm the patients. The aim of this study was to evaluate the influence of tablet splitting on dose uniformity of diazepam by the utilisation of Ph. Eur. 9.0 and FDA recommendations.
Methods: Mass variation of whole and half-tablets in parallel with the determination of their content uniformity were performed according to the pharmacopoeial methods. The weight loss after tablet splitting was assessed by employing FDA guidelines. It was also investigated if tablet splitting influenced the *in vitro* dissolution properties of diazepam tablets.
Results: Diazepam whole tablets fulfilled the pharmacopoeial requirements in regard to all the investigated properties. The weight uniformity of scored diazepam tablets ranged from 63.80% to 122.55% label claim. The losses of mass after splitting diazepam tablets were 5.71%. Despite the average content of diazepam in half-tablets was found to be 104.24% label claim, the requirements of Ph. Eur. were not fulfilled. Diazepam content in half-tablets ranged from 0.76 mg to 1.21 mg, thus, patients might receive doses that vary by as much as 45%. However, after weight adjustment, diazepam content in each of the tested half-tablets was in the range of 85-115% of the average drug content meeting the Ph. Eur. criteria. Dissolution profiles of whole and half-tablets were found to be similar, following the Hixson-Crowell kinetic model.
Conclusion: According to the results, splitting of diazepam tablets greatly influenced the drug content in the obtained parts, ie the dose accuracy was fully dependent of the ability to score the tablet into exactly equal halves.

Key words: tablet splitting, diazepam, tablet scoring, half-tablets, dose adjustment.

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INTRODUCTION

Since patients show a large variability in body surface area and weight, there is a broad variation in drug response among the patients. In order to accomplish proper drug treatment, a large variation of tablet strengths is required, but this is not always provided. Besides, adverse effects of drugs, which are considered as one of the major problems in modern pharmaceutical practice, are dose dependent. Despite the manipulation of medicines renders their use unlicensed, tablet splitting is commonly used in clinical practice as an approach to attain a desired drug dose and/or reducing its side effects, particularly among paediatricians and psychiatrists.[1-4] Healthcare professionals often prescribe half-tablets either to achieve lower drug doses than the lowest com-

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mercially available strength or to reduce treatment costs because different dose strengths of the same drug frequently have similar prices[1] or higher-strength tablets are payable by insurance companies, unlike lower drug doses.[5] Another reason for tablet scoring is a facilitated drug administration due to ease of swallowing.[6, 7]

On the other side, there are many potential concerns associated with tablet splitting. The most important problems are variation in weight and drug content in half-tablets, as well as drug stability of halves obtained by splitting whole tablets. As a result of uneven tablet scoring, administered dose can significantly fluctuate, especially in case of drugs with narrow therapeutic index, where subpotency or superpotency of drugs might harm the patients.[1-3, 8, 9]

Tablets can be either hand-split along a scored line or the scoring can be obtained by using a knife or specially designed tablet splitter (Figure 1). Because some tablets can break into more than two parts, the occurrence of tablet wasting is possible. Several studies have reported weight differences among split medications. However, some of these studies have evaluated uniformity of drug content solely by means of variation in weight of half- tablets,[5, 7] while a few studies have evaluated the drug content in the halves.[1, 4, 8]

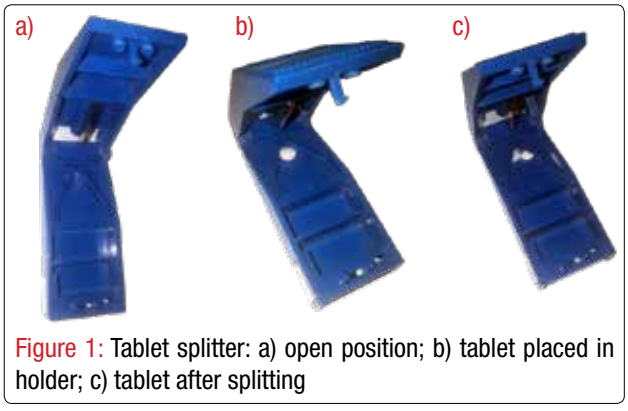

Figure 1: Tablet splitter: a) open position; b) tablet placed in holder; c) tablet after splitting

To address these issues, the European Pharmacopoeia 4.0 (Ph. Eur.)[10] introduced guidelines for measuring the dosing accuracy of subdivided scored tablets. Hence, this assessment became mandatory in many European countries in order to provide accuracy in dosing of split tablets. However, a score line on tablets can be misleading, as not all scored tablets are suitable for splitting.[8] According to the rules of Ph. Eur. and Guideline on Summary of Product Characteristics (SmPC) adopted by the European Commission, one of the following phrases should be used in the SmPC for tablet designed with a score line:[6]

- "The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses"
- "The tablet can be divided into equal halves"
- "The tablet must not be divided at all"

This information is significant to both healthcare professionals and patients as well, because it is believed among patients that the score line on a tablet represents a sign that the tablet can be split.[6]

It is also important to note that until now guidelines for the assessment of the drug content of split tablets have not been established in any official pharmacopeia. However, as a response to problems concerning tablet splitting, the US Food and Drug Administration (FDA) developed Guidance for Industry on tablet scoring,[11] providing the criteria for scored tablets, as a part of the FDA drug reviewing process. According to the Guidance,[11] the split tablets should fulfil the same requirements as the whole tablets having equal strength

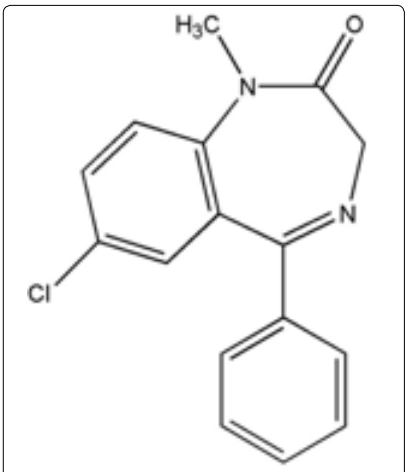

Figure 2: Chemical structure of diazepam

Diazepam (Figure 2) is one of the most prescribed benzodiazepines[12] with sedative, anxiolytic, anticonvulsant, muscle relaxant and amnestic action, which is mediated by enhancement of the activity of gamma-aminobutyric acid (GABA), a major inhibitory neurotransmitter in the brain.[13] In clinical practice, it is used in the short-term treatment of severe anxiety disorders, insomnia and for premedication and sedation. Diazepam is also indicated in the treatment of status epilepticus and febrile convulsions, as well as in the control of muscle spasm. The use of diazepam is associated with the risk of dependence, which is very much affected by the given dose and treatment duration. Therefore, doses of diazepam should be the lowest that can control symptoms and courses of treatment

should not be longer than 4 weeks, with the drug being withdrawn gradually. Dosage reduction may also be required in elderly and debilitated patients, as well as patients with hepatic or renal impairment. Also, low doses of diazepam may be given to children (ie in children 1–12 months diazepam is given initially 250 microgram/kg twice daily for the treatment of muscle spasm in cerebral spasticity or in postoperative skeletal muscle spasm; 1 to 5 mg at bedtime have been used in children and adolescents aged from 12 to 18 years to treat night terrors and sleepwalking).[13-15]

The aim of this study was to evaluate the effect of tablet splitting on dose uniformity of diazepam by the utilisation of Ph. Eur. 9.0[16] and FDA recommendations.[11] For this purpose, determined mass variation of whole and half- tablets was determined in parallel with the determination of their content uniformity. The weight loss after tablet splitting was also evaluated. Finally, the authors were interested to investigate if tablet splitting influenced dissolution properties of diazepam tablets.

METHODS

Reagents

All chemicals used in this study were of analytical grade. Sulphuric acid, methanol and hydrochloric acid (35%) were purchased from Lach-Ner (Neratovice, the Czech Republic).

Tablets

Diazepam tablets (2 mg) were obtained from the local market. Tablets were round, convex, without score lines, with average diameter and thickness of 8.07 ± 0.02 and 4.30 ± 0.04 mm, respectively. Inactive ingredients were: lactose monohydrate, corn starch, povidone and magnesium stearate.

Tablet splitter

In this work tablet splitter (Romed - Holland) was used. Tablet splitter was opened (Figure 1a) and the investigated tablet was positioned and scored by closing the splitter (Figure 1b). The weight of tablets was measured before and after scoring (Analytical balance, TE214S, Sartorius, Goettingen, Germany).

Uniformity of mass of whole tablets

Mass uniformity of whole tablets was determined according to Ph. Eur. 9.0. monograph "Uniformity of mass of single dose preparations".[16] Twenty randomly taken tablets were weighted and the average mass was calculated. In order to pass the test, not more than two of the individual masses should differ from the average mass by more than 7.5% and none more than 15%.

Subdivision of tablets

According to the European Pharmacopoeia "Test for subdivided scored tablets",[16] thirty tablets of the chosen product were selected at random. These thirty tablets were split and assessed to have passed the test if no more than one individual mass was not within 85-115% of the average mass and if no individual mass was outside the limits of 75-125% of the average mass. Additionally, the limit for relative standard deviation (RSD) from the United States Pharmacopeia[17] (USP) was applied, stating that the product passed the test if the RSD is less or equal to 6%. However, the USP has a somewhat different method for making a decision which halves to weigh. Namely, all of the weighed tablet parts must be within the 85-115% range of the target tablet weight. Thus, in this study the Ph. Eur. criteria[16] were used with the addition of the RSD limit from the USP.[17]

Loss of mass after scoring the tablets

In accordance with the requirements of the FDA tablet scoring guidance for industry,[11] splitability of diazepam tablets was checked by calculating a loss of mass obtained by scoring fifteen tablets. The difference in mass of split tablet portions when compared to the whole tablets-should be less than 3%.

Content uniformity of whole and scored diazepam tablets (Ph. Eur. 9.0)[16]

The individual content of diazepam of ten randomly taken tablets was determined. The tablets comply with the test if individual content is range of 85% and 115% of the average content. The tablets fail to comply with the test in the case of more than one individual content being outside the above-mentioned limits. Any of individual contents also must not be out of the boundaries of 75-125% of the average content. In the cases when one individual content falls outside the range of 85-115% but within the limits of 75-125%, another twenty tablets randomly selected should be analysed on drug content. In order to pass the test, not more than one of the individual contents of thirty units is out of the range of 85-115% and none being outside the limits of 75-125% of the average drug content.

In this study, ten randomly selected diazepam tablets were tested. Because FDA Guidance11 recommends that the scored tablets should fulfil the same criteria as the whole tablets, five tablets taken at random were split and the content of the drug was also measured in ten obtained half-tablets.

Drug assay

Content of diazepam in tablets and half-tablets was determined according to the British Pharmacopoeia[18] as follows. Firstly, 1 ml of water was added to one tablet. The tablet was then allowed to disintegrate for 15 minutes. Afterwards, 80 ml of a 0.5% w/v solution of sulphuric acid in methanol was added and then shaken for 15 minutes. Sufficient volume of the methanolic sulphuric acid was added to produce 100 ml and filtered. The absorbance of the filtrate was measured at 284 nm and diazepam content was calculated according to the value of A (1%, 1 cm) at 284 nm (UV-1800 spectrophotometer, Shimadzu, Japan), which is 450.

Microsoft Office Excel was employed for all calculations.

Dissolution test

The dissolution test of whole and half-tablets was carried out according to the USP42-NF37[17], by using apparatus 1 (Erweka 726) at a stirring speed of 100 rpm. Temperature was maintained at 37°C during the entire experiment. The test was performed in 900 ml of 0.1 M hydrochloric acid. Dissolution samples in the amount of 5 ml were taken at the following intervals (after 10, 20 and 30 min). Withdrawn samples were supplemented with the same volume of freshly prepared dissolution medium to maintain sink conditions. The acquired samples were filtered using 0.22 μm membrane filters (Chromafil®X-tra PTFE-20/25, Macherey-Nagel, Düren, Germany). Diazepam concentration was determined by using UV-VIS spectroscopy, at 242 nm (UV-1800 spectrophotometer, Shimadzu, Japan). If necessary, the samples were diluted with dissolution medium prior to drug quantification.

As oral bioavailability of diazepam is fully dependent on dissolution of a dosage form, the evaluation of dissolution properties and the comparison of dissolution profiles for whole and scored tablets are very important. The obtained dissolution profiles were compared by utilising a model-independent approach, which includes the determination of a difference factor (f1) and a similarity factor (f2),[19] according to the equations (1) and (2) as follows:

$$f_1 = \frac{\sum_{t=1} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \times 100 \quad (1)$$

$$f_2 = 50 \times \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\} \quad (2)$$

where n is the time points number, Rt is the dissolution value of the reference product (whole tablets) at time t, and Tt is the dissolution value of the test product (half-tablets) at time t. The assessment of similarity of dissolution profiles was based on f1 and f2 values, which should be in a range of 0-15 and 50-100, respectively.[20] In addition, drug release data were fitted to different kinetic models (Table 1) and the linear regression was evaluated by using R^2 (squared correlation coefficient) as the main criterion concerning the selection of the model best describing diazepam dissolution from the investigated whole and half-tablets.

Table 1: Mathematical models applied to dissolution profiles of diazepam whole and half tablets[18]

Model	Equation
Zero order	$Q_t = Q_0 + K_0 t$
First order	$\log Q_t = \log Q_0 - K_1 t/2.303$
Higuchi	$Q_t = Q_0 + K_H t^{1/2}$
Korsmeyer-Peppas	$Q_t = K_{KP} t^n$
Hixson-Crowell	$Q_0^{1/3} - Q_1^{1/3} = K_{HC} t$

Q_t: amount of drug released in time t; Q_0: initial amount of drug in dissolution media; K_0, K_1, K_H, K_{KP}, K_{HC}: release rate constants.

Data analysis

Dissolution tests results obtained with six replicates were presented as the average amount of diazepam dissolved (%) ± SD. The statistical analysis was carried out by using Student's t-test. p values lower than 0.05 were considered as statistically significant. Microsoft Excel software package was employed for all analyses.

RESULTS

Uniformity of mass of whole tablets

Table 2 shows mass of twenty whole tablets (g) and whether the weight of each investigated sample fitted in the range of 85-115% of the average tablet weight. Average mass of twenty diazepam tablets was found to be 201.87 mg.

Table 2: Results of mass uniformity for whole diazepam tablets.

Sample number	Weight of whole tablet (g)	85-115% of the average mass
1	0.2077	Yes
2	0.1980	Yes
3	0.2038	Yes
4	0.2027	Yes
5	0.2053	Yes
6	0.2022	Yes
7	0.2032	Yes
8	0.2014	Yes
9	0.2039	Yes
10	0.2020	Yes
11	0.1969	Yes
12	0.1959	Yes
13	0.2012	Yes
14	0.1987	Yes
15	0.2047	Yes
16	0.2104	Yes
17	0.2010	Yes
18	0.1939	Yes
19	0.2040	Yes
20	0.2004	Yes
Average	0.2019	
SD	0.0039	
RSD	1.95	
Meet Ph. Eur. ac-ceptance criteria	Yes	

Uniformity of mass of half tablets

Masses of thirty half-tablets (g) were determined (Table 3) and it was evaluated if they were in a range of 85-115% and 75-125% label clam. Average mass of thirty half-tablets was 93.7 mg, which represents 92.83% of the predicted mass of half-tablet. The weight uniformity of scored diazepam tablets ranged from 64.4 mg to 123.7 mg, which is equivalent to 63.80% to 122.55% label claim. Also, the weight of twelve samples of scored tablets was not beyond the limits of 85-115% of the average mass, with four of them outside 75-125% of the average (Table 3).

Loss of mass after scoring the tablets

The mass loss (g) produced by scoring the tablets was expressed as % of the whole tablet weight. As can be seen from Table 4, on average 5.71% of tablet mass was lost during the scoring procedure.

Table 3: Results of mass uniformity for diazepam half tablets.

Sample number	Weight of whole tablet (g)	85-115% of the average mass	75-125% of the average mass	Sample number	Weight of whole tablet (g)	85-115% of the average mass	75-125% of the average mass
1	0.1183	No	No	16	0.1237	No	No
2	0.0806	Yes	Yes	17	0.0943	Yes	Yes
3	0.1112	No	Yes	18	0.0958	Yes	Yes
4	0.0976	Yes	Yes	19	0.1063	Yes	Yes
5	0.1012	Yes	Yes	20	0.1072	Yes	Yes
6	0.0881	Yes	Yes	21	0.0767	No	Yes
7	0.1149	No	Yes	22	0.0784	No	Yes
8	0.0817	Yes	Yes	23	0.1032	Yes	Yes
9	0.1011	Yes	Yes	24	0.0908	Yes	Yes
10	0.0719	No	Yes	25	0.0964	Yes	Yes
11	0.1145	No	Yes	26	0.0764	No	Yes
12	0.0692	No	No	27	0.0916	Yes	Yes
13	0.1020	Yes	Yes	28	0.0644	No	No
14	0.0997	Yes	Yes	29	0.0892	Yes	Yes
15	0.0895	Yes	Yes	30	0.0738	No	Yes
Average	0.0937						
SD	0.0154						
RSD	16.49						
Pass	No						

Content uniformity of whole and scored diazepam tablets

In this part of the study, uniformity of diazepam content in whole and half-tablets was determined and the obtained results were presented in Table 5. The average content of diazepam in ten randomly taken whole tablets was 105.98%

Table 4: Mass losses obtained by scoring diazepam tablets using tablet splitter

Sample number	whole tablet mass (g)	1/2 tablet mass (g)	2/2 tablet mass (g)	Loss of mass (%)
1	0.2037	0.0945	0.0850	11.88
2	0.2041	0.1054	0.0930	2.79
3	0.2047	0.1121	0.0918	0.39
4	0.1999	0.0926	0.0897	8.80
5	0.2026	0.0968	0.0955	5.08
6	0.2027	0.0969	0.0951	5.28
7	0.2000	0.1000	0.0905	4.75
8	0.2041	0.0868	0.1016	7.69
9	0.1993	0.1010	0.0888	4.77
10	0.2029	0.1030	0.0967	1.58
11	0.2078	0.1219	0.0846	0.63
12	0.2003	0.0976	0.0883	7.19
13	0.2047	0.0843	0.1060	7.03
14	0.2043	0.0976	0.0981	4.21
15	0.2027	0.0852	0.0901	13.52
Average loss (%)	5.71			
SD	3.79			
RSD	66.38			
Pass	No			

label claim, whereas half-tablets contained on average 104.24% label claim of the drug.

In addition, adjustment of drug content for weight of half-tablets was made and it was revealed that diazepam content in weight-adjusted half-tablets was less variable and similar to the drug content in whole tablets (105.05%).

Dissolution test

In vitro dissolution test revealed that drug dissolved (%) from whole and half-tablets in 30 minutes was 96.48±1.35 and 96.16±4.88, respectively (Figure 3). In addition, dissolution profiles of whole and half-tablets were found to be similar as depicted in Figure 3. This is also

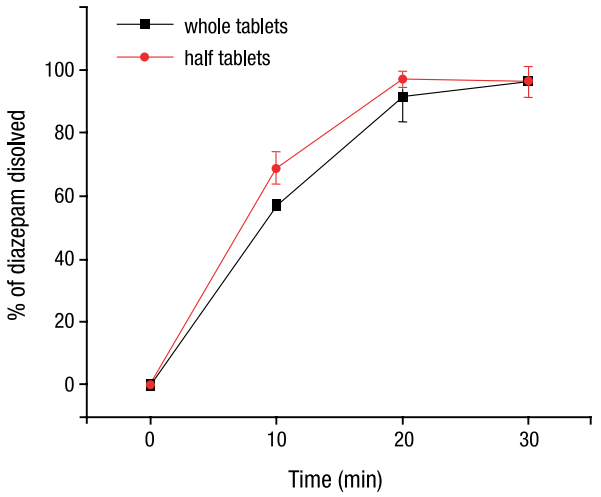

Figure 3: Dissolution profiles of whole and half diazepam tablets

Table 5: Results of content uniformity for whole and half diazepam tablets

Sample number	whole tablets		half tablets			weight-adjusted half tablets	
	Content of diazepam (% of label claim)	85 -115% of the average content	Content of diazepam (% of label claim)	85 -115% of the average content	75-125% of the average content	Content of diazepam (% of label claim)	85 -115% of the average content
1	107.78	Yes	115.78	Yes	Yes	103.16	Yes
2	99.78	Yes	120.22	No	Yes	95.27	Yes
3	106.11	Yes	104.89	Yes	Yes	103.32	Yes
4	110.33	Yes	94.67	Yes	Yes	101.66	Yes
5	112.67	Yes	110.67	Yes	Yes	96.89	Yes
6	105.00	Yes	120.89	No	Yes	103.18	Yes
7	105.89	Yes	94.22	Yes	Yes	117.47	Yes
8	108.44	Yes	75.56	No	No	112.45	Yes
9	103.11	Yes	97.78	Yes	Yes	105.36	Yes
10	100.67	Yes	107.78	Yes	Yes	111.71	Yes
Average	105.98		104.24			105.05	
SD	4.07		14.05			6.97	
RSD	3.84		13.64			6.64	
Pass	Yes		No			Yes	

confirmed with the values of f1 and f2 which were 7.25 and 55.96, respectively.

The values of correlation coefficients (R^2) obtained by fitting the drug release data are presented in Table 6. As can be noticed the drug release from whole and half-tablets followed the same kinetics, ie the Hixson-Crowell kinetic model.

Table 6: The values of correlation coefficients (R^2) obtained by fitting the drug release data

Sample	Model				
	Zero order	First order	Higuchi	Korsemeyer -Peppas	Hixson -Crowell
whole tablets	0.84	0.98	0.98	0.97	**0.99**
half tablets	0.72	0.97	0.95	0.98	**0.99**

DISCUSSION

Uniformity of mass of whole tablets

Taking into account that not one individual mass was outside the limits of 92.5-107.5% of the average mass, diazepam tablets fulfilled the Ph. Eur. requirements as expected.

Uniformity of mass of half tablets

According to the results obtained in this part of the study, the requirements for mass uniformity of split tablets were not fulfilled. Moreover, according to the calculated RSD, which was found to be 16.49, diazepam tablets did not pass the test for uniformity of mass. These results can be attributable to the small size and round shape of tablet, which is in line with earlier findings,[8, 21]

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where tablets having diameter smaller than 8 mm showed poor splitting behaviour. Besides, a lack of a score line on the tablets, generally, makes the tablets difficult to split evenly.[8, 21]

Loss of mass after scoring the tablets

In agreement with mass variation of half-tablets, manipulation of whole tablets led to an increased friability of the investigated solid dosage form of diazepam. As expected, the losses of mass after splitting diazepam tablets exceeded 3%. Thus, the FDA requirements were not fulfilled. In addition, it should be noted that there was high variability among the tested samples, with up to 13.52% of the tablet mass lost during the scoring procedure. Taking into account these results coupled with weight uniformity of the half-tablets, high variations in drug content of scored tablets can be expected.

Content uniformity of whole and scored diazepam tablets

As presented in the Results section, content of the drug for whole tablets ranged from 99.78% to 112.67% label claim, indicating that the whole tablets fulfilled the Ph. Eur. acceptance criteria regarding drug uniformity.

On the other hand, despite the average content of diazepam in half-tablets was found to be close to the label claim, the requirements of Ph. Eur. were not fulfilled.[16] Actually, four samples contained diazepam outside the limits of 85-115% label claim. However, the drug content of all ten samples of half-tablets was in range of 75-125% label claim. In addition, three samples were not beyond the boundaries of 85-115% of the average drug content in half-tablets, while one of them also did not fit to the range of 75-125% of the average drug content. Because diazepam content in half-tablets ranged from 0.76 mg to 1.21 mg, patients might receive doses that varied by as much as 45%. This finding correlates well with the results of weight uniformity. However, in order to deeper investigate the cause for these results, the drug content was adjusted for weight of half-tablets, since it is supposed that the drug in tablets is dispersed uniformly. Thus, it is presumed that the drug content in half-tablet with known weight is proportional to the ratio of the half tablet's weight to the whole tablet's weight:

$$\text{weight-adjusted target drug content} = \frac{\text{measured half tablet weight} \times \text{target drug content for whole tablets}}{\text{measured whole tablet weight}}$$

Then the difference (%) between weight-adjusted drug content and the label diazepam content of half-tablet was calculated. Accordingly, after weight adjustment, a large reduction in drug content variation was found. Moreover, one half-tablet felt outside the limits of 85-115% label claim, but still inside the range of 75-125%. In addition, diazepam content in each of the tested half-tablets was in the range of 85-115% of the average drug content meeting the Ph. Eur. criteria.[16] Taking into account these results, it could be concluded that the weight of half-tablets directly correlated with the content of diazepam and it is the main reason for diazepam content variation. Therefore, the administration of required dose of diazepam is determined by the patient's ability to split tablets perfectly in equal parts.

Dissolution test

The obtained results revealed that the whole tablets as well as half-tablets met USP42-NF37 requirements[17] (not less than 85% of the label amount of diazepam is dissolved in 30 minutes). As the major quantity of diazepam was dissolved within the first 20 minutes, the drug product is expected to exhibit fast action.

Furthermore, Hixson-Crowell kinetic model best describing drug release from whole as well as from half-tablets indicated that the change in tablets' surface area and diameter occurred during the release process. Hence, this model assumes that drug release rate is not limited by diffusion, but rather by drug particles dissolution rate.[22] In the case of diazepam whole and half-tablets, the obtained f1 and f2 factors, similar amounts of the drug dissolved in each time point of the experiment as well as similar dissolution mechanisms suggested that the dissolution properties of whole tablets would not be altered by their manipulations, such as scoring and dividing. Therefore, if tablet splitting could be performed without significant mass losses, the tablet scoring could be suggested as a mean of a swallowing facilitation.

CONCLUSION

According to the results, splitting of diazepam tablets greatly influenced the drug content in the obtained parts, ie the dose accuracy was fully dependent on the ability to score the tab-

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let into exactly equal halves, which was somehow expected. On the other hand, dissolution profiles of scored tablets were similar to the *in vitro* release kinetic of whole diazepam tablets, indicating that the investigated tablets can be split in order to facilitate swallowing of the tablets. Also, if tablets are scored perfectly into two equal parts, dissolution properties of a half- tablet would be the same as in the case of taking the whole tablet and thus similar bioavailability could be presumed.

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CONFLICT OF INTEREST

None.

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ORIGINAL ARTICLE

The Degree of Tooth Colour Change After Using Different Concentrations of Carbamide Peroxide

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ABSTRACT

Background: Depending on the cause of discoloration, bleaching materials and other factors, vital dental bleaching techniques may be professional (in-office dental bleaching), at-home night-guard bleaching and combined.
The main objective of this study was to determine, in vitro, tooth colour change using external dental bleaching techniques with 16% and 30% carbamide peroxide gel and to investigate the effect of concentration of carbamide peroxide gel on the bleaching success.
Method: This study included 20 extracted intact human teeth. Teeth were divided into two groups of ten each: the first group was bleached with 16% and the second group with 30% carbamide peroxide gel. The procedure was repeated three times for each tooth. The existing colour on each tooth was recorded using VITA classical shade guide A1-D4 before treatment, after each session and after bleaching was completed.
Results: A significant difference ($p < 0.01$) was found between the first and the second bleaching treatment, for both concentrations (Exact binomial test). A significant difference ($p < 0.05$) was also present between the second and the third treatment, while no statistically significant difference was found between the first and the third bleaching treatment, for both concentrations. There was no statistically significant difference between groups based on degree of tooth shade ($\chi 2$ test).
Conclusion: The teeth bleaching technique with 16% carbamide peroxide gel and the teeth bleaching technique with 30% carbamide peroxide gel have shown the same efficiency in changing the tooth colour.

Keywords: carbamide, peroxide, tooth, gels.

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INTRODUCTION

Dental bleaching is one of the fastest growing areas in restorative and aesthetic dentistry in the last few years. Earlier, it was thought that enamel colour was responsible for tooth colour. Later on, research has shown that four dental tissues: pulp, dentin, enamel and cement are involved in creating the final shade of each tooth. Any change in one of these structures leads to the tooth colour change, which is reflected on transmission change and light reflection. Dental discolorations have different aetiologies, locations, frequency and affinities to dental tissue. [1-3]

Depending on the cause of discoloration, bleaching materials and other factors, vital dental bleaching techniques may be professional (in-of-

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CONTENT

fice dental bleaching), at-home night-guard bleaching and combined. In recent years, over-the-counter dental bleaching products have become very popular. They are based on low concentrations of bleaching agents (3-6% hydrogen peroxide gel) in the form of coloured rubber bands, splints, toothpastes. These self-applied bleaching treatments are administered without the consultation and supervision of a dentist.[1, 4-9]

In-office dental bleaching techniques use high concentrations of hydrogen or carbamide peroxide gel. The gel is placed on a specific surface of the tooth and then activated chemically or by various light and heat sources. The main advantages of in-office bleaching technique are: procedure is completely under the control of the dentist, the soft tissue of the oral cavity is protected during the procedure and faster colour change.[1, 4-10]

A very popular and effective dental bleaching technique of vital teeth is at-home night-guard bleaching, conducted by patient itself. The advantages of this technique are simple application and low concentration of bleaching agent (10-16% carbamide peroxide gel). The process involves making a soft, vinyl individual spoon or tray for bleaching gel application. Bleaching treatment with this technique lasts from two to six weeks, depending on the intensity of tooth discoloration. Regular dental check-ups are needed to determine colour change as well as possible soft tissue damage and sensitivity. Increased salivation occurs frequently in patients while wearing a splint, which is a common occurrence due to pH change in the mouth.[1, 3, 5, 8-17]

Zekonis et al. examined colour change, recurrence of discoloration and tooth sensitivity after performing two different dental bleaching techniques in the same patient. In-office bleaching technique with 35% hydrogen peroxide gel was used on one half of the upper jaw of the subjects, while at-home night-guard bleaching technique with 10% carbamide peroxide gel was applied on the other half. The results of the study showed that 84% of respondents consider that home night-guard bleaching techniques are more effective in colour change. There was no statistical difference between dental bleaching techniques related to tooth sensitivity in patients.[18]

The bleaching effect depends on various factors such as dental plaque, temperature, pH, tooth isolation and most importantly, on bleaching gel concentration and the application time. The application time is directly proportional to the positive tooth colour change.[1]

The main objective of this study was to determine, in vitro, tooth colour change by using external dental bleaching techniques with 16% and 30% carbamide peroxide gel and to investigate the effect of concentration of carbamide peroxide gel on the bleaching success.

METHOD

The study is a part of dissertation conducted on Faculty of Medicine, University of Banja Luka and included 20 extracted intact human teeth. All teeth were extracted at the Public Health Institute of Dentistry Banja Luka for orthodontic or periodontal reasons. Teeth were cleaned of soft deposits and calculus and kept in saline until the experiment. They were divided into two groups of ten teeth each: the first group was bleached with 16% carbamide peroxide gel (Vivastyle 16%, Ivoclar Vivadent, Liechtenstein) and the second group with 30% carbamide peroxide gel (Vivastyle 30%, Ivoclar Vivadent, Liechtenstein).

Before treatment, the existing colour of every tooth was recorded by using VITA classical shade guide A1-D4 (VITA Zahnfabrik, Bad Säckingen, Germany). External bleaching technique was done for all teeth.

In the first group, 16% carbamide peroxide gel (Vivastyle 16%, Ivoclar Vivadent, Liechtenstein) was applied to the vestibular surface of each tooth for 30 minutes, then the tooth was washed with water and dried, and the procedure repeated three times. This method of dental bleaching is equivalent with at-home night-guard vital teeth bleaching technique, modified for the purposes of this study.

In the second group, 30% carbamide peroxide gel (Vivastyle 30%, Ivoclar Vivadent, Liechtenstein) was applied to the vestibular surface of each tooth for 15 minutes, after that, washed with water and dried. This procedure was repeated twice. Performed method of tooth bleaching is equivalent with in-office professional teeth bleaching technique, modified for the purposes of this study.

The bleaching process was repeated in same manner after seven and fourteen days. In between, teeth were stored in fresh sterile saline. Overall, bleaching process was performed three times. If the tested tooth did not change its shade after two bleaching processes it was excluded from the third procedure.[1]

After each procedure, the tooth colour change was evaluated based on the 'dark-light scale' (Table 1). On this scale, each tooth shade was assigned a corresponding number from one to 16, so that statistics could be done. The lightest colour on the scale (B1) corresponds to number one, while the darkest colour (C4) corresponds to number 16. One degree of shade change is represented by moving from a higher to a lower number on the scale (eg from shade C2 to C1, means from number 7 to 6), two degrees for two numbers (eg from B4 to B3 is actually from 13 to 11) and consequently, three degrees for three numbers (eg from A2 to colour A1 or from 5 to 2).[1, 19]

Statistical data processing was done using $\chi 2$ and exact binomial test.

Table 1: Dark-light scale of tooth shade

Vita shade guide	B1	A1	B2	D2	A2	C1	C2	D4	A3	D3	B3	A3,5	B4	C3	A4	C4
Shade number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16

RESULTS

Bleaching with 16% carbamide peroxide was unsuccessful in all ten teeth (100%) as seen in Table 2. After the second treatment, six teeth (60%) changed their shade to the lighter, while in third treatment no change of shade was observed in any of the six tested teeth (four teeth were excluded from the third process due to the unchanged shade after the first two procedures). High statistically significant difference was found ($p < 0.01$) between the first and the second bleaching treatment (exact binomial test). A statistically significant difference ($p < 0.05$) was also present between the second and third treatments. No statistically significant difference was found between the first and the third bleaching treatments.

In a group of teeth bleached with 30% carbamide peroxide, only one tooth (10%) after the first treatment changed its shade into the lighter. After the second treatment eight teeth (80%) underwent a shade change and after the third process, only two of them underwent a shade change (20%) (Table 2). In this group results of exact binomial test showed that there was a highly statistically significant difference ($p < 0.01$) between the first and the second treatment, while the difference between the first and the third treatment was not significant. A statistically significant difference was also found between the second and the third treatment ($p < 0.05$).

In a group of teeth bleached with 16% carba-

Table 2: Success rate of teeth bleaching with two different carbamide peroxide concentracion depending on the number of treatments.

Carbamide peroxide concentration		**After first treatment**		**After second treatment**		**After third treatment**	
		n	**%**	**n**	**%**	**N**	**%**
16%	teeth that have changed their color	0	0	6	60	0	0
	teeth that have not changed their color	10	100	4	40	6	100
30%	teeth that have changed their color	1	10	8	80	2	20
	teeth that have not changed their color	9	90	2	20	6	80

Table 3: Degrees of success of teeth bleaching with two different concentrations of carbamide peroxide

Carbamide peroxide concentration	One degree		Two degree		Three degree		Total		X^2 test
	n	%	n	%	n	%	n	%	
16%	5	83.33	1	16.67	0	0	6	100	p>0.05
30%	6	75.00	2	25.00	0	0	8	100	

p= statistic value, X^2test= test- Hi quadrate test

mide peroxide, five teeth (83.33%) underwent one-degree of shade change, while only one tooth (16.67%) underwent two degrees. No tooth changed its shade for three degrees (Table 3).

In a group of 30% carbamide peroxide six teeth (75.00%) changed their shade for one degree, two teeth (25.00%) for two degrees, while no tooth had a three-degree change (Table 3).

χ2 test showed no statistical difference between groups based on degree of tooth shade change (Table 3).

DISCUSSION

Tooth discoloration is a major aesthetic problem. In modern dentistry, there is a tendency for patients and dentists to restore discoloured teeth to the natural colour of their teeth, to achieve the best possible aesthetics and to avoid prosthetic dental rehabilitation.

Observing the colour change through the number of bleaching treatments for both gel concentrations (16% and 30%), bleaching was most effective after the second treatment. Colour change did not occur in any of teeth after the second treatment. It can possibly be explained with so called 'Saturation point'. Carbamide peroxide dissolves in situ to urea, ammonia, carbon dioxide, water and hydrogen peroxide, which is the active substance. Hydrogen peroxide diffuses throughout the organic matrix and releases free radicals. Further on, these free radicals break down the double unsaturated bonds of the pigment molecules that produce smaller molecules that reflect less light. This is a bleaching process. If the process continues at some point the 'saturation point' is reached. The 'saturation point' is the point when the maximum bleaching is achieved. From this stage, the pigments are no longer bleached, and the bleaching agent begins to act on other carbon compounds, such as enamel matrix proteins and at this point, a loss of tooth structure can start. Therefore, a clinician needs to know when to stop the bleaching process. If it continues, complete disintegration of hard dental tissues can appear. [1, 20]

The results of this study showed the same efficiency in the degree of tooth colour change in group of teeth bleached with a higher carbamide peroxide concentration (30%) - shorter exposition time (two applications for a duration of 15 min) and in the group of teeth bleached with a lower (16%) carbamide peroxide concentration - longer exposition time (three applications for a duration of 30 min). This study confirmed that the application time of bleaching agent played a major role in the success of vital teeth bleaching. The application time is directly proportional to the positive tooth colour change. Low concentrations of bleaching agents can achieve satisfactory and equally good teeth bleaching results as agents with high concentrations, if the agent is applied to the tooth for an extended period of time.[1, 18, 21-23]

Meireles et al also showed that the time of exposure to a bleaching agent is a more important factor than gel concentration itself. A satisfactory tooth colour was achieved with multiple treatments despite the carbamide peroxide concentration. Therefore, the authors propose the use of low carbamide peroxide concentrations for vital teeth bleaching, and that is in line with American Dental Association (ADA) proposal. [21]

Other authors examined the colour change on intact bovine incisors. Tooth colour was determined by a spectrophotometer (Easyshade, Vita Zahnfabrik, Germany). Teeth were bleached

with 10% and 16% carbamide peroxide (four hours a day, for two weeks) and 37% carbamide peroxide (three times for 20 minutes in one session, for three sessions). This study showed that after the first week of bleaching, 10% and 16% of carbamide peroxide were significantly more effective than 37% of carbamide peroxide. At the end of the bleaching treatment, there was no statistically significant difference in the bleaching success among the 10%, 16%, and 37% carbamide peroxide. The same efficiency of at-home and in-office-bleaching techniques was observed. The authors recommend the use of low concentrations of bleaching agents and the use of at-home bleaching technique.[21]

Moghadam at al examined the success of colour change, long term effect and teeth sensitivity associated with in-office and at-home bleaching techniques. Half of the subjects were involved in at-night bleaching of maxillary teeth (Opalescence 15%, Ultradent, South Jordan, UT, USA) and in-office bleaching of mandibular teeth (WHITE XTRA 38%, Bydental, Maltinti, Italy), while the other half of subjects were assigned for office bleaching of maxillary teeth and at-home bleaching of mandibular teeth, with same agents. Participants were followed for two weeks and one, three and six months after the bleaching process. Tooth colour in all patients was determined by using a colour key and a spectrophotometer. This study showed that there was no difference in the degree of colour change between two bleaching techniques or in terms of colour regression immediately after bleaching and at two weeks, one month and three months from the end of treatment. The both bleaching methods are clinically identical at different time intervals in post-treatment sensitivity.[22]

Mounika et al examined the effectiveness of different concentrations of carbamide and hydrogen peroxide on the degree of colour change of vital teeth. Teeth were bleached by in-office bleaching technique with 35% hydrogen peroxide, three times for 15 minutes per session, in three sessions and at-home bleaching technique with 16% carbamide peroxide, three weeks, eight hours a day. The colour assessment was performed with a spectrophotometer before the bleaching process and after one, two, three and four weeks, or three and six months after the bleaching process was completed. The results of this study showed the same efficacy in tooth colour changes with both bleaching techniques, which confirms the findings of other studies that tooth exposure time to the bleaching agent is more important in the bleaching process than the agent concentration. The dye regression occurred between three and six months after the bleaching process in both techniques.[23]

Using at-night and in-office vital teeth bleaching techniques, Matis et al tested the effects of different concentrations of hydrogen peroxide (15%, 25%, 30%, 35%, 40%) on colour changes and its persistence after the bleaching process was completed. Tooth colour was determined before bleaching, immediately after bleaching process and one, two, four and six weeks after the bleaching treatment using a colorimeter and colour key. All types of agents have shown efficacy in colour changes. Three of the four bleaching agents with the lowest concentration had the largest colour changes immediately after bleaching, while the three bleaching agents with the shortest contact time showed the smallest colour changes. From the results of this study it can be concluded that the contact time of the bleaching agent with the tooth was more important than the concentration of the agent.[24]

In conclusion, the teeth bleaching technique with 16% carbamide peroxide gel and the teeth bleaching technique with 30% carbamide peroxide gel have shown the same efficiency in tooth colour changes.

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CONFLICT OF INTEREST

None.

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ORIGINAL ARTICLE

The Characteristics of the Outpatient Utilisation of Medicines in the Republic of Srpska in the period 2009-2017

Vanda Marković-Peković[1], Ljubica Bojanić[2], Svjetlana Stoisavljević-Šatara[3]

ABSTRACT

Background: Monitoring and measuring of the medicine utilisation enables to assess the quality of use of medicines, providing the evidence-based data for the improvement of the prescribing practice and a more rational use of medicines. The aim of this study was to analyse utilisation patterns of medicines and to compare the results with other countries.
Methods: A retrospective, observational study to analyse outpatient medicines utilisation in the Republic of Srpska between 2009 and 2017. Data of medicines utilisation were retrieved from the national database in the Public Health Institute of the Republic of Srpska and calculated and analysed by using the Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) methodology. The results were expressed as Defined Daily Doses (DDDs) per 1,000 inhabitants per day.
Results: Total medicines utilisation increased, from 448 DDDs in 2009 to 1,036 DDDs in 2017. Cardiovascular medicines (group C) were the most used medicines, and their share in the total utilisation increased from 36.6% in 2009 to 44.4% in 2017. Among them, the most frequently used were angiotensin-converting enzyme inhibitors, plain and in combinations with diuretics, namely enalapril. The share of medicines used in diabetes in the total utilisation increased from 3.9% in 2009 to 5.1% in 2017. Metformin and glimepiride accounted for about 83% of the blood glucose lowering medicines group (A10B). Among the antithrombotic medicines, the most frequently used were platelet aggregation inhibitors (B01AC), mainly acetylsalicylic acid whose use tripled since 2009. Diclofenac was the most frequently used non-steroidal anti-inflammatory and antirheumatic drug (M01).
Conclusion: The trend of increased medicines utilisation was observed in this study. This finding is comparable with other countries. Variations between countries in the preferred medicines within a class as well as the extent of medicines use were observed. These differences were probably consistent, but not solely attributable, to differences in local guidelines and reimbursement policies.

Key words: utilisation of medicines, ATC/DDD methodology, international comparisons, rational use.

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INTRODUCTION

Medicines are only one component in the maintenance and restoration of the health of communities and individuals, and are segment in the prevention, diagnosis and treatment of diseases. If used appropriately, medicines have the potential to relieve suffering from disease and to restore health, which is why they are placed amongst the top priorities in every health sys-

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CONTENT

tem.[1] With their pharmacological properties, economic impact on health systems and environmental impact, utilisation of medicines exerts important effects on health systems. As in general, consumption of medicines continues to increase,[2-4] the knowledge of the quantitative and qualitative patterns of medicines use is a key element for allocation of health care resources and development of sustainable health policy. In 2016, after inpatient and outpatient care, medicines represented the third largest item of health care spending and accounted for one-sixth of health expenditure in the European Union, thus confirming the vital role that medicines have in the health system.[5]

Systematic use of routinely collected data on medicines can be employed in assessing the value of medicines in use in health care systems, and can give an insight in the efficiency, quality and fairness of health services.[6] Monitoring and measuring of the medicines use enables to assess quality use of medicines, to identify areas of suboptimal medicines use and provide feedback to prescribers, and thus improvement of pharmacotherapy. The volume of prescribed medicines may be affected by a number of factors, such as population size and age, disease prevalence, changes in medical practice, prescriber and patient behaviour, developments in medical practice, new medicines, reimbursement policies, new guidelines that adjust the recommended treatment per patient or which enlarge the population of patients who would benefit from the treatment.[7, 8] Our country, like other countries in transition, is characterised by the demographic shift, with an increase in life expectancy and population aging.[9] So, the major burden of diseases is shifted toward the whole range of chronic diseases, and clinical guidelines were developed for the most common non-communicable diseases.[10] At the same time the legislative and organisational system for collecting the data on the medicines utilisation has been established.

Previous studies conducted by our research group have shown the importance of continuous monitoring and analysing of medicines utilisation and expenditure patterns in the population.[4, 8] These studies enabled us to assess the influence of multiple measures introduced in our healthcare system in recent years to increase prescribing efficiency, and furthermore to suggest additional reforms or measures to further enhance the prescribing efficiency. With the aging of our population and the increasing prevalence of multiple medicinal conditions in the elderly, the share of the long-term medicine use has increased proportionally. This points out the public health importance of the utilisation patterns analyses in the elderly population with the aim to optimise drug prescribing for this group. Understanding of current patterns in medicines use is important to support pharmaceutical policy implementation as a part of a sustainable health policy, considering the expected health outcomes and the related impact to the medication expenditure.

In order to continue with the monitoring and evaluation of the utilisation of medicines in our country, the aim of this study was to analyse the utilisation patterns of medicines and to compare the results with the ones in other countries.

METHODS

This was a retrospective, observational study on outpatient medicines use over the period from 2009 to 2017. Data was retrieved from the national database located in the Public Institute of Health (PHI). Reports on all medicines dispensed to the patients in all retail pharmacies were sent annually to PHI for collation. This period was chosen as PHI has been collecting and processing data since 2009.

Medicines utilisation was calculated using the Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) methodology,11 as the internationally accepted methodology for measuring medicines utilisation.12-16 The ATC system classifies medicines into different groups according to the organ or system on which they act and their chemical, pharmacological and therapeutic properties. Medicines were classified into ATC groups by its international non-proprietary name. The results were expressed as a DDD per thousand inhabitants per day (DDDs). DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. It is a technical, statistical unit of measurement and does not necessarily reflect the recommended or actual used daily dose. DDD is a tool for national and international compar-

isons between different geographical areas and health facilities.11 Descriptive analyses on the data were performed. Data were expressed as absolute numbers with or without percentages. All analyses were undertaken using Microsoft Excel 2010 program. The results were presented in tables.

RESULTS

Total medicines utilisation increased, from 448 DDDs in 2009, to 1036 DDDs in 2017. The utilisation increased in almost all anatomical groups, and the highest increase was observed in groups C (cardiovascular system), B (blood and blood forming organs) and A (alimentary tract and metabolism). Group C medicines share in the total utilisation of medicines increased from 36.6% in 2009, to 44.4% in 2017 (Table 1).

Medicines acting on the renin-angiotensin system (C09) and calcium channel blockers (C08) had a highest utilisation in the group C. The C09 group share in the total medicine utilisation increased from 15.7% (2009) to 24.6% (2017) (Table 2), and the most prescribed were angiotensin-converting enzyme inhibitors (ACEIs), plain (C09A) and in combinations (C09B) (Table 3). The share of the medicines used in diabetes (A10) in the total medicine utilisation increased from 3.9% (2009) to 5.1% (2017) (Table 2). In total medicines utilisation, the share of psycholeptics (N05) ranged from 4.5% (2009) to 3.4 % (2017) and of psychoanaleptics (N06) from 1.3% (2009) to 1.9% (2017) (Table 2). Anxiolytics were the most prescribed among psycholeptics (Table 3), namely diazepam followed by alprazolam. Utilisation of antidepressants has grown steadily and has increased 3.5-fold during the observed period (4.7 DDDs in 2009 vs 16.7 DDDs in 2017).

Utilisation of drugs for obstructive pulmonary diseases (R03) has increased 2.5-fold in number of DDDs and the share in the total medicine utilisation increased from 1.4% (2010) to 1.9% (2017) (Table 2).

Among calcium channel blockers (CCBs), selective CCBs with mainly vascular effects (C08C) were prescribed the most, with about seven percent share in total medicines utilisation (Table 3). A continuous increase in the utilisation of drugs for acid-related disorders (A02) was

Table 1: Total utilisation of medicines at the level of main anatomical groups (ATC level I), in number of DDDs

ATC code	Anatomical group	2009	2010	2011	2012	2013	2014	2015	2016	2017
C	Cardiovascular system	163.8	242.9	294.4	285.4	300.9	338.7	348.7	422.9	460.2
B	Blood and blood forming organs	52.8	82.7	99.4	94.3	97.1	111.2	127.6	130.2	131.3
A	Alimentary tract and metabolism	60.3	70.8	105.6	105.3	106.7	110.4	108.1	123.1	126.6
N	Nervous system	74.1	93.5	94.0	94.3	99.5	102.4	99.3	84.8	96.0
M	Musculo-skeletal system	17.1	39.6	48.2	47.7	50.4	56.5	55.5	65.6	71.1
R	Respiratory system	24.2	26.5	27.3	23.9	26.3	30.7	34.6	39.5	39.2
G	Genito urinary system and sex hormones	6.7	12.3	13.9	15.4	14.9	16.2	18.3	21.9	24.5
D	Dermatologicals	10.3	15.4	19.9	22.4	23.2	28.0	20.4	24.0	23.6
J	Antiinfectives for systemic use	20.7	18.1	18.0	16.0	18.7	15.8	17.7	20.0	23.2
H	Systemic hormonal preparations, excl. sex hormones and insulins	10.0	8.5	11.2	12.2	11.8	14.8	14.8	20.2	21.7
S	Sensory organs	7.3	9.4	10.9	10.6	10.9	12.8	13.3	14.8	15.9
L	Antineoplastic and immunomodulating agents	0.7	2.5	1.9	2.1	2.1	2.2	2.7	2.5	2.9
P	Antiparasitic products, insecticides and repellents	0.7	2.5	1.9	2.1	2.1	2.2	2.7	2.5	2.9
	Total	**448.2**	**622.3**	**746.5**	**731.5**	**764.3**	**841.7**	**861.2**	**969.5**	**1036.3**

CONTENT

Table 2: Total medicines utilisation of 20 most prescribed therapeutic groups (ATC level II), in number of DDDs

ATC code	Therapeutic group	2009	2010	2011	2012	2013	2014	2015	2016	2017
C09	Agents acting on the renin-angiotensin system	70.4	106.4	138.7	135.8	148.6	167.8	187.5	229.2	254.8
B01	Antithrombotic agents	30.3	46.8	54.8	55.1	58.9	67.9	86.6	84.9	89.5
C08	Calcium channel blockers	30.5	42.5	50.3	48.4	53.8	64.2	56.6	70.0	72.4
A10	Drugs used in diabetes	17.3	23.2	34.3	33.5	35.5	39.1	41.9	52.3	52.8
M01	Antiinflamatory and antirheumatic products	16.1	25.3	30.4	30.5	31.7	35.4	34.9	40.8	46.1
B03	Antianemic preparations	21.2	34.6	43.7	35.3	34.5	39.8	35.5	44.8	41.4
C07	Beta blocking agents	11.9	16.4	21.3	20.6	22.8	25.5	26.9	34.1	40.2
N05	Psycholeptics	20.0	29.2	33.2	29.3	29.4	31.7	33.7	36.5	35.5
A02	Drugs for acid related disorders	10.9	12.9	19.3	21.7	21.3	23.2	21.9	28.0	30.4
A11	Vitamins	24.0	22.1	38.4	31.7	32.7	30.3	24.9	27.6	29.0
C03	Diuretics	11.4	21.0	20.5	21.7	20.3	22.0	24.4	27.0	28.9
C01	Cardiac therapy	20.9	27.9	33.2	31.5	27.4	28.8	23.1	26.7	27.3
N02	Analgesics	41.0	46.7	39.1	42.3	54.0	44.9	37.9	16.5	25.0
J01	Antibacterials for systemic use	20.2	17.6	17.5	15.7	18.4	15.6	16.8	19.8	23.1
M02	Topical products for joint and muscular pain	0.3	13.2	16.2	15.3	16.5	18.5	18.6	21.7	21.7
N06	Psychoanaleptics	5.7	7.9	11.0	11.9	12.5	14.3	14.4	17.6	20.4
C10	Lipid modifying agents	7.8	12.8	9.1	9.6	10.2	12.3	13.5	18.8	20.0
R03	Drugs for obstructive airway diseases	8.1	8.6	10.4	9.7	10.6	12.3	15.2	19.3	19.6
H03	Thyroid therapy	8.1	8.6	10.4	9.7	10.6	12.3	15.2	19.3	19.6
G04	Urologicals	1.6	2.3	4.6	5.9	6.5	8.2	10.2	12.6	15.0

observed, with the share in the total medicine utilisation of about 3% (Table 2). The most prescribed were drugs for peptic ulcer and gastro-oesophageal reflux disease (A02B) (Table 3), namely proton pump inhibitor pantoprazole and H2-receptor antagonist ranitidine (Table 4).

Table 3: Total utilisation of ten most prescribed pharmacological groups (ATC level III), in number of DDDs

ATC code	Pharmacological group	2009	2010	2011	2012	2013	2014	2015	2016	2017
C09	Angiotensin-converting-enzyme (ACE) inhibitors, plain	46.7	70.9	93.7	91.6	96.8	109.3	118.7	147.2	154.8
B01A	Antithrombotic agents	46.7	70.9	93.7	91.6	96.8	109.3	118.7	147.2	154.8
C09B	Angiotensin-converting-enzyme (ACE) inhibitors, combinations	30.3	46.8	54.8	55.1	58.9	67.9	86.6	84.9	89.5
C08C	Selective calcium channel blockers with mainly vascular effects	27.8	39.0	46.5	45.1	50.8	61.2	53.7	66.7	69.5
M01A	Antiinflamatory and antirheumatic products, non-steroids	16.1	25.3	30.3	30.5	31.7	35.4	34.9	40.8	48.1
A10B	Blood glucose lowering agents, excl. insulins	12.7	18.0	28.9	28.3	30.4	34.5	35.8	44.9	46.8
C07A	Beta blocking agents	11.9	16.4	21.3	20.6	22.7	25.4	26.7	33.8	37.8
B03B	Vitamin B12 and folic acid	15.3	27.1	35.6	30.0	29.6	33.9	30.9	35.3	32.1
A02B	Drugs for peptic ulcer and gastro-oesophageal reflux disease	10.3	11.9	18.6	21.1	20.8	22.6	21.6	27.6	30.3
N5B	Anxiolytics	17.5	24.9	28.8	25.5	25.2	27.4	28.8	30.4	30.0

Among the antithrombotic medicines (B01A), the most frequently used were platelet aggregation inhibitors excluding heparin (B01AC), namely acetylsalicylic acid whose use tripled since 2009 (Table 4). The most frequently used were blood glucose lowering medicines, excluding insulin (A10B) (Table 3), namely metformin and glimepiride who accounted about 83% of A10B group utilisation (Table 4). Non-steroid (M01A) medicines were the most used among anti-inflammatory and antirheumatic medicines (M01) (Table 3), specifically diclofenac (Table 4).

Four out of five most prescribed medicines were cardiovascular medicines. Plain ACEI enalapril was the most frequently used, with the increased share in the total medicines' utilisation from 7.6% (2009) to 9.3% (2017). Amlodipine was the dominantly prescribed selective CCBs. Consumption of non-opioid analgesics (N02B) dominated among analgesics (N02), namely the combination of paracetamol with caffeine, codeine and propyphenazone. The high-ceiling diuretics comprised about 2/3 of diuretics (C03) utilisation and furosemide was the most prescribed (Table 4).

Table 4: Twenty most prescribed medicines, in DDDs

ATC code	INN	2009	2010	2011	2012	2013	2014	2015	2016	2017
C09AA02	enalapril	34.3	49.0	63.3	61.7	67.2	74.5	80.3	94.0	96.5
B01AC06	acetylsalicylic acid	45.7	45.5	49.6	50.1	53.6	63.1	81.0	78.2	82.2
C08CA01	amlodipine	32.6	35.5	41.6	40.1	45.0	53.6	45.9	53.8	53.8
C09BA02	enalapril, hydrochlorothiazide	15.5	23.1	28.8	27.6	32.0	33.1	39.1	41.7	52.7
C09AA05	ramipril	3.1	6.1	11.1	12.6	13.0	13.8	17.6	26.3	30.3
A10BA02	metformin	5.1	7.6	11.1	15.9	13.6	16.2	18.0	23.6	26.1
M01AB05	diclofenac	10.3	16.2	19.1	19.5	19.4	20.5	20.7	21.6	25.0
B03BB01	folic acid	0.6	0.7	20.3	21.1	18.5	17.8	18.3	22.4	21.4
N02BE51	codeine, caffeine, paracetamol, propyphenazone	3.4	26.3	19.8	22.1	20.3	19.5	19.0	16.8	20.2
C03CA01	furosemide	5.5	11.1	10.6	12.8	11.3	12.3	13.5	16.8	18.4
N02BE01	paracetamol	3.1	3.4	4.3	5.6	9.2	6.8	7.5	9.6	18.2
C07AB02	metoprolol	5.9	8.6	10.6	10.1	11.2	12.3	12.1	14.2	17.0
A02BC02	pantoprazole	0.6	1.2	2.1	2.8	4.1	7.0	7.3	11.4	14.0
A02BA02	ranitidine	7.2	6.8	11.9	14.2	13.0	12.6	12.0	14.0	13.8
A11GA01	ascorbic acid	16.1	13.3	12.7	10.7	16.0	13.7	12.4	12.8	13.6
H03AA01	levothyroxine	4.0	3.0	5.6	5.6	6.3	8.5	8.1	11.8	13.1
C09AA03	lisinopril	2.2	3.3	5.1	5.6	5.9	6.7	8.1	10.8	12.7
A10BB12	glimepiride	0.5	1.4	2.6	3.8	5.8	8.3	9.0	12.1	12.5
C10AA05	atorvastatin	4.5	7.8	5.5	5.2	5.6	7.6	8.0	11.7	12.4
C07AB07	bisoprolol	0.5	0.1	2.1	2.6	3.8	5.1	6.4	9.8	12.0

INN, International Non-proprietary Name

DISSCUSION

This study revealed an increasing trend toward the utilisation of medicines, and given the previous studies[17,18] it was not a surprising finding. Similar trend was observed in other studies.[2-4, 7] The quantity of medicines tends to increase over time in most therapeutic classes, which may be explained by population ageing, the rise in the prevalence of chronic diseases such as cancer and diabetes, the availability of new medicine treatments or changes in the physicians' prescribing practices,[19] that may have had an influence on our patterns of medicines utilisation, too.

Medicines classes used for treatment of the most common chronic non-communicable diseases were of the highest degree of utilisation,[9, 20] as in other countries.[21-26] Premature mortality related to the major non-communicable diseases can be reduced if appropriate, timely and collective action is taken.[27-29] Among the other activities undertaken towards improvement of health of the population,[30] an update of reimbursable medicines list was carried out precisely to provide better therapeutic choice of medicines, contributing thus to the reduction of morbidity and mortality. Although major non-communicable diseases affect people of all ages, they are often associated with older age groups. Our population is evidently aging as the share of elderly (≥ 65 years) has increased, from 18% (2007) to 22% (2014), and of people aged 50-64 years, from 19% (2010) to 23% (2014). As the trend in ageing of population has significantly increased over the time, it directly influenced the volume of medicines needed for care of elderly people since they have multiple chronic diseases and requires larger number of prescriptions. A recent study among elderly patients has showed an increase of those who use more medicines for longer period of time, with an increased polypharmacy prevalence (use of ≥ 5 different medicines).[8]

Cardiovascular (CV) medicines were the most frequently prescribed, like in other countries.[21-26, 31, 32] The trend of steady increase in the CV medicines use has been seen over the last few decades[33] as they are key elements in preventing and treating CV diseases, which are the leading cause of death and disability worldwide.[34-36] It has also been a leading cause of our population's mortality for the last 20 years.[9, 37] The health policy planners therefore focused their attention on a national CV programme, implementation of the national and European guidelines[38-42] and selection of the reimbursed medicines. A decrease in CV mortality, from 53.6% in 2002 to 48.7% in 2016[9, 17] might be attributable to improved CV care, including pharmacotherapy, as the association between the increase in CV medicines use and a decrease in CV mortality was confirmed.[43,44] Despite the significant increase in CV medicines use, the mortality rate was rather high and CV diseases has remained a leading cause of morbidity and mortality.[44]

The highest utilisation of antihypertensive medicines, such as ACEIs, CCBs and beta blockers, and the increased utilisation of diuretics, are in accordance with clinical guidelines for hypertension. These medicines, with ARBs, are major classes for the treatment of hypertension, used either as monotherapy or in combination with other drugs (mainly diuretics). Over the past 20 years a constant increase in utilisation of these classes was noticed.[45] Enalapril as a monotherapy and in combination with hydrochlorothiazide was the most used ACEI, followed with ramipril (monotherapy) and lisinopril (combination). As a monotherapy, the ACEIs were also frequently prescribed in Serbia,[21,23] Finland[46] and Norway.[31] High use of ACEIs in combination with diuretics was not surprising, because treatment of hypertension should be preferentially based on combinations of ACEIs or ARBs with a CCB and/or a thiazide diuretic as the most effective evidence-based treatment strategy to improve blood pressure.[42] These combinations are available on our market in a single pill and in a range of doses, enabling simplification of treatment, flexible prescribing and better patient adherence. Country differences were noticed in the preferred ACEIs [23, 24, 26, 31, 32, 47] and ARBs.[23, 24, 31, 46] They may be influenced by the recommendation to assess the clinical effects, which are proven to be divergent today, of each medicine and their indications in light of the comorbidities.[48]

Although amlodipine was the most preferred CCB, an increase in lercanidipine utilisation was notable (rising from 0.5 DDDs in 2011 to 11 DDDs in 2017). This trend was noticed in other countries[23-25, 31], and could be explained by more favourable tolerability profile.[49] It is a medicine of a higher cost within the class,[50, 51] and value for money is also an important consideration when choosing a preferred medicine. Patients should be provided with a medication appropriate to their clinical needs and at the lowest cost to them and health system. Acetylsalicylic acid was the most frequently used among the antithrombotic medicines, as generally considered effective for the secondary prevention of cardiovascular disease and one of the most frequently used drugs worldwide.[52]

Among statins, atorvastatin was the most prescribed, with the growth in rosuvastatin use (0.7 DDDs in 2011; 5.6 DDDs in 2017). The cross-country variations in the statin use was also noticed by other authors.[53] Atorvastatin reference prices were higher than those of simvastatin, while rosuvastatin was the most expensive

statin. Therapeutic switch from rosuvastatin to atorvastatin was not associated with any differences in safety or lipid control, but resulted in significant drug cost savings.[54] Some studies suggest a continued suboptimal prescribing of lipid lowering medicines in CV population along with the expansion of its use, a shift in use towards asymptomatic and older populations, and overtreatment of people who are unlikely to benefit from this therapy.[33] Further studies of statin use are needed for deeper analysis.

Diabetes was the fifth leading cause of death in women and the seventh in men in 2016.[9] Endocrine, nutritional and metabolic diseases (ICD E00-E90) accounted for about 3% in the total morbidity since 2010.[9, 55] This chronic disease requires continuous medical care, including expenditure in pharmaceutical supplies. Therefore, besides biguanides and sulphonylureas (SUs), during this follow-up period new oral antidiabetic medicine classes became reimbursed, as dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogues and sodium-glucose co-transporter 2 (SGLT2) inhibitors. An increasing trend in the utilisation of metformin and glimepiride may be influenced by the guidelines that suggest metformin as a first choice[56-58] and SUs as an initial drug treatment if metformin is contraindicated or not tolerated, or as a dual therapy with metformin if initial treatment with metformin has not reached the patient's individual goals.[57] International comparisons showed an increasing trend in metformin use, and at the same time by decrease in SUs use.[46, 59-61] We have also noticed a decrease in the use of other available SUs, except for glimepiride. Pharmaceutical marketing might have had some influence on prescribing the first choice among the SUs, as pointed out by Pavlov in Croatia.[62] This possible influence should be clarified in future research. DPP-4 and GLP-1 were less frequently used but an increase in their use was also observed.

Utilisation of proton pump inhibitors (PPIs) and especially of pantoprazole has steadily grown, as elsewhere.[24, 25, 31, 46] Several PPIs, including pantoprazole, were reimbursed, and pantoprazole is the only one also available on the market as a non-prescription medicine (20 mg dose). Ranitidine utilisation was high compared to the other countries.[24, 25, 31,46] At low doses (75 mg) it is available on our market as an over-the-counter (OTC) medicine. The reason for its still wide use, despite the availability of the more effective acid-suppressant PPIs, is to be further explored. A decreasing trend in the use of diclofenac was expected regarding the new scientific evidences about its safety profile, i.e. cardiovascular side effects, as informed by the Agency of Medicines and Medical Devices of Bosnia and Herzegovina at the beginning of 2014. Moreover, this is a sole prescription medicine for oral use. In other countries ibuprofen is preferred due to a better safety profile and more OTC medicines available in pharmacies because of which diclofenac exhibits a declining trend.[24, 25, 31, 46] Ibuprofen utilisation has grown over the period.

The strength of this study is a nine-year follow-up period, a timeline that is long enough to allow for the determination of the existing trends. The medicines utilisation data came from the official national source, thus providing robustness. Data built on the medicines dispensed to patients were considered as a strength, although there was awareness that it does not necessarily ensure that the medicine was taken by the patient. The nature of the data in this administrative database that allowed only determination of trends may be considered as a limitation. More in depth analysis could be performed with available data on the age, gender, diagnosis, clinical information, changes in medicines use, therapy intensification, medication duration etc. Beyond the limitations, these results can serve as a starting point for further studies about the use of medicines and its rationality.

CONCLUSION

The utilisation of medicines showed an increasing trend, which is similar to other countries. In addition to the similarities, certain differences in the use of medicines were also observed among the countries, as variations in the preferred medicines within a class and the extent of medicines use. These differences were probably consistent, but not solely attributable, to differences in local guidelines and reimbursement policies. Value for money, for health system and patients who pay for their own medicines, is an important consideration when choosing a preferred medicine according to scientific evidence and the patient's needs.

CONTENT

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CONFLICT OF INTEREST

None.

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Austrian Measures for Prevention and Control of the Plague Epidemic Along the Border With the Ottoman Empire During the 18th Century

Boro Bronza[1]

ABSTRACT

Throughout centuries, policies of states in the Western Balkan region were largely shaped in accordance with the infection outbreaks and consequences of plague epidemics. Austrian policy was not out of the line in this context, so the general aspects of dealing in organisation of military border with the Ottoman Empire were always crucially connected with the reactions towards epidemics. Especially in the 16th and 17th centuries, Austria battled hard to stop expansion of epidemics that during those times mainly fluxed in from the side of the Ottoman Empire. The decisive change came in the 18th century. During this period, the Austrian reaction to plague outbursts at the area of south-eastern Europe was already a product of general rise of sanitary standards in western European regions, where attempts for implementation of some of newest qualities in perception of the quarantine requirements and medicine applications met with complex aspects of life in a turbulent area of military border. Efficiency of measures was instant and sustainable in the long term.

Key words: plague, Austrian Empire, Ottoman Empire, epidemics, quarantine.

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Some crucial movements in the aspect of political shaping of south-eastern Europe during last several millennia were firmly connected with the directions and timing of plague epidemics. Such patterns have also been pretty much present at the area of western Balkans throughout era of confrontations between the Habsburgs (the Austrians) and the Ottomans (the Turks), especially in the 17th and 18th century. Special breakthrough in the taming of the rage in the destructive epidemics came in the 18th century, when the Austrian side started the series of measures that in the long term completely eliminated plague as significant factor in the political calculations and also as essential threat to the regions next to Ottoman border.

The significance of plague outbreaks

The penetration of the Habsburgs into the interior of the Bosnian Pashalik (the territory governed by pasha) was to some extent prevented by the plague epidemics, which were relatively frequent in the Pashalik area during the 17th century. News from Dubrovnik on the events in Bosnia throughout the Great Vienna War (1683-1699) between the Austrians and the Ottomans also reported on the details of the plague outbreaks. In Bosnia, the epidemics raged constantly in the period 1686-1690, and then again in 1694.[1] Probably one such epidemic was the cause of the stalemate of a large and very successful offensive of the Austrian army, which, during the winter of 1688/89, moved from northern Serbia,[2] through Zvornik and Srebrenica (eastern Bosnia), to the plateau of Romanija, and in fact to the entrance to Sarajevo.[3]

Plague epidemics were very common throughout the 18th century in the Ottoman Empire. Out of a total of 100 years of that century, the plague itself was present in Istanbul for as long as 64

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years.[4] Istanbul, as the largest city and largest meeting point of the Empire, was the destination where epidemics were most common. Other parts of the Ottoman state were affected by epidemics at very different frequencies. In Wallachia and Moldova, the plague has raged for a total of 45 years, in Serbia, Bosnia and Herzegovina for 41 years, in Bulgaria for 18 years, and in Mesopotamia for only 4 years.[4] At the beginning of the century, the plague was still present in western and central Europe. It was raided in parts of the Habsburg Monarchy between 1700 and 1714. New epidemics occurred in 1726, 1729-1732, 1738-1739 and 1743.[5] With the passage of the 18th century, the number of epidemics was decreasing. The development of a sanitary cordons at the border with the Ottomans was of great importance for such an outcome.

Quarantine stations, as a system to prevent the spread of the plague infection, existed in some coastal cities, such as Dubrovnik, as early as the late Middle Ages. Since the plague infection at the territory of the Ottoman Empire was largely viewed through the prism of a religious fatalism, implying that epidemics were seen as a "*divine punishment*" against which nothing could be done, there was no fundamental change during the 18th century in relation to the most dangerous infectious disease at those times.[6] The Habsburg Monarchy was greatly affected by epidemics, as it shared a long land border with the Ottoman Empire. Therefore, one of the most important forms of the Habsburg border organisation according to the Ottomans was the establishment of an efficient sanitary cordon. During the 18th century, the military landscape of the Habsburg Monarchy stretched from Bukovina to the Adriatic Sea, approximately 1,900 kilometres long (Figure 1). The depth of its territory varied from 15 to 50 kilometres. The total area of this specific military zone was 47,400 square kilometres. In addition to all its functions related to the defensive and offensive plans of the Ottoman Empire, the accumulation of manpower for military purposes, the transmission of trade activities, etc was significant. The military landscape served as a sanitary "shield" for the inland Austrian regions.

The institutional development of a system to prevent the spread of the plague epidemic to

Figure 1: Habsburg Monarchy borders throughout 18th century

the Habsburg Monarchy ran through the whole of the 18th century.

As early as during the reign of Leopold I (1658-1705), the rule was that all forms of traffic with the Ottoman Empire should be interrupted during the plague epidemic.[6] The first official regulatory document on border behaviour to prevent the spread of the epidemic was the so-called "Plague patent" ("Pestpatent") from 1710. This action was not yet strictly of sanitary character and not entirely successful, as the Habsburg countries were also affected by the plague epidemic of 1713-1715. In Vienna in 1718, on the occasion of the previous epidemic, the Court Sanitary Commission (Sanitäts Hofkomission) was established, and for the first time medical personnel were deployed at the border.[4] However, the real beginning of the sanitary cordon was linked to the year 1728 and the patent for the construction of a quarantine system, which was issued by Charles VI on 22 October that year. From that moment on, the Military Frontier functioned as a "living wall" towards Ottoman Empire.

In accordance with the patent of 1728, on 3 October 1731, a rule on quarantine and hygienic behaviour at the border was also issued ("Contumaz- und respective Reinigungs-Ordnung").[6]

Figure 2: The Plague Doctor 17th -18th century

That rule strictly prescribed a system of behaviour at the border. In the quarantine stations there had to be one lieutenant with 30 horsemen and three border guards. In each quarantine, there had to be one doctor (Figure 2), who examined the people coming to the border crossings, with whom the quarantines were mandatory. The mandatory implementation of these rules, which entailed structural reform of the Habsburg border system and large accompanying investments, could not be implemented quickly and easily.

During the reign of Charles VI, wars were the primary component of the operation of the Habsburg court in the southeast, so that there was no time or resources to concentrate on building a sanitary cordon. The government of the Austrian Empress Maria Theresa intended from the beginning to concentrate more on the formation of a system of protection at the border, but even in the period 1740-1763 it was also occupied by major wars in the north and west. This is why the creation of a dense quarantine system in the true sense began only after 1763. Special sanitary commissions were established, with their headquarters in Karlovac, Zagreb, Osijek, Timisoara and Sibiu. Lazarettes, as institutions for the accommodation of patients directly related to quarantines, were located along the border in places such as Rudenovac, Slunj, Maljevac, Kostajnica and Brod. The 'rastels', which used to be rehabilitation centres, were located along the border in Gradiška, Kobaš and Mitrovica.[4] Quarantine and lazarette in Kostajnica (northern Bosnia) played a special role in view of the heavy traffic of people, especially during migration. The importance of quarantine in Kostajnica was reflected primarily in the fact that Kostajnica was located on the Sarajevo-Banja Luka-Zagreb-Ljubljana-Verona-Milano trade route.[4]

Centralisation of institutions

Special regulations have been made in Vienna to schedule the obligations of border guards who were in service at the quarantine stations. According to them, one border guard had to spend exactly 52 days on quarantine, and 49.5 days he had to spend in his regiment, wherever he was. In addition, he was required to spend 48 days in

military exercises, which in total meant that he had to spend five months a year under arms. For the remaining seven months he was obliged to farm. Under the normal circumstances, the total cadre of sanitary cordons at its 1,900 km length was 4,000 people. If plague occurred in Istanbul, the number of people hired would increase to 7,000. If the plague were to occur in Wallachia and Moldova or Bosnia and Serbia, or at the borders of the Monarchy, the number of people involved would be 11,000.[6]

In the Bosnian pashalik, plague was quite common during the 18th century. The Austrians have always made every effort to find out whether such epidemics are present in certain areas of Bosnia and Herzegovina. Thus, through Dubrovnik they learned that the plague epidemic had been present in Herzegovina in 1722-1723, and again in 1782-1783.[7] Austrian spies informed the authorities about the details connected with the outbreak of plague in Bihać and Banja Luka in 1733-1734, and again in 1741-1743.8 The plague outbreak in Bosnia was recorded again in 1787.[1]

One of the most specific points of the Austrian sanitation policy was the determination of the number of days that travellers to Austrian countries had to spend quarantined at the border. In the 1760's the rule was that, at the time of the well-established plague epidemic on the borders of the Monarchy, the mandatory quarantine time had to be 84 days, and in situations where it was only assumed that the plague existed, a stay of 42 days in the quarantine was mandatory. When it was certain that there was no plague, the passengers were quarantined for 21 days. Such strictly formulated hygiene regulations were a good prevention of the spread of the plague, but they drastically reduced mobility at the border, which reflected very poorly on the development of trade. The new sanitary norm of 1770 fixed that quarantine would last 42 days in the case of plague, and in the case of no plague, it would still be 21. Neither was enough to gain trade momentum. It was not until 1785, on the recommendations of Adam Chenot, a special medical advisor who came from Luxembourg to Vienna, that the quarantine in the plague period was 21 days, in the situation of a presumption of a plague epidemic 10 days, and when the Austrian authorities were sure that there was no plague the quarantine was completely abolished.[6] This decision allowed for a much more intensive flow of people and goods at the border, which greatly encouraged trade in the years before the new Austrian-Turkish War of 1788-1791.

The Austrian protection system has proven to be very effective. After its introduction, the plague appeared only in Hungary and Croatia during the great epidemic of 1739-1742.[9] When the system was fully built, after 1763, the plague epidemic no longer appeared on the territory of the Habsburg lands. At the same time, the plague epidemic was quite common in the Ottoman Empire, Russia, Poland, Wallachia, Moldova, and Venice until 1785.[4] This was proof that the system of measures taken by Austria to prevent the spread of a dangerous disease outweighed its neighbours' modest attempts to build their sanitary cordon systems. Some Austrian historians treat the effective actions of the Habsburgs in preventing the spread of the plague epidemic as "saving all of Europe".[6]

Consequences for the trade

The new dimension of trade with the East also entailed regulating trade with the Bosnian Pashalik, with such regulation also being substantially related to the global perception of human and goods traffic in the area of the new border on the Una and the Sava rivers, especially given the more stringent sanitary measures that increasingly developed within the Military Landscape. On 25 August 1742, the Court of War Council sent a directive to General Quadanji to find the most suitable place at the border for the construction of larger capacity quarantines, which would, in fact, create the conditions for centralisation of border traffic in one location (*"... die erbau- und herstellung eines eigenen Contumazhausses zwischen Bosnien und Croathen disseiths der Vuna ohnweith Novi von seithen des Militaris nur nöthig seye, damit zu errichtung sothanen Gebaües ein bequemmen Plaz ausfindig gemacht, und assigniret werde..."*).[10] At that moment, the Council did not have the right information on the quality and quantity of work of the already existing quarantine in Kostajnica. General Quadanji was told that he should first inquire about the details of the quarantine operation in Kostajnica,[11] in order to be convinced at all of the necessity of building a new quarantine facility, which, roughly, should be located near Novi (north-west Bosnia). In this regard, representatives of the higher directorate of the Slavonian Chamber, Johann Wilhelm Vogt and Johann Paul Passardi, sent a letter from Osijek to the Court Chamber on 31 August 1742, with their opinion on the eventual establishment of the new quarantine. Repre-

sentatives of the Slavonian Chamber said that the quarantine in Kostajnica is very necessary, especially in the context that the new border is still very vulnerable, especially in the Dubica area (*"welcher ratione deren zwischen denen Türckhen in Bosnien und Croathen zu Dubitza annoch schwebenden Graniz-strittigkeithen zu aussmachung der sache sich ehehin alda in Loco befindet... "*).[10] The cost for establishment of a new quarantine was estimated at 4,000 ducats. Due to all of the above, they concluded that the quarantine in Kostajnica was still necessary, and that there was no particular need to build a new quarantine at Novi (*"Bey allem deme scheinet es, dass.. die Absicht das erösterte Contumaz Hauss zu Novi errichten zu lassen, nun umb so viellmehr zerfalle, alss eben ein dergleichen Gebaüde alschon zu Kostaniza ohnweith von obigen Orth vorhanden seye..."*).[10]

The following year, it was definitely decided to build a new quarantine, but in the immediate vicinity of the old one, in Kostajnica. Quarantine was built on the Balanka River Island. On 21 June 1743, Ban Bacanyi informed the Court of the War Council of Valpovo about the great expenses that were necessary to build the new, huge building, but also about the extraordinary benefits it would bring to the Monarchy. The main engineers for the quarantine construction were Lazzeni and Griesseyssen. The Quarantine looked like a lavish fort. The Ban emphasised that construction was not about aesthetics, but about the quality and purpose of the material, so that the building could last for as long as possible and serve its purpose (*"... ein solches Gebaü blos zur wohlfahrt, und sicherheit des landes anzusehen, also auch hieran weiter keine Zierd erforderlich ist, folgends nur dauerhafte, und diensam gute Bau-materialien fürgekehrt..."*).[10] Baron Patačić, the Commander of Kostajnica, made the keynote address on the procurement of the construction materials and all other quarantine-related matters. With the completion of operations, Kostajnica definitely became a key quarantine and border centre on the left bank of the Una and the Sava rivers (Figure 3), which implied that in the following decades its importance in the context of trade traffic has grown tremendously.

Figure 3: Map from 1725, with the border between the Habsburg Monarchy and the Ottoman Empire at parts of the Una and the Sava (orientation towards south)

The Kostajnica quarantine was also often visited by the Serbian traders from Sarajevo. Todor Rajović, Jovan Mihadović and Andrija Vuković arrived in the quarantine on 21 December 1754.

There, the quarantine surgeon on duty, Wisinger, concluded that all traders were healthy and that their further journey to the Monarchy did not present a danger in terms of transmitting infectious and other diseases (*"Kommen aus der Türkey v[on] Sarajeva der Totor Rayovich, Jovan Mihadovich und Andrea Vukovich, 3 Grichische Handels-leuth; Seynt Gesund befunden."*).[10] The quarantine policy in Kostajnica, by the way, was very strict throughout 1754, due to the frequent news of the plague epidemics in Bosnia, Serbia and other parts of the Ottoman Empire.[12] On 28 May, the quarantine surgeon Wisinger informed the Banska Krajina Command that the first news of the spread of the infection from Turkey had arrived in Kostajnica from the Karlovac General's area. The contagion spread across the mainland, south of Novi. This is why particularly tight controls have been established in that part of the border (*"Übrigens Habe ich gantz Jüngst zwahr noch per indirectum Ir doch eine Bestättige nachricht erhalten, welcher gestalten man in dem Benachbarten Generalat Carlstatt aus aus dem Türkischen gebieth neuerliche Spuren einer Contagiosen Infection habe, und daher auch schon ein scharfer Cordon an dortigen Granitzen gezogen worden seye..."*).[10] The visitor concluded that it was necessary to establish a frequent patrol system on the left bank of the Una river as well, and to prevent all contact with the other bank in order to prevent infection from spreading in the Banska Krajina area (*"Es ist also die Vordorge erfoderen... und Veranstalten, dass an denen Gräntzen des Vuna Flusses auf das fleisigste patroulliret, und alle abseitige communication und postirungen wohl entgegen Zustehen, und solche einzustrecken."*).[10]

This meant that during 1754 not only a strict quarantine (Figure 4) was introduced for the transport of people and livestock, but also for all the merchandise. Several deliveries of cotton coming from Macedonia, then heavily affected by the plague epidemic, as well as tobacco, imported from Bosnia by the traders Ivan Parlo and Todor Jurić, were halted in July (*"Es zeichten Ivan Parlo und Thodor Jurich bey mir an, wie dass selbige einigen Vorrath Türkischen blätter Tabak in 60 Cent[ner]s Bestehend in Bossnien erkauft Hätten, und solchen nun gerne Herüber Bringen mögten..."*).[10] The purchase of hay from the Bosnian Pashalik area has been a constant in Austrian trade policy. In the conditions of rigorous regulation of the traffic of people and goods, alternative ways had to be found to maintain the continuity of that essential aspect of trade. On 29 July, the Banska Krajina governor from Petrinja informed Colonel Kleefeld that future hay purchases made it necessary for the Krajina officers to be present with the buyers themselves, and that the Turkish side should oblige its officers to be present with the sellers. When picking up the goods, it was not allowed for Habsburg representatives to come into long contact with the hay sellers from Turkey, or to talk to them for long, but after the goods were taken, they should leave the place of purchase as soon as possible (*"... niemand von denen Türkischen Unterthanen mit denen unsrigen Granitzern einen Umgang pflegen, viel weniger einen Handel, und Wandel treibe..."*).[10]

The Ottomans were also surprised by the tightening of sanitary criteria at the border. In a letter sent on 15 January 1756, Captain of the fortress in Novi, Rustem-beg Cerić, expressed amazement at the Commander of Kostajnica, Major Kristof Vojković, because the Turkish aga carrying a letter to the Krajina general had to spend 21 days in quarantine (*"... tako razumesmo da na Szkeloi vassi pregye y 21 dan daga metnete na Stalliu, Krainszke navade doszada ni billo, koiszu G-dina G-dina Passe sz-lisztma dohodili Age, Tergovichkim putem nehode dabisze vu Stalliu metalli..."*).[10] Since this had not been the case before, the captain sought an explanation. Despite the protests, the Austrian side has been very consistent and rigorous in its approach to the quarantine. During 1756, quarantine and borders were completely closed for travellers from Turkey after any news of the plague epidemic. This also happened on 10 August, when the director of the quarantine, Xaver Anton Natterhürn, issued special regulations on maintaining cleanliness, especially in and around pig holding rooms ("Schwein-ställe"). With a special consternation, Naterhirn referred to the attempts to smuggle six bales of sheepskin from the Bosnian Pasalik at a market in Zagreb. The smuggling was again attempted by boats across the Una river, during the night, with the agreement of some merchants from the Ottoman and Austrian sides. Even Empress Maria Theresa reacted to such quarantine policy disciplines, and in a letter to the Croatian ban from 1 Oc-

tober 1756, threatened that all those who would not comply with the quarantine policy would be sentenced to death by crossing the border.[10]

In some cases, Austrian hypocrisy within the framework of the sanitary border policy was evident. Namely, the transitions of the Austrian encroachments into the territory of the Bosnian Pashalik, which also took place on a tentative basis, mostly during the night, regardless of the epidemiological situation in the Ottoman Empire, were not subject to the strict sanitary regulations. Such a case, among others, occurred in 1755, when Dubica's commander, Captain Wollgemuth, sent his spy for information into the interior of the Pashalik (*"... zur Einholung der Wahrheit einen Vertratuen Mann in das Türkische abgeschickt..."*).[10]

Problems with violations of the sanitary regulations, that is, continuous attempts to smuggle goods for trade, followed the Austrian border-quarantine policy during the 1760's. Then the quarantine director at Kostajnica, Philippus Haller frequently reported to the Banovina authorities about the traffickers' attempts to smuggle fish, iron, tobacco and other articles into the Military Frontier, violating sanitary regulations, because the Ottoman side of the border was dominated by the plague infection. The situation was particularly dramatic in 1766. On 29 November, Empress Maria Theresa sent a strict order to the Croatian Ban to take maximum precautionary measures for the possible spread of the plague epidemic from Bosnia, before she had already learned that the plague infection was spreading across Bihac and Novi (*"über Bihacz herwers bis Novi bereits vorgreifenden Pest-Übel..."*).[10]

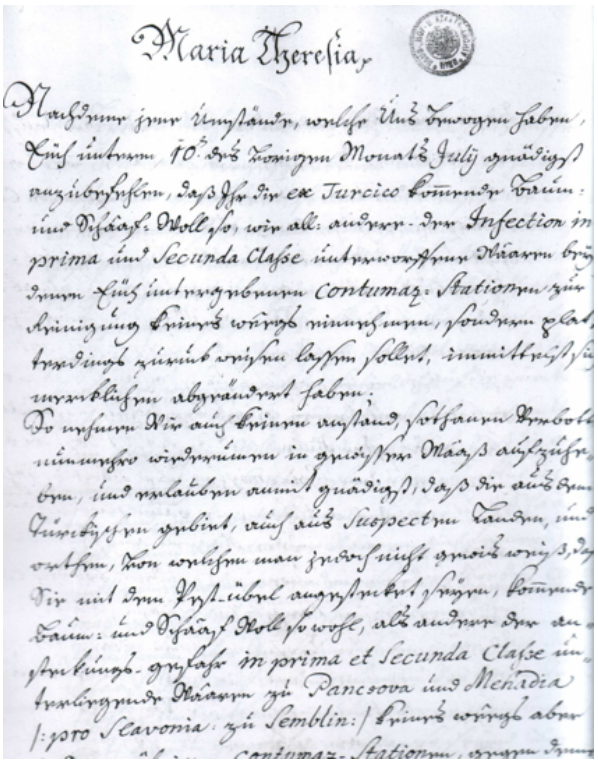
Maria Theresia

Figure 4: Proclamation of the Empress Maria Theresa about measures against plague epidemics at the border with the Bosnian Pashaluk from 1754, HHStA, Staatskanzlei, Provinzen, Illyrien, Kart. 1, Fasz. ad 1753 (1-192), Fol. 118

Throughout the next decades there was significant decrease in the number of plague cases at the border. Until the end of the century, different measures helped in further successful confrontation with the plague epidemic from the side of the Habsburg Empire (for example, in the context of burials, ie prevention of inadequate burials).[14] On the other hand, the perception of plague was not changed among the Ottomans, and the epidemics ravaged around south-eastern Europe deep into the 19th century.

CONCLUSION

Besides some short-term setbacks, the Austrian sanitary cordon fulfilled its primary task in great extent throughout the 18th century. Success in dealing with the epidemics of plague and total elimination of the disease at the area of Habsburg lands assured the Austrian court in orientation towards further implementation of modern scientific measures in facing with the challenges of medicine. Of course, it was still impossible for medicine of that period to isolate bacterium *Yersinia* pestis as a cause of disease.[13] The development in medicine and optics for such level of perception and analysis was not achieved before the very end of 19th century. However, it was exactly this success around the border that implied huge scientific breakthrough in the development of medicine in Vienna during last several decade of 18th century, and especially helped to foster brave scientific experiments in the decade of rule of the Emperor Joseph II (1780-1790). Efforts of Joseph II have been crowned with the construction of a large hospital in Vienna, (*Allgemeines Krankenhaus*), which was opened in 1784.[15] Through the building of this institution, Vienna paved its way towards dominance in the medical field during next century.

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CONTENT

Seifert and Jaganjac. Scr Med 2019;50(4):185-7. DOI:10.5937/scriptamed50-24215

CASE REPORT

Uncommon Diagnosis of an Emphysematous Cystitis: a Case Report

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ABSTRACT

A case of a 79-year-old woman who developed emphysematous cystitis (EC) prior to scheduled lower back surgery, suffering from severe back pain was presented. She had neither of the known EC risk factors (diabetes mellitus, immunodeficiency, neurogenic bladder and recurrent urinary tract infections) and presented herself without classical signs of EC (dysuria, haematuria, abdominal pain, pollakiuria, pneumaturia). She had a persistent back pain that was masked by her chronic back condition, leukocytosis and increased C-reactive protein (CRP) concentrations. The abdominal ultrasound showed a suspiciously impeded, cloudy vision in the lower pelvis and a blurry, thickened presentation of the wall of the urinary bladder with high echogenicity. A CT scan of the abdomen was performed and confirmed the diagnosis of an emphysematous cystitis, as well as a secondary pyelonephritis Escherichia coli was isolated from urine and blood and successfully treated with ciprofloxacin. Contrast-enhanced CT imaging is the diagnostic method of choice.

Key words: emphysematous cystitis; computerised tomography; diagnosis; pyelonephritis; Escherichia coli; ciprofloxacin.

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INTRODUCTION

Emphysematous cystitis (EC) is a relatively uncommon disease of the lower urinary tract characterised by a diffuse inflammation of the urinary bladder wall with presence of intraluminal and/or intramural gas. EC can be caused by various pathogens, in most cases as a result of a bacterial infection. It is most commonly found in elderly women suffering from diabetes mellitus, which is the primary risk factor for EC. It is associated with a fairly high mortality due to the risk of the developing secondary pyelonephritis and/or urosepsis, and therefore requires early diagnosis and adequate treatment.[1–3]

The report presented here is on the case of a 79-year-old female who developed EC prior to lower back surgery. She was suffering from severe back pain, which made it difficult to distinguish the cause of the symptoms at first.

This case shows an unusual and unsuspected lower urinary tract infection that was diagnosed by abdominal ultrasound with subsequent confirmation on CT imaging.

CASE HISTORY

A 79-year old female was transferred to the hospital with heavy back pain for surgical treatment of a known lumbar spinal stenosis. Her medical history included hypertension, hypothyroidism and arteriosclerosis. She did not suffer from diabetes mellitus.

Routine presurgical blood tests revealed a rapid increase of the inflammation factors with an elevated white blood cell count up to 12.2/nl and an elevated CRP of 297 mg/l with an unclear focus. A chest x-ray was inconspicuous. Urinalysis (test strip) was strongly positive for erythrocytes and haemoglobin and weakly positive for nitrite;

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it was negative for leucocytes. She did not present herself with fever, nor did she suffer from any urinary infection-related symptoms, such as dysuria, pollakiuria, macrohaematuria or pneumaturia. The abdominal ultrasound (Figure 1) showed a suspiciously impeded, cloudy vision in the lower pelvis (a) and a blurry, thickened presentation of the wall of the urinary bladder with high echogenicity (b).

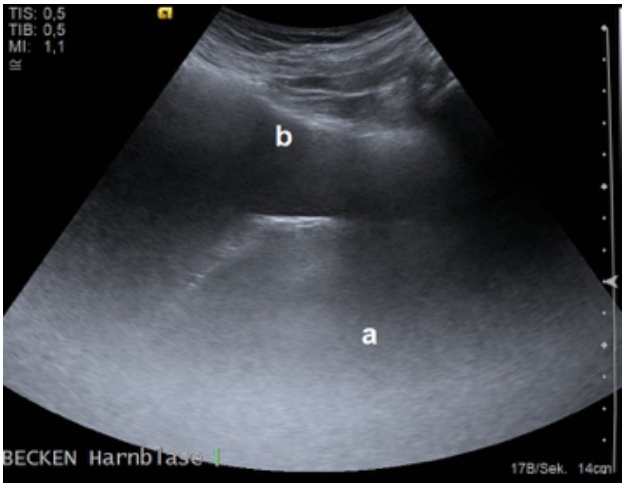

Figure 1: Ultrasound image of the pelvic region (a) including the urinary bladder (b)

The following CT scan of the abdomen (Fig. 2) confirmed the diagnosis of an emphysematous cystitis with countless gas bubbles both intramurally and intraluminally in the bladder, continuing into the wall of the right ureter (arrow), as well as a secondary pyelonephritis with ambilateral contrast uptake of the pelviocaliceal system (Fig. 3).

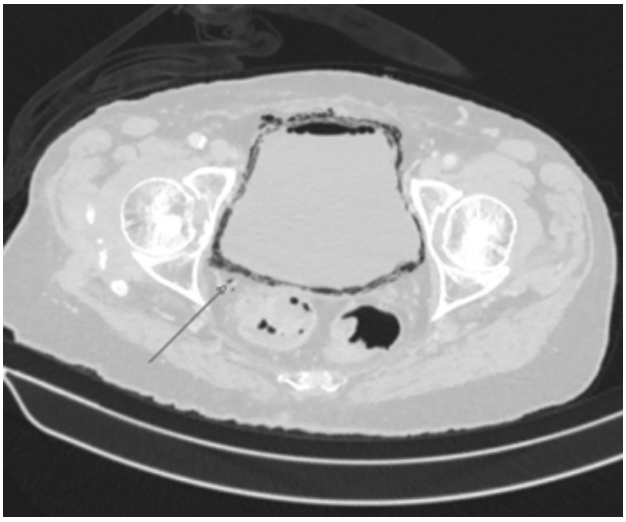

Figure 2: Contrast-enhanced CT of the abdomen (lung window) shows intramural and intraluminal air in the bladder, continuing within the wall of the right ureter (arrow)

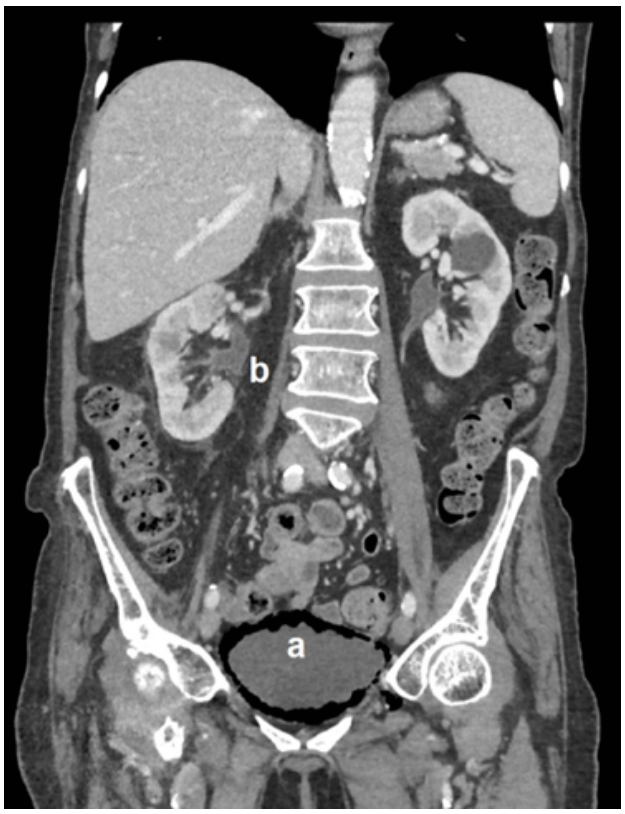

Figure 3: Coronal view of the contrast-enhanced abdominal CT shows intramural gas in the bladder (a), as well as an ambilateral contrast uptake of the pelviocaliceal system (b)

The patient was transferred to the intermediate care unit, where she was catheterised transurethrally for 8 days in total for sufficient bladder decompression and urinary drainage, and received intravenous antibiotics, initially ceftriaxone and metronidazole. Eventual microbial blood culture and culture of the urinalysis revealed *Escherichia coli* sensitive to ciprofloxacin, so the antibiotic therapy was altered accordingly.

The patient responded well to therapy with a quick decrease of inflammatory parameters and a good clinical recovery. She was dismissed from the intermediate care unit after four days and discharged from the hospital eight days after admission. The initially planned back surgery was postponed.

DISCUSSION

Emphysematous cystitis is a somewhat rare condition of the urinary bladder, mostly caused by bacterial infections. The most common organism causing EC is *Escherichia coli* (*E. coli*), followed by *Klebsiella pneumoniae, Enterobacter*

and *Clostridium* species, *Staphylococcus aureus, Proteus mirabilis,* or *Candida* species.[1,2] This corresponds well with the case presented here, as the patient's urinalysis and blood culture identified *E. coli* as the pathogen. EC is more common in elderly women in their 6th and 7th decade, with a 2:1 female vs male ratio. The main underlying conditions involve diabetes mellitus, immunodeficiency, neurogenic bladder and recurrent urinary tract infections.[1, 2, 4] This patient did not suffer from any of the risk factors above, which is a special finding.

Symptoms are similar to those of uncomplicated cystitis and can range from dysuria, haematuria, abdominal pain, and pollakiuria, to fever and sepsis. A unique and typical symptom for EC is pneumaturia.[1] This patient did not suffer from any of those listed symptoms, but a repeated back pain. In this case it was difficult to distinguish between the pre-existing back pain due to spinal stenosis and flank pain due to the later diagnosed secondary pyelonephritis.

Regarding imaging, ultrasound is usually the initial diagnostic investigation performed; it can show an abnormal diffuse urinary bladder wall thickening with high echogenicity along the wall and in the pelvis, such as in this patient. A plain radiography may also be helpful by revealing a radiolucent line of intramural gas bubbles outlining the bladder wall. The standard for confirming the diagnosis of EC and ruling out other pathologies such as enterovesical fistula is contrast-enhanced CT-imaging, as it is the most sensitive and specific diagnostic tool.[1, 3, 5]

Adequate therapy of EC includes sufficient bladder decompression and drainage via catheterisation. Antibiotic or antifungal coverage as per culture and sensitivity is also indispensable.[1, 6] In this case, the identified pathogen was E. coli sensitive to ciprofloxacin. In case of diabetes mellitus, strict glyceamic control, as well as treatment of other relevant comorbidities are needed to secure a good outcome for the patient. In severe case of necrosis, bladder rupture, obstructions, anatomic abnormalities or secondary causes such as bladder stones, surgical intervention can also be necessary for treatment.[1]

Literature describes mortality rates of EC of up to 10%.[7–9] As a severe and potentially fatal condition, awareness and early detection as well as prompt treatment are necessary for a good recovery and outcome for the patient.

CONCLUSION

Emphysematous cystitis is an uncommon infectious disease of the urinary bladder with the detection of intramural and/or intraluminal gas. It has a strong female predominance and is mostly found in the elderly; main risk factors include diabetes mellitus and immunosuppression. Contrast-enhanced CT imaging is the diagnostic method of choice. Prompt recognition and adequate treatment, including sufficient drainage of the bladder, antibiotic therapy and strict glycaemic control, are required to prevent secondary complications such a urosepsis, and to secure a good outcome for the patient.

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None.

CONFLICT OF INTEREST

None.

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Stajić and Maksimović. Scr Med 2019;50(4):188-90. DOI:10.5937/scriptamed50-22410

CASE REPORT

Aripiprazole as a Mood Stabiliser in Postpartum Depression With Premorbid Passive-Dependent Personality Structure: a Case Report

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ABSTRACT

Depression is becoming a widespread illness. One of the most dangerous types of depression is postpartum depression. In the presented case of postpartum depression, aggravating factor was patient's personality structure. With the frequent giving up on previous therapy, frequent mood swings, and the present feeling of helplessness, the very treatment of depressive episode within the postpartum depression was difficult. In this case report, the introduction of aripiprazole as a drug with a proven effect on mood swings and tendency to mood stabilisation resulted with complete and long-lasting remission.

Key words: postpartum depression, premorbid personality structure, aripiprazole.

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INTRODUCTION

Postpartum depression is a serious health problem. Studies indicate that the prevalence of postpartum depression in new mothers runs at about 10-15%. Some studies report on a risk as high as 35%. Given the wide spectrum of clinical features and the existence of multiple forms in which this disorder manifests itself, individual studies have shown that a severe depressive episode appears in 7.1% of mothers postpartum.[1, 2]

Clinical studies point out the importance of premorbid personality traits for the development of depressive episodes and/or bipolar disorder. The most important traits of personality are the passive, dependent, and obsessive-compulsive ones dominated by introvertity.[3]

CASE HISTORY

Patient AC, 28 years old, primipara, had an appointment with a family doctor due to anxiety, sadness, loss of appetite, fear and guilty feeling of "not being a good mother". The problems occurred immediately after discharge from the hospital after delivery. Patient was mainly complaining of reduced social functioning and the inability to fulfil her mother's duties.

During examination the patient had a bent forward posture, looked scruffy, with expressed vascular markings and most of the time was avoiding eye contact. She was cracking knuckles during our conversation and bouncing her legs. The patient had slightly extended latency of response time and tenacity focused on blaming herself for the entire course of pregnancy and peripartum period.

From the medical records and conversation, it was found out about patient's visits to a psychiatrist and a psychologist and about her history of depression. It was also found out about the existence of a passive-dependent personality struc-

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ture, and that the patient had also been treated for a while under the diagnosis of bipolar disorder. After each previous commencement of medication and psychotherapy, the patient would stop using therapy at the first sign of improvement until the next deterioration of her health status. She repeatedly mentioned mood swings: "Several times a week I happen to be either overly happy or sad, for no specific reason. Earlier, these episodes were much less frequent."

The previous therapy included mainly antidepressants like mirtazapine, venlafaxine, sertraline, and lamotrigine as mood stabilisers. However, the patient stated that despite the slight initial improvement, there had never been a drastic improvement in the symptoms while using these medications. "Depressive mood swiftly improves, but sudden mood swings remain, only at a lower intensity." This is stated as the main reason for giving up therapy because “no drug is good enough to cure me". At every attempt to rationalise the problem, the patient would respond: "You are right, but what I can do – I am sick."

During the further diagnostic and therapeutic procedure, after excluding the possibility of harming herself or the child, the patient was sent by her family doctor to see a psychiatrist and a psychologist, to do the basic laboratory tests and to check the hormonal status of the thyroid gland. The family doctor prescribed sertraline 25 mg qd and aripiprazole 2.5 mg qd until seeing the psychiatrist.

Laboratory results and examination of the thyroid gland showed values within the limits of reference interval for age and gender. After examination, the psychiatrist and the psychologist confirmed the initial working diagnosis of postpartum depression with features of a severe depressive episode, and began the pharmacological treatment of acute symptoms, with the aim of introducing her into psychotherapeutic protocols based on the existing passive-dependent personality traits. Aripiprazole and sertraline were confirmed by the psychiatrist as therapy, with daily monitoring of the patient. Over the next 7 days, a gradual improvement in the voluntary-instinctive sphere took place, the patient began to feel better, becoming "happier while being with the child", and thoughts of incompetence and hopelessness disappeared. Later, the patient, with addition of aripiprazole 2.5 mg qd, was introduced into psychotherapeutic cognitive behavioural treatment (CBT). While adhering to psychopharmacotherapy and regular control and treatment of psychologists and psychiatrists, sudden mood swings disappeared, only the spirit was on a higher level, and the patient began to feel "as a parent ready to give all her love to her child."

DISCUSSION

In the presented case, the patient suffering from postpartum depression with a feature of major depressive episode, who had a pre-diagnosed passive-dependent personality and a bipolar disorder, is described. It is considered that the structure of the personality contributes to the previous withdrawal from therapy, which implied mainly antidepressants. Numerous studies have demonstrated a high degree of withdrawal from therapy in patients with a personality disorder, ranging from 37.5% to 58% .[4, 5]

It is believed that in the case of sudden mood swings (within cyclothymia, bipolar disorder, etc), the dominant benefit for the patient comes from using mood stabilisers, while antidepressants are useful in depressive phases. The antidepressants themselves, without mood stabilisers, increase the risk of a manic "switch", and the consequent withdrawal from therapy.[6-8]

The patient in the presented case previously used sertraline, for which she stated that she "believed most" and was a logical choice as an antidepressant in the treatment of the current depressive episode. Having in mind the patient’s personality structure and sudden mood swings, it was decided to introduce a mood stabiliser. Aripiprazole has proven to be a good mood stabiliser in numerous studies. A small recommended dose and once-daily administration is one of the features of a drug that was expected to ensure a good patient's compliance. Further, compared to other antipsychotics and mood stabilisers, aripiprazole shows better tolerability and safety profile.[9, 10]

Aripiprazole is first antipsychotic (followed by quetiapine ER and olanzapine) that according

to the United States Food and Drug Administration (FDA) received approval for use in addition to antidepressants in the treatment of a severe depressive episode.[11-14]

In this case, it was shown that the combination of antidepressants with aripiprazole led to the withdrawal of the symptoms of depression, with long-term persistence and without the occurrence of subsequent sudden mood disorders. Bearing in mind the long history of use of antidepressants and psychotherapy combined, which gave no desired results, it was concluded that adding of aripiprazole as an additional therapy proved to be extremely useful.

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None.

CONFLICT OF INTEREST

None.

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Papers should be written on PC or MAC, using 12 pt font, double-spacing, with 4 cm left margin. Bold letters should be reserved for subtitles. Expressions like *in vitro, in vivo, in situ* and other ones taken from Latin should be written in *italic*. Routes of administration should be written without dots and italicised (eg im, instead of i.m.). Original articles, reviews and articles from history of medicine should not exceed 16 pages; special articles 10; case reports 6; letters to the editor 3, and congress reports and book reviews 2.

All measurements should be reported in the metric system of the International System of Units (SI), and the standard internationally accepted terms (except for mmHg and °C).

MS Word is recommended for word processing. Illustrations should be made using standard graphic formats (*pdf, *Ai, *cdr).

Photos should be delivered in *jpg format, 1:1, 300 Dpi as separate files.

Papers should be prepared in accordance with the Vancouver Convention.

Preparation of the manuscript
Parts of the manuscript are: Title page; Abstract with Key words; Text; Acknowledgements (optional), References.

1. Title page

a) The title should be concise but informative, while subheadings should be avoided;

b) Full names of the authors marked with ascending Arabic numerals in superscript (eg 1, 2, 3).

c) Exact names and places of department(s) and institution(s) of affiliation where the studies were performed, city and the state for any authors, clearly marked by standard footnote signs;

d) Contact data of the corresponding author.

2. Abstract and key words.
The second page should contain the title of the article and a structured abstract (250-300 words for original articles). In short, clear sentences the authors should write the Background/Aim, major procedures – Methods (choice of subjects or laboratory animals; procedures, methods for observation and analysis), the obtained findings – Results (concrete data and their statistical significance), and the Conclusion. It should emphasize new and important aspects of the study or observations. A non-structured abstract of maximum 150 words should be used for editorials, review articles, current topics, special articles, professional articles, history of medicine articles and case reports. *In memoriam* articles do not have an abstract. Below the abstract 3-5 key words should be provided that describe the topic of the article. The key words should be selected from Medical Subject Headings (MeSH).

3. Text
The text of the articles includes the following chapters: Introduction, Methods, Results and Discussion. Longer articles may need subheadings within some sections to clarify their content. Case reports should have four sections: Introduction, Case history, Discussion and Conclusion.

Introduction. After the introductory notes, the aim of the article should be stated in brief (the reasons for the study or observation), only significant data from

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the literature, but not extensive, detailed consideration of the subject, nor data or conclusions from the work being reported.

Methods. The selection of study or experimental subjects (patients or experimental animals, including controls) should be clearly described. The methods, apparatus (manufacturer's name and address in parentheses), and procedures should be identified in sufficient detail to allow other workers to reproduce the results. Also, give references to established methods, including statistical ones. Identify precisely all drugs and chemicals used, with generic name(s), dose(s), and route(s) of administration. State the approval of the Ethics Committee for the tests in humans and animals.

Results should be presented in logical sequence in the text, tables and illustrations. Emphasize or summarize only important observations.

Discussion is aimed to emphasize the new and significant aspects of the study and the conclusions that result from them. Relate the observations to other relevant studies. Link the conclusions with the goals of the study, but avoid unqualified statements and conclusions not completely supported by your data. Conclusion could be a separate chapter or the last paragraph of the discussion;

References should be superscripted and numerated consecutively in the order of their first mentioning within the text. All the authors should be listed, but if there are more than 6 authors, give the first 6 followed by et al. Do not use abstracts, secondary publications, oral communications, unpublished papers, official and classified documents. References to papers accepted but not yet published should be cited as ”in press“. Information from manuscripts not yet accepted should be cited as ”unpublished data“. Data from the Internet are cited with the date of citation.

Examples of references:

Gillespie NC, Lewis RJ, Pearn JH, Bourke ATC, Holmes MJ, Bourke JB, et al. Ciguatera in Australia: occurrence, clinical features, pathophysiology and management. Med J Aust 1986;145:584-90.

Hull J, Forton J, Thompson A. Paediatric respiratory medicine. Oxford: Oxford University Press; 2015. Bydder S. Liver metastases. In: Lutz S, Chow E, Hoskin P, editors. Radiation oncology in palliative cancer care. Chichester (UK): John Wiley & Sons, Ltd.; 2013. p. 283-298.

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.

Polgreen PM, Diekema DJ, Vandeberg J, Wiblin RT,

Chen YY, David S, Rasmus D, Gerdts N, Ross A, Katz L, Herwaldt LA. Risk factors for groin wound infection after femoral artery catheterization: a case-control study. Infect Control Hosp Epidemiol [Internet]. 2006 Jan [cited 2007 Jan 5];27(1):34-7. Available from: http://www.journals.uchicago.edu/ICHE/journal/issues/v27n1/2004069/2004069.web.pdf.

Tables

Each table should be typed double-spaced on a separate sheet, numbered in the order of their first citation in the text in the upper right corner and supplied with a brief title each. Explanatory notes are printed under a table. Each table should be mentioned in the text. If data from another source are used, acknowledge fully. Each table should be named in order to indicate the author's name the number of the table, (eg Johnson_Table 1). The place of the table in the text should be marked as in the following example: “(Table 1 near here)”.

Illustrations

Any forms of graphic enclosures are considered to be figures and should be submitted as additional databases in the System of Aseestant. Letters, numbers, and symbols should be clear and uniform, of sufficient size that when reduced for publication, each item will still be legible. Each figure should be named in order to indicate the author's name and the number of the figure (eg Johnson_Figure 1). If a figure has been published, state the original source.

Captions for illustrations are typed on a separate page, with Arabic numbers corresponding to the illustrations. If used to identify parts of the illustrations, the symbols, arrows, numbers, or letters should be identified and explained clearly in the legend. Explain the method of staining in photomicrographs. Captions should be detailed enough to allow for understanding of the content of the figure without previous reading of the text. The place of the figure in the text should be marked as in the following example: “(Figure 1 near here)”.

Abbreviations and acronyms

Authors are encouraged to use abbreviations and acronyms in the manuscript in the following manner: abbreviations and acronyms must be defined the first time they are used in the text and thereafter must be consistently used throughout the whole manuscript, tables, and graphics; abbreviations should be used only for terms that appear more than three times in text; abbreviations should be sparingly used. Use of abbreviations in the titles should be avoided. Even if used after its definition in the abstract, the same definition and repetition of the abbreviation should be performed the first time it is used in the text.

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