

## ORIGINAL PAPER

doi: 10.5455/medarh.2019.73.326-330

MED ARCH. 2019 OCT; 73(5): 326-330

RECEIVED: JUN 22, 2019 | ACCEPTED: SEP 25, 2019

# Diabetes Mellitus Type Has Impact on Cutaneous Silent Period

Senad Drnda<sup>1</sup>, Enra Suljic<sup>2</sup>

<sup>1</sup>Department for Urgent Neurology, Clinic for Neurology, Clinical Centre University of Sarajevo, Sarajevo, Bosnia and Herzegovina

<sup>2</sup>Department for Science, Teaching and Clinical Trials, Clinical Centre University of Sarajevo, Sarajevo, Bosnia and Herzegovina

**Corresponding author:** Prof. Enra Suljic, MD, PhD. Department for Science, Teaching and Clinical Trials, Clinical Centre University of Sarajevo, Sarajevo, Bosnia and Herzegovina. E-mail: neurofiziologija@kcus.ba. ORCID ID: <https://orcid.org/0000-0003-0858-4621>.

### ABSTRACT

**Introduction:** Neurophysiological tests allow accurate assessment of the function of the peripheral nervous system. Detection of neurophysiological changes allows us to understand the neurological clinical symptoms and signs of patients with type 1 and type 2 diabetes and the possibility for their symptomatic treatment. **Aim:** Evaluate the effect of diabetes mellitus on the “cutaneous silent period” in detecting diabetic polyneuropathy. **Material and Methods:** The study included 150 subjects, 90 suffering from diabetes, divided into three groups of 30, depending on the disease duration, and a control group of 60 respondents not suffering from diabetes or other polyneuropathies. The control group are referred for EMG analysis on another basis (cervical radiculopathy, brachialgia, etc.). Group 1 consisted of 30 subjects with diabetes mellitus type 2 and duration of illness up to 5 years. Group 2 consisted of 30 subjects with type 2 diabetes mellitus 2 and illness duration from 5 to 10 years. Group 3 consisted of 30 patients with type 1 diabetes mellitus. The study groups consisted of patients referred for EMNG analysis to the EMG office of the Clinical Center of Sarajevo University, Neurology Clinic and the Neurophysiology Laboratory in Ljubljana, from July 1, 2011 to May 1, 2016. All patients were examined neurologically and electroneurographic analysis was performed. **Results:** A statistically significant difference was found in the incidence of pathologic CSP with respect to the study groups,  $\chi^2 = 26.153$ ;  $p=0.001$ . Pathologic CSP was more common in group 1 and group 2 of subjects (56.17%) compared to group 3 and control subjects, where it occurred in 13.3% of the cases. **Conclusion:** The pathological cutaneous period of silence was more frequent in subjects of group 1 and group 2, that is, in subjects with DM type 2, compared to subjects with DM type 1.

**Keywords:** diabetes mellitus, polyneuropathy, neurophysiology, cutaneous silent period.

## 1. INTRODUCTION

Neuropathy is a common complication of diabetes mellitus and can cause dysfunction of thicker myelin fibers ( $A\alpha$ ), thin myelin fibers ( $A\delta$ ) and non-myelin fibers (C-fibers). In some patients with diabetic neuropathy, thinner fibers may be more severely affected than thicker fibers (1, 2). Thin fibers are more susceptible to damage, and their damage precedes damage to thick fibers in the development of diabetic neuropathy (3). Diabetics with neuropathy often complain of a burning sensation and tingling, especially in the distal parts of the extremities (4, 5). This presentation may underlie thin-fiber neuropathy. Thin-fiber neuropathy cannot be easily detected with standard electrophysiological tests, and the patient may exhibit normal strength, normal reflexes and electrophysiology. Therefore, standard clinical tests are not sensitive enough to detect initial changes on thin fibers, leaving initial sensory neuropathy undiagnosed. Despite its high frequency

and clinical relevance, there are only a few methods for quantifying dysfunction of peripheral thin fibers. These include quantitative sensory testing (6), analysis of heart rate variability, assessment of motor-axon reflexes (7), or skin biopsy (8). However, the availability of these procedures in clinical practice is limited, and the sensitivity of these methods is questionable. Early detection of thin-fiber dysfunction would reduce severe neuromuscular complications and facilitate epidemiological monitoring of the incidence of neuropathy in diabetics. Clinical interest in the cutaneous silent period originates from its potential utility for evaluating segments and components of sensory nerves that are not well evaluated by standard electrophysiological methods (9). In addition, it provides information for understanding central nervous system disorders and their impact on motor and sensory function (10, 11). CSP is a potential electrophysiological method for the diagnosis of dysfunction of

© 2019 Senad Drnda, Enra Suljic

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

peripheral thin fibers. During the cutaneous period of silence, temporary suppression of muscular contraction is achieved through postsynaptic inhibition of motor neurons or presynaptic inhibition of excitatory inputs of motor neurons reflecting voluntary contraction. Cutaneous afferent neurons are associated with various levels of the nervous system, so they have an effect on motor activity. During motor nerve stimulation, a mixture of excitatory and inhibitory effects is produced, which depends on the location and intensity of inputs, the specific muscles involved, and whether the task requires contraction or muscle relaxation. Electromyographic activity, one of the most powerful cutaneous reflexes, determines the cutaneous silent period, and it consists of a short break in the voluntary contraction after extensive stimulation of the cutaneous nerve and is useful for studying the circular flow of sensorimotor integration at the spinal and supraspinal levels (10). CSP is a transient suppression of the electrical activity of a muscle, during maximum effort, after vigorous stimulation of its nerves. The main hypothesis of electrical generation during the cutaneous silent period involves spindle afferents, cutaneous afferents, inhibitory spinal reflex systems, internuncial neurons, and descending active inhibitions from the motor cortex (12, 13). According to various reports, the cutaneous silent period is a combination of temporary cessation of muscle discharge of spindles, Golgi tendons, and cutaneous afferent nerve fibers (14). The cutaneous silent period is thought to arise from thin myelin high threshold cutaneous nerve fibers with slow conduction. The cutaneous silent period is an inhibitory spinal reflex, mediated by cutaneous A $\delta$  afferent fibers (15,16). There are also studies to support the following theory. High intensity stimulations, usually 10 times the perceptual threshold, are required to evoke the cutaneous silence. Strong cutaneous nerve stimulation was then followed by a synchronized cutaneous silence period in several muscle groups. The characteristic distribution between the upper and lower extremities and cranial muscles depends on the site of stimulation (16).

## 2. AIM

Evaluate the effect of diabetes mellitus on the cutaneous silent period in detecting diabetic polyneuropathy.

## 3. MATERIAL AND METHODS

The study included 150 subjects, 90 suffering from diabetes, divided into three groups of 30, depending on the disease duration, and a control group of 60 respondents not suffering from diabetes or other polyneuropathies. The control group consisted of 60 subjects not suffering from diabetes mellitus or some other polyneuropathies and who are referred for EMG analysis on another basis (cervical radiculopathy, brachialgia, etc.). Group 1 consisted of 30 subjects with diabetes mellitus type 2 with up to 5 years duration of illness. Group 2 consisted of 30 subjects with type 2 diabetes mellitus 2 and duration of illness from 5 to 10 years. Group 3 consisted of 30 subjects with type 1 diabetes mellitus. The groups studied consisted of patients referred for EMNG analysis to

the EMG laboratory of the Clinical Center of Sarajevo University, Neurological Clinic and the Neurophysiological Laboratory in Ljubljana, from July 1, 2011 to May 5, 2016. The study is of a prospective, experimental-laboratory, clinical and applied character. The three groups included subjects of both sexes suffering from diabetes mellitus. The control group included the following subjects: healthy volunteers, subjects of both sexes, over 18 years of age, with negative anamnestic data in terms of the existence of any metabolic disease, or other types of polyneuropathies, normal cognitive parameters, psychologically healthy persons capable of adequately completing the forms foreseen for this study. All subjects were analyzed for the neurophysiological parameter of the peripheral nerves, or the angular period of silence. The computer neurophysiological system of MedelecSinergy, USA, was used. Standard electrodes from Viasys were used as electrodes, namely the large bipolar stimulator (W/O 256644) and the registration electrodes (09497). The apparatus for EMNG analysis in Ljubljana is identical to that at the Clinical Center of Sarajevo University, Neurological Clinic–Medelec Synergy. The examination is done without anesthesia and is not painful if there is cooperation with the patient. It lasts from 30 to 45 minutes and can be more or less uncomfortable. The test is performed on technologically highly computerized apparatus, in this research the Sinergy EMNG machine, where the conductivity of peripheral nerves, motor and / or sensory, is usually first examined.

## 4. RESULTS

Figure 1 shows the average values of the first latency of the cutaneous period. The mean values of L1 in the subjects of group 1 were  $101.93 \pm 2.47$  ms and were 10.76% higher than the values determined in the control group of subjects ( $92.36 \pm 1.21$ ). This difference was statistically significant ( $p < 0.001$ ). In group 2 subjects, the values of the first latency of the cutaneous silent period were  $100.93 \pm 2.40$  and were 9.7% higher than the values determined in the control group. Also, this difference was statistically significant ( $p < 0.002$ ). However, the values of the first latency of the cutaneous silence period in group 3 did not differ significantly from the values determined in

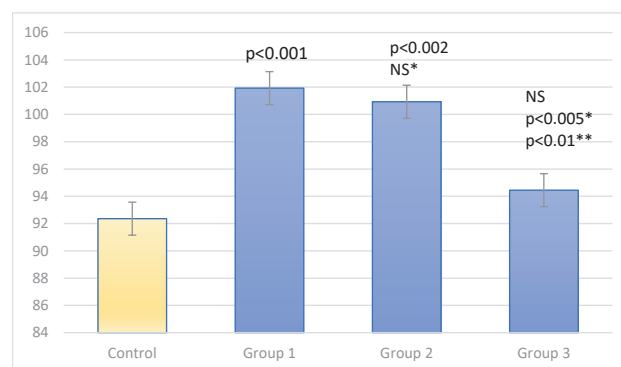


Figure 1. Values of the first latency (L1) of cutaneous silent period in patients with diabetes mellitus. The average values of the first latency (L1) of the cutaneous period of silence ( $X \pm SEM$ ) in the control group and the subjects with diabetes mellitus are presented. p—significance, NS—not significant, \*—in relation to Group 1, \*\*—in relation to Group 2

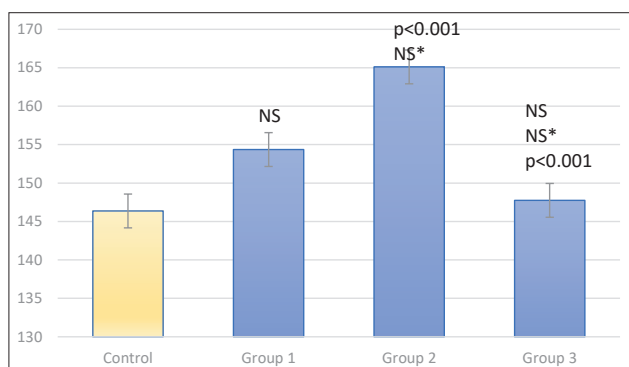


Figure 2. Values of second latency (L2) of cutaneous silent period in patients with diabetes mellitus. Average latency (L2) values of cutaneous silent period (X±SEM) in the control and diabetic subjects were presented. p–significance, NS–not significant, \*–in relation to Group 1, \*\*–in relation to Group 2

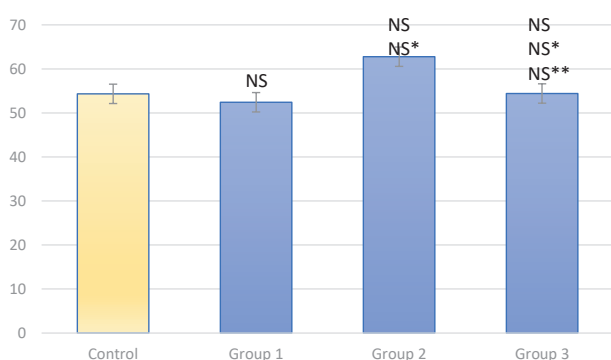


Figure 3. Differences in mean values of second and first latency of cutaneous silent period in patients with diabetes mellitus. The differences between the mean values of the second and first latencies of the cutaneous silent period (X±SEM) in the control group and the subjects with diabetes mellitus were presented. p–significance, NS–not significant, \*–in relation to Group 1, \*\*–in relation to Group 2

the control group. No statistically significant difference was found between group 1 and group 2 in the mean values of the first latency of the cutaneous silent period. However, statistically significant lower first latency was observed in group 3 subjects compared to group1 and group 2 subjects (p<0.005; p<0.01).

Figure 2 shows the average values of the second latency of the cutaneous silent period. The mean L2 values in the subjects of group 1 were 154.36±4.09 ms and were 5.5% higher than the control group (146.37±2.2). This difference was not significant. In group 2 subjects, the mean values of the second latency of the cutaneous silent period were 165.11±4.05 ms and were 12.8% higher than the values determined in the control group of subjects. This difference was statistically significant (p<0.001). The average values of the second latency of the cutaneous silent period in the group 3 subjects were 147.75±2.29 ms and were not statistically significant compared to the values determined in the control group of subjects. There was no statistically significant difference between group 1 and group 2 as well as between group 1 and group 3 in the average values of the second latency of the cutaneous silent period. However, a statistically lower average value of the second latency of the cutaneous silence period in

group 3 was found compared to the values determined in group 2.

Figure 3 shows the differences in the average values of the second and first latencies of the cutaneous silent period. The average values of the difference between the second and the first latency in the group 1 subjects was 52.42±3.85 ms, and in the group 2 subjects it was 62.77±4.47 ms (6.3-128). In group 3 it was 54.41±1.95 ms, and in the control group subjects it was 54.33±1.98 ms. No statistically significant difference was found in the mean values of the difference between L2 and L1 KPT between the tested groups with diabetes mellitus and the control group of subjects, as well as between individually between each group of subjects with diabetes mellitus.

GROUPS	CSP			
	Physiological		Pathological	
	N	%	N	%
Control	52	86.7	8	13.3
Group 1	13	43.3	17	56.7
Group 2	13	43.3	17	56.7
Group 3	26	86.7	4	13.3
Total	104	69.3	46	30.7

Table 1. Frequency of pathologic findings of cutaneous silent period (CSP) in subjects with diabetes mellitus. Numerical and percentage incidence of physiological and pathologic findings of cutaneous silent period in the control and diabetic subjects were presented.

Using the chi-square test in Table 1, a statistically significant difference in the incidence of pathologic CSP was found with respect to the study groups,  $\chi^2=26.153$ ; p=0.001. Pathologic CSP was more common in group 1 and group 2 subjects (56.17%) compared to group 3 and control subjects, where it occurred in 13.3% of the subjects. No correlation was found between CSP and biochemical parameters in subjects with diabetes in all three study groups.

## 5. DISCUSSION

By analyzing the latency of the cutaneous silent period in this study, we came to the following data. The mean L1 values in the group 1 subjects were 101.93±2.47 and were 10.76% higher than the values determined in the control group (92.36±1.21). This difference was statistically significant (p<0.001). In Group 2 subjects, the values of the first latency of the cutaneous silent period were 100.93±2.40 and were 9.7% higher than the values determined in the control group. Also, this difference was statistically significant (p<0.002). However, the values of the first latency of the cutaneous silent period in group 3 did not differ significantly from the values determined in the control group. No statistically significant difference was found between group 1 and group 2 in the mean values of the first latency of the cutaneous silent period. However, statistically significant lower first latency was observed in group 3 subjects compared to group1 and group 2 subjects (p<0.005; p <0.01). The mean L2 KPT values in the subjects of group 1 were 154.36±4.09 and were 5.5% higher than the control group (146.37±2.2). This difference was not significant. In group 2 subjects, the mean values of the second latency of the cuta-



neous silent period were  $165.11 \pm 4.05$  and were 12.8% higher than the values determined in the control group of subjects. This difference was statistically significant ( $p < 0.001$ ). The average values of the second latency of the cutaneous silent period in the group 3 subjects was  $147.75 \pm 2.29$  and were not statistically significant compared to the values determined in the control group of subjects. There was no statistically significant difference between group 1 and group 2 as well as between group 1 and group 3 in the average values of the second latency of the cutaneous silent period. However, a statistically lower average value of the second latency of the cutaneous silent period in group 3 was found compared to the values determined in group 2.

Kim et al. (17) performed a study to evaluate whether the cutaneous silent period was metrically useful for detection thin-fiber neuropathies in diabetics. The cutaneous silent period was measured on the abductor pollicis brevis muscle in 30 healthy subjects and 110 diabetics, which were divided into three subgroups (subjects with neuropathies of thick fibers, thin fibers and asymptomatic patients). The relationship between the cutaneous silent period and clinical characteristics between groups was analyzed. The group of patients had a significant delay of the cutaneous silent period relative to the control group, which was correlated with the results of this study. The authors conclude that delays in the cutaneous silent period can be a useful tool in assessing damage to thin neural fibers in diabetics.

Onal et al. (18) conducted a study aimed at assessing changes in the cutaneous silent period in patients with type 2 diabetes mellitus. The study included 43 subjects with type 2 diabetes mellitus and 41 healthy subjects as a control group. They investigated the duration of CSP latency as well as the difference between the upper and lower extremities. CSP delay was longer at the lower extremities ( $122.1 \pm 15.5$  vs.  $96.4 \pm 6.4$  ms;  $p < 0.001$ ). CSP duration was shorter ( $29.5 \pm 8.9$  vs.  $43.1 \pm 5.0$  ms;  $p < 0.001$ ), and the delay difference was longer ( $48.1 \pm 12.6$  vs.  $22.7 \pm 3.7$ ;  $p < 0.001$ ) in subjects diagnosed with diabetes mellitus than in control subjects. The difference was more significant in patients with neuropathic pain present. Evaluation and upper extremity CSP revealed a significant difference. Which is correlated with the results of the conducted study. In conclusion, the authors state that evaluation of CSP, together with nerve conduction studies, has been proven useful and that the latency difference performance and length of CSP may be valuable parameters in the electrophysiological evaluation of diabetics with thin-fiber neuropathies.

Pinar et al. (19) conducted a study to verify the parameters of the cutaneous silent period (latency and duration) in symptomatic diabetics, with clinically defined thin-fiber neuropathy and normal nerve conduction. The study included 31 diabetics and 30 healthy control subjects. The results indicate that the parameters of the cutaneous silent period did not differ statistically between the studied groups, while in the lower extremities patients with diabetes had an extended latency of the cutaneous silent period ( $p = 0.018$ ) and a shortened duration of the cutaneous silent period ( $p < 0.001$ ). The upper latency limit of the cutaneous silent period was 115.9 ms and the lower 31.5 ms. According to these values, 4 (12.9%) of the subjects had an abnormal

delay of the cutaneous silent period and 10 (32.3%) of them had an abnormal duration of the cutaneous period. The sensitivity of the cutaneous silence method in this study was 32.6% and the specificity was 96.7%.

## 6. CONCLUSION

The cutaneous silent period (CSP) is a sensitive method for the early detection of diabetic polyneuropathy, with the measurement of other neurophysiological parameters. CSP was directly related to the duration of diabetes and pathological findings were more common in DM type 2 subjects compared to DM type 1 and control subjects. No correlation was found between CSP and biochemical parameters in subjects with diabetes in all three study groups.

- **Declaration of patient consent:** The authors certify that they have obtained all appropriate patient consent forms.
- **Author's contribution:** Both authors gave substantial contribution to the conception or design of the work and in the acquisition, analysis and interpretation of data for the work. Each author had role in drafting the work and revising it critically for important intellectual content. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- **Conflicts of interest:** There are no conflicts of interest
- **Financial support and sponsorship:** Nil.

## REFERENCES

1. Lequesne PM, Fowler RCJ, Parkhouse N. Peripheral neuropathy profile in various groups of diabetics, *J. Neurosurg. Psychiatry.* 1990; 53: 558-563.
2. Navarro X, Kennedy WR, Fries TJ. Thin nerve fiber dysfunction in diabetic neuropathy. *Muscle Nerve.* 1989; 12: 498-507.
3. Stevens MJ, Edmonds ME, Foster AV, Watkins PJ. Selective neuropathy and preserved vascular responses in the diabetic charcot foot. *Diabetologia.* 1992; 35: 148-154.
4. Hanson P, Schumacker P, Debugne TH, Clerin M. Evaluation of somatic and autonomic Thin fibers neuropathy in diabetes. *Am J Phys Med Rehabil.* 1992; 71: 44-47.
5. Lacomis D. Thin-fiber neuropathy, *Muscle Nerve.* 2002; 26: 173-188.
6. Low PA, Caskey PE, Tuck RR, Fealey RD, Dyck PJ. Quantitative sudomotor axon reflex test in normal and neuropathic subjects. *Ann Neurol.* 1983; 3: 573-580.
7. Polydefkis M, Hauer P, Griffin JW, McArthur JC. Skin biopsy as a tool to assess distal Thin fiber innervation in diabetic neuropathy. *Diabetes Technol.* 2001; 3: 23-28.
8. Floeter MK. Cutaneous silent periods. *Muscle Nerve.* 2003; 28: 391-401.
9. Inghilleri M, Cruccu G, Argenta M, Polidori L, Manfredi M. Silent period in upper limb muscles after noxious cutaneous stimulation in man. *Electroencephalogr. Clin Neurophysiol.* 1997; 105: 109-115.
10. Shefner JM, Logigian EL. Relationship between stimulus strength and the cutaneous silent period. *Muscle Nerve.* 1993; 16: 278-282.
11. Leis AA, Kofler M, Ross MA. The silent period in pure sensory neuropathy. *Muscle Nerve.* 1992; 15: 1345-1348.
12. McLellan DL. The electromyographic silent period produced by supramaximal electrical stimulation in normal man. *J Neurol Neurosurg Psychiatr.* 1973; 36: 334-341.
13. Cantello R, Gianelli M, Civardi C, Mutani R. Magnetic brain stimulation: the silent period after the motor evoked potential. *Neurology.* 1992; 42: 1951-1959.
14. Metron PA. The silent period in a muscle of the human hand. *J Physiol.* 1951; 114: 183-198.
15. Cruccu G, Agostino R, Inghilleri M, et al. Mandibular nerve in-



- volvement in diabetic polyneuropathy and chronic inflammatory demyelinating polyneuropathy. *Muscle Nerve*. 1998; 21: 1673-1679.
16. Ertekin C. Sentral ve periferik EMG (Anatomi-Fizyoloji-Klinik), Bölüm 19: Refleksoloji ve geç yanıtlar. Meta Basım Matbaacılık Hizmetleri, İzmir 2006: 777-846.
  17. Kim BJ, Kim NH, Kim SG, Roh H, Park HR, Park MH, et al. Utility of the cutaneous silent period in patients with diabetes mellitus. *J Neurol Sci*. 2010; 293(1-2): 1-5.
  18. Onal MR, Ulas UH, Oz O, Bek VS, Yucel M, Taslipinar A, et al. Cutaneous silent period changes in Type 2 diabetes mellitus patients with Thin fiber neuropathy. *Clin Neurophysiol*. 2010; 121(5): 714-718.
  19. Koytak P, Isak B, Borucu D, Uluc K, Tanridag T, Us O. Assessment of symptomatic diabetic patients with normal nerve conduction studies: utility of cutaneous silent periods and autonomic tests. *Muscle Nerve*. 2011; 43: 317-323.

**HYPRESSIN®**  
perindopril

**HYPRESSIN Plus®**  
perindopril+indapamid

NOVO

**IZNAD OČEKIVANJA**

Potpuna i stabilna 24-satna kontrola krvnog pritiska

**HYPRESSIN®:**  
tablete, 30 x 2 mg (br. rješenja: 04-07.3-1-3222/15)  
tablete, 30 x 4 mg (br. rješenja: 04-07.3-1-3223/15)  
tablete, 30 x 8 mg (br. rješenja: 04-07.3-1-3224/15)

**HYPRESSIN Plus®:**  
tablete, 30 x 2 mg/0,625 mg (br. rješenja: 04-07.3-1-4436/16)  
tablete, 30 x 4 mg/1,25 mg (br. rješenja: 04-07.3-1-4437/16)

Lijek se izdaje uz ljekarski recept.  
Bosnalijek d.d., Jukićeva 53, Sarajevo, BiH

**ODOBRENE INDIKACIJE:** HYPRESSIN®: Hipertenzija, zatajenje srca i stabilna bolest koronarnih arterija; HYPRESSIN Plus®: Esencijalna hipertenzija

**KONTRAINDIKACIJE:** Preosjetljivost na aktivne supstance (perindopril, indapamid), na bilo koju od pomoćnih supstanci, ili na bilo koji drugi lijek iz grupe ACE inhibitora ili grupe sulfonamida; angioedem u povezanosti s ranijom primjenom nekog lijeka iz grupe ACE inhibitora (u anamnezi pacijenta); hereditarni ili idiopatski angioedem; drugo i treće tromjesežne trudnoće; istovremena primjena perindopрила i lijekova koji sadrže aliskiren, kontraindicirana je u pacijenata s dijabetes mellitusom ili s bubrežnim oštećenjem (GFR < 60 mL/min/1,73 m<sup>2</sup>), teško oštećenje bubrega; teško oštećenje jetre; hipokalijemija; kombinacija sa nearitmijским lijekovima koji uzrokuju torsades de pointes; laktacija.

**POSEBNA UPOZORENJA I MJERE OPREZA PRI PRIMJENI:** Ukoliko se epizoda nestabilne angine pektoris (značajna ili ne) pojavi u toku prvog mjeseca liječenja sa perindoprilom, prije nastavka liječenja treba izvršiti brzi procjenu odnosa dobiti i rizika. Simptomatska hipertenzija se rijetko javlja u nekomplikiranih hipertenzivnih pacijenata, a vjerovatnije je da će se javiti u pacijenata s deplecijom tečnosti izazvanom npr. liječenjem s diureticima, s dijetalnom restrikcijom soli, dijalizom, dijarejom ili s povraćanjem, ili u pacijenata s teškim oblikom hipertenzije koja je ovisna o reninu. Perindopril bi trebalo s oprezom primjenjivati u pacijenata sa stenozom mitralnog zaliska i opstrukcijom isticanja krvi iz lijeve komore poput aortne stenozе ili hipertrofične kardiomiopatije. Ne preporučuje se istovremena primjena kombinacije perindopril i indapamida i litija kao i svih lijekova koje povećavaju količinu kalija u organizmu. Lijek primjenjivati krajnje oprezno u pacijenata sa kolagenskom vaskularnom bolešću, pacijenata koji primaju imunosupresivnu terapiju, terapiju s alopurinolom ili s prokainamidom. Tiazidi i tiazidima srodni diuretici mogu uzrokovati reakcije fotosenzitivnosti. Perindopril i indapamid ne utiču izravno na sposobnost upravljanja motornim vozilima ili rukovanja mašinama, ali individualne reakcije povezane sa niskim krvnim pritiskom, mogu oslabiti sposobnost upravljanja vozilima ili rukovanja mašinama. Pacijenti s rijetkim nasljednim poremećajem nepodnošenja galaktoze, nedostatkom „Lapp laktaze“ ili glukoza-galaktoza malapsorpcijom, ne bi trebali primjenjivati ove lijekove.

**NEŽELJENA DJELOVANJA:** Najčešći neželjeni događaji vezani uz perindopril: omaglica, glavobolja, parestezija, vrtoglavica, poremećaji vida, tinitus, hipertenzija, kašalj, dispneja, abdominalni bol, konstipacija, dijareja, disgeuzija, dispepsija, mučnina, povraćanje, svrbež, osip, mišićni grčevi i astenija; vezani uz indapamid: bol u epigastriju, anoreksija, nemakulopapilarna erupcija.

**DOZIRANJE I NAČIN UPOTREBE:** HYPRESSIN®: Hipertenzija: Uobičajena preporučena početna doza je 4 mg perindopрила, jedanput na dan, ujutro. Nakon mjesec dana liječenja, doza se može povećati na 8 mg perindopрила, jedanput na dan. Simptomatsko zatajenje srca: Preporučena početna doza je 2 mg primijenjena ujutro. Ova doza se nakon dvije sedmice može povećati na 4 mg jedanput na dan, ukoliko postoji dobra podnošljivost. Prilagodavanje doze bi se trebalo izvršiti na temelju individualnog kliničkog odgovora pacijenta. Stabilna bolest koronarnih arterija: Liječenje bi trebalo započeti s dozom od 4 mg, jedanput na dan, tokom dvije sedmice, a potom je povećati na 8 mg, jedanput na dan, u zavisnosti od funkcije bubrega i pod uslovom da se doza od 4 mg dobro podnosi. Preporučuje se primjenjivati HYPRESSIN® jedanput na dan, ujutro prije jela. HYPRESSIN Plus®: Esencijalna hipertenzija: Jedna tableta 2mg/0,625mg, jedanput na dan. Ako se nakon mjesec dana liječenja ne postigne zadovoljavajuća kontrola krvnog pritiska, doza se može udvostručiti.

BH/HYP2018.07.

Za sve detaljnije informacije o lijeku koristiti zadnji odobreni Sažetak glavnih karakteristika lijeka i Uputstvo o lijeku.

