DOI: https://doi.org/10.25121/PNM.2018.31.1A.65 Post N Med 2018; XXXI(1A): 65-70

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Hydroxychloroquine – drug characterization and the most frequently observed adverse reactions in the group of patients with diagnosed alopecia cicatricans

Hydroksychlorochinina – charakterystyka leku i najczęściej obserwowane działania niepożądane w grupie pacjentów z łysieniem bliznowaciejącym

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Keywords

hydroxychloroquine, adverse reactions, alopecia cicatricans

Słowa kluczowe

hydroksychlorochina, działania niepożądane, łysienie bliznowaciejące

S u m m a r y

Hydroxychloroquine is an antimalarial drug commonly used in the therapy of rheumatoid arthritis and other diseases of the connective tissue. Its toxicity and number of interactions with other preparations are relatively low, so it easily allows one to limit the use of glycocorticosteroids. In alopecia cicatricans beside topically or systemically applied glycocorticosteroids doctors are inclined to apply hydroxychloroquine.

The aim of this study was to determine frequency of the adverse events during hydroxychloroquine therapy.

A group of patients with diagnosed alopecia cicatricans who were treated with hydroxychloroquine in terms of the observed reactions was analyzed. The studied group consisted of 52 women and one man.

The adverse reactions reported by the patients included (in descending order): increased gastric symptoms (n = 16), vision disturbances (n = 9), discolorations (n = 3), skin pruritus (n = 3), muscle power decrease/muscle pain (n = 2), vertigo (n = 1), headache (n = 1), urticaria (n = 2) and elevated liver enzymes (n = 1). Most adverse reactions were reported within up to three months after the hydroxychloroquine therapy initiation.

To sum up, hydroxychloroquine is a drug with a good safety profile and is increasingly often prescribed by dermatologists.

S t r e s z c z e n i e

Hydroksychlorochina jest lekiem przeciwmalarycznym, powszechnie używanym w terapii reumatoidalnego zapalenia stawów i innych chorób tkanki łącznej. Jej toksyczność oraz liczba interakcji z innymi lekami są relatywnie niewielkie, co pozwala ograniczyć stosowanie steroidoterapii. W leczeniu łysienia bliznowaciejącego poza miejscowymi steroidami lekarze są skłonni do stosowania hydroksychlorochiny.

Celem pracy było ustalenie częstości występowania działań niepożądanych podczas terapii hydroksychlorochiną.

Grupa pacjentów ze zdiagnozowanym łysieniem bliznowaciejącym była analizowana pod kątem występowania działań niepożądanych w trakcie terapii. Oceniano 52 kobiety oraz jednego mężczyznę.

Zgłaszane działania niepożądane (w kolejności malejącej): dolegliwości gastryczne (n = 16), zaburzenia widzenia (n = 9), zaburzenia widzenia kolorów (n = 3), świąd skóry (n = 3), osłabienie siły mięśniowej/bóle mięśniowe (n = 2), zawroty głowy (n = 1), bóle głowy (n = 1), pokrzywka (n = 2) oraz podwyższone enzymy wątrobowe (n = 1).

Podsumowując, hydroksychlorochina jest lekiem o dobrym profilu bezpieczeństwa i jest coraz częściej stosowana przez dermatologów.

Conflict of interest
Konflikt interesów

None
Brak konfliktu interesów

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INTRODUCTION

Hydroxychloroquine is an antimalarial drug commonly used in the therapy of rheumatoid arthritis and other diseases of the connective tissue. Since its discovery in 1955, it has found other numerous applications and occupies an important position in the derma-

tological treatment repertoire. Its toxicity and number of interactions with other preparations are relatively low, so it easily allows one to limit the use of glycocorticosteroids and consequently, inter alia, to reduce the number of secondary infection cases. The exact mechanism of action of this drug has not been fully explained yet, but numerous clinical observations and experimental studies have recorded its antithrombotic, hypoglycemic and hypolipidemic properties (1).

Alopecia cicatricans (fig. 1) is a rare disease characterized by a progressive course and permanent damage to hair follicles. Despite the unambiguous hyperactivity of the immune system, the etiology of the disease still raises many doubts. Due to a significant deterioration of the patients' quality of life, lack of social acceptance as well as accompanying symptoms such as pruritus, the burning sensation and considerable hypersensitivity of the scalp, it is often necessary to initiate systemic treatment (2). Beside topically or systemically applied glycocorticosteroids, doctors are increasingly inclined to apply non-biological drugs modifying the course of the disease, which include hydroxychloroquine.

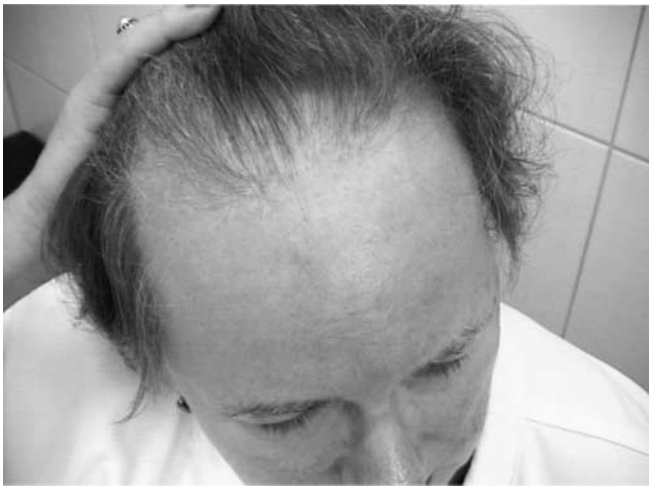

Fig. 1. A female patient with frontal fibrosing alopecia

PHARMACOLOGICAL PROPERTIES OF HYDROXYCHLOROQUINE

Hydroxychloroquine belongs to the group of antimalarial drugs. It is used to treat malaria, rheumatoid arthritis and lupus. It is also applied in dermatology due to its anti-inflammatory properties. Its mechanism of action has not been fully explained yet: it includes, inter alia, influence on lysosomes, phospholipase A2 inhibition, phagocytosis suppression, peroxide synthesis inhibition and intracellular pH increase. This results in a decreased activity of CD4 lymphocytes, inhibition of cytokine release from monocytes and inhibition of antibody production. Due to the observed affinity to pigments, including melanin, the drug may increase the risk of retinopathy development. Moreover, it is applied in cutaneous porphyria because it binds to porphyrins, facilitating their elimination with urine. Literature also mentions aldosterone concentration increase caused by hydroxychloroquine. Its bioavailability is nearly complete, but it should nonetheless be taken during meals to increase its absorption. It reaches the highest serum concentration after approx. 1-3 hours, binding to proteins in approx. 55%. In the case of rheumatoid diseases, the onset of its action may be observed as late as after approx. 4-6 months. It is metabolized mainly in the liver and eliminated mainly via the kidneys. One must exercise caution in pregnant women because the drug penetrates the placental barrier (3-6).

HYDROXYCHLOROQUINE DOSAGE SCHEME

The appropriate dosage scheme does not depend on the patient's actual weight because the preparation deposition in the fatty tissue is scant. It should not exceed 6.5 mg/kg of body weight for so-called ideal weight, even in patients with significant obesity. If the patient's weight falls within the correct BMI range or is lower than that, the optimal dose of hydroxychloroquine is 5.0 mg/kg of body weight. In most descriptions of dermatological diseases and in the cases of good tolerance, a dose of 400 mg/day was applied. Clinical experience has shown that a bigger dose does not result in the expected improvement and increases the risk of retinopathy development instead. The pharmacokinetic properties of the drug allow one to apply alternative doses in order to optimize the daily dose. This means that one can apply a scheme consisting of alternating 200 mg/day and 400 mg/day doses in order to achieve a daily dose of 300 mg/day. If an adequate response does not follow, one can determine the blood level of hydroxychloroquine, which should equal 750 ng/ml at the initial stage and 500 ng/ml during the administration of the maintenance dose. Given the fact that full saturation with the preparation may take up to several months, one can consider an initial dose of 1,200 mg/day at the beginning of the therapy depending on the clinical situation. Unfortunately, gastric complaints make the abovementioned dosage scheme impossible to apply in most cases. The common view that assumes the influence of smoking on the hydroxychloroquine dosage scheme is rather unclear. Nevertheless, all patients should be educated about the harmful influence of nicotinism, especially if other immunosuppressive drugs are applied. Based on the current findings of experts, it is permissible to administer hydroxychloroquine to pregnant women despite the placental barrier penetration if the therapy brings noticeable results. Dosage modification is related to special clinical situations and aimed at reducing the risk of retinopathy, which is one of the most serious treatment complications. In patients with liver dysfunctions and elderly patients, the drug must be applied with caution because the two factors are characterized by impaired metabolism of the drug, even though they do not increase the risk of retinopathy. Hydroxychloroquine may cause hypoglycemia, which is a very important fact when treating patients who take antidi-

abetic drugs. In the event of recurring hypoglycemia episodes, the dosage scheme must be reviewed. Special caution must also be exercised when treating patients with kidney dysfunctions (the risk of retinopathy doubles) and women who take tamoxifen (the risk of retinopathy increases five times). Hydroxychloroquine should be avoided in patients with retina dysfunctions, blood picture disturbances, glucose-6-phosphate dehydrogenase deficiency as well as severe stomach and intestine disorders. One must remember that hydroxychloroquine may aggravate the course of psoriasis, porphyria and myasthenia (3-9).

SIGNIFICANT INTERACTIONS WITH OTHER MEDICINAL PRODUCTS

Contrary to the common opinion about low toxicity of hydroxychloroquine and the small number of its interactions, one must remember that certain medicinal products constitute a serious threat, while others require particular caution (tab. 1).

Tab. 1. Significant interactions of hydroxychloroquine with other medicinal products

- Adalimumab
- Alefacept
- Anakinra
- Anthrax vaccine
- Anti-thymocyte globulin
- Azathioprine
- Live BCG vaccine
- Cyclosporin
- Digoxin
- Diphtheria and tetanus toxoids
- Diphtheria and tetanus vaccine/cell-free pertussis vaccine
- Inactivated polio vaccine
- Etanercept
- Golimumab
- Hemophilus influenzae type B vaccine
- Inactivated hepatitis A vaccine
- Hepatitis B vaccine
- Human papillomavirus vaccine, bivalent, quadrivalent
- Infliximab
- Influenza vaccine, quadrivalent, intranasal
- Leflunomide
- Measles, mumps and rubella vaccine, live
- Measles, mumps, rubella and varicella vaccine, live
- Mycophenolate
- Pneumococcal vaccine, 13-valent, heptavalent
- Rabies vaccine
- Rilonacept
- Rubella vaccine
- Sirolimus
- Tacrolimus
- Temsirolimus
- Tocilizumab
- Tofacitinib
- Typhoid polysaccharide vaccine
- Ustekinumab
- Varicella virus vaccine, live
- Yellow fever vaccine
- Shingles vaccine
- Astragal
- Cholera vaccine
- Topically administered dapsone
- Denosumab
- Echinacea
- Mercaptopurine
- Methotrexate
- Ocrelizumab
- Tobramycin

In the event of parallel administration of cyclosporin, one should consider determination of its level due to the possibility of its blood concentration elevation with concurrent increased nephrotoxicity. Common agents neutralizing the gastric juice reaction, including aluminum, calcium and magnesium salts, reduce hydroxychloroquine absorption. Therefore, the interval between taking the abovementioned preparations must equal at least two hours. Concurrent administration of hydroxychloroquine and amiodarone is absolutely contraindicated due to a high risk of severe cardiac rhythm disturbances. Hydroxychloroquine probably increases digoxin concentration, which may also cause cardiological disturbances. Hydroxychloroquine weakens the action of neostigmine and pyridostigmine, which may considerably complicate the therapy of myasthenia with a significant intensification of symptoms. If it is necessary to apply a rabies vaccine, hydroxychloroquine administration must be put off or discontinued due to the possibility of a diminished antibody response (1, 3, 10-14).

PATIENT MONITORING

It is advised that the patient undergo periodic ophthalmological examinations during the therapy with hydroxychloroquine due to the increased risk of retinopathy. A short-term therapy (under five years) does not increase the risk of retinopathy if there are no initial disturbances within the retina. The risk group includes patients with impaired metabolism and/or elimination of hydroxychloroquine, which increases its toxic action (liver or kidney insufficiency, old age). If the daily dose exceeds 5 mg/kg of the actual body weight, the risk of retinopathy is significantly increased: it equals 10% in the first ten years and 40% after twenty years. A dose below 5 mg/kg of the actual body weight reduces the risk to 2% in the first ten years and 20% after twenty years of hydroxychloroquine application. In most cases, the described disturbances are observed after exceeding the cumulative dose of 1,000 grams. The current guidelines assume the first ophthalmological examination in the first year of treatment, with a reservation that the examination does not have to precede the initiation of hydroxychloroquine therapy because the full action of this drug develops after approx. 3-6 months of therapy. Annual ophthalmological follow-ups are advised for the group of patients taking hydroxychloroquine for over five years. If the risk of retinopathy is increased, one should consider annual or more frequent follow-ups without the waiting period. In selected cases, one can consider further administration of hydroxychloroquine despite the disturbances within the retina, with an indication of an ophthalmological follow-up every three months. Except the observed hydroxychloroquine deposition in the pigmented layer of retina, the mechanism of drug-induced retina degeneration has not been fully explained. If degeneration symptoms are established, one must discontinue the treatment and recommend

an examination in an ophthalmological outpatient clinic because the degeneration may progress despite the discontinuation. It is recommended, based on a similar mechanism, that patients avoid UV radiation due to the risk of discoloration development. Patients with a history of epilepsy require a clear-cut determination of therapeutic benefits due to the increased risk of convulsions. Given the abovementioned hypoglycemic properties of hydroxychloroquine, patients with diagnosed diabetes must be treated with particular caution due to the possibility of life-threatening complications. The glycemia level must be measured regularly and the patients must be educated about alarming symptoms. During follow-ups, the patients must be assessed in terms of their muscle power and if any irregularities are discovered, the treatment must be discontinued. The suggested laboratory tests and consultations are listed in table 2 (15-20).

Tab. 2. Suggested laboratory tests and specialist consultations during the therapy with hydroxychloroquine

- Morphology before every follow-up visit
- Creatinine before every follow-up visit
- ALAT and AspAT before every follow-up visit
- Glucose before every follow-up visit
- Ophthalmological consultation at least once a year (more frequently for patients in the retinopathy risk group)
- ECG once a year

Adverse reactions in the group of patients with diagnosed alopecia cicatricans

The possible adverse reactions to hydroxychloroquine are described quite well (tab. 3) (1, 3).

Unfortunately, no data are available regarding the exact frequency of the described events. Therefore, we analyzed a group of patients with diagnosed alopecia cicatricans who were treated with hydroxychloroquine in terms of the observed reactions. The studied group consisted of 52 women and one man. Their age was 29 to 72, with an average age of 58.3 years ± 10.5 years. The treatment time equaled 1 to 27 months, with an average time of 12.4 months 4.9 months. The adverse reactions reported by the patients included (in descending order): increased gastric symptoms (n = 16), vision disturbances (n = 9), discolorations (n = 3), skin pruritus (n = 3), muscle power decrease/muscle pain (n = 2), vertigo (n = 1), headache (n = 1), urticaria (n = 2) and elevated liver enzymes (n = 1). The observed adverse reactions are presented in figure 2 in a graphic form. Only in two cases was the treatment discontinued due to urticaria. In the remaining cases, the dosage was changed to 200 mg/day, which allowed for controlling the reported symptoms and simultaneous maintenance of the therapeutic effect. Most adverse reactions were reported within up to three months after the hydroxychloroquine therapy initiation.

DISCUSSION

Hydroxychloroquine is a well-described antimalarial preparation with an immunomodulating action (3). Until recently, it was associated mainly with the treatment of rheumatoid arthritis and connective tissue diseases. Nowadays, literature contains numerous descriptions of beneficial hydroxychloroquine application in dermatology concerning, inter alia, atopic dermatitis, localized scleroderma, necrobiosis lipoidica diabeticorum, polymorphous light eruption, cutaneous porphyria, frontal fibrosing alopecia, sarcoidosis, granuloma annulare, lichen planus, lichen sclerosus and urticarial (4, 21, 22). Contrary to glycocorticosteroids and other non-steroidal anti-inflammatory drugs, it is characterized by a relatively low onset of action (3-4 months), but does not cause the unfavorable adverse effects associated with long-term steroid therapy. The mechanism

Tab. 3. Possible adverse reactions during the therapy with hydroxychloroquine

- Nausea/vomiting
- Headache
- Vertigo
- Muscle power weakening
- Aplastic anemia, leucopenia, thrombocytopenia, hyperleukocytosis
- Lesions or deposits in the cornea (vision disturbances, blurred vision, photophobia; reversible after therapy discontinuation)
- Damage to the cornea during long-term use
- Alopecia
- Pruritus
- Weight loss, anorexia
- Cardiomyopathy (rare)
- Hemolysis (persons with glucose-6-phosphate dehydrogenase (G6PD) deficiency)
- QT interval prolongation
- Ventricular rhythm disturbances and torsade de pointes
- Tinnitus
- Nystagmus
- Sensorineural deafness
- Irreversible retinopathy with pigmentation changes (bull's eye image)
- Field of vision disturbances (paracentral scotoma)
- Vision (visual acuity) disturbances
- Maculopathy (macula degeneration)
- Diminished adaptation of sight to darkness
- Color vision disturbances
- Corneal lesions (edema and loss of transparency)
- Abdominal pain
- Fatigue
- Deviations of liver parameters
- Acute liver failure
- Urticaria
- Angioneurotic edema
- Bronchospasm
- Diminished appetite
- Hypoglycemia
- Porphyria
- Sensory and motor disorders
- Myopathy of skeletal muscles and neuromyopathy
- Convulsions
- Ataxia
- Extrapyramidal symptoms such as dystonia
- Dyskinesia
- Tremor
- Dyspigmentation of the skin and mucous membranes
- Change of hair color
- Bullous diseases with erythema multiforme
- Stevens-Johnson syndrome
- Toxic epidermal necrolysis
- Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome)
- Hypersensitivity to light

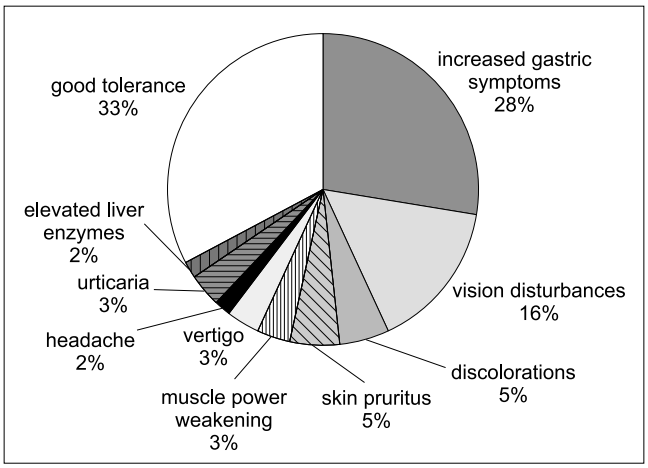

Fig. 2. Adverse reactions in the group of patients with diagnosed alopecia cicatricans

of the anti-rheumatic action is based on intracellular pH increase, which, inter alia, reverses the protein degradation metabolism to the lysosomal one. This implicates disturbances within macrophages and other antigen-presenting cells during the antibody production process (10, 15). The hydroxychloroquine dose should not exceed 5.0 mg/kg of the patient's optimal body weight. In most cases, a bigger dose does not improve the therapeutic effect, but is related to increased gastric symptoms instead. Due to the proposed hydroxychloroquine action mechanism, one must exercise particular caution when administering immunosuppressive drugs such as cyclosporin, biological drugs and other preparations (e.g. vaccines) which would interact with the immune system in an inappropriate manner. Correct patient monitoring is aimed at reducing the possibility of developing the most dangerous complication – hydroxychloroquine-induced retinopathy (16). According to new guidelines, if initial risk factors (such as liver or kidney insufficiency, old age or exceeding the daily dose of 5 mg/kg of the actual body weight) are not established, regular annual monitoring in an ophthalmological outpatient clinic can commence five years after the beginning of the therapy. The most frequently reported adverse reactions include gastric symptoms in the form of nausea and diarrhea. The observations recorded in the group of patients with FFA confirm the literature data: 26% of the studied group reported those symptoms. One must highlight that the symptoms regressed after modifying the daily dose to the level of 200 mg/day. Literature mentions skin and mucous membrane discolorations as frequent complications. According to our observations, they affected only 5% of the studied group, which may be related to the fact that the patients correctly obeyed the photoprotection recommendations. Only two patients showed acute skin reactions in the form of urticaria, which forced premature therapy discontinuation. Serious disturbances such as hemolytic anemia or severe hypoglycemia were not observed. According to the available literature data, it is recommended to monitor morphology once a year. Only one patient demonstrated elevated liver enzymes, but they did not require additional interventions except dosage modification. On the basis of our observations and the literature data, the relationship between hydroxychloroquine and topical aggravation of psoriasis is not unambiguous. Approx. 3% of patients from the observed group reported muscle power weakening which regressed after dose reduction. Despite the lack of clear-cut guidelines concerning the method of monitoring patients who take hydroxychloroquine in terms of possible cardiological disturbances, one must bear in mind the possible interactions (amiodarone, digoxin) and perform electrocardiogram once a year. To sum up, hydroxychloroquine is a drug with a good safety profile and is increasingly often prescribed by dermatologists. On condition that the suggested follow-up schedule is obeyed and bearing in mind that the full effect is achieved after approx. 3-4 months, one can expect that hydroxychloroquine is going to become more widespread.

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received/otrzymano: 6.02.2018
accepted/zaakceptowano: 27.02.2018