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New pharmaceutical formulations and new indications for an old drug - methotrexate

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PSP-20

NOVE FORMULACIJE I NOVE INDIKACIJE JEDNOG STAROG LEKA – METOTREKSATA

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Od 1953.god. metotreksat (MTX) je korišćen parenteralno za lečenje kancera, psorijaze i reumatoidnog artritisa. Cela doza se može primeniti odjednom ili podeliti u tri doze koje se uzimaju u periodu od 24 sata (na 8h). MTX se može davati kod ektopične trudnoće kako bi se izazvao hemijski pobačaj. MTX je takođe efikasan u lečenju drugih bolesti, poput: astme, sistemskog eritematoznog lupusa, Kronove bolesti, miozitisa i vaskulitisa. Terapija malom dozom MTX postiže se efikasnost kao kod steroida.. Neželjeni efekti MTX-a kao što su stomatitis, slabost, mučnina, povraćanje, dijareja, glavobolja i blaga alopecija, umor, promena raspoloženja, vrtoglavica, temperatura, mialgija i poliartralgija nisu opasne po život, ali se javljaju kod 20-30 % pacijenata. Većina manjih neželjenih efekata je povezana sa iscrpljenjem folne kiseline. Za sve pacijente treba razmotriti dodatak folata sa 1 mg dnevno ili 7 mg jednom nedeljno. Ozbiljna neželjena dejstva MTX, poput: poremećaja rad jetre, bubrega, pluća i koštane srži, javljaju se ređe. Da bi se poboljšala terapijska efikasnost i bezbednost MTX-a, razvijene su nove farmaceutske formulacije kao što su injektabilni termosenzitivni hidrogelovi koji sadrže metosfere na bazi MTX-a, nanočestice folne kiseline-hitosan-MTX, termosenzitivne sisteme pripremljene na biokompatibilnom polimeru Pluronic F127 kao nosač, MTX napunjene mikročestice alfa-laktalbumina, konjugati MTX monoklonskih antitela, MTX u nanokeramičnom nosaču magnezijum aluminijum hidroksid, obložen sa poli (D, L laktid-ko-glikolidom).
Nove farmaceutske formulacije su superiorne u poređenju sa konvencionalnim formulacijama MTX u smislu isporuke leka, dugotrajnog oslobađanja leka i dobre biokompatibilnosti. Topikalne formulacije MTX su namenjene za upotrebu u lečenju psorijaze. Neke od ovih formulacija sa pojačanom penetracijom MTX u kožu su mikroemulzije, nanogelovi, niosomi, lipozomalni hidrogelovi, deformabilni lipozomi, čvrste lipidne nanočestice, nanovezikule, bioadhezivni sistemi surfaktanta koji sadrže polisorbat 60 ili 80 kao surfaktante. Pametni gel na bazi MTX NLC koji se sastoji od lipida, surfaktanta Tween 80 i ko-surfaktanta PEG 400, formulisan je za intraartikularnu administraciju koja može dati specifično isporuku leka u reumatske zglobove. MTX je formulisan kao transdermalni flasteri sa različitim odnosima etilceluloze i hidroksipropilmetilceluloze, i pojačivača permeacije Tween 80, Span 80, dimetil sulfoksid i izopropil miristat. Nove MTX farmaceutske formulacije, imaju smanjenu toksičnost, bolje farmakokinetičke osobine, ciljano oslobađanje i veću efikasnost i bezbednost.

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NEW PHARMACEUTICAL FORMULATIONS AND NEW INDICATIONS FOR AN OLD DRUG – METHOTREXATE

Svetlana Goločorbin-Kon[1], Nebojša Pavlović[1], Saša Vukmirović[2], Maja Djanić[2], Boris MilijaSević[2], Milica Paut Kusturica[2], Ana Tomas[2], Bojan Stanimirov[4], Hani Al-Salami[3], Momir Mikov[2]

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Since 1953., Methotrexate (MTX) has been used as a parenteral formulation for cancer treatment, the treatment of psoriasis and rheumatoid arthritis. The entire dose can be administered at once or divided into three doses taken over a 24h period (every 8h). MTX could be given as a safe treatment for the ectopic pregnancy treatment to induce a chemical abortion. MTX has also been found efficacious in the treatment of other diseases, including asthma, systemic lupus erythematosus, Crohn's disease, myositis and vasculitis. Due to its steroid-sparing properties where low-dose therapy achieves efficacy while minimizing side effects. Minor side effects of MTX such as stomatitis, malaise, nausea, vomiting, diarrhea, headaches and mild alopecia, fatigue, mood alteration, dizziness, fever, myalgia and polyarthralgia are not life threatening but occur in 20- 30 % of patients. Most minor side effects are associated with depletion of folate. Folate supplementation with 1 mg daily or 7 mg once weekly should be considered for all patients. Major side effects of MTX, such as hepatic, renal, pulmonary and bone marrow disorders, occur less frequently. In order to improve therapeutic efficacy and safety of MTX, new pharmaceutical formulations have been developed like injectable thermosensitive hydrogels containing MTX loaded chitosan based microspheres, folic acid chitosan MTX core shell nanoparticles, thermosensitive systems prepared on biocompatible polymer Pluronic F127 as a vehicle, MTX loaded alpha lactalbumin microparticles, MTX monoclonal antibody conjugates, MTX intercalated in a nanoceramic vehicle magnesium aluminium layered double hydroxide, coated with poly (D,L lactide-co-glycolide). These new pharmaceutical formulations were superior compared to the conventional formulations of MTX in terms of localized drug delivery, long-term sustained drug release, and good biocompatibility. Topical formulations of MTX have been evaluated for the use in the treatment of psoriasis. Some of these formulations with enhanced skin penetration of MTX include microemulsions, nanogels, niosomes, liposomal hydrogels, deformable liposomes, solid lipid nanoparticles, nano-vesicles bioadhesive surfactant systems containing polysorbate 60 or 80 as surfactants. MTX NLC based smart gel composed of lipids, surfactant Tween 80 and co-surfactant PEG 400, was formulated for intra-articular administration that could give site-specific delivery of a drug to the rheumatic joints. MTX has been formulated as transdermal patches with different ratios of ethyl-cellulose and hydroxypropylmethyl-cellulose, and permeation enhancers Tween 80, Span 80, dimethyl sulphoxide and isopropyl myristate. Novel MTX pharmaceutical formulations, which have reduced toxicity, better pharmacokinetic properties and targeted delivery, have improved efficacy and safety. Acknowledgement: This research was supported by HORIZON 2020 MEDLEM project Grant No.690876 and Project for Scientific and Technological Development of Vojvodina No.114-451-2072-/2016-02