TOPICAL FORMULATIONS OF PROPRANOLOL HYDROCHLORIDE FOR INFANTILE HEMANGIOMA – A COMPARATIVE STUDY ON *IN VITRO* DRUG RELEASE

Milica Kaurin*, Nataša Bubić Pajić

University of Banja Luka – Faculty of Medicine, Department of Pharmaceutical Technology and Cosmetology, Banja Luka, Republic of Srpska, Bosnia and Herzegovina

*natasa.bubic.pajic@med.unibl.org

Oral administration of propranolol, the first-line treatment for infantile hemangioma, can sometimes cause several adverse effects, such as bradycardia, hypotension and hypoglycemia. Topical formulations of propranolol hydrochloride (PRO-CL) are considered as an appealing approach to selectively deliver the drug at the focal sites of disease, developing on/under the skin surface, and thus to address the abovementioned issues (1,2). The objective of this study was to rationalize the selection of PRO-CL topical formulations by investigating their *in vitro* drug release patterns. Conventional official bases (hydrophilic petrolatum ointment, amphiphilic cream, carbomer gel and carmellose gel) prepared according to Magistral formulae 2008 of the Republic of Serbia or DAC/NRF 2018 and two microemulsions were used as vehicles for PRO-CL-loaded (1%, w/w) formulations. *In vitro* drug release tests were performed using Franz diffusion cells equipped with polycarbonate membrane. The obtained results suggested that PRO-CL release was strongly influenced by the inner structure and physicochemical properties of the vehicles. The cumulative drug amount released from the tested samples over 24h ranged from 90.83 μg/cm^2 to 3546.95 μg/cm^2. PRO-CL liberation from lipophilic vehicle was extremely limited. The best results were obtained by using carmellose gel, making it the most promising formulation for PRO-CL dermal delivery. Interestingly, PRO-CL reached receptor medium from microemulsions was significantly lower than by utilization of both investigated gels. The outcomes of the current research may be of particular interest to pharmacists in community and hospital pharmacies. However, the effectiveness of the tested samples should be further verified on appropriate skin models.

References

1. Casiraghi A, Musazzi UM, Rocco P, Franze S, Minghetti P. Topical Treatment of Infantile Haemangiomas: A Comparative Study on the Selection of a Semi-Solid Vehicle. Skin Pharmacol Physiol. 2016;29(4):210-9.
2. Nagata E, Kashiwagura Y, Okada E, Tanaka S, Sano S, Nishida M, et al. Efficacy and safety of propranolol cream in infantile hemangioma: A prospective pilot study. J Pharmacol Sci. 2022;149(2):60-5.

Acknowledgements

This research was financially supported by the Ministry for Scientific-Technological Development, Higher Education and Information Society, Republic of Srpska, through the Project 19.032/961-149/19.

FORMULACIJE PROPRANOLOL-HIDROHLORIDA ZA TOPIKALNU PRIMJENU KOD INFANTILNOG HEMANGIOMA – KOMPARATIVNA STUDIJA *IN VITRO* OSLOBAĐANJA LIJEKA

Milica Kaurin*, Nataša Bubić Pajić

Univerzitet u Banjoj Luci – Medicinski fakultet, Katedra za farmaceutsku tehnologiju i kozmetologiju, Banja Luka, Republika Srpska, Bosna i Hercegovina

*natasa.bubic.pajic@med.unibl.org

Peroralna upotreba propranolola (PRO), kao prvi izbor u liječenju infantilnog hemangioma, može ponekad uzrokovati ozbiljne neželjene efekte, kao što su bradikardija, hipotenzija i hipoglikemija. Topikalne formulacije propranolol-hidrohlorida (PRO-CL) se mogu smatrati atraktivnim izborom za selektivnu isporuku lijeka na fokalna mjesta bolesti, koja se mogu razviti na i ispod površine kože, čime se ujedno mogu riješiti i gore pomenuti problemi (1,2). Cilj ove studije je bio da se racionalizuje izbor topikalnih formulacija za PRO-CL kroz istraživanje njihovih *in vitro* profila oslobađanja lijeka. Konvencionalne oficinalne podloge (mast hidrofilnog vazelina, ambifilni krem, hidrofilni gel karbomera i hidrofilni gel karmeloze-natrijum), izrađene prema propisima Magistralnih formula 2008 Republike Srbije ili DAC/NRF 2018, i dvije mikroemulzije su korišćene kao nosači za izradu formulacija sa 1% (m/m) PRO-CL. *In vitro* testovi oslobađanja lijeka su izvođeni upotrebom Francovih difuzionih ćelija sa polikarbonatnim membranama. Dobijeni rezultati ukazuju da je oslobađanje PRO-CL bilo pod značajnim uticajem unutrašnje strukture i fizičkohemijskih osobina nosača. Kumultivna količina lijeka oslobođena iz ispitivanih uzoraka nakon 24h po jedinici površine membrane varirala je od 90,83 μg/cm^2 do 3546,95 μg/cm^2. Oslobađanje PRO-CL iz lipofilne podloge je bilo veoma ograničeno. Najbolji rezultati su dobijeni upotrebom hidrofilnog gela karmeloze-natrijum, što ga čini najperspektivnijom formulacijom za dermalnu isporuku lijeka. Zanimljivo je i to da je prolazak PRO-CL u receptorski medijum iz mikroemulzija bio značajno niži u odnosu na oba ispitivana gela. Rezultati trenutnog istraživanja bi mogli biti od posebnog interesa za farmaceute u javnim i bolničkim apotekama. Međutim, efikasnost testiranih uzoraka treba dodatno provjeriti korišćenjem odgovarajućih modela kože.

Literatura

1. Casiraghi A, Musazzi UM, Rocco P, Franze S, Minghetti P. Topical Treatment of Infantile Haemangiomas: A Comparative Study on the Selection of a Semi-Solid Vehicle. Skin Pharmacol Physiol. 2016;29(4):210-9.
2. Nagata E, Kashiwagura Y, Okada E, Tanaka S, Sano S, Nishida M, et al. Efficacy and safety of propranolol cream in infantile hemangioma: A prospective pilot study. J Pharmacol Sci. 2022;149(2):60-5.

Zahvalnica

Ovo istraživanje je finansijski podržano od strane Ministarstva za naučnotehnološki razvoj, visoko obrazovanje i informaciono društvo Republike Srpske kroz projekat 19.032/961-149/19.