APPLICATION OF ADJUSTED INDIRECT COMPARISONS TO ASSESS BIOEQUIVALENCE AND SWITCHABILITY BETWEEN GENERIC DRUGS – EXAMPLE OF CLOPIDOGREL

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Generic medicines are bioequivalent (BE) and switchable with the reference medicine, however, between generics BE is not demonstrated. In practice, patients are often offered generic substitution, where information on BE between generics may be useful, especially when there is a doubt that substitution may potentially pose a risk to the patient. These information can be obtained by assessing BE between generics, applying the method of adjusted indirect comparison (AIC). This method is based on data from BE studies in which generics were compared with the same reference medicine. Thus, it is possible to identify generics for which efficacy and safety problems are not expected upon substitution (1,2). The AIC was used to compare four generic clopidogrel medicines. Publicly available data from original BE studies, in which each generic medicine was compared with the reference medicine Plavix film-coated tablets 75 mg, were analysed. Generics were considered BE if the 90% confidence interval (CI) for the ratio of their pharmacokinetic parameters maximum plasma concentration (C_{max}) and area under the curve up to the last measurable concentration (PIK_{0-t}), was within the acceptance range 80.00-125.00%. In all the tested combinations, 90% CIs for PIK_{0-t} were within the acceptance range, while for C_{max} 90% CIs were within or very close to the limits, with the point estimate being within the range in all cases. The results obtained by the AIC indicated that the bioavailability of these four generic clopidogrel medicines is very similar, therefore they can be considered switchable with each other in clinical practice.

References

1. Gwaza L et al. Statistical approaches to indirectly compare bioequivalence between generics: A comparison of methodologies employing artemether/lumefantrine 20/120 mg tablets as prequalified by WHO. Eur J Clin Pharmacol. 2012;68(12):1611–8.
2. Yu Y et al. Investigation into the interchangeability of generic formulations using immunosuppressants and a broad selection of medicines. Eur J Clin Pharmacol. 2015;71(8):979–90.

PRIMENA METODE PRILAGOĐENOG INDIREKTNOG POREĐENJA U PROCENI BIOLOŠKE EKVIVALNETNOSTI I ZAMENJIVOSTI GENERIČKIH LEKOVA – PRIMER KLOPIDOGRELA

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Generički lekovi su biološki ekvivalentni (BE) i zamenjivi sa referentnim lekom, međutim, između samih generičkih lekova BE nije potvrđena. Pacijentima se u praksi često nudi odgovarajuća generička zamena, pri kojoj od koristi mogu biti informacije o BE između generika, naročito u slučaju kada postoji sumnja da zamena generika može potencijalno predstavljati rizik za pacijenta. Ove informacije mogu se dobiti procenom BE između generičkih lekova metodom prilagođenog indirektnog poređenja, na osnovu podataka iz već sprovedenih individualnih studija BE u kojima su generički lekovi poređeni sa istim referentnim lekom. Na taj način identifikuju se generički lekovi za koje se prilikom zamene u praksi ne očekuju problemi u pogledu efikasnosti i bezbednosti (1,2). Navedena metoda korišćena je za poređenje četiri generička leka koji sadrže klopidogrel. Analizirani su javno dostupni podaci iz studija BE u kojima je svaki generički lek poređen sa referentnim lekom Plavix film tablete 75 mg. Dva generička leka smatraju se BE ukoliko je 90% interval pouzdanosti (CI) za odnos njihovih farmakokinetičkih parametara maksimalna koncenracija u plazmi (C_{max}) i površina ispod krive do poslednje merljive koncentracije (PIK_{0-t}), unutar raspona 80,00-125,00%. U svim ispitanim kombinacijama 90% CI za PIK_{0-t} bili su unutar dozvoljenog raspona, dok su 90% CI za C_{max} bili unutar ili veoma blizu granica ovog raspona, pri čemu je *point estimate* u svim slučajevima bio unutar raspona. Rezultati dobijeni metodom prilagođenog indirektnog poređenja pokazali su da je biološka raspoloživost ova četiri generička leka koja sadrže klopidogrel veoma slična, te se oni mogu smatrati međusobno zamenjivim u kliničkoj praksi.

Literatura

1. Gwaza L et al. Statistical approaches to indirectly compare bioequivalence between generics: A comparison of methodologies employing artemether/lumefantrine 20/120 mg tablets as prequalified by WHO. Eur J Clin Pharmacol. 2012;68(12):1611–8.
2. Yu Y et al. Investigation into the interchangeability of generic formulations using immunosuppressants and a broad selection of medicines. Eur J Clin Pharmacol. 2015;71(8):979–90.