1130-0108/2013/105/5/305-306
Revista Española de Enfermedades Digestivas

Rev Esp Enferm Dig (Madrid)
Vol. 105, N.° 5, pp. 305-306, 2013

Letters to the Editor

Dosage adjustment for hepatic dysfunction

Key words: Liver disease. Dosage adjustment. Pharmacokinetics.

Dear Editor,

Periáñez-Párraga et al. (1) provide dose adjustment recommendations for 186 drugs in hospitalized patients with chronic liver dysfunction (LD). In this article, a literature review about dosage adjustment was performed and, in case no information was found, the adjustment recommendations were given according to the process defined by Delcò et al. (2).

The final recommendation was established for 186 reviewed drugs; 73.1 % of them needed quantitative or qualitative adjustment. Recommendation was defined according to the product characteristics summary in 92 drugs (49.5 %), DrugDex Micromedex 49 (26.3 %) and WHO 35 (18.8 %). The recommendations of 6 drugs (3.2 %) were based on previous publications for the group of antimicrobials in 2009 and in 4 drugs a theoretical adjustment recommendation based on the proposal defined by Delcò et al. (2) was given.

We performed a literature search in Medline database using the combination of the following keywords: "pharmacokinetics", "liver disease", "hepatic metabolism", "dose adjustment" and the specific generic name of each drug evaluated. The references of the papers found were screened for additional information in product characteristics summary, DrugDex-Micromedex (3); Drug information handbook (4); British National Formulary (5); FDA (6) and EMEA (7) guidelines as well as WHO recommendations (8). Final recommendation is different in 46 drugs comparing with those provided by Periañez-Parraga et al. (1) (Table I).

In this review, 136 drugs needed dose adjustment, requiring qualitative recommendation in 64.7 % of them. In our review, 195 drugs need dose adjustment (oncology therapy was not included); 69.7 % of the recommendations obtained were unspecific. Protein binding ≥ 90 % was registered in 75 (38.5 %) drugs, < 90 % in 109 (55.9 %) drugs and no data was obtained in 11 (5.6 %) drugs. Hepatic extraction ratio (E) was < 0.3 in 19 drugs (31.6 % of drugs with E data available). These data coincide with

Table I. Differences between the recommendations of Periáñez-Párraga L et al. and our review

Number of drugs	*Drugs*	*Recommendation in our review*
32	Amitriptyline, amlodipine, amoxicillin, azathioprine, carbamazepine, caspofungin, clomipramine, darunavir, efavirenz, furosemide, hidroclortiazide, ibuprofen, isoniazid, lopinavir, mercaptopurine, methadone, methyldopa, nevirapine, ribavirin, nifedipine, sodium nitroprussiate, piperacillin/tazobactam, pyrazinamide, pyrimethamine, procainamide, saquinavir, simvastatin, trimethoprim/sulfamethoxazole, morphine, zidovudine	More strict
5	Atazanavir, erithromycin, morphine, ofloxacin, valproic acid	Less strict
10	Azithromycin, aztreonam, ceftriaxone, didanosine, gentamicin, linezolid, metoclopramide, rifabutin, rifampicin	Dosage adjustment is required (not needed in Periáñez L et al. review)

those obtained by Periáñez-Párraga L et al. (1). In 60 drugs (30.8 %), E was obtained through the bibliography, while Periañez-Párraga L et al. (1) only found information of 11.5 % of the reviewed drugs.

Moreover, for 103 drugs not included in their review, dosage adjustment requirements in LD were found: Albendazole, alfentanil, magnesium hydroxide, amiodarone, amodiaquine, amprenavir, atorvastatin, bisoprolol, bupropion, buspirone, candesartan, carvedilol, chloramphenicol, chlomethiazole, clorphenamine/clorpheniramine, cholestyramina, cinacalcet, clofazimine, clomiphene, clonidine, colestipol, dabigatran, dapsone, diltiazem, dipyridamole, disopyramide, eprosartan, ergometrine (ergonovine), escitalopram, esomeprazole, ethionamide, everolimus, fenofibrate, fentanyl, flecainide, fluphenazina, fluvastatin, fusidic acid, galantamine, gemfibrozil, hydroxyzine, isosorbide dinititrate/mononitrate, labetalol, levetiracetam, losartan, lovastatin, magnesium sulphate, mebendazole, mefloquine, melarsoprol, meperidine, metoprolol, midazolam, moxifloxacin, naproxen, neomycin, nicotinic acid/niacin, nimodipine, nisoldipine, nitroglycerin, norethisterone, ondansetron, oxytetracycline, peginterferon alfa-2a and 2b, pentazocine, pilocarpine, pravastatin, praziquantel, prazosin, propafenone, propylthiouracil, pyrantel pamoate, quetiapine, quinidine, quinine, roxithromycin, sertraline, sildenafil, sirolimus, solifenacin, spiramycin, sulfadoxine, suramin, telmisartan, terbinafine, testosterone, tetracycline, thiopental, ticlopidine, tirofiban, torasemide, vardenafil, venlafaxin and zaleplon.

As mentioned in the article published by Periáñez-Párraga (1), lack of information and clinical trials in patients with hepatic insufficiency make it difficult to recommend specific dosage adjustments leading to a lack of consistency in dosage adjustment recommendations. Dosage recommendations and pharmacokinetic parameters are not coincident in different scientific sources, as it is shown in the differences between both reviews.

Núria Padullés-Zamora, Elisabet Leiva-Badosa
and Ramón Jodar-Masanes

Department of Pharmacy. Hospital Universitari de Bellvitge. IDIBELL. Hospitalet de Llobregat, Barcelona. Spain

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