Esters Twin Drugs of Metronidazole: Synthesis, Physicochemical properties, Kinetic studies and Antigardial activity.


Abstract:

Abstract A series of identical twin esters 3a-e of metronidazole was synthesized and evaluated as potential prodrugs with improved physicochemical and pharmacokinetic properties. The synthesis of the twin esters 3a-e was achieved by interaction of metronidazole with the respective dicarboxylic acid anhydride or their dichloride. Their structures were verified by elemental and spectroscopic analyses. The lipophilicity of metronidazole and the prodrugs 3a-e, expressed as Rm values, were determined using reversed-phase TLC and revealed enhanced lipophilic properties compared with metronidazole. Reversion kinetics of the parent drug from its twin esters was investigated in aqueous buffer solutions (pH 1.2 and 7.4) as well as in biological media (80% human plasma and 20% rat liver homogenate) at 37 °C using HPLC. In all cases, the hydrolysis followed pseudo-first-order kinetics in a two-step reaction (k1 and k2) via the intermediate formation of the respective metronidazole hemiester. All the synthesized twin ester prodrugs 3a-e were proved to be chemically stable at acidic pH (t1/2 ~ 25-72 h) and also at the physiological pH (t1/2 ~ 13-40 h). Meanwhile, the release of the first molecule of metronidazole from its twin esters 3a-d ensued rapidly in 80% human plasma (t1/2 ~ 10-150 min) and in rat liver homogenate (t1/2 ~ 4-55 min). The resulting hemiesters 2a-d showed a sustained release of the second molecule in the same biological fluids (t1/2 ~ 3-9 h and 1-11 h respectively). In vivo evaluation studies of metronidazole and its twin esters 3a-d in mice and 3b in rabbits revealed that the prodrugs have been absorbed almost unhydrolyzed with considerable higher plasma level. Antiparasitic activity of the synthesized compounds was evaluated in mice against Giardia muris, the prodrug 3b showed improved antigiardial activity compared to the parent drug. These results suggest that the synthesized identical twin esters 3a-d may be useful as a promising new prodrug form of metronidazole for oral drug delivery.

Keywords:

Metronidazole twin ester prodrugs... , physicochemical , hydrolysis... kinetics ..... antigiardial

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