GATEKEEPING PROCEDURES FOR DOSE FINDING WITH MULTIPLE ENDPOINTS

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In many dose finding studies there are hierarchically ordered endpoints (e.g., primary, secondary, etc.) and a given dose is compared with a control on any endpoint conditional on the tests on all the higher-ranked endpoints being significant (called serial gatekeeping). It is required to control the familywise error rate at a designated level α taking into account multiplicity of tests. We give a closed procedure (Marcus, Pertiz and Gabriel 1976) for this problem which uses weighted Bonferroni tests for intersection hypotheses. For an easier implementation of this closed procedure, we give an equivalent stepwise procedure. The stepwise procedure uses a penalized Bonferroni test for each endpoint except the last, for which it uses a penalized Holm test. The penalty charged at each step of testing is inversely proportional to a so-called rejection gain factor, which depends on the number of rejections at earlier steps and the weights assigned to those rejected hypotheses. The method is applied to a type II diabetes drug trial data with three endpoints. Extensions involving replacing the Bonferroni test with the Simes or resampling or the Dunnett test are indicated.