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Baclofen (4-amino-3-p-chlorophenylbutyric acid), a p-chlorophenyl analogue of γ-aminobutyric acid, is widely used in the treatment of spastic disorders as a skeletal muscle relaxant. The enantiomers of baclofen differ in their pharmacodynamic and toxicological properties: the R-(-)-enantiomer is much more active but also more toxic than the S-(+)-enantiomer. Besides, the "ineffective" S-(+)-enantiomer antagonizes the action of the effective R-(-)-enantiomer, so that the R-(-)-enantiomer is also substantially more effective than racemic baclofen. Because the kinetic disposition of the two enantiomers may be different, the investigation of the pharmacokinetic behavior of both enantiomers is often desirable. In this study, the optimal enantiomeric separation of baclofen and the validation of the method for its accurate and precise assay in human plasma will be discussed by capillary electrophoresis using highly sulfated γ-cyclodextrins as chiral additives.

[PD4-13] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

New reagent for the enantiospecific analysis of primary or secondary amino group via High-Performance Liquid Chromatography

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The synthesis and analytical testing of new ultraviolet active chiral derivatizing agent, (S)-[3-(3-Fluoro-4-morpholin-4-yl-phenyl)-2-oxo-oxazolidin-5-ylmethyl]-2,5-dioxo-pyrrolidin-1-yl ester were investigated. In a rapid, one-step procedure, the compound reacts with primary or secondary amino group of β-blockers(acebutolol, arotinolol, betaxolol, bisoprolol, celiprolol, metoprolol, pindolol and propranolol) to form stable asymmetric urea derivatives. Studies on derivatization conditions demonstrate excellent derivative yield in mild organic base solutions. With excess of 20 times molar or more of chiral derivatizing agent, chiral derivatization reactions were completed within one hour at room temperature. Diastereomeric derivatives of β-blockers were well resolved in the ODS-C8 column using acetonitrile-methanol-water as mobile phase.
A reversed-phase high performance liquid chromatographic method was developed to determine the optical purity of propranolol enantiomers. The enantiomers were converted to diastereomeric derivatives using this new chiral derivatizing agent. Separation of the enantiomers as diasteromers was achieved by reversed phase HPLC within 35 min using Develosil C8 column. This method allowed determination of 0.05% of either of the enantiomers in the presence of its stereoisomer and method validation showed adequate linearity over the required range. Owing to the reaction condition during the derivatization with (S)-[3-(3-Fluoro-4-morpholin-4-yl-phenyl)-2-oxo-oxazolidin-5-ylmethyl]-2,5-dioxo-pyrrolidin-1-yl ester, the possibility of racemization had to be established. Different ratios of (R)-(+)-prorpranolol and (S)-(-)-propranolol were prepared. Enantiomeric separation of these mixtures took place on a chiracel OD column or, after derivatization with (S)-[3-(3-Fluoro-4-morpholin-4-yl-phenyl)-2-oxo-oxazolidin-5-ylmethyl]-2,5-dioxo-pyrrolidin-1-yl ester, on a Develosil C8 column. The results from these two independent separation systems were compared with trace racemization and were in very good agreement. No racemization was found during the experiment.

[PD4-14] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Influence of temperature and time differences on contents of cefaclor in dried-syrup.

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The stability of cefaclor monohydrate syrup was studied under various temperature and time differences. Refrigerated condition(4℃), room temperature and accelerated condition(40℃) were investigated for temperature differences and 4h., 8h., 12h., 24h., 2 days to 20 days(every day) were investigated for time differences.
The contents of cefaclor monohydrate was determined for 9 commercial dried cefaclor-syrup by High Performance Liquid Chromatography with Hypersil ODS column and triethylamine/glacial acetic acid/acetonitrile/D.W = 5/20/25/875 mobile phase. The detection was performed at 254nm.
The calibration curves showed a good linearities having r value of 0.99935 and detection limit was 0.953ppm.
At 40℃, the rate of degradation was significantly higher than that of the others. By the time passed, the pH of the syrup was decreased.
At room temperature, the rate of degradation was slightly decreased. The result showed that cefaclor monohydrate content to be stable for at least 5 days at room temperature and at least 14 days at refrigerated condition.

[PD4-15] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

A Collaborative Study to Establish a Korean Reference Standard for Factor VIII:C Concentrate

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A collaborative study was carried out to evaluate the suitability of the candidate preparation to serve as a Korean Reference Standard for Factor VIII:C concentrate. Five laboratories including three manufacturers and two national control laboratories participated in this study, and the potency of this candidate was determined using two different methods. The one is the one-stage clotting method, described in the Minimum Requirements for Biological Products, and the other is the chromogenic assay, described in the European Pharmacopoeia. To minimize possible substantial discrepancies among laboratories and between assay methods, the following recommendations by the International Society on Thrombosis and Haemostasis were adopted for the assays , e.g., pre-dilution of samples in FVIII-deficient plasma, inclusion of 1% albumin in the dilution buffer and calibration against the 6th International Standard for blood coagulation Factor VIII:C, coded 97/616. The results of this study were in good agreements among laboratories with the inter-laboratory coefficient of variations of 10.51%. The mean value for estimates obtained by the one-stage clotting method was 8.27 IU/vial, and that by the chromogenic assay was 6.88 IU/vial. Based on the results of the collaborative study, the candidate reference standard is judged to be suitable to serve as the National Reference Standard for Factor VIII:C Concentrate.

[PD4-16] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Comparison of the Chromogenic Assay and Clotting Assay Methods for the Potency Test of the Intermediate and High Purity Factor VIII:C Concentrates in Korea

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The clotting assay was replaced by the chromogenic substrate assay which is recommended by the