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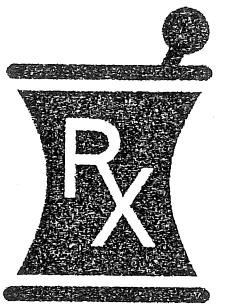

POSTER PRESENTATIONS
SATURDAY, JULY 25, 1998
BPK/PD SESSION

Pharmacodynamic Studies On Some Amide Proline –[2,1-f]-Theophylline Derivatives*

B. Filipek[1], J. Sapa[1], M. Zygmunt[1], D. Maciag[1], M. Pawlowski[2]
[1]Laboratory of Pharmacological Screening, Collegium Medicum Jagiellonian University, 19 Krakowska St., 31-062, Krakow, Poland
[2]Department of Pharmaceutical Chemistry, Collegium Medicum Jagiellonian University, 9 Medyczna St., 30-688 Krakow, Poland

A series of amide proline-[2,1-f]-theophylline derivatives was synthesized and tested for electrocardiographic and antiarrythmic activity in vivo (protection against adrenaline-induced arrhythmia in anaesthetized rat). Some of the compounds of this series slightly decreased the heart rate, prolonged P-Q, Q-T intervals and QRS complex. Two compounds, given 15 minutes before arrythmogen in doses of 1/20-2/5 LD_{50} iv, attenuated or completely prevented against the symptoms of adrenaline-induced arrhythmia. The antiarrhythmic properties of this compounds were comparable to that reported for quinidine in the same experimental procedure. These results indicate that the some prolinetheophyline derivatives possesses potent antiarrythmic properties although their precise mechanism of actions to be further studied.

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Pharmacodynamic Studies On Novel 7,8-Disubstituted Theophylline Derivatives With Antiarrythmic, Antihipertensive, And α-Adrenoceptor Blocking Activity

J. Sapa[1], M. Zygmunt[1], B. Filipek[1], S. Charakchieva-Minol[2], M.J. Mokrosz[2], G. Chlon[3], A. Zejc[3]
[1]Laboratory of Pharmacological Screening, Collegium Medicum Jagiellonian University, 19 Krakowska St., 31-062, Krakow, Poland
[2]Institute of Pharmacology, Polish Academy of Science, 12 Smetna St., 31-343 Krakow, Poland
[3]Department of Pharmaceutical Chemistry, Collegium Medicum Jagiellonian University, 9 Medyczna St., 30-688 Krakow, Poland

Previous pharmacological screening for new cardiovascular drugs led us to discover the anthiarrythmic, antihypertensive activity of 7-β-hydroxy-γ-(N4-phenoxy-ethylpiperazine)-propyltheophylline (CH-1). In continuation of our research a series of new analogous CH-1 with benzylamine substituent in 8 position of theophylline moiety were synthesized and tested for electrocardiographic, antiarrythmic and antihypertensive activity as well as for α_1- and α_2-adrenoceptors binding affinities.

The antiarrythmic activities of the compounds were investigated in experimentally induced arrhythmia in anesthetized rats. Antihypertensive activity was evaluated after single i.v. administration to normotensive rats. Displacement of [3H]clonidine specifically bound to synaptosomal fraction of the cortex was measured to asses [3H] prazosin and the affinity of the compounds to α_1- and α_2-adrenoceptor, respectively. Some of the tested compounds prevented or attenuated the adrenaline-induced arrhythmia, reduced significantly the blood pressure in normotensive anesthetized rats and reversed the pressor response to adrenaline, and displayed low (nM or mM) binding affinity for α_1- and α_2-adrenoceptors. These results suggest that the antiarrythmic and hypotensive effect of tested compounds are related to their adrenolytic properties.

Pharmacodynamic Studies On Aminoalkanolic Derivatives With Potential Antiepileptic Activity

Z. Gorka[1], H. Marona[2], K. Kiec-Kononowicz[2]
[1]Department of Pharmacodynamics and [2]Department of Chemical Technology of Drugs, Collegium Medicum, The Jagiellonian University, Krakow, Poland

Antiepileptic drugs are a group of drugs with a still increasing differentiation of the chemical structure (Prominal, Phenytoin, Trimethadione, Ethosuximide, Diazepam, Vigabatrin, Progabide, Nimodipine, Lamotrigine, etc.) and their chemical classification is more and more difficult. Searching for compounds with potential antiepileptic action we have obtained some aminoisopropanoloxy derivatives of 2-xanthone (3-12) and subjected them to pharmacological screening. The compounds were prepared by the amination of 2-[(2,3-epoxy)-propoxy]-xanthone or 2-(3-chloro-2-hydroxy-propoxy)-xanthone. Preliminary pharmacological tests of all the synthesized compounds have been provided by the Antiepileptic Drug Development Program, Epilepsy Branch, Neurological Disorders Program, National Institutes of Neurological and Communicative Disorders and Stroke Bethesda, MD, USA. The obtained compounds were evaluated for anticonvulsant activity in the maximal electroshock (MES)- and subcutaneous pentylenetetrazole (scMet)-induced seizures and for neurotoxicity in the rotorod test in mice and rats. Anticonvulsant quantification, i.e. the doses of drug required to produce the biological responses in 50% of animals (ED_{50}), and the respective 95% confidence intervals, were determined on selected compounds displaying sufficient antiepileptic activity and low neurotoxicity from the above primary evaluations by means of a computer program using probit analysis. The most promising compounds seem to be 3-(tert.-butyl-amino)(3), 3-[N-methyl-(tert.butyl)-amino] (12) and 3-[4-(benzyl)-1-piperazinyl] (5) substituted of 2-hydroxy-1-(2-xanthonoxy)-propane from which 3 and 5 were active in both the anticonvulsant tests. The protective index (TD_{50}/ED_{50}) in MES in mice for 3 and valproate, as well as for 12 and phenytoin or carbamazepine, is similar.

In vitro Biopharmaceutical Study of Hydrogel Containing Diethylammonium Salt of 2,5-dihydroxy-benzenesulfonic acid (Etamcylate)

T. Nikova
Department of Industrial Pharmacy, Faculty of Pharmacy, Medical University, Sofia, Bulgaria

Diethylammonium salt of 2,5-dihydroxy-benzenesulfonic acid (Etamcylate) is a potent homeostatic introduced into clinic practice in early sixties. Both, in the form of ampoules for i.v. and i.m. injection and in the form of tablets are commercially available.

The aim of this study was to estimate in vitro biopharmaceutical behavior of Etamcylate from hydrogel for local application.

The experiments were carried out by modified method described by Olszewski Z. Et all.The release rate K_d [$cm.min^{-1}$], diffusion constant D[cm^2/sec], permeation constant P[cm/sec], and partition coefficient base/membrane K_p [cm/sec] were calculated. The stability at "stress" conditions was also studied by means of TLC-analysis.

Sustained Release of Drugs From Hydrogels On The Basis On Chemically Cross-Linked Polyacrylic Acid

M. Dimitrov, St. Tsankov, N. Lambov
Department of Pharmaceutical Technology with Biopharmacy, Faculty of Pharmacy, Medical University, Sofia, Bulgaria

The possibility for sustained release of drugs from hydrogels on the basis of chemically cross-linked with anhydrides and urethane fragments polyacrylic acid has been studied. The obtained nets in contact with water swelling (from 115% to 150% for 3 h), without dissolving. The extended release of model drugs, loading in matrices before and after cross-linking was proved. (t_{50}>12 hours). During in vitro investigations the influences of basic factors determining the rates of drug release from hydrogels were studied:

- **Degree of cross-linkage of matrix:** variation of the concentration (from 1:2 to 1:0.3) and kind of cross-linkage agent (polypropylenglycol, polytetramethylenglycol, polyethylenglycol). The increase of concentration of cross-linking agent leads to a decrease in drug release.
- **Drug concentration:** The increase in drug concentration over 5% leads to a sharp increase in the rate of drug release.
- **Methods of drug loading:** The loading during cross-linkage showed significantly prolonged drug release in comparison with the soaking drugs into the solution of already prepared net
- **pH of eluents.**

Cross-linked Polyethylene Oxide Hydrogels: Evaluation of Factors, Determined of Drug Release

N. Lambov, M. Dimitrov, St. Tsankov
Department of Pharmaceutical Technology With Biopharmacy, Faculty of Pharmacy, Medical University, Sofia, Bulgaria

Hydrogels obtained after irradiation (γ-rays) induced cross-linking of high molecular weight polyethylene oxide were studied. Diclofenac sodium, Acebutalol hydrochloride and Piroxicam were used as a model drugs. The release of the drugs depends on:

- Drug releated factors (solubility, concentration of the drug)
- Matrix related factors (irradiation dose and state of the matrix-dry or wet)

Generally, the release take places as an anomalous diffusion (release exponent n=0.53÷0.86). The rate and kinetics of release ($t^{1/2}$or zero order prevailing) depend mostly on the drug content in the matrices and the irradiation dose.

It can be concluded that it is not only the type of the matrix (dry or wet) but also irradiation and drug concentration determining the release kinetics.

Determination of Steady State Plasma Concentrations of Tenoxicam In Osteoarthritic Patients Using HPLC

İ. Ağabeyoğlu[1], Z.Ş. Teksin[1], S. Çubukçu[2], V. Sepici[3]
[1]Department of Pharmaceutical Technology, Faculty of Pharmacy, Gazi University, Ankara, Turkey
[2]Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Pamukkale University, Denizli, Turkey
[3]Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Gazi University, Ankara, Turkey

Tenoxicam is a nonsteroidal anti-inflammatory drug, which displays good efficacy and tolerability in therapy for the rheumatic diseases. It is administered once daily. It is bound extensively to albumin (>99%) and has a half-life of 60-80 hours in normal subjects. Steady state plasma concentrations of about 11μg/ml are achieved in 10 to 12 days after administration of tenoxicam, 20 mg once daily. The pharmacokinetics of tenoxicam show significant interindividual variability.

Determination of steady state plasma concentrations and protein binding of tenoxicam was studied in twenty patients with ostheoarthritis (13 women, 7 men) in the age range between 43 and 70. Patients' total protein and albumin contents in plasma were assessed by modified Biuret method and a bromocresol green method. Mean total protein concentrations and mean total albumin concentrations were found to be 7.6 g/100 ml and 4.0 g/100 ml, respectively. Patients had been taking Tilcotil® tablet with a dosage of 20 mg/day for two weeks. 10 ml blood samples were collected from each patient on the fifteenth day, at two hours after dosing.

Tenoxicam in plasma was measured by an HPLC method. This sensitive method is specific for tenoxicam. Extraction and HPLC conditions in the literature were modified for shorter separation times. Chromatographic parameters were determined. Extraction method was used for sample preparation. Linear correlations between peak-height ratio and concentration of tenoxicam in plasma were used in drug assay. Steady-state plasma concentrations were found to be 12.0μg/ml.

The pharmacokinetic parameters and plasma profiles of tenoxicam were found with a healthy volunteer and a patient with osteoarthritis at steady state using HPLC. Pharmacokinetic calculations were performed using programs ESTRIP, LSNLR (Marquardt algorithm) and IKIKOMP.

Comparative Dissolution Studies of Diclofenac Sodium Retard Dosage Forms

Ö.H. Ocak, G. Yetkin, Z.I. Parlatan
Department of Pharmaceutical Technology, Faculty of Pharmacy, Gazi University, Etiler, Ankara 06330, Turkey

Diclofenac sodium (DS) is widely used as an anti-inflammatory drug. Its absorption depends on gastrointestinal pH. The solubility of DS is poor in the gastric medium, and it can cause local irritation.

In this study, the dissolution kinetics of three different retard oral dosage forms of DS were compared. The continuous flow through cell was used as the dissolution apparatus. Five different buffer solutions were used as dissolution medium. The pH of these buffer solutions were 1.2, 4.5, 5.5, 6.5, 7.5. Dissolution studies were performed for 24 hours. Different time intervals were selected for each pH medium. The flow rate of dissolution medium was 4 ml/min.

The dissolution profile of each dosage form was plotted on 3D graphs. Dissolution data of each pH interval were evaluated. Drug release rates were calculated and compared to other dosage forms.

Investigation On The Qualities And In Vitro Dissolution Rates of Flutamide Tablets Marketed In Turkey

N. Gönül, Ö. Taygal, A.B. Ölçer, T. Baykara
Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Ankara, 06100 Tandoğan, Ankara, Turkey

Flutamide is a nonsteroidal antiandrogen agent that specifically blocks the androgen receptor. It has been used in the treatment of prostate cancer, hyperplasia, hirsutism, and virilism.

Flutamide tablets of two different brands are being imported and are available in Turkish drug market. The quality and the pharmaceutical dosage form of a medicine have great importance in the treatment. The quality of a medicine affects directly or indirectly the safety, effectiveness and acceptability of the product. Therefore its pharmaceutical properties should meet the specifications.

In this study, the pharmaceutical properties of two batches which belong to two different commercial brands of flutamide tablets were investigated. The quality control methods such as diameter-thickness, weight variation, friability, hardness, disintegration time and content uniformity were studied on the tablets. Furthermore, the dissolution tests were carried out on the tablets and the data obtained was evaluated kinetically.

As a result, all the tablets investigated were found to be in compliance with the specifications.

Cationic Surfactant, CTAB Enhanced Coadsorption of Hydrophobic Drug On Nonionic Surfactant, TX100 Coated Silicas

Cherkaoui[1], C. Vaution[1], C. Treiner[2]
[1]Laboratoire de Pharmacie Galénique, URA CNRS 1218, Université Paris-Sud 5 Rue J.B. Clément, 92296 Chatenay Malabry, France, [2]Laboratoire d'Electrochimie, URA CNRS 430, Université Pierre et Marie Curie, 4 Place Jussie, Bat. 74, 75005, Paris, France.

Surfactants are used in numerous applications such as flotation, surfactant separation process or drug controlled-release. Practical applications, usually consist of a mixture of surface active compounds. These systems are then of great interest either in scientific or in technological fields.

While, adsorption from mixed surfactants have been studied widely both on hydrophilic substrate or hydrophobic one, the coadsorption in such systems did not receive the same attention. The aim of this work was then to study the effect of a TX100/CTAB mixed admicelle, on the adsolubilization (coadsorption) of a hydrophobic drug (progesterone) onto two different silicas (A200 and R974).

It was found that, while the cationic surfactant enhanced the adsolubilization of the steroid onto both substrates, the nonionic one, on the contrary, decreased it. Moreover, the same phenomenon (decrease) was observed with solubilization of the molecule in the mixture, compared to the pure surfactant compounds. The relative importance of mixed micelles to mixed admicelles in coadsorption of the drug is discussed.