Suven Research Publications in 2012

1. Bioorg Med Chem Lett. 2012 Dec 15; 22(24):7431-5.

Design, synthesis and pharmacological evaluation of 4-(piperazin-1-yl methyl)-N1 - arylsulfonyl indole derivatives as 5-HT$_6$ receptor ligands.

Nirogi RV, Badange R, Kambhampati R, Chindhe A, Deshpande AD, Tiriveedhi V, Kandikere V, Muddana N, Abraham R, Khagga M.

Source

Discovery Research, Suven Life Sciences Limited, Serene Chambers, Road-5, Avenue-7, Banjara Hills, Hyderabad 500 034, India. nvsrk@suven.com

Abstract

4-(Piperazin-1-yl methyl)-N(1)-arylsulfonyl indole derivatives were designed and synthesized as 5-HT(6) receptor (5-HT(6)R) ligands. The lead compound 6a, from this series shows potent in vitro binding affinity, good PK profile, no CYP liabilities and activity in animal models of cognition.

PMID: 23141912

2. Bioorg Med Chem Lett. 2012 Nov 15; 22(22):6980-5.

N,N-Dimethyl-[9-(arylsulfonyl)-2,3,4,9-tetrahydro-1H-carbazol-3-yl]amines as novel, potent and selective 5-HT$_6$ receptor antagonists.

Nirogi RV, Konda JB, Kambhampati R, Shinde A, Bandyala TR, Gudla P, Kandukuri KK, Jayarajan P, Kandikere V, Dubey PK.

Source

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Abstract

The design, synthesis and SAR of novel tetrahydrocarbazole derivatives having 5-HT(6) receptor antagonist activity is presented. The racemic compound 15e was found to possess desirable pharmacokinetic properties, adequate brain penetration and activity in animal models of cognition.

PMID: 23036955

3. J Med Chem. 2012 Nov 8; 55(21):9255-69.

Design, synthesis, and pharmacological evaluation of piperidin-4-yl amino aryl sulfonamides: novel, potent, selective, orally active, and brain penetrant 5-HT$_6$ receptor antagonists.

Nirogi R, Shinde A, Daulatabad A, Kambhampati R, Gudla P, Shaik M, Gampa M, Balasubramaniam S, Gangadasari P, Reballi V, Badange R, Bojja K, Subramanian R, Bhyrapuneni G, Muddana N, Jayarajan P.

Source

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Abstract

Our initial findings around aryl sulfonamide series led to N-(3,5-dichloro-2-methoxyphenyl)-3-(1-methylpiperidin-4-ylamino)-4-methoxy benzenesulfonamide as potent and selective 5-HT(6) receptor (5-HT(6)R) antagonist with reasonable pharmacokinetic properties and activity in animal models of cognition. However, lack of brain penetration and P-glycoprotein liability makes this scaffold unsuitable for further development. Our goal was to identify small molecule 5-HT(6)R antagonist with adequate brain penetration, acceptable ADME properties, no P-glycoprotein, and no hERG liability. Several structural modifications including bringing conformational constraint around the sulfonamide -NH group and introduction of a heteroatom to modulate the physicochemical properties were attempted. This effort culminated in the discovery of series of novel, potent, selective, orally bioavailable, and adequately brain penetrant compounds with no hERG liability. These compounds showed activity in animal models of cognition like object recognition task and water maze and in brain microdialysis studies at lower doses.

PMID: 23006002

4. J Chromatogr B Analyt Technol Biomed Life Sci. 2012 Oct 15;

Dried blood spot analysis of an iron chelator--deferasirox and its potential application to therapeutic drug monitoring.

Nirogi R, Ajjala DR, Kandikere V, Aleti R, Srikakolapu S, Vurimindi H.

Source

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Abstract

Deferasirox is an iron chelating agent for the treatment of transfusional iron over load in patients with chronic anemia. These anemic patients require close monitoring of the deferasirox exposures for ensuring its therapeutic efficacy. Dried blood spot (DBS) sampling methodology has the advantages of low volume of blood withdrawal and ease of transportation and storage

over liquid blood methods. A LC-MS/MS based analytical method was developed using reversed phase column with gradient elution program and quantitated in MRM mode. Linearity range for the liquid blood was 1-1000 ng/mL and for DBS was 5-5000 ng/mL under similar mass spectrometry conditions. The method was validated with respective (M-H)(-) ions, m/z 372→118 for deferasirox and m/z 410→348 for fluvastatin (internal standard). The validated method was applied for the analysis of DBS samples from a rat pharmacokinetic study and results were compared against liquid blood samples from the same animal. The mean C(max) from DBS sample (1121 ng/mL) was comparable to mean C(max) found in blood samples (1015 ng/mL) at 2h after oral dose of deferasirox. All the other calculated pharmacokinetic parameters were quite comparable for both liquid blood and DBS samples.

PMID: 23036906

5. Beilstein J Org Chem. 2012; 8:1366-73.

A novel asymmetric synthesis of cinacalcet hydrochloride.

Arava VR, Gorentla L, Dubey PK.

Source

R&D Laboratory, Suven Life Sciences Ltd., Hyderabad, India.

Abstract

A novel route to asymmetric synthesis of cinacalcet hydrochloride by the application of (R)-tert-butanesulfinamide and regioselective N-alkylation of the naphthyl ethyl sulfinamide intermediate is described.

KEYWORDS:

(R)-tert-butanesulfinamide, asymmetric synthesis, cinacalcet hydrochloride, naphthyl ethyl sulfinamide, regioselective N-alkylation

PMID: 23019473

6. J Neurosci Methods. 2012 Aug 15; 209(2):379-87

Approach to reduce the non-specific binding in microdialysis.

Nirogi R, Kandikere V, Bhyrapuneni G, Benade V, Saralaya R, Irappanavar S, Muddana N, Ajjala DR.

Source

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Abstract

Measurement of unbound test compound concentrations at the biophase is routinely carried out in the drug discovery. Microdialysis is an established sampling technique for in vivo measurement of endogenous and exogenous compounds and it is commonly used for monitoring true concentrations. Endogenous compounds like neurotransmitters and neuropeptides in the brain are routinely evaluated as a proof of pharmacological activity of test compounds. Although, microdialysis offers several advantages over the conventional techniques for its use in brain pharmacokinetics, the absolute determination of extracellular concentrations of test compound depends on the predictable non-specific binding to the tubing and probe membrane. In the present investigation, we have demonstrated steps to predict non-specific binding and described approaches to reduce while working with compounds having different degree of adsorption properties. Non-specific binding to the tubing was measured in vitro for seven structurally diverse compounds and based on the binding characteristics, changes were adapted in study conditions. In vitro probe extraction efficiency was evaluated by gain and loss, which was further used as a second layer of measurement for non-specific binding. For selected compounds, in vivo probe extraction efficiencies were carried out and brain pharmacokinetics was evaluated in the prefrontal cortex of male Sprague-Dawley rats. Thus, the present approach demonstrates a systematic approach for evaluating and reducing the non-specific binding of test compounds to the microdialysis tubing and probe membranes. The stepwise approach described will strengthen the applicability of microdialysis in brain pharmacokinetics.

PMID: 22732212

7. Biopharm Drug Dispos. 2012 Jul;33(5):265-77.

Pharmacokinetic profiling of efavirenz-emtricitabine-tenofovir fixed dose combination in pregnant and non-pregnant rats.

Nirogi R, Bhyrapuneni G, Kandikere V, Muddana N, Saralaya R, Komarneni P, Mudigonda K, Mukkanti K.

Source

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Abstract

During pregnancy, the disposition of various drugs is altered due to changes in physiological condition, maternal gastrointestinal absorption, gastric secretion and motility. A fixed dose combination of antiretrovirals is commonly prescribed for the treatment of HIV infection. There is a need to understand the pharmacokinetics and placental transfer of efavirenz-emtricitabine-tenofovir in fixed dose combination during pregnancy. The pharmacokinetics and placental transfer of efavirenz-emtricitabine-tenofovir fixed dose combination was evaluated in timed pregnant and non-pregnant Sprague-Dawley rats at 30, 10, 15 mg/kg p.o., respectively. The plasma, placental tissue, amniotic fluid and fetal tissue concentrations were measured using high performance liquid chromatography combined with tandem mass spectrometric detector (LC-MS/MS). To summarize, the pharmacokinetic profile of efavirenz remained similar in the pregnant and non-pregnant rats. However, a considerable difference in the pharmacokinetics of emtricitabine and tenofovir was observed in pregnant and non-pregnant rats. Efavirenz and emtricitabine showed appreciable placental, amniotic fluid and fetal exposure compared with tenofovir. The present study suggests that a profound impact on antiretroviral pharmacokinetics was observed during pregnancy and there is a need to monitor the exposure levels of each drug

when administered as a fixed dose combination during pregnancy. Further studies to explore the pharmacokinetic parameters of fixed dose antiretrovirals during the preclinical stage in a timed-pregnancy rat model are required. Such studies can help in the development of safe and effective medications with a reduced risk of perinatal transmission of HIV-1 infection.

PMID: 22610784

8. J Pharmacol Toxicol Methods. 2012 Jul; 66(1):22-8. doi: 10.1016/j.vascn.2012.05.003. Epub 2012 May 16.

Methyllycaconitine: a non-radiolabeled ligand for mapping α7 neuronal nicotinic acetylcholine receptors - in vivo target localization and biodistribution in rat brain.

Nirogi R, Kandikere V, Bhyrapuneni G, Saralaya R, Muddana N, Komarneni P.

Source

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Abstract

INTRODUCTION:

Reduction of cerebral cortical and hippocampal α7 neuronal nicotinic acetylcholine receptor (nAChR) density was observed in the Alzheimer's disease (AD) and other neurodegenerative diseases. Mapping the subtypes of nAChRs with selective ligand by viable, quick and consistent method in preclinical drug discovery may lead to rapid development of more effective therapeutic agents. The objective of this study was to evaluate the use of methyllycaconitine (MLA) in non-radiolabeled form for mapping α7 nAChRs in rat brain.

METHODS:

MLA pharmacokinetic and brain penetration properties were assessed in male Wistar rats. The tracer properties of MLA were evaluated in rat brain by dose and time dependent differential regional distribution studies. Target specificity was validated after blocking with potent α7 nAChR agonists ABBF, PNU282987 and nicotine. High performance liquid chromatography combined with triple quad mass spectral detector (LC-MS/MS) was used to measure the plasma and brain tissue concentrations of MLA.

RESULTS:

MLA has shown rapid brain uptake followed by a 3-5 fold higher specific binding in regions containing the α7 nAChRs (hypothalamus - 1.60 ng/g), when compared to non-specific regions (striatum - 0.53 ng/g, hippocampus - 0.46 ng/g, midbrain - 0.37 ng/g, frontal cortex - 0.35 ng/g and cerebellum - 0.30 ng/g). Pretreatment with potent α7 nAChR agonists significantly blocked the MLA uptake in hypothalamus. The non-radiolabeled MLA binding to brain region was comparable with the α7 mRNA localization and receptor distribution reported for [(3)H] MLA in rat brain.

DISCUSSION:

The rat pharmacokinetic, brain penetration and differential brain regional distribution features favor that MLA is suitable to use in preclinical stage for mapping α7 nAChRs. Hence, this approach can be employed as an essential tool for quicker development of novel selective ligand to map variation in the α7 receptor densities, as well as to evaluate potential new chemical entities targeting neurodegenerative diseases

PMID: 22609758

9. J Pharmacol Toxicol Methods. 2012 Jul; 66(1):8-13. doi: 10.1016/j.vascn.2012.04.006. Epub 2012 Apr 30.

Comparison of manual and automated filaments for evaluation of neuropathic pain behavior in rats.

Nirogi R, Goura V, Shanmuganathan D, Jayarajan P, Abraham R.

Source

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Abstract

INTRODUCTION:

The most commonly used Von Frey filaments are productive in evaluating behavioral responses of neuropathic pain in preclinical and clinical research. To reduce the potential experimenter bias, automated instruments are being developed for behavioral assessment. In preclinical research, neuropathic pain models of nerve injury with varied etiology like partial sciatic nerve ligation (PNL), chronic constricted injury (CCI) and spinal nerve ligation (SNL) are employed to screen the analgesic drugs to treat symptoms like allodynia and hyperalgesia. The current study was aimed to validate and compare conventionally used Von Frey monofilaments and automated dynamic plantar aesthesiometer using three different pain models.

METHODS:

PNL, CCI and SNL rats were used to compare and validate the assessment of neuropathic pain using Von Frey monofilaments and automated dynamic plantar aesthesiometer.

RESULTS:

Mechanical allodynia was assessed at various time points to mimic drug testing conditions in neuropathic pain models and anticipated to observe reliable and reproducible paw withdrawal threshold measurements across these models. Consistent paw withdrawal thresholds were observed in all the three models of neuropathic pain with Von Frey monofilaments, whereas variable paw withdrawal thresholds were noticed in PNL and CCI models but not in SNL model with dynamic plantar aesthesiometer.

DISCUSSION:

Manually used Von Frey filaments can be used in assessment of mechanical allodynia in all the three models, whereas dynamic plantar aesthesiometer is suitable for assessing mechanical allodynia in SNL but not in PNL and CCI models. The reason for variable paw withdrawal thresholds during assessment of mechanical allodynia in PNL and CCI models with dynamic plantar aesthesiometer may be due to the paw deformity and change in foot posture.

PMID: 22575456

10. J Pharmacol Toxicol Methods. 2012 May-Jun; 65(3):136-41.

Rat thalamic α4β2 neuronal nicotinic acetylcholine receptor occupancy assay using LC-MS/MS.

Nirogi R, Kandikere V, Bhyrapuneni G, Saralaya R, Muddana N, Ajjala DR.

Source

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Abstract

INTRODUCTION:

In vivo brain receptor occupancy has been the key assay in driving preclinical drug discovery program and there is a need to hasten this screening step. Radiolabeled methods, which are time consuming and expensive, are most widely employed to measure receptor occupancy. Thus we sought to develop and validate an alternative novel approach for measuring rat brain α4β2 neuronal nicotinic acetylcholine receptor occupancy using high performance liquid chromatography combined with tandem mass spectrometric detector (LC-MS/MS).

METHODS:

Tracer optimization studies like in vivo dose and time dependent brain regional distribution; saturation binding and blocking study with nicotine and atropine were carried out for ZW-104 in rats. Assay validity was tested by pretreatment with potent α4β2 ligands; TC-1734, cytisine, ABT-089, ABT-594 and A-366833. Receptor occupancy along with plasma and brain exposure levels of α4β2 ligand was measured in the same set of animals.

RESULTS:

The regional distribution of ZW-104 in rat was found to be, thalamus>frontal cortex>striatum>hippocampus>cerebellum, and is in accordance with the distribution and regional densities of α4β2 nAChRs measured using [^{18}F]ZW-104 in mice and baboons. Pretreatment with nicotine and α4β2 ligands dose dependently reduced the binding of ZW-104 in the thalamus. Non-nicotinic antagonist atropine did not alter the binding of ZW-104 in the thalamus, indicating the tracer specificity. The ED_{50} values calculated for occupancy were found

to be 3.01, 0.83, 14.81, 0.001 and 0.11 mg/kg for TC-1734, cytisine, ABT-089, ABT-594, and A-366833, respectively.

DISCUSSION:

These findings demonstrate that non-radiolabeled ZW-104 is suitable for determining the α4 β2 receptor occupancy in rat brain. The LC-MS/MS based receptor occupancy assay is a rapid method and allows the generation of occupancy data along with the brain and plasma concentration in the same group of animals.

PMID: 22546347

11. J Pharmacol Toxicol Methods. 2012 May-Jun; 65(3):115-21.

In vivo receptor occupancy assay of histamine H3 receptor antagonist in rats using non-radiolabeled tracer.

Nirogi R, Kandikere V, Bhyrapuneni G, Muddana N, Saralaya R, Ponnamaneni RK, Manoharan AK.

Source

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Abstract

INTRODUCTION:

Rapid and reliable preclinical receptor occupancy measurement at the target organ in relevant species is critical in accelerating the drug hunting process. The aim of this study was to develop in vivo receptor occupancy assay for histamine H3 receptors (H3 R) using the non-radiolabeled GSK189254 as a tracer and to correlate the occupancy-exposure relationship for H3 R antagonists in the rats.

METHODS:

In vivo tracer characterization studies like brain regional distribution, dose and time dependent uptake were carried out for GSK189254 in the male Wistar rats after intravenous administration. The tracer specificity was validated by pretreatment with H3 antagonists like ciproxifan, thioperamide, and GSK334429. The brain regional tracer levels and H3 R antagonist concentrations in plasma and brain were quantified using liquid chromatography tandem mass spectrometry. Receptor occupancy was calculated using the ratio of total binding (striatum or frontal cortex) to the nonspecific binding (cerebellum) of the tracer in animals pretreated with H3 R antagonist.

RESULTS:

High degree of selective distribution of GSK189254 was found in striatum, frontal cortex, and low level in the cerebellum. Regional distribution of GSK189254 in the rat brain was consistent to that of H3 R distribution mapped using ^{3}H or ^{11}C-GSK189254 in human, porcine, and rat. The

calculated occupancy ED_{50} values in the frontal cortex were 0.14, 1.58, and 0.14 mg/kg for ciproxifan, thioperamide, and GSK334429, respectively. The plasma EC_{50} values (ng/mL) were found to be 2.33, 292.2, and 3.54 for ciproxifan, thioperamide and GSK334429, respectively.

DISCUSSION:

Results from mass spectroscopy based approach to determine H3 R occupancy in rat brain is comparable with reported radiolabeled method by scintillation spectroscopy. In conclusion, non-radiolabeled GSK189254 was successfully employed as a tracer for assessing the H3 R occupancy in rats and it can be used as a preclinical tool for evaluation of novel H3 R ligands in the drug discovery.

PMID: 22487318

12. Brain Res. 2012 May 9; 1453:40-5.

Difference in the norepinephrine levels of experimental and non-experimental rats with age in the object recognition task.

Nirogi R, Abraham R, Jayarajan P, Medapati RB, Shanmuganathan D, Kandikere V, Irappanavar S, Saralaya R, Benade V, Bhyrapuneni G, Muddana N.

Source

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Abstract

In the present study, we investigated the performance of adult and juvenile rats in the Object Recognition Task (ORT). While it is well known that the performance of rat in ORT differs with age, the reason for the difference as well as the underlying neurotransmitter that may have led to these differences were investigated. In the present study, juvenile rats of postnatal day 40-45 (PND 40-45) and adult rats of postnatal day 60+ (PND 60+) were subjected to a two trial ORT. The juvenile rats did not discriminate between the novel object and the familiar object, while the adult rats discriminated the novel from the familiar object. On estimating brain concentrations of norepinephrine (NE), it was observed that the NE level in MTL (medial temporal lobe) of adult experimental rats was significantly higher than the adult non-experimental rats. In juvenile rats, no significant difference was observed in the NE levels of experimental rats in comparison to its non-experimental counterparts. Administration of yohimbine (α(2A) adrenergic receptor antagonist) enhanced the level of NE in juvenile rats and reversed the difference seen with age. From the present study, we conclude that the deficit in memory seen is likely due to the difference in NE levels with task and this can be reversed by yohimbine which enhance NE levels.

PMID: 22464882

13. Biomed Chromatogr. 2012 Feb 16. doi: 10.1002/bmc.2718. [Epub ahead of print]

Exploring dried blood spot sampling technique for simultaneous quantification of antiretrovirals: lamivudine, stavudine and nevirapine in a rodent pharmacokinetic study.

Nirogi R, Kandikere V, Komarneni P, Aleti R, Padala N, Kalaikadhiban I, Bhyrapuneni G, Muddana N.

Source

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Abstract

A high-performance liquid chromatography/positive ion electrospray tandem mass spectrometry method for the simultaneous quantification of lamivudine, stavudine and nevirapine was developed and validated in dried blood spot (DBS) cards. The analytes were separated using an isocratic mobile phase on a reverse phase column and analyzed by MS/MS in the MRM mode using the respective [M+H](+) ions, m/z 230-112 for lamivudine, m/z 225-127 for stavudine, m/z 267-226 for nevirapine, m/z 383-337 for zidovudine (IS). The lower limit of quantification was 1 ng/mL for both lamivudine and stavudine and 10 ng/mL for nevirapine. Acceptable precision and accuracy were obtained for concentrations over the standard curve range. The method was successfully applied to quantify them in a rat pharmacokinetic study in whole blood, plasma and DBS cards after a single oral co-administration at the dose of 10, 2 and 13 mg/kg for lamivudine, stavudine and nevirapine, respectively, to male Wistar rats. Following oral administration the pharmacokinetic results in all the matrices are in close agreement. Thus accomplishment of this method would facilitate the ease of collection of clinical samples on DBS cards for lamivudine, stavudine and nevirapine during human clinical trials and therapeutic drug monitoring.

PMID: 22344535

14. Eur J Drug Metab Pharmacokinet. 2012 Feb 3. [Epub ahead of print]

Concurrent administration of atypical antipsychotics and donepezil: drug interaction study in rats.

Nirogi R, Bhyrapuneni G, Kandikere V, Benade V, Muddana N, Saralaya R, Irappanavar S, Ponnamaneni R, Mukkanti K.

Source

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Abstract

Psychotic and behavioral symptoms are common in patients with dementia. Thus, it is rational to assume that patients with dementia would gain benefit from combination therapy of an antipsychotic agent and a cognitive enhancer. Antipsychotics are not approved by the US FDA in elderly patients with dementia but their use is still prevalent in other population. In the current study, we investigate the effect of atypical antipsychotics on acetylcholine modulation by donepezil. In addition, the plasma pharmacokinetics on concurrent administration of these drugs

was studied. Acetylcholine modulation was carried out in the ventral hippocampus of Sprague-Dawley rats using brain microdialysis technique. In a parallel group of animals, pharmacokinetic parameters were evaluated on administration of donepezil (5.0 mg kg(-1), ip) alone and in combination with olanzapine, clozapine, or quetiapine. Donepezil produced 348% increase in hippocampal acetylcholine levels. Coadministration of olanzapine and donepezil produced 393% increase in extracellular acetylcholine, and the effect was supported by a significantly ($p < 0.05$) decreased clearance of donepezil in plasma. Whereas, other plasma pharmacokinetic parameters of donepezil "AUC(0-24h), T (1/2) and T (max)" were moderately altered after this combination treatment. Concurrent administrations of clozapine or quetiapine with donepezil produced a non-significant change in acetylcholine levels in comparison to donepezil alone. The plasma pharmacokinetics of donepezil was unaltered. Results from this preclinical investigation indicate that extrapyramidal side effects may precipitate upon coadministration of donepezil with olanzapine. Care must be exercised by physicians and caregivers while administering these two drugs together.

PMID: 22302541

15. Biomed Chromatogr. 2012 Jan 4. doi: 10.1002/bmc.2670. [Epub ahead of print]

LC-ESI-MS/MS method for quantification of ambrisentan in plasma and application to rat pharmacokinetic study.

Nirogi R, Kandikere V, Komarneni P, Aleti R, Padala N, Kalaikadhiban I.

Source

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Abstract

A sensitive high-performance liquid chromatography-positive ion electrospray tandem mass spectrometry method was developed and validated for the quantification of ambrisentan in plasma. The analyte and the internal standard (armodafinil) were extracted from plasma by acetonitrile precipitation and they were separated on a reversed-phase C(18) column with a gradient program. The MS acquisition was performed with multiple reaction monitoring mode using the respective [M□+□H](+) ions, m/z 379-347 for ambrisentan and m/z 274-167 for the IS. The assay exhibited a linear dynamic range of 1-2000□ng/mL for ambrisentan in plasma. Acceptable precision (<10%) and accuracy (100□±□8%) were obtained for concentrations over the standard curve range. The method was successfully applied to quantify ambrisentan concentrations in a rodent pharmacokinetic study after a single oral administration of ambrisentan at 2.5□mg/kg to rats. Following oral administration the maximum mean concentration in plasma (C(max) ; 1197□±□179□ng/mL) was achieved at 1.0□±□0.9□h (T(max)), and the area under the curve (AUC) was 6013□±□997□ng□h/mL. Therefore, development of such a simple and sensitive method in rat plasma should translate into a method for ambrisentan in human plasma for clinical trials.

PMID: 22222607

16. J Pharmacol Toxicol Methods. 2012 Jan; 65(1):37-43.

Comparison of whole body and head out plethysmography using respiratory stimulant and depressant in conscious rats.

Nirogi R, Shanmuganathan D, Jayarajan P, Abraham R, Kancharla B.

Source

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Abstract

INTRODUCTION:

Assessment of respiratory safety is one of the most important requirements for new chemical entity (ICH Guideline S7A). The aim of the present study was to compare and validate respiratory safety pharmacology models in conscious rats, to find out the most appropriate method for detection of drug-induced adverse effects on respiratory function in preclinical safety studies.

METHODS:

Head out plethysmography and whole body plethysmography methods were used to monitor typical parameters of ventilatory function like respiratory rate (RR), tidal volume (TV), minute volume (MV) and mid expiratory flow (EF50). The effects of respiratory stimulant theophylline (100mg/kg) and respiratory depressant chlordiazepoxide (100mg/kg) were evaluated in both models. Propranolol (60mg/kg) was also used to compare head out and whole body plethysmography because of its bronchoconstrictor effects on airway function.

RESULTS:

Theophylline caused a significant increase in TV, EF50 and MV in both whole body and head out plethysmography. In whole body plethysmography, theophylline significantly increased RR, but this increase was not observed in head out plethysmography. Chlordiazepoxide significantly decreased RR, TV, EF50 and MV in head out plethysmography, but it significantly reduced only TV in whole body plethysmography. A significant reduction in TV was observed with propranolol in both whole body and head out plethysmography.

DISCUSSION:

We conclude that ventilatory function can be accurately assessed using head out plethysmography compared to whole body plethysmography. Our experimental results of EF50 from non-invasive methods suggest that reliable assessment of airway function demand additional invasive methods

PMID: 22019985