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Noωrrelation betweeß side-chaiø of prøpraaolol oxidation and S-mephenytoin 4"-hydro rlase activit)

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LoUHOJmgEHd5(2p arlntJC eneticsRmuchhmw 4Z UM4hmeoh
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KEY WORDS propranolol; mephenyω ; cyω-chrome P-450; hy ocylases;ωMmedm pharmaα19tmetics

AIM: To determine any rrelation betw n the side-chain idative capacity for propranolol and S-tnephepytoin 4hydroxyl < ωhrome P-45D 2C19 CYP2C19) acti ty in hmi . y Chine of E n nationalily. ME1HODS: S-mephemytoin öxida e metabolite 4'- hy mephenytom (4'-OH-M) S- and R-mephenytoin and naphthoxyl-aetic Beid (NLA) exa d mume d pmpramolol in pl a were meastl ed after 14 healthy extensive mtZMizasofS mepfmy D.dation were given å itagle al do f m mie meph wtGD 100 mg and mic propranolol 80 mg rE tively. S/R-mephetlyto : he was det ned by cbiraf capary s ehxomst :Faphy with mtrogen-phQspl ros detection 4'-OH...M in urine by revl -phpe ltquide Dl_a Qphy (RPLC)' with ultraviolet det tion and plasna propranolol or uôjI8fy' NLA by e RPLC wi ce ætectiQn. RES1JL1'S: Ne sω ela :ωns w nndbetw n the p al metal: lic c1 tance (αm) Tof propranolo1ωNLA d8 inary S/R m n of 1l1fpkly D ('s=- ω ;] P=0.869§} nor between theαmmdlogmof8h ary excretion :eti0f of " M (rs:: ()).1 {J77; P=ä.7140). CONαUSIONS: CYF C19 is not a princi .pal P-4Sø im me res:r:nsiJle for the zyiωside-êhain ondatiQp of }0toptanoll m:the ()hin

Propranolof undergα s extensive first-pass metabelism by h Hanlre :r m croSOmÆ} crtooru.nome P450 (CYF) proteins via 3 main 'rathwall aromatic naph e hng h oxylatioIrl and 5-positions side-chain oxidatiop (N desisop opyb.tion 0 N...deaJkýla:i0D) d ectn glucuror d wMd e aromatic hydroxylation is catalyzed predonllrumtly_by h_ debrisDquine 4-hydro rlase (ωCmE)(2-5L e N-desiSop 0plyati ib0n ŭf prop'ranolol to a hthoxyae tlllc acicl (NLA) i d pendent p ωl on hmma (ωCYP2Cαlω9)'62 However the sid haiñ N desisoWlfo pylatiojft ÏJs mediated pr ncipa.Jy b7 bői.hdle recombinant and/or cloned human CYPIA2) and human liver microsomal CYFli\? 45 but not by human liver mlcrosomal CYP2C19(agreer ent with a lack of inhibition of propranolol N-desisopropyl e etivlity by meph qtda h human liver micr-osomes(3); propranolol N-desisopropylation was rrdated weZ y CYP2C content (== ()40<<&) hexob; 1 1'. hydroxylation (==0.161)(4) catalyzed larg' by CYP2C19(8) and S mepnenytom 4)-hyclr y i ==0.60 ; P == 0..ns)(5J implying that çY C19 may Qot he a mqjn :PA50 isozyrne in propranølol N-de isdi>:lfopyrãtiøn. Thus a ruajð role pla' by CYFIA2 in the involvement oi prop17allolo1 -N-desisopropylation was prúposed e basis of above evidence4-7 and the fact that the pM I metabplite cleaJ calllce (αm) Qf propraflolol to 1_ _j[ ) was much higher in srnQkearlin nonpokgs cilue cbieiyωtn@ induct4on ci CWl W smoking(10j and a cQntroversy Inçerning the relative ntribution Qf' CYP2Cl'9 aorivi y ø pzoprain01013s gdechain o dation i h MRSJ ts

ZELt4LtitJJLtz;

yω etation 1lletween tliiè sid dhain d capacity for .pròpranolol and ' CYP2C19 activí h atthy CNnese.

[1] Froject s po ed by de NaJmnd N al imce tlndlartion of αúna NQα9200154 and F3 9330230 and by Chrr.m 11 c& 1'd of New York USA Na 92-568.
SCOFf pond ce to Prof ZHαJ Høng-
ReGei ed 1996-09]3 AecepteJ t'99'7-0-11-27

SUBJECTS ANDMETHODS

The Han Chinese (7F 7M) 21 sh

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and renal or hyatic functions. NC

?d?ddω0 . 8 h urine (mωω) beiω 10d thept 8 h urinary on of 4' wxmephwo l-OH M) bei 90 %-1 d S-mephenytoin d (19 D %). The studly prot o. w approved by e Ethics t O{HZJTZ IJrlivmity and writtm idoomed nsent was each subject.

pmtMcmc19acMty d ch subj was determined by taking 8J single øral do 01 10@ raeem1c mephenytoin (Mesantoin⁹ ndoz) after an overnight fast. Urine w Uocted during the xstdose period of 0 8 h and m limot stored at-30 .4'-OH-M levds m mne w e L by an ùnproved LC method(11) and amounts of S- and R-meph ytoin in U!in@ by cl al capillrury gas ; m th a sli t nlodification[13']. The CYP2C19 ac vity was pressed S/R ratio or 19 D %.

At least 2 wk after the mephenytoin test each subject received a single oral dose of 80 mg of racemic propranolo1 h hloride (lnderal tablet 10 mg each Beijing 2nd pharmacMid Co)Using a si protocolω 1Jhat o mephenytoin t t urine was J. ected for 24 h. Urin y NLAwasmωured by HPLC[14] _ t mination of NLA in reolicate urine samples w s done within 1 d. Estimate ai the fraction d to d excreted λin the urine (fro) w mean va.1ue of t e 2 pa:allet samples of each subject. Venous blcx(10 mL) was heparinized before and alter oral propranoloL Pl ma propranolol w quantitated by HPLC

using 4-methylpropranolol stand d.

Data analysis lndividual elimination rate constant (K_e) was timated from the slope of the terminal phase (3 −24 h) of the log plasma ncmtation-timeα rrve. The oral clærance of propranolol (Cl 0) w: calculated with tne equations: Cl_o = d /AUC Cl_m = j x Cl_o , 1n which f_m is the fraction of the total dose excreted as the n1etabolite NLA in urine. CO elation between Cl_m of propranolo1 to NLA and CYP2C19 activity (S/R ratio 19 D %) was analyzed by nonparametic Speaman's r lk rrelation with e use of the SAS syst (SAS 6.10 version SAS lnstitute C NC USA).

RESULTS AND DISCUSSION

In this stl1dy relationship hetween S/R ratio and Cl_m (r_s = 0.0484; P = 0.8695) or between ig D% dclm(fs=-0.1077;P=0.7140 had no sismificant Irrelations in the EM subjects with a lazprange of cymc19acdvity(Fig1).Although

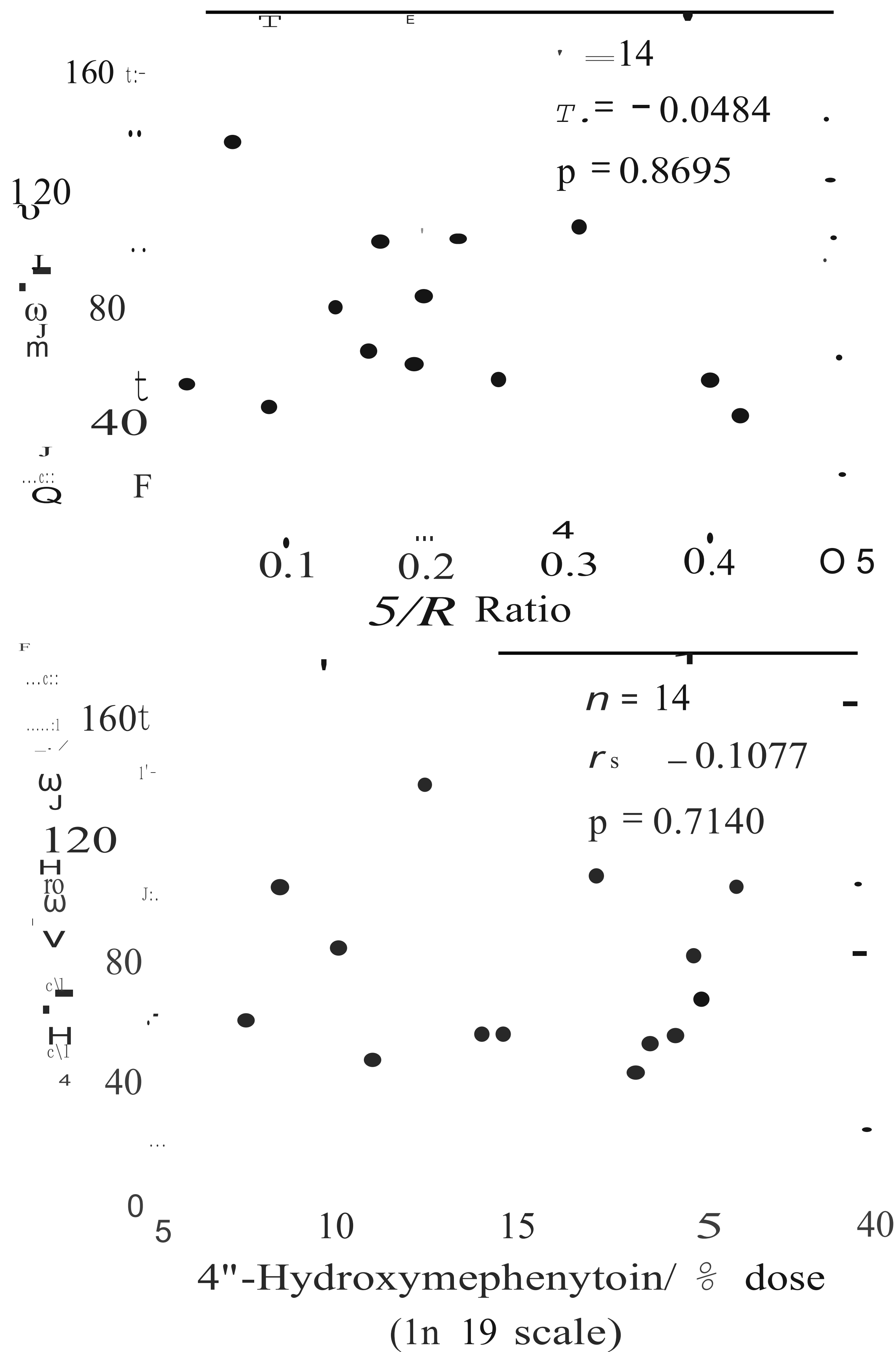

Fig 1. Correla nbe een Cl_m of propranolol to NLA and S/R ratio of mephenytoin (up) and 4'-OH-M % d f S-mephenytoin (lower) excre d in the ineO-8h i1stdωe.

Ward et aZ(2) found that the Cl_m of propranolol to NLA a further oxidative metabolite of N-desisopropylpropranolol correlated highly with the S/R ratio of mephenytoin in the postdose 0 − 8 h urine samples (r = 0.80') and was somewhat lower in the p r metabolizers (PM) of S-mephenytoin than in the EM subjects they also suggested that other CYF iso mes may be capable of catalyzing tbe same m.etaoolic reaction. Thus an under-

standing of PTOFra110loi TRetaboiimmust take lHto ac unt fhe inwivernent of thc rnuitipk liver CY? isofommi11eachmetalmiicmute{0} the relative mtztbutkm o{the dibrent immmlOlh1. nletal ωT the iFI :ehr ha mω(Kn xω d 1 ance Knl) of '(Hh rrrbi and

and disc nCq3y d i)_htl i11 '(dO d jFI Yf studiC even lhe ìnterindividual é ld/or jnl cret htHC differentTSiudnlg nttaim!ism-1o our kno -ledgc thit udy for the fint tinl offered the prcliminaryevidence that iFtuitxypropranoiol-s -Y- immη-latiomwmt bemdia lnainly by CYfC19 ωntent váth the other in 'oithη α)11 1ncllIszconclUSIOns(5)

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b lù Y Hα ;kawa Se 1'S UH 1lohzod S Kjlad'a M, et al. Cy hrome' fP45ID i zym wdlved m pπ)Jr 101ol melabolísm in h1!1an liver rmierosomes: e dle ·f CYP2 ring hy xy seancl CYF1A2 N-d prop se. U Metab Dispos 1994 22: 90-15.

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6 C0h1lg MS cM. Nib3 ke CoGha Ibnt8l HTu Jlk RHJ mh)(.(} Prnw or 4t. 1fi hyc d iωpr'pylatiøn by doωJ huυ in (yl(ωxhlmrne P450 1 nl P450 1A2. TJr1Jg M ab Dispc 199 ;24: 692 -4.

7 f 11m K. Ildi8 SW LcrmωEd MS Tdckωr (Vυriable αtributk H of c. Yf [)6 tl t. N dcalkylalion c.f S (-)-prn>pranoloJ Ly hurr liver rm Br J CIlH Phannucol 199642! 390 3.

8 2 f7 :tjijr:rt :j,S/tw 1 hfi tp tok se IJynlO ;I: lit-:

Adàitional cffects on rer 1clear ce oI me holil J Pharmaωi EXP Ther i987324611928-33.

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11 HG H' U SL Zhou H:th-perfomlhmee líquid chrornat Taphlç defl Urisl 6ry4'"hydFOXYTEIephmyudfha mdakk m ket: fl hÜBtic ø ne CYP2C19" hwn]Chmmtogr : Biomcd Appl 1995 : 125...

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: S- (S :p)

酶(CYP2C19) ( )

: 14 S-M pp

Mψplω

80

S- R-M 4

(4 OH-M)

:0-8 S/R 4

19D%

(rs — 0.0484 0.1071).

cYP2 19 Pro

P -450 -