# PHARMACOLOGICAL EVALUATION OF THE ANTIARRHYTHMIC ACTIVITY OF TOCAINIDE IN EXPERIMENTAL ANIMALS

THESIS

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BY

MOHAMED AHMED ABDEL - BARY

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Demonstrator in Pharmacology Department


Supervisors


Prof. Dr. HANIA MOHAMED ALI

Prof. & Head Of Pharmacology Department

Dr. ZEINAB M. LABIB

Ass. Prof. Of Pharmacology

Dr. GABER ABDEL - SABOUR ALI

Lecturer Of Pharmacology

Department Of Pharmacology

Faculty Of Medicine, Ain Shams University


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# A C K N O W L E D G E M E N T S

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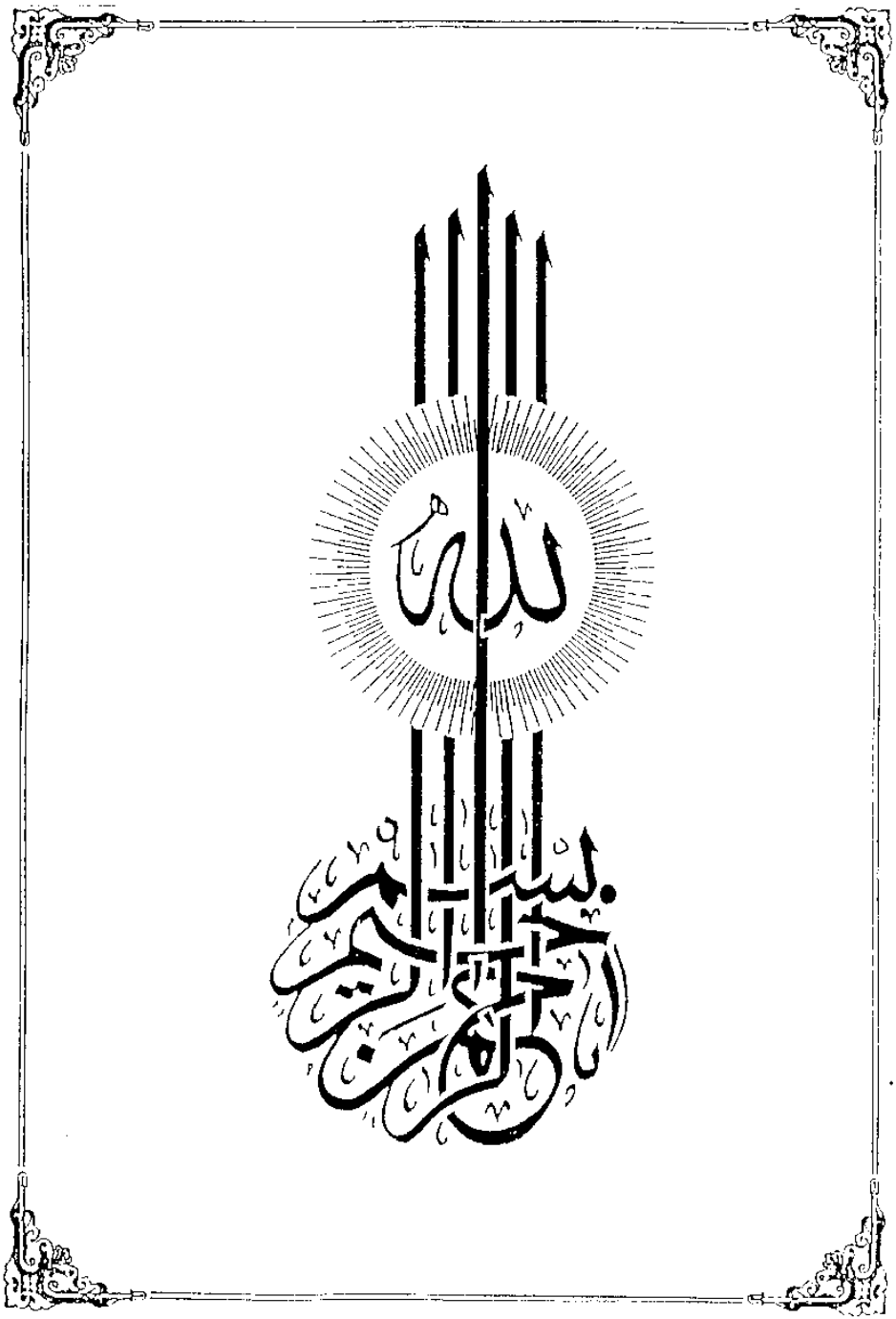

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# C O N T E N T S

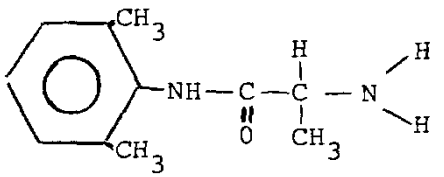
# INTRODUCTION

# I N T R O D U C T I O N

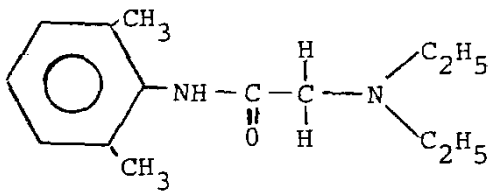
Although a number of new antidysrhythmic agents have been used for clinical trials, there continues to be a need to find more potent and safer ones ( Harrison et al., 1977 and Zipes and Troup, 1978 ) .

Tocainide was introduced by Astra Laboratories in the early seventies . It has been experimentally proved to be orally-effective long-acting antidysrhythmic agent (Smith and Duce, 1971; Smith et al., 1972 and Duce et al., 1973). It is a structural analogue of the parent compound lidocaine ( Figure 1 ) .

The modification of the amine end of lidocaine resulted in lowered lipophylicity of tocainide base ( Smith, 1979 ). The carbon atom number " 2 " is a chiral atom . This chiral center confers optical activity on the R-(-) and S-(+) enantiomers and more importantly, it makes them react at different rates towards chiral reagents , solvents and catalysts ( Meislich et al., 1983 ) . The two enantiomers have different pharmacokinetic as well as pharmacodynamic properties ( Sedman et al., 1984 ) .



Tocainide ( 2-amino-2',6' propionoxylidide ) .



Lidocaine ( Diethylglycine xylidide ) .

Figure 1 - Structural formulae of tocainide and lidocaine

Pharmacokinetics :

In human, the plasma profile of tocainide suggests an initial distribution phase and is best described by biexponential equation . In some cases, a distribution equilibrium is immediately reached indicating a mono-exponential behaviour . This is more true after oral administration where equilibrium between absorption , distribution and elimination phases seems to occur rapidly ( Graffner et al., 1980 ) . In rats, the kinetics can be described by a linear 2-compartment model with a distinct but short distribution phase up to a dose level of 15 mg/kg b.wt. At doses higher than 20 mg/kg b.wt., non-linear kinetic behaviour is evident .

Tocainide pharmacokinetic properties suggest its suitability for oral use . Bioavailability after oral administration is nearly complete . The rate of absorption is the same after different dose regimens ; but the extent is increased proportional to increase of the dose . Although the rate of absorption may be reduced by food, its extent is not changed ( Winkle et al., 1976 ) .

In human, tocainide is rapidly distributed with mean total apparent volume of distribution ($V_\beta$) = 2.3 l/kg b.wt.

The mean volume of the central compartment ( $V_c$ ) and the mean volume of distribution at steady state ( $V_{ss}$ ) are equal to 0.8 and 1.45 l/kg b.wt. respectively ( Meffin et al., 1977 ) . The percentage of the drug bound to plasma protein varies between 10 and 50 % . Two classes of binding sites were identified : one with low capacity and high affinity and a second with relatively low affinity and high capacity ( Lalka et al., 1976 and Elvin et al., 1982 ) . The binding of the R-(-) is slightly less than the S-(+) isomer but the difference is of little clinical significance . Binding is independent of serum tocainide concentration within therapeutic range of 4 to 12 µg/ml ( Sedman et al., 1982 ) .

Elimination of tocainide is achieved through both enzymatic degradation and renal excretion . The total body clearance ( Cls ) ranges from 122 to 197 ml / minute ( = 1.61 - 2.6 ml/kg/minute ), of which about 64 - 70 ml / minute are of renal origin . The mean elimination half-life ( $t_{\frac{1}{2}}$ ) ranges from 11.3 to 13.5 hours ( Woosley et al., 1975 ) .

In human , metabolism of tocainide is mainly through two pathways : conjugation and oxidative deamination (Elvin et al., $1980_{a,b}$ and Ronfeld et al., 1982 ) .

Tocainide glucuronide( TOCG ) is formed in two steps ; first, tocainide combines with $CO_2$ to form carbamic acid then, carbamic acid is conjugated with glucuronic acid to form carbamyl O-β-D-glucuronide . The enzymes needed to produce TOCG may be wide spread in animal kingdom but the capacity to produce substantial amounts has only been documented following oral administration suggesting that gut flora may have a role ( Gipple et al., 1982 ) .

Conjugation of tocainide in human -unlike rats (Venkataramanan and Axelson, $1980_b$ and Bennett et al., 1980)- is not inducible by sedative doses of barbiturates nor by other substrates for glucuronyl transferase . The authors explanation is that tocainide carbaminic acid formation is a rate-limiting step in TOCG synthesis in rats . TOCG represents 23% of tocainide elimination, is mainly excreted by glomerular filtration and its $t_{\frac{1}{2}}$ is slightly lower than that of tocainide.

Deaminated metabolite ( LX ) is also synthesized through a number of intermediates . It is 25 % as potent as tocainide but it has no detectable central nervous system toxicity . Its $t_{\frac{1}{2}}$ is greater than twice that of tocainide and only about 2 % are recovered in urine , suggesting further metabolic degradation .

The metabolism of R-(-) enantiomer is more active than that of S-(+) enantiomer (Gal et al.,1982) and this may be responsible for the longer $t_{\frac{1}{2}}$ of S-(+) (= 16.7 h) relative to R-(-) enantiomer ( = 10.3 h ) ( Sedman et al., 1984 ) .

complicated by left ventricular failure ( Macmahon et al., 1985 ) suggest that tocainide kinetics are not affected neither by reduction of cardiac index nor elevation of pulmonary artery pressure . However, there is trend towards high plasma concentrations and low volume of distribution . The pharmacokinetic data also suggest that the drug can be used in patients with substantial renal impairment ( Lalka et al., 1976 ), however, TOCG tends to accumulate so that in patients with severe impairment, it may be higher than tocainide itself ( Ronfeld et al.,1982 ).

Pharmacodynamics :

In canine Purkinje fibers bathed in low potassium Tyrode solution ( 2.7 mmol/l ), tocainide at concentrations of 40 - 60 µg/ml increased excitability threshold so that greater current was required to elicit action potential during repolarization . The supernormal phase of excitability was shortened at concentration of 40 µg/ml and was completely eliminated at concentration of 60 µg/ml (Moore et al., 1978) . In high potassium Tyrode solution ( 4.5 mmol/l ), Kinnaird and Man ( 1984 ) found that the increase in activation voltage occured at tocainide concentrations of 2 - 5 µg/ml and that it was more pronounced with decrease in cycle length . The authors explained this on the basis that hyperpolarization occured during increased rates of stimulation ( Vasslle, 1977 ) .

In dogs, tocainide increased ventricular fibrillation threshold ( VFT ) in a dose-dependent manner during both normal sinus rhythm and programmed premature ventricular depolarization . However, at any given plasma concentration, the increase in VFT was more after a premature complex than during sinus rhythm . The maximum observed increase in VFT was at concentration of 33 and 48 µg/ml respectively ( Moore et al., 1978 and Schnittger et al., 1979 ) .

On sinoatrial node ( SAN ) automaticity, tocainide mildly increases sinus node cycle length ( SNCL ) at a concentration of 10 µg/ml in both dogs ( Coltart et al., 1974 ) and guinea pigs ( Naumann d'Alnoncourt and Luderitz, 1979 ) . Dose-dependent increase up to complete suppression occured in the concentration range of 30 - 200 µg/ml .

In human, infusion of tocainide at a rate of 0.5 - 0.75 mg/ kg/ minute for 15 minutes ( corresponding blood levels = 3.1 - 10 µg/ml ) resulted in mild decrease ( Anderson et al., 1978 ) or no change ( Horowitz et al., 1978 ) in SNCL .

The epinephrine-enhanced automaticity of guinea pig Purkinje fibers was more susceptible than the SAN . It was depressed in the concentration range of 5 - 10 µg/ml ( Naumann d' Alnoncourt and Luderitz, 1979 ) . In rats, Tejerina et al. ( 1983 ) found that the drug prolonged the sinus node recovery time ( SNRT ) at concentration of $10^{-4}$ M (= 19.2 µg/ml ) ,

while in human, at concentration up to 10 µg/ml SNRT as a ratio of SNCL was not significantly affected as demonstrated by Anderson et al. ( 1978 ) .

On canine atrioventricular node ( AVN ) conduction, tocainide caused linear depression being maximal at 50 µg/ml ( Moore et al., 1978 ) while in rabbits, no consistent changes occured up to a concentration of $3 \times 10^{-5}$ M ( = 5.8 µg/ml ) as proved by Ronfeld et al. ( 1982 ) . In human, Anderson et al. ( 1978 ) reported decrease in AVN effective refractory period ( ERP ) but not in AVN functional refractory period ( FRP ), while Horowitz et al., in the same year, found insignificant change in refractoriness and conduction at therapeutic concentrations .

As regards the His-Purkinje conduction, tocainide increased conduction time at concentrations higher than 20 µg/ml in both dogs ( Kinnaird and Man, 1984 ), rabbits ( Ronfeld et al.,1982) and guinea pigs(Almotrefi and Baker, 1980 ) . Complete block was reported at concentrations higher than 60 µg/ml ( Ronfeld et al., 1982 ) .

In human, however, conduction was not significantly changed in the therapeutic range ( Anderson et al., 1978 ) .

The different phases of action potential are affected by the drug as shown by Moore et al. (1978) . They found that tocainide concentration of 10 - 50 µg/ml caused dose-dependent shortening of the plateau ( phase 2 ) and $APD_{50}$, but not the duration of complete repolarization . Although the ERP was not prolonged, the ratio of ERP to action potential duration ( APD ) increased in a dose-dependent fashion. The maximum upstroke velocity ( $V_{max}$ ), the level of overshoot and the resting membrane potential were not affected .

Recently, Gintant et al. ( 1983 ) and later Kinnaird and Man ( 1984 ), with high potassium concentrations (>4 mmol/l) showed that dose- and rate-independent depression of $V_{max}$ at all cycle lengths ( even after long quiescence up to 8 minutes) occured at concentrations of 10 - 20 µg/ml . Both $APD_{50}$ and $APD_{90}$ were decreased at all cycle lengths but the ERP was only shortened by concentration of 20 µg/ml and at cycle length of 1 second . This is consistent with what was reported earlier by Man and Dresel ( 1979 ) who noticed that tocainide depressed the conduction of mid-range extrasystoles ( coupling interval = 250 - 500 ms ) but not upper-range extrasystole ( coupling interval > 500 ms ) . Oshita et al. ( 1980 ) demonstrated similar effects in guinea pigs at potassium concentrations > 4.5 mmol/l, but not at high calcium concentrations ( 7.2 nM/l ) . In some cases, a slow component was recorded at pacing rate of 0.25 Hz .