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A Molecular Modelling Analysis of the Metabolism of Mexiletine

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Abstract: In this study, molecular modelling analyses based on molecular mechanics, semi-empirical (PM3) and DFT (at B3LYP/6-31G* level) calculations have been carried out to obtain information on the toxicity of mexiletine (MEX) and its metabolites. The results of the analyses show that MEX and its metabolites have moderately large to large LUMO-HOMO energy differences ranging from 5.4 to 6.4 eV indicating that the compounds would be inert kinetically, with the parent drug being most inert. The molecular surface of one of the metabolites namely HMMEX is found to possess significant amount of positively charged electron-deficient regions so that it may be subject to nucleophilic attacks by glutathione and nucleobases in DNA, thus causing cellular toxicity due to glutathione depletion and DNA damage due to oxidation of nucleobases. However, because of kinetic inertness of the molecule, the rate of such adverse reactions is expected to be low.

Key words: Mexiletine, anti-arrhythmic agent, schizophrenia, diabetes mellitus, molecular modelling

INTRODUCTION

Mexiletine [2-(2,6-dimethylphenoxy)-1-methylamine; MEX] is an orally active antiarrhythmic agent used to treat ventricular arrhythmias (De Bellis *et al*., 2006). It is also effective against myotonia and neuropathic pain. The drug is rapidly and almost completely absorbed following oral administration with a bioavailability of about 90%. Peak plasma concentration is reached within 1 to 4 h after oral administration and its plasma half-life is 10 to 12 h. A linear relationship is found to exist between dose and plasma concentration of the drug. MEX is sometimes used along with psychotic drugs in patients with depression, schizophrenia or sleep disorder (Hara *et al*., 2005). Neurologicl side effects of MEX therapy include tremor, ataxia, dizziness, blurred vision, diplopia, drowsiness, psychosis and memory loss (occurring in approximately 10% of patients) while gastrointestinal side effects include nausea, anorexia and gastric irritation (Manolis *et al*., 1990).

MEX is extensively metabolized in humans by C- and N-oxidation, catalysed mainly by CYP2D6 and to a lesser extent by CYP1A2. Eleven metabolites are known. The major metabolites are: p-Hydroxy-mexiletine (PHMEX), Hydroxy-methyl-mexiletine (HMMEX), M-hydroxy-mexiletine (MHMEX) and N-hydroxymexiletine (NHMEX). PHMEX, HMMEX and NHMEX may be glucorinated to produce corresponding phase II metabolites. Little information is available on the pharmacodynamic properties of metabolites of MEX (De Bellis *et al*., 2006). HMMEX can be further oxidized to produce Carboxy-mexiletine (CMEX). Another metabolite is 2,6-dimethylphenol (TSDMP). MEX is an optically active molecule existing in R- and S-enantiomers. Figure 1 summarizes the major metabolic pathways for MEX. The two isomers appear to differ in the ease of oxidation Mao and Zeng, 2005).

The renal clearance of R-MEX is found to be higher than that for S-MEX. MEX is known to alter metabolism of other drugs such as caffeine and theophylline (Labbe and Turgeon, 1999). In this study,

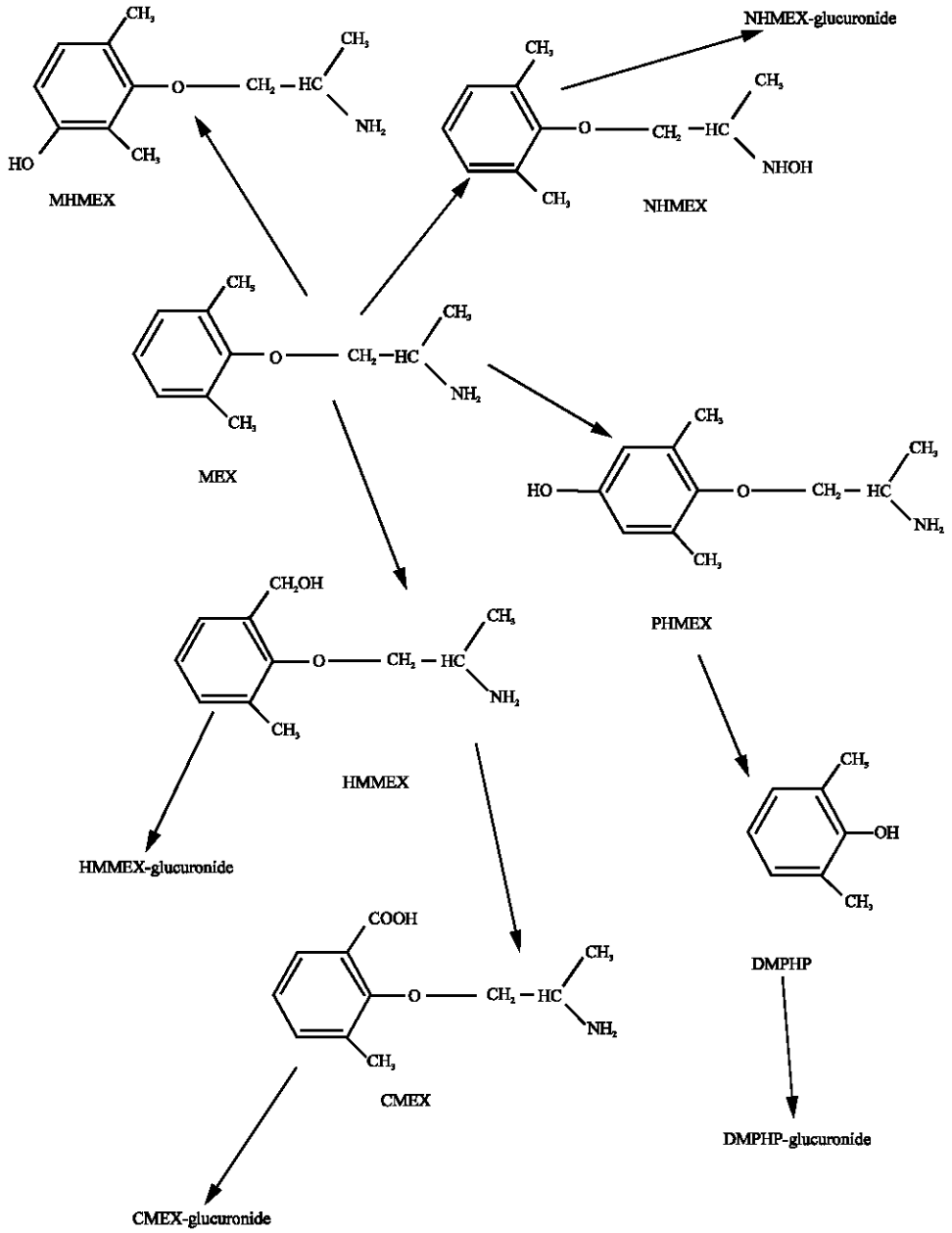

Fig. 1: Metabolic pathways for MEX in humans (Labbe and Turgeon, 1999)

molecular modelling analyses have been carried out using the program Spartan '02 (Spartan, 2002) of MEX and its metabolites PHMEX, HMMEX, NHMEX, TSDMP and CMEX, with the aim of providing a better understanding of their relative toxicity. The study was carried out in the Discipline of Biomedical Science, School of Medical Sciences, The University of Sydney during January to February 2007.

COMPUTATIONAL METHODS

The geometries of MEX, PHMEX, HMMEX, NHMEX, TSDMP and CMEX have been optimized based on molecular mechanics, semi-empirical and DFT (density functional theory) calculations, using the molecular modelling program Spartan 02. No calculations were done for the glucuronides produced in phase II reactions. Molecular mechanics calculations were carried out using MMFF force field. Semi-empirical calculations were carried out using the routine PM3. DFT calculations were carried at B3LYP/6-31G* level. In optimization calculations, a RMS gradient of 0.001 was set as the terminating condition. For the optimized structures, single point calculations were carried out to give heat of formation, enthalpy, entropy, free energy, dipole moment, solvation energy, energies for HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital). The order of calculations: molecular mechanics followed by semi-empirical followed by DFT ensured that the structure was not embedded in a local minimum. To further check whether the global minimum was reached, some calculations were carried out with improvable structures. It was found that when the stated order was followed, structure corresponding to the global minimum or close to that could ultimately be reached in all cases. Although RMS gradient of 0.001 may not be sufficiently low for vibrational analysis, it is believed to be sufficient for calculations associated with electronic energy levels.

RESULTS AND DISCUSSION

Table 1 gives the total energy, heat of formation as per PM3 calculation, enthalpy, entropy, free energy, surface area, volume, dipole moment and energies of HOMO and LUMO as per both PM3 and DFT calculations for MEX, PHMEX, HMMEX, NHMEX, TSDMP and CMEX. Figure 2-8 give the regions of negative electrostatic potential (greyish-white envelopes) in (a), HOMOs (where red indicates HOMOs with high electron density) in (b), LUMOs in (c) and density of electrostatic potential on the molecular surface (where red indicates negative, blue indicates positive and green indicates neutral) in (d) as applied to optimized structures of MEX, PHMEX, HMMEX, NHMEX, TSDMP and CMEX.

The LUMO-HOMO energy differences for MEX, PHMEX, HMMEX, NHMEX, TSDMP and CMEX from DFT calculations are found to range from 5.4 to 6.4 eV, indicating that MEX and its metabolites would be kinetically inert.

The solvation energies of MEX, PHMEX, HMMEX, NHMEX, TSDMP and CMEX obtained from PM3 calculations are found to range from -4.24 to -11.55 kcal mol^{-1}, indicating that the

Table 1: Calculated thermodynamic and other parameters of MEX, PMEX, HMMEX, MHMEX, NHMEX, TSDMP and CMEX

Molecule	Calculation type	Total energy (kcal mol^{-1} /atomic unit*)	Heat of formation (kcal mol^{-1})	Enthalpy (kcal mol^{-1} K^{-1})	Entropy (cal mol^{-1} K^{-1})	(kcal mol^{-1}) Free energy	Solvation energy (kcal mol^{-1})
MEX	PM3	-37.86	-33.62	172.35	114.78	137.13	-4.24
	DFT	-555.38		174.19	120.33	138.31	-3.38
PHMEX	PM3	-87.18	-78.67	176.55	120.14	140.73	-8.51
	DFT	-634.61		176.05	177.49	143.83	-8.41
HMMEX	PM3	-81.39	-73.65	122.96	121.27	139.89	-7.74
	DFT	-634.6		178.23	120.71	142.24	-7.09
MHMEX	PM3	-84.77	-7700.00	176.36	121.87	140.02	-7.77
	DFT	-634.61		177.74	121.49	141.52	-7.95
NHMEX	PM3	-49.34	-44.20	175.98	118.21	140.74	-5.14
	DFT	-634.54		177.44	123.73	140.55	-2.17
TSDMP	PM3	-42.35	-38.09	106.38	89.96	79.55	-4.26
	DFT		-386.11	106.29	90.15	79.41	-4.45
CMEX	PM3	-124.58	-113.03	165.87	122.08	129.47	-11.55
	DFT	-708.62		167.10	121.81	130.78	-9.77

Table 1: Continued

Molecule	Calculation type	Area (Å2)	Volume (Å3)	Dipole moment (debye)	HOMO (eV)	LUMO (eV)	LUMO-HOMO (eV)
MEX	PM3	231.38	209.38	0.3	-9.30	0.26	9.56
	DFT	236.52	210.69	1.2	-6.15	0.24	6.39
PHMEX	PM3	240.59	216.80	1.6	-8.98	0.16	9.14
	DFT	245.41	217.83	2.2	-5.57	-0.16	5.41
HMMEX	PM3	243.87	217.34	1.5	-9.52	0.06	9.58
	DFT	242.91	217.72	2.1	-6.43	-0.06	6.37
MHMEX	PM3	239.73	216.75	1.6	-8.95	0.13	9.08
	DFT	244.33	217.65	1.4	-5.62	0.26	5.88
NHMEX	PM3	240.91	218.26	1.9	-9.44	0.18	9.62
	DFT	243.85	219.12	2.5	-5.87	0.10	5.97
TSDMP	PM3	160.73	141.95	1.2	-8.96	0.30	9.26
	DFT	161.09	142.00	1.5	-5.72	0.29	6.01
CMEX	PM3	242.41	218.94	4.5	-9.71	-0.52	9.19
	DFT	246.91	220.56	5.2	-6.58	-0.54	6.04

*In atomic units from DFT calculations

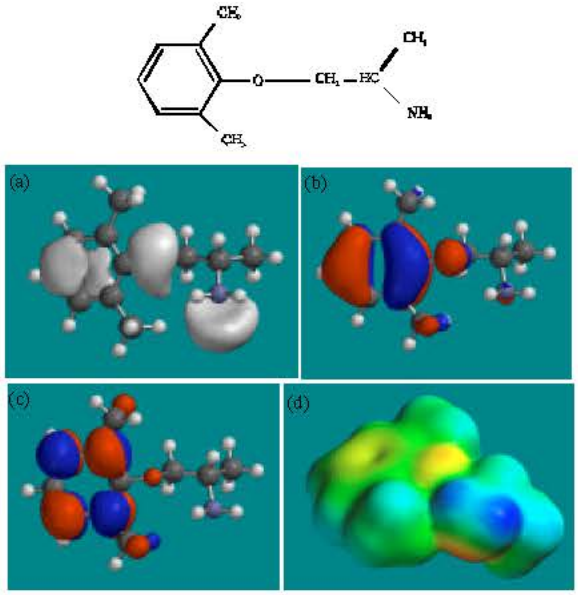

Fig. 2: Structure of MEX giving in: (a) the electrostatic potential (greyish envelope denotes negative electrostatic potential), (b) the HOMOs, (where red indicates HOMOs with high electron density) (c) the LUMOs (where blue indicates LUMOs) and in (d) density of electrostatic potential on the molecular surface (where red indicates negative, blue indicates positive and green indicates neutral)

compounds would vary in their solubility in water. The parent drug MEX is expected to be least soluble in water.

In the case of MEX, PHMEX, MHMEX, HMMEX and NHMEX, the electrostatic potential is found to be more negative above and below the phenyl ring, around oxygen and nitrogen atoms, indicating that the positions may be subject to electrophilic attack. In the case of TSDMP also, the electrostatic potential is found to be more negative around oxygen and nitrogen atoms, indicating that the positions may be subject to electrophilic attack.

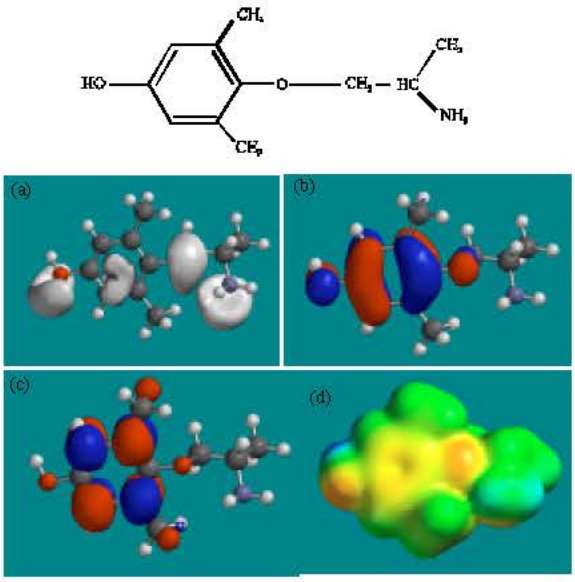

Fig. 3: Structure of PHMEX giving in: (a) the electrostatic potential (greyish envelope denotes negative electrostatic potential), (b) the HOMOs, (where red indicates HOMOs with high electron density) (c) the LUMOs (where blue indicates LUMOs) and in (d) density of electrostatic potential on the molecular surface (where red indicates negative, blue indicates positive and green indicates neutral)

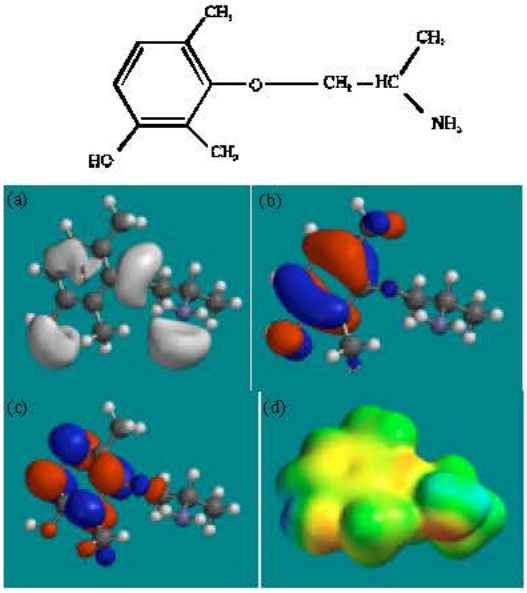

Fig. 4: Structure of MHMEX giving in: (a) the electrostatic potential (greyish envelope denotes negative electrostatic potential), (b) the HOMOs, (where red indicates HOMOs with high electron density) (c) the LUMOs (where blue indicates LUMOs) and in (d) density of electrostatic potential on the molecular surface (where red indicates negative, blue indicates positive and green indicates neutral)

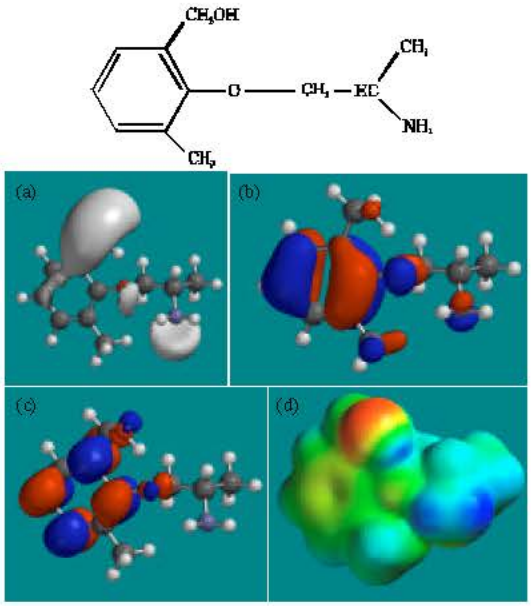

Fig. 5: Structure of HMMEX giving in: (a) the electrostatic potential (greyish envelope denotes negative electrostatic potential), (b) the HOMOs, (where red indicates HOMOs with high electron density) (c) the LUMOs (where blue indicates LUMOs) and in (d) density of electrostatic potential on the molecular surface (where red indicates negative, blue indicates positive and green indicates neutral)

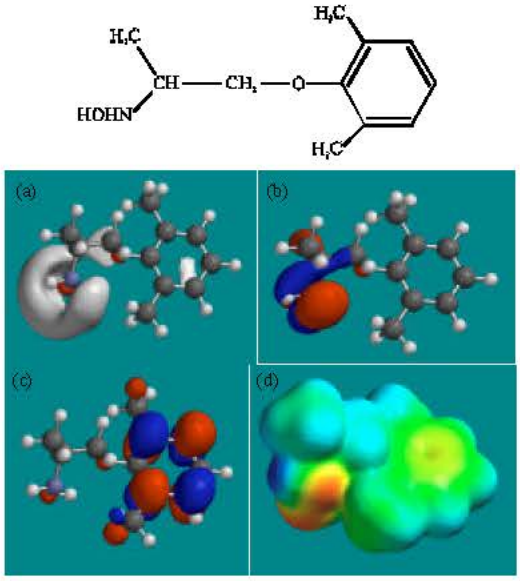

Fig. 6: Structure of NHMEX giving in: (a) the electrostatic potential (greyish envelope denotes negative electrostatic potential), (b) the HOMOs, (where red indicates HOMOs with high electron density) (c) the LUMOs (where blue indicates LUMOs) and in (d) density of electrostatic potential on the molecular surface (where red indicates negative, blue indicates positive and green indicates neutral)

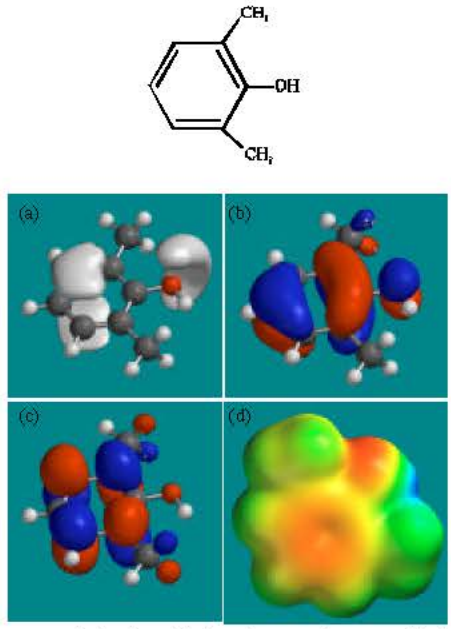

Fig. 7: Structure of TSDMP giving in: (a) the electrostatic potential (greyish envelope denotes negative electrostatic potential), (b) the HOMOs, (where red indicates HOMOs with high electron density) (c) the LUMOs (where blue indicates LUMOs) and in (d) density of electrostatic potential on the molecular surface (where red indicates negative, blue indicates positive and green indicates neutral).

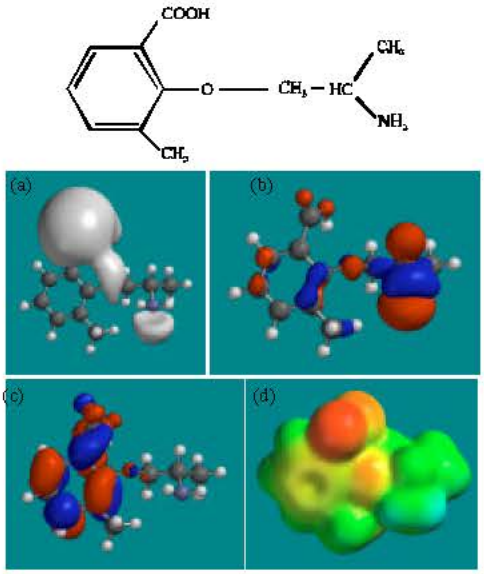

Fig. 8: Structure of CMEX giving in: (a) the electrostatic potential (greyish envelope denotes negative electrostatic potential), (b) the HOMOs, (where red indicates HOMOs with high electron density) (c) the LUMOs (where blue indicates LUMOs) and in (d) density of electrostatic potential on the molecular surface (where red indicates negative, blue indicates positive and green indicates neutral)

In the case of MEX, PHMEX, HMMEX and TSDMP both the HOMOs with high electron density and the LUMOs are found to be centred mostly on the non-hydrogen atoms of the phenyl ring. In the case of NHMEX, the HOMOs with high electron density are found to be centred on the non-hydrogen atoms of the N-hydroxymethylamine side chain whereas the LUMOs are centred on the non-hydrogen atoms of the phenyl ring.

The overlap of HOMO with high electron density and region of negative electrostatic potential at some positions, gives further support to the idea that the positions may be subject to electrophilic attack.

The molecular surfaces of MEX, PHMEX, HMMEX, NHMEX, TSDMP and CMEX are found to possess neutral (green), electron-rich (red and yellow) regions so that they may be subject to lyophilic and electrophilic attacks. The molecular surfaces of HMMEX and NHMEX are also found to possess some electron-deficient (blue) regions so that they may be subjected to nucleophilic attacks such as those by glutathione and nucleobases in DNA. Reaction with glutathione would induce cellular toxicity by compromising the antioxidant status of the cell whereas that with nucleobases in DNA could cause DNA damage. However, as stated earlier, since HMMEX and NHMEX are expected to be kinetically inert, the rates of such adverse reactions are expected to be low unless speeded up enzymatically.

CONCLUSION

Mexiletine (MEX) is an orally active antiarrhythmic agent used to treat ventricular arrhythmias. Molecular modelling analyses based on molecular mechanics, semi-empirical (PM3) and DFT (at B3LYP/6-31G* level) calculations show that MEX and its metabolites have moderately large to large LUMO-HOMO energy differences ranging from 5.4 to 6.4 eV indicating that the compounds would be inert kinetically, with the parent drug being most inert. Thus, although the molecular surfaces of HMMEX and NHMEX have significant amounts of electron-deficient (blue) regions so that they may be subject to nucleophilic attacks such as those by glutathione and nucleobases in DNA, in actual fact the rates of such adverse reactions are expected to be low unless speeded up enzymatically.

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