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Topical Pressure Lowering Drug: Racial Respond Variation and Pharmacogenetics

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1. Introduction

Racial factor has been identified as a risk factor of glaucoma. African derived population is at higher risk of developing primary open angle glaucoma (POAG). African Americans were found to be at greater risk for open-angle glaucoma (Tielsch et al, 1991). The prevalence of OAG in populations of African descent was 7-fold greater than in Caucasians age 40–49, but due to the steeper increase of OAG in Caucasians at older age, the difference between the 2 populations dropped to 2.5-fold in the 80–89 year-old age bracket (Quigley et al, 1999). Although the prevalence of OAG in Caucasians and Asians aged 40–49 are similar, Caucasians as a whole demonstrate a greater prevalence. On the other hand, Asians are more predisposed to angle closure glaucoma.

African derived population is believed to have more severe and progress faster than Caucasian with higher rate of blindness (Sommers et al, 1991a; Sommers et al, 1991b). Angle closure glaucoma (ACG) behaved differently in Asian population. ACG is responsible in more blindness in Asian than in Caucasian population. Laser peripheral iridotomy do not confer strong protection in prevention of progression to glaucoma post acute angle closure in Asians (Ang and Ang, 2008). African derived population response differently to medical and surgical intervention. Racial influence does not only affect susceptibility to glaucoma but also response to glaucoma treatment.

In addition, individual variation has also exerted its effect to management of glaucoma patient. Individual variation in drug response poses a significant clinical problem, ranging from failure to respond to a drug to life threatening adverse drug reactions. The causative factors are genetic, physiological, pathophysiological, and environmental. Quantification of pharmacokinetics and pharmacodynamics of topical ophthalmic drugs is technically more difficult as compared to systemic drugs. It is considered quite difficult and dangerous to obtain aqueous or any ocular fluid sample sequentially to determine the concentration of drug in human. Tracer such as technetium makes it possible. Ophthalmic drug once given topically is absorbed to systemic circulation directly by passing hepatic first pass effect. Low availability of ophthalmic drug in the target tissue may cause the needs for higher concentration of the drug and higher likelihood for systemic side effects. The concentration of ophthalmic drug in the blood circulation is certainly not reflective the actual concentration at the target tissue. The pharmacokinetic of the ophthalmic drug is affected by the absorption at the corneal and conjunctiva, rate of blinking, tears concentration and

nasolacrimal duct (NLD) system. Moreover, the definitive mechanism of action of ophthalmic drug especially pressure lowering drugs are not well understood.

In general the effectiveness of pressure lowering drugs in glaucoma management is based on the amount of pressure reduction. While in longitudinal studies, the progression of glaucoma in term of visual field defect or structural changes of optic disc were defined as an end point such as in Advanced Glaucoma Intervention Study (AGIS) (The AGIS investigators, 2000). The AGIS found that the risk of progression of visual field defects was reduced when intraocular pressures (IOPs) were maintained $>18\text{mmHg}$. On another longitudinal study, it was suggested lower IOP $<15\text{mmHg}$ prevent further progression of visual field loss in advanced glaucoma (Shirakashi et al, 1993).

2. Melanin

The variation of response was first observed with topical mydriatic drugs; topical epinephrine 4% and homatropine 4% in 1971 (Emiru VP). Full mydriasis was observed within 40 minutes post instillation of topical epinephrine on the right eye and topical homatropine on the left eye in European eyes but much longer time was needed to achieve similar effect in African eyes. The amount of melanin was then implicated (Garde et al, 1978). Melanin is highest in the eye compared to other organ in the body (Potts, 1964). Most lipophilic and basic drugs have the ability to bind to the melanin (Leblanc et al, 1998). The binding is via electrostatics, van der Waals or simple charge transfer that may reduce the effectiveness of drug at the target tissue.

It is known that Asians and African Americans have larger amount of melanin compared to Caucasians. There was no statistical different of the amount of melanin between Asians and African Americans but Asians have smaller mean total melanocytes number and mean cellularity (Albert et al, 2003). Unlike skin melanocytes, ocular melanocytes are not affected by melanin stimulating hormone (MSH). Melanocytes are not mere important to determine the iris colour but also perhaps susceptibility of certain ocular disease such as Harada disease. Most importantly there is also possible association between melanin and topical drug especially pressure lowering drugs.

For decades, timolol is known as the most effective topical pressure lowering drug in almost all type of glaucoma. Timolol has high affinity for and easily bind to melanocyte especially isolated melanocytes compare to tissue melanocytes (Menon et al, 1989). Dark-pigmented rabbits demonstrated higher concentration of timolol maleate in the iris ciliary body when compared to albino rabbits, reducing the amount of active ingredient available for pharmacological action (Menon et al, 1989). Menon et al (1989) found that the binding was quick at the beginning then later decelerated. It is believed the possible binding is achieved through van der Waals binding, hydrophobic interaction, ionic interaction and several other types of binding. Abrahamson et al (1988) found that the binding of timolol to melanin is not proportionate with the release of timolol from the melanin containing tissue. In fact the release of melanin into aqueous humour is much faster resulted in higher concentration of timolol in the aqueous. Moreover, the accumulative effect of melanin binding is seen over a prolong period of treatment (Salminen and Urtili, 1984). Melanin near to the site of pharmacological action did not inactivate the active drug. Paradoxically, melanin competitively inhibits timolol. The net effect is that highly pigmented eyes require a higher concentration (0.5%) than less pigmented eyes (0.25%), which is reflected in clinical observations in Asians and Africans (Ong et al, 2005; Otaleju and Ajayi, 1999; Katz and

Berger, 1979). Caucasians with brown or dark brown irides have higher possibility for discontinuation of treatment due to inadequate pressure lowering (Katz and Berger, 1979). Perhaps, the variation of respond to management of medical treatment is not entirely due to racial differences but more of the amount of iris melanocytes.

Theoretically, the reversible binding of timolol and melanocytes should provide protective effect against the unwanted systemic side effect such as cardiorespiratory impairment. It is known that systemic drugs such as systemic beta blockers and antimalarial drugs bind to melanin. The binding of timolol and melanin do not confer any protective effect against ocular toxicity (Leblanc et al, 1998). However, there is no such study looking into the protective effect of melanin binding of topical drugs against unwanted systemic side effect. A prospective study on 63 Asians glaucoma patients receiving topical timolol gel forming solution for 6 months found that 6 patients developed respiratory outflow obstruction [Selva Raja V et al, 2006]. The incidence was only 10% as compared to the previous clinical studies in Caucasians (Diggory et al, 1998; Waldock et al, 2000). Diggory and associates (1998) reported incidence of 25% and Waldock et al (2000) reported slightly higher incidence of 28%. However, the former study was using timolol gel forming solution that has longer ocular retention and reduced systemic absorption (Hashimoto et al, 2001). Thus direct comparison of the possibility of protective effect of melanin bound timolol is not possible.

Another example is pilocarpine, a parasympathomimetic drug used to treat various type of glaucoma especially angle closure glaucoma. Pilocarpine is available in 0.25% to 10% concentration. The pressure lowering effect of pilocarpine is observed with concentration of 1 to 4% in Caucasians or lighter irides individual. African-Americans patients demonstrated much lower mean IOP reduction (1.2mmHg) as compared to 2.3mmHg in Caucasian patients with pilocarpine 4% (Harris and Galin, 1971). Caucasian with blue coloured iris achieved hypotensive effect even with pilocarpine 1%, while those with brown eyes required pilocarpine 4% to achieve the similar effect (Harris and Galin, 1971). Higher concentration even up to 8% is required in African-American to achieve similar effect (Harris and Galin, 1971). The effect of melanin to pilocarpine is not extensively studied but it is a strong postulation that pilocarpine has similar affinity towards melanin (Meilikian et al, 1971). Inactivation of pilocarpine was more pronounced (2-3 folds more) in pigmented uveal tissue compared to albino tissue (Lyons and Krohn, 1973).

Brominidine, an alpha agonist is effective as adjunctive, combination and replacement therapy in glaucoma management. Brominidine provide significant pressure lowering effect in various type of glaucoma and in various populations (Adkins and Balfour, 1998). A post hoc analysis was conducted on 460 patients involved in multicenter open label control trial to determine the effectiveness of brominidine as replacement therapy (Lee, 2000). African-Americans and Hispanic patients demonstrated better IOP reduction and almost similar to Caucasians with green or hazel eye colour. Brominidine is most effective as replacement therapy in Caucasians with green or hazel irides but less effective in Asian patients with mean IOP reduction of 1.54mmHg (Lee, 2000). In contrary, the pressure reduction of brominidine as monotherapy was almost similar to other populations based on a randomized control trial conducted in Taiwanese patients (Chen et al, 2003). A pharmacokinetics study was conducted on albino and pigmented rabbits using 14C-brominidine solution (Acheampong et al, 1995). The absorption of brominidine was rapid at the rate of 0.67 hour in both pigmented and albino rabbits. The half life was just 1 hour for both pigmented and albino rabbits but followed by slower declined in pigmented rabbits. The terminal half-life in pigmented rabbit was 160 hours suggesting the high affinity of

brominidine towards melanin-containing tissue (Acheampong et al, 1995). Clinically, brominidine was found to be as effective as timolol 0.5% but with safer systemic profile; minimum effect on the cardiorespiratory system.

On the other hand, pressure lowering drugs are also found to induce pigmentation and melanin deposition. Melanin deposition (adenochrome) on the conjunctival is a common side effect with topical epinephrine. In certain extreme cases, the deposition melanin even causes blockage of lacrimal sac and 'black cornea' (Barishak et al, 1969; Kaiser et al, 1992). Black cornea is deposition of melanin in the cornea usually occurs in prolong treatment with epinephrine (Kaiser et al, 1992). The deposition is unwanted side effect without compromising the effectiveness of epinephrine as pressure lowering drug (Corwin and Spencer, 1963). There is no racial different in the tendency of melanin deposition. The effectiveness of dipivefrin in African-American patients was almost similar to Caucasians (Drake et al, 1993).

Topical prostaglandin analogues are currently replacing topical beta blockers as the first line drug in glaucoma management. Unlike timolol or any topical beta blockers, prostaglandin analogues do not bind to melanin. Instead, darkening of the iris, eyelashes and even eyelids were reported. This peculiar side effect was first noted in monkeys during the pre-clinical trial of latanoprost (Bito, 1997). Latanoprost is among the first commercially available topical prostaglandin analogue in the market. Iris darkening was initially observed to be more prominent in those with mixed colouring of hazel irides especially those with brown patches on blue, gray, green or yellow (Watson and Stjernschantz, 1996). As the popularity of latanoprost escalated and spread to all part of the world, iris darkening was also found in homogenous dark brown irides of Japanese and South East Asians (Chiba et al, 2004; Chou et al, 2005).

The mechanism of prostaglandin induced iridial pigmentation (PIIP) is not clear. Three possible mechanisms have been widely discussed; increased in iris stromal melanocyte numbers, increased melanogenesis and redistribution iris stromal melanocytes to the anterior border region without increasing number of melanocytes or melanin (Watson and Stjernschantz, 1996; Grierson et al, 2001; Cracknell et al, 2007). It was also noted that incidence of PIIP is time dependant; PIIP tends to occur within the first 8 months post initiation of treatment. After 2 years, over 90% of those that are going to develop iris darkening have already done so (Alm et al, 2004). After 3 years there was no evidence of increase in pigmentation (Alm et al, 2004). Older patients were more at risk to develop PIIP (Arranz-Marquez and Teus, 2007). However, to our knowledge, there is no evidence that the effectiveness of prostaglandin analogues is affected by the presence of PIIP. The effectiveness of latanoprost was also not affected by the iris colour. Those with blue, brown and hazel irides demonstrated almost similar pressure lowering effect (Bayer et al, 2005). PIIP remains as cosmetic concern rather than functional, although it is indeed affect the persistency and adherence to medications. Unlike PIIP, the severity of conjunctival hyperaemia induced by latanoprost is associated with significant better IOP reduction (Kobayashi and Kobayashi, 2011). Conjunctival hyperaemia can be used as predictor of effectiveness of topical latanoprost.

A pooled data analysis of eight different clinical trials involving African-Americans, Asians, Caucasians and Mexicans glaucoma patients was conducted to compare the pressure lowering effect between latanoprost and timolol (Hedman and Larsson, 2002). Latanoprost reduced mean diurnal pressure more than timolol. A significant greater difference in mean diurnal pressure between latanoprost and timolol was observed in the Asian and Mexican

patients than European and American patients (Hedman and Larsson, 2002). Comparatively lack of effectiveness of timolol in Asian and Mexican patients was postulated due to reversible timolol and melanin binding. The mean diurnal pressure of African-American patients was almost similar to the Caucasian. Travaprost is found to be more effective in African-American compared to latanoprost and timolol (Netland et al, 2001).

In vitro spectrometric and in vivo study was conducted on timolol, betaxolol, carteolol, pilocarpine, epinephrine, prostaglandin A2, F2 alpha and E2 analogues to determine the binding ability of drug to synthetic melanin on pigmented and non-pigmented rabbits (Nagata et al, 1993). Beta blockers exhibited the highest binding rate of 80 to 85% followed by epinephrine 50% and pilocarpine 40%. Binding of prostaglandin analogues and synthetic melanin was almost absent. As expected, significant IOP reduction was observed in albino rabbits treated with timolol 0.5% and pilocarpine 3% compared to pigmented rabbit. Epinephrine 1% was effective in both pigmented and albino rabbits but with slightly better effect on albino rabbits. Prostaglandin analogues provide good pressure reduction on pigmented and albino rabbits. Based on this animal experimental study, the binding of pressure lowering drugs to melanin is a strong predictor to predetermine the effectiveness of the drugs in lowering the pressure in different population. Thus, iris colour plays an important role in selecting the drug of choice in glaucoma management of certain population. Table 1 provide a summary of possible interaction between drug and melanin. For example timolol 0.25% is certainly not a good choice for first line management in Asians. However, prostaglandin analogue is indeed a better choice in achieving target pressure.

Drug	Drug-melanin interaction	Implications
Beta blockers Timolol Betaxolol	Reversible binding	Higher concentration in pigmented iris
Parasympatomimetics Pilocarpine	Reversible binding	Higher concentration in pigmented iris
Alpha agonists Brominidine	Reversible binding	Less effective in pigmented iris
Adrenergic Dipivefrin	Deposition of melanin	Adenochrome
Prostaglandin analog Latanoprost Travaprost	Induced pigmentation	Side effect- prostaglandin induced iris pigmentation (PIIP)

Table 1. The possible interaction between topical pressure lowering drugs and melanin

3. Genetics and pharmacogenetics

Drug interaction with Melanin may explain the racial variation of drug respond but not individual respond in the population. Individual variation in drug response poses a significant clinical problem, ranging from failure to respond to a drug to life threatening adverse drug reactions. The possible causative factors include genetic, physiological, pathophysiological, and environmental. Genetics play an important role in drug absorption, distribution, metabolism, and drug-drug interactions. Although genetics is believed to play a major role, it

is interrelated with other causative factors. It is estimated that genetics is responsible for 15–30% of variation in drug responsiveness (Evan and McLeod, 2003). However, in certain drugs, genetic factors could contribute up to 95% of variation. Pharmacogenetics aims to understand how genetic variations contribute to variations in response to medicines.

Genetic variations may influence drug action by affecting its pharmacokinetics, which includes absorption, distribution, metabolism, and excretion, or its pharmacodynamic properties (what the drug does to the body), which involves target receptors, enzyme targets, and disease modifiers. Single nucleotide polymorphisms (SNPs) are naturally occurring variations that may not cause disease but are responsible in altering the products they encode and have a reported frequency of more than 1% of the population (Ford, 1940). The variations in all genes are believed to cause different individuals or populations to express different forms of proteins also known as gene products, including those responsible for metabolizing the drug or the site of drug action. Genes encoding drug transporters were also identified as potential factors causing alteration in drug response (Evans and McLeod, 2003).

The variation of drug response can be divided into Gaussian variation and monogenic (all-or-none) variation. The initial understanding of pharmacogenetics is based on monogenic variation (all-or-none); the impact of a single gene product may lead to all-or-none responsiveness (Kalow, 1997). Gaussian variation is a mathematically calculated variation in the form of median effective or lethal dose of a drug (ED_{50} or LD_{50}) and determined mainly by environmental factors but with hereditary elements (Vesell, 1992; Trevan, 1927). The principle is based on a distribution curve of the frequency of response to a standard drug dose in a group of individuals. A majority of the known drugs demonstrate a unimodal distribution similar to a bell-shaped or Gaussian curve (Turner et al, 2001). Gaussian distribution represents the effect of multifactorial determinants by interaction of genetic and environmental factors without any single factor having a discernibly large effect on the response. Thus, it is more difficult to identify the effects of individual genes. Bimodal distribution is due to separate subpopulations with distinctly different drug responses suggesting that a single factor, possibly segregation of alleles at a single genetic locus, has a large effect on drug response (Murphy, 1964). Responders and non-responders to a certain drug may be represented as a bimodal distribution curve (McLaren and Moroi, 2003).

Pharmacogenetics is potentially important in customizing or personalizing medication. Tailoring the medication according to the predicted response, minimizing the side effects, and maximizing the expected drug response is ideal to promote compliance and persistency of medication especially in chronic diseases. ‘Candidate gene’ or ‘candidate pathway’ approaches have been adopted to predict the disposition or response to a given drug. So far, polymorphisms are the most studied genetic variations. Polymorphisms can be homozygous or heterozygous, depending on how many copies of a variant or wild-type allele are present. Based on the balanced polymorphism concept, a double dose of a variant allele (homozygous mutant) may exert a detrimental effect but a single copy may increase fitness (heterozygous mutant) (Ford, 1940).

However, the concept of single gene has been left behind in the pharmacogenetics field. The drug-response phenotype is not governed by a single gene (monogenic trait) but by multiple genes (polygenic) that has spawned the term ‘pharmacogenomics’. The effects of most drugs are determined by many proteins and composite genetic polymorphisms in multiple genes coupled with non genetics factors are postulated to be responsible in drug response. For example; HT_3 antagonist tropisetron, a CYP2D6 substrate if given to patient with high

enzyme activity due to gene duplication will not achieve effective drug concentrations. Inability to achieve effective drug concentration is not entirely due to the CYP2D6 polymorphism but may be due to other factors influencing the entire pathway before reaching the target organ or tissue. As HT₃ antagonist is also a phagocytic glycoprotein (Pgp) substrate, the level of Pgp expression will affect ability of HT₃ antagonist to transfer from blood to the brain. Once the drug reach the HT₃ receptor, the magnitude of response will depend on the drug concentration, neurotransmitter concentration in the synaptic cleft and genetic polymorphisms of the receptor. Moreover, serotonin concentration is further influenced by proteins involved in biosynthesis, transport and catabolism. Thus, the pharmacogenetic analysis of poor response to HT₃ antagonist should include all of these candidate genes that involved in the pathway of this drug before reaching the target tissue.

The impact of polymorphisms of cytochrome P450 (CYP) enzymes and thiopurine methyltransferase (TPMT) are the most established and well studied (Idle and Smith, 1979). Cytochrome P450s are a multi-gene family of enzymes found predominantly in the liver, the most important site for metabolic elimination of most drugs. Cytochrome P450 CYP2D6 (known as debrisoquine hydroxylase), CYP2C9, and CYP2C19 are among the most studied cytochrome P450s and affect the metabolism of 20–30% of clinically used drugs (Kirchheiner et al, 2004; Kirchheiner and Brockmoller, 2005).

Polymorphisms in CYP2D6 result in different metabolic capacities for antidepressants, anti-hypertensives such as β -blockers, and antipsychotic drugs. Some mutations in CYP2D6 result in complete loss of enzyme activity and severely compromises drug metabolism; this is known as the 'poor metabolisers' (PMs) phenotype. Other mutations or duplications of CYP2D6 produce increased metabolic capacity; individuals with such variation are known as ultra-rapid metabolisers (UMs). Those with wild-type levels of activity are known as extensive metabolisers (EMs). PMs require low doses of a drug or higher doses if it is a prodrug, while UMs and EMs require higher doses or a more frequent dose administration regime. An individual can be a PM of one drug and EM of another. There is evidence of racial influence in phenotypic of CYP2D6. It is believed due to the effect of selective breeding rather than direct racial influence. CYP2D6 PMs were found in 6–10% of Caucasians, fewer in African populations (5%), and even fewer in Asians (less than 1%) (Kalow, 1991; Marez et al, 1997; Masimirembwa et al, 1993).

Pharmacogenetics studies have been conducted with various systemic drugs but minimal emphasis has been given to topical ophthalmic drugs. Timolol can be given orally as in hypertensive treatment and CYP2D6 polymorphisms are known to affect the metabolism of oral timolol. In spite of given topically, timolol especially in the aqueous form has poor ocular bioavailability due to large amount (up to 80%) of topical timolol is absorbed to systemic circulation upon instillation through nasal mucosa (Shell, 1982). High systemic absorption of topical timolol is based on clinical observation of the fellow untreated eye that demonstrated lesser but significant IOP reduction (Zimmerman and Kaufman, 1977). It is most significantly, explained the systemic adrenergic beta-blocking that result in life-threatening side effect such as bradycardia and respiratory impairment in certain susceptible individuals (Zimmerman and Kaufman, 1977; Zimmerman et al, 1983). A drop of 0.5% timolol aqueous solution to each eye is approximates to a 10mg oral dose. The hepatic metabolism is important in pharmacokinetic of topical timolol. Naturally, CYP2D6 play a role in pressure lowering effect as well as cardiopulmonary side effect of topical timolol.

Edeki and co-workers (1995) was among the first investigators attempted to determine the role of CYP2D6 in the metabolism of topical timolol. Topical timolol was instilled through the nose to ensure no spill-over of the medication through eye drop application in a known EMs and PMs. Oral quinidine was also given as CYP2D6 inhibitor to EMs randomly. Plasma timolol concentration was significantly higher in PMs compared to EMs suggesting the role of CYP2D6 in metabolism of topical timolol. Greater heart rate reduction and higher plasma timolol concentration was observed in EMs, signified not only the importance of CYP2D6 in timolol metabolism but the possibility of oral-ophthalmic drug interactions. Nasal instillation of topical timolol in this study may not represent the actual clinical situation; overestimation of the oral-ophthalmic interaction is inevitable. Additional reduction of heart rate and IOP was also observed in 12 healthy Japanese volunteers who were given oral cimetidine (CYP2D6 inhibitor) prior to topical timolol instillation (Ishii et al, 2000). This finding further reaffirms the role of CYP2D6 in topical timolol metabolism.

CYP2D6 gene has been extensively studied in various populations and is known to be highly polymorphic. Arg296Cys (rs16947) and Ser486Thr (rs1135840) has been widely studied. The polymorphism of CYP2D6 is commonly pooled together and defined based on the functional activity such as EMs, intermediate metabolisers (IMs), PMs and UMs. There is no conclusive definition, which further complicate the analysis. A pilot genotype-phenotype study was conducted on glaucoma patients and healthy volunteers instilled with timolol aqueous solution and hydrogel 0.1% (Nieminen et al, 2005). The CYP2D6 PMs had higher maximum plasma concentrations, longer elimination half lives and higher area-under-curve than EMs, IMs and UMs. However, this effect was not significant in those treated with timolol hydrogel 0.1%. Theoretically, PMs should have poorer pressure reduction. Surprisingly, CYP2D6 polymorphisms were not associated with meaningful pressure reduction of timolol based on the finding from Marshfield Clinic Personalized Medicine Research project (PMRP) (McCarty et al, 2008). Marshfield Clinic PMRP is a population-based bio bank project that has extensive medical record for phenotyping and stored DNA for genotyping. The meaningful pressure reduction was defined as IOP reduction of more than 20% from the baseline pressure. Similar finding was also noted in Asian populations (Yuan et al, 2010). There was no significant different between CYP2D6 SNPs rs16947 and rs1135840 with mean IOP reduction 24 hours post topical timolol instillation. Contradicting evidence was found in the previous study from the same group of investigators using different laboratory technique; CYP2D6 rs16947 TT genotype was associated with poor timolol-induced ocular hypotensive effects (Yang et al, 2009). There was no significant different between the findings of two different laboratory technique but the later study (Yuan et al, 2010) recruited more subjects. Most likely by chance more subjects with rs16947 polymorphism and those with poorer respond to timolol were recruited. However, consistently both studies found that timolol-induced bradycardia was significantly associated with rs16947 CT and TT phenotypes (Yuan et al, 2010; Yang et al, 2009).

CYP2D6 rs16947 plays a role on inter-individual difference of timolol-induced side effect. Evidently, CYP2D6 is a potential pharmacokinetic candidate gene in predicting the susceptibility to timolol-induced bradycardia. Detection of CYP2D6 can be done with ease and inexpensive. Customizing the prescription of timolol according to polymorphism of CYP2D6 will promote compliance and prevent life threatening side effect. Timolol is a non-selective beta adrenergic antagonist but acts more on beta 2 receptor. Although the mechanism of action of timolol and other beta antagonist is unclear, it is believed to act on beta adrenergic receptor particularly in the ciliary body. Since beta adrenergic agents play a

significant role in IOP regulation, the presence of beta adrenergic receptor in ocular cells is of physiological and clinical importance (Nathanson, 1981). Both beta 1 (ADRB1) and beta 2 (ADRB2) adrenergic receptors are present in the ciliary body and trabecular meshwork with predominantly beta 2 (Wax and Molinoff, 1987). The reversible binding of beta antagonist prevents binding of catecholamine that in turn prevents activation of intracellular adenylate cyclase and reduces the intracellular concentration of cAMP at the ciliary body. Through an unknown mechanism, this process reduces aqueous humour production (Neufeld, 1979). The basal level of cAMP is maintained, as is the response to other transmitters. cAMP is an important second messenger in the intracellular cascade. Since the understanding of aqueous humour production is imprecise, the mechanism of action of topical beta antagonist remains unknown.

Beta adrenoreceptor gene (*ADRB*) controls the function of receptor. Any polymorphism or mutation of *ADRB* is certainly affecting drug-receptor binding and function. Beta2 adrenoreceptor gene (*ADRB2*) has been widely studied in hypertension, cardiovascular, respiratory and other diseases. Thus so far, 20 important SNPs were found in *ADRB2* but only certain SNPs were functionally important (Table 2). In addition, the frequency of the SNPs differs according to population (Table 2). The phenotype of *ADRB2* is based on the effect of beta agonist on *ADRB2* receptor.

Codon	Amino Acid	SNP	Caucasians	African	Asian	Latino	Phenotype
-20		T>C	NA	NA	NA	NA	Increased expression
-47	-19	C>T					
	Arg		65.0**	79.0**	92.0**	82.4#	Increased expression
	Cys		35.0	21.0	8.0	17.6	expression
46	16	A>G					
	Arg16		45.7*	48.8*	58.7*	57.9#	
	Gly16		54.3	51.2	41.3	42.1	
79	27	C>G					Increased desensitization
	Gln27		65.2*	79.3*	92.8*	NA	
	Glu27		34.8	20.7	7.2		
491	164	C>T					Reduced desensitization
	Thr164		96.0@	98.0@	99.0@	97.0@	
	Ile164		4.0	2.0	1.0	3.0	
							Reduced coupling

*Xie et al, 1999; #Litonjua et al, 2004; **McGraw et al, 1998; @Small et al, 2003

NA: not available

Table 2. Allele frequencies and possible phenotypes of *ADRB2* polymorphisms

It was found that polymorphism of beta 2 adrenergic receptor gene (*ADRB2*) was not responsible in susceptibility to glaucoma in Caucasian, African, Turkish and Japanese population (McLaren et al, 2007; Güngör et al, 2003; Inagaki et al, 2006). Although, it was

found those with Gly16 was associated with POAG at younger age and higher baseline IOP with 27Glu in Japanese population (Inagaki et al, 2006). It was then postulated that polymorphisms of *ADRB2* may play a role in predicting the effectiveness of beta blocker. Fushjager et al (2005) conducted a study on 270 healthy non smoking Caucasian males. Topical timolol was instilled and IOP was taken at 8, 12 and 16 hours post instillation. Genotype for *ADRB2* was also done using allele-specific real time PCR to detect polymorphisms at codon 16 and 27. There was no association of *ADRB2* polymorphisms at codon 16 and 27 with short term ocular hypotensive effects of topical timolol. However, this study was conducted on healthy individual that may not represent glaucoma patients. Furthermore, the IOP was taken for such a short period.

Marshfield Clinic PMRP conducted a similar study on 210 Caucasian glaucoma patients who were treated with topical timolol and defined meaningful IOP reduction as more than 20% from the baseline. Homozygous wild CC for codon 27 was significantly associated with good pressure lowering effect of timolol (more than 20% reduction from the baseline). Gln27Glu was associated with 2-fold greater odds of a clinically meaningful IOP (McCarty et al, 2008). Another study in Asian population found that Arg16Gly of *ADRB2* was associated with pressure lowering effect of timolol (Liza Sharmini, 2011). Gly16 of *ADRB2* was also found to increase the risk of respiratory impairment and T-20C was found to confer protective effect against respiratory impairment in a study involving 63 Asian glaucoma patients [Selvaraja, 2006]. Evaluation of respiratory function was conducted 6 months post instillation of topical timolol-XE 0.5% in newly diagnosed non-smoker glaucoma patients. *ADRB2* is not only important in predicting the efficacy of timolol but a good predictor for the side effect of timolol. The current available research findings highlight the potential of *ADRB2* as pharmacodynamic candidate gene. However, more research work is needed especially to study the potential tagging markers of *CYP2D6* and *ADRB2* in predicting the efficacy of timolol.

Since timolol is non-selective beta blocker antagonist, the potential role of β_1 adrenoreceptor gene (*ADRB1*) polymorphisms was also studied on patients treated with topical timolol (Nieminen et al, 2005). There was no association between Arg389Gly and Ser49Gly polymorphism to the side effect of timolol aqueous and gel form. Reduction of heart rate, systolic and diastolic blood pressure in supine, upon head-up tilt or during exercise was not associated with *ADRB1*. Lack of effect as potential pharmacodynamic predictor is due to the lesser effect of timolol on β_1 compared to β_2 receptor. The potential role of *ADRB1* polymorphism is best studied in betaxolol, a cardioselective topical beta blocker acts on *ADRB1* receptor. Betaxolol is more protective against cardiorespiratory side effects but less efficacious compared to timolol. In a small pilot study involving 48 healthy volunteers treated with betaxolol hydrochloride 0.5% for 6 weeks, polymorphism at codon 389 (Arg389) of *ADRB1* was found to be associated with significant IOP reduction from baseline (Schwartz et al, 2005). In fact, those with Arg389 recorded higher baseline IOP. However, in a larger study on 210 glaucoma patients in Marshfield Clinic PMRP, *ADRB1* failed to show any significant association with meaningful IOP reduction (McCarty et al, 2008). The role of *ADRB1* in effectiveness of topical beta blocker is still inconclusive. Similarly, in spite of extensive studies on *ADRB1* and *ADRB2* in systemic diseases especially in hypertension and asthmatic patients, the possible association is still inconclusive. The population variation in allele frequency of *ADRB1* and *ADRB2* polymorphisms is perhaps the major contribution.

Prostaglandin analogues have gained popularity recently and replacing topical beta blockers as first line drug in many countries. Currently, there are at least 3 major popular prostaglandin analogues that act on prostaglandin receptors. Latanoprost and travaprost act on FP receptor that regulate by prostaglandin F_{2α} receptor gene (*PTGFR*), while bimatoprost acts on EP receptor. EP receptor is regulated by prostaglandin E₂ receptor gene. Thus, *PTGFR* is potentially a pharmacodynamic candidate gene that may be associated with pressure lowering effect and side effect of latanoprost. Most of the studies on *PTGFR* were conducted in myometrium and corpus luteum to understand the contractility of uterus as well the effect of prostaglandin agonist on myometrium especially pre-term labour. Screening of *PTGFR* in 100 Japanese healthy volunteers found 10 single nucleotide polymorphisms in the promoter, coding and non-coding region (Sakurai et al, 2007). Two SNPs rs3753380 at the promoter region and rs3766355 at introns 1 (non-coding region) were found to significantly associated with meaningful IOP reduction of more than 20% from baseline post instillation of topical latanoprost. In a pilot study of 30 Asian glaucoma patients receiving topical latanoprost as an adjunctive therapy to topical timolol, the genetic polymorphism in the coding region of *PTGFR* was not associated with the level of HLA-DR on conjunctival impression cytology. HLA-DR level is a good predictor in subconjunctival inflammation as well as conjunctival hyperaemia induced by topical latanoprost [Cheong, 2007].

Currently, there are a number of on-going studies on the pharmacogenetics of topical antiglaucoma drugs. The potential role of genetics polymorphism in predicting the effectiveness and side effects of topical antiglaucoma drug is undeniable but strong powerful scientific evidences are needed to further support this observation.

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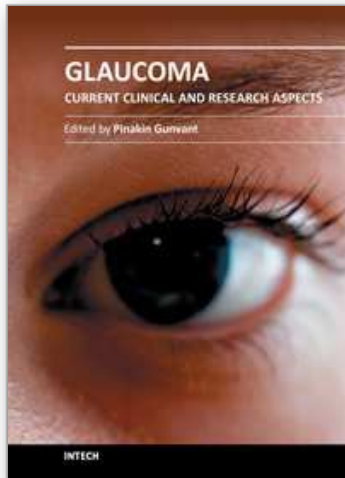
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