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Adrenergic beta blockers: A review

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Abstract

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ADRENERGIC BETA BLOCKERS: A REVIEW

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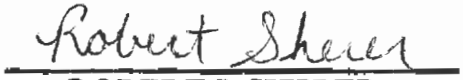

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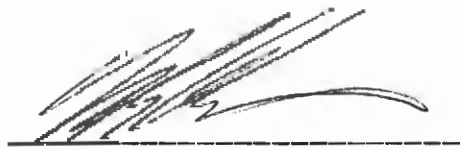

DR. MARK WILLIAMS

BIOGRAPHY

I am a native Montanan and love to hunt and fish. I received my undergraduate degree from Montana State University in Business Management and am currently finishing my Doctorate of Optometry at Pacific University College of Optometry. My plans for the future are to enter private practice in Great Falls, Montana in the summer of 1991.

ABSTRACT

This thesis deals with the Adrenergic Beta Receptor Blocking drugs. It covers some aspects of general pharmacology that must be considered when prescribing beta blocker drugs. The eleven beta blockers that have currently met FDA approval are then detailed with respect to their specific clinical applications, pharmacology, side effects, contraindications, and advantages and disadvantages.

The Adrenergic Beta Receptor Blocking drugs, more commonly referred to as the beta-blockers, are a class of drugs that are expanding at a phenomenal rate. The amount of research on beta blockers has been large yet they are still not well understood. Their two main areas of use are in heart therapy for managing hypertension, angina, and arrhythmias and in the management of open angle glaucoma by lowering intraocular pressure in the eye. This paper will deal with the pharmacology, clinical applications, side effects, contraindications, and the advantages and disadvantages of the most common beta blockers. A section on some of the general pharmacological aspects of the beta blockers will be covered first and then the eleven most commonly used beta blockers that have met Federal Drug Administration(FDA) approval, Timolol, Betaxolol, Levobunolol, Metipranolol, Propranolol, Nadolol, Acebutolol, Atenolol, Pindolol, Labetalol, and Metoprolol will be covered in detail. The numerous other beta blockers that are currently being researched but have not achieved FDA approval will not be included in this paper.

Many factors must be considered when a beta blocker is being considered for systemic or ocular therapy. The more important ones that will be covered are beta receptor selectivity, lipophilicity, systemic effects with ocular administration, long-term drift, intrinsic sympathomimetic activity, hepatic affect, active metabolites, first-pass metabolism, protein binding, and renal affects. Of these beta receptor selectivity will be covered first.

The beta receptors are part of the larger Autonomic Nervous System that regulates the activities of smooth muscle, cardiac muscle, and glands. The Autonomic System is divided into two large divisions, the sympathetic and the parasympathetic. Most organs and muscles receive input from both of these systems with one division stimulating the muscle or organ and the other division inhibiting it. There are two main classes of adrenergic receptors in the Autonomic System, alpha and beta. The alpha receptors are usually excitatory causing smooth muscle contraction, peripheral vasoconstriction, increased cardiac output and exocrine gland secretion, and pupillary dilation from dilator muscle contraction. The beta receptors are subdivided into two classes, $beta_1$ and $beta_2$ receptors. This division is based on the relative concentrations of the receptors in different parts of the body. The $beta_1$ receptors are found mainly in the heart while the $beta_2$ receptors are located in the lungs, the ciliary body in the eye, the liver, the pancreas, and in peripheral blood vessels. The $beta_1$ receptors in the heart are excitatory causing an increased heart rate. The $beta_2$ receptors in the lungs induce bronchiodilation, in the ciliary body they stimulate aqueous humor production, in the liver they stimulate glycogenolysis which results in glucose release, in the pancreas they stimulate insulin release, and in the peripheral blood vessels they stimulate vasodilaton.

Each beta blocker exhibits a certain receptor selectivity from non-selective, which blocks both $beta_1$ and beta $_2$, to only blocking one or the other type of beta receptor. The particular selectivity of a specific drug then should theoretically affect one receptor group

more than the other. A $beta_2$ blocker should inhibit dilation of the bronchioles and decrease aqueous humor production. In reality though, it only follows theory partially. It is known that if enough $beta_1$ blocker is present that it will also block $beta_2$ receptors and visa versa. Theory has enough validity though to warrant consideration when prescribing a beta blocker. This can be shown with Betaxolol, a $beta_1$ cardio-selective blocker, which has been shown to cause fewer problems in patients with bronchiole asthma.[16] (Refer to Appendix 1 for the beta receptor selectivity of the different beta blockers).

Even with topical administration of a beta blocker on the eye there are systemic side effects that can occur.[1] This happens when the beta blocker is absorbed directly into the blood stream in the conjunctivial and nasal mucosal capillaries as the drop leaves the eye through the lacrimal drainage system. This systemic absorption can be significantly decreased though by simply occluding the nasal-lacrimal drainage system with digital pressure or by closing the eyelids for five minutes.[32] Without either of these measures being applied with ocular administration, systemic side effects such as dyspnea, bradycardia, decreased cardiac output, increased peripheral vascular resistance, and CNS penetration resulting in depression, hallucinations, and confusion can occur.

Long-term drift is a consideration when using topical beta blockers to lower IOP in the eye. This occurs slowly over the first several years as the IOP will sometimes drift back up again even with continued beta blockade. Therefore it should not be assumed that the IOP will stay under control if control is achieved initially. A

patient's IOP should be checked every month for the first three months and then every three months thereafter to assure that long-term drift does not occur.

Another consideration in prescribing a beta blocker is Intrinsic Sympathomimetic Activity. By definition, beta blockers are antagonistic to the beta adrenergic receptors which makes them sympatholytic drugs; they decrease the sympathetic tone within the body. Some of the beta blockers, Pindolol, Labetalolol, and Acebutolol, have also shown a certain degree of agonistic ability which has been termed Intrinsic Sympathomimetic Activity or ISA. If ISA is present it will decrease the magnitude of beta blockage by also slightly increasing the amount of agonistic activity. Interestingly, if the intrinsic sympathomimetic activity is $beta_2$ type it should, in theory, actually cause slight bronchiole dilation. The ISA effect is actually dependent on the overall sympathetic tone of the body though. During exercise, when sympathetic tone is strong, there is no ISA effect but when tone is low, like when a person is sleeping, a beta blocker with $beta_2$ type ISA actually showed a slight increase in heart rate. [27] A beta blocker with ISA also causes less beta blockade hypersensitivity. In prolonged systemic beta blockade a hypersensitivity to catecholamines can develop so that if they are abruptly withdrawn, it can cause a large rush of sympathetic input that can actually lead to heart failure. Therefore a beta blocker with ISA does not need to be withdrawn as carefully as one without it. This could be critical in an emergency. There is also evidence that ISA beta blockers have less of a disturbance in certain metabolic

processes such as lipid metabolism and the break down of liver metabolized drugs. [27]

The lipophilicity of a beta blocker must also be considered. If a beta blocker is to be administered topically on the eye it must have the right balance of lipophilicity and hydrophilicity. To penetrate the cornea, a beta blocker must pass through the epithelium, which is lipophilic, then the stroma, which is hydrophilic, and last of all, the endothelium which is lipophilic. Lipophilicity is measured by log P, log P being the logarithm of the partitioning of a compound in oil to its partitioning in water. The corneal permeability of the beta blockers plateaus at log P values greater than 2.5.

The lipophilicity of the beta blockers is provided by their carbon ring component that is partially or completely aromatized. Their hydrophilicity originates from their OH group and/or the oxygen with the lone pair of electrons that all beta blocker chemical structures contain. Therefore, one of the important aspects of administering a topically applied beta blocker is that it has the proper balance of lipophilicity and hydrophilicity so that it can penetrate the cornea and reach the ciliary body through the aqueous humor. Lipophilicity must also be considered in hepatic function and metabolism.

Lipid soluble beta blockers are largely metabolized by the liver. [18] This has three important implication: the first is the possibility of major first-pass metabolism; secondly, if hepatic function is impaired, it can cause an accumulation of beta blocker in the blood stream; and last of all, the metabolism that occurs can sometimes produce active metabolites. First-pass metabolism occurs

in the liver mainly with oral administration of a drug. The liver breaks down the drug before it has a chance to act which means a larger dose of the drug must be given to get a sufficient amount of drug through the liver unmetabolized to achieve high enough plasma levels to be effective. Active metabolites are merely metabolites that can produce a systemic effect. If active metabolites are produced, they must be identified so their affects can be considered in the overall decision of which beta blocker would be most effective and in what amount. If hepatic function is impaired, a decrease in liver metabolism will cause the beta blocker to accumulate in the blood. Patient's with impaired hepatic function, in general, should not be put on lipid soluble beta blockers because the risk of beta blocker accumulation leading to overdose is too great.

Protein binding is another important consideration in determining the proper dosage of a beta blocker. Protein binding of some beta blockers to certain blood plasma proteins can be significant. The degree of binding will affect the amount of drug that is available for beta blockage and, once again, the dosage will have to be adjusted accordingly. Protein binding, along with first-pass metabolism, occurs to differing degrees from person to person and thus the bioavailability of a beta blocker can be highly variable. Renal function is also important in prescribing a beta blocker.

The more hydrophilic beta blockers, along with liver metabolized active metabolites that are excreted renally, can produce an important systemic effect. If a patient has impaired kidney function, an accumulation of the beta blocker or active metabolite can occur in the blood stream. As a possible overdose of beta

blockers could have fatal implications, a patient with renal dysfunction must be considered carefully before a beta blocker is prescribed.

Having covered the most important general pharmacological effects of the beta blockers, they will now be covered one at a time in detail.

Timolol

(Timoptic, Blocadren, Timoptol, Chibro-Timoptol)

Timolol, a non-selective beta blocker, is by far the most used beta blocker in the management of glaucoma. It comes in concentrations of 0.25%(blue top) and 0.50%(yellow top). In the management of glaucoma, Timolol is normally started at 0.25% twice a day. If control of the IOP is not achieved the concentration is increased to 0.50% twice a day. Since more than 0.50% Timolol twice a day has not shown more of a decrease in IOP some different drugs must be added to the therapy if control is to be achieved. Epinephrine derivatives, miotics, and carbonic anhydras inhibitors can be added one at a time to the therapy program until control is achieved. In the event that visual field changes are still occurring with maximum medications then a filtering bleb or Argon Laser Trabeculoplasty(ALT) is indicated. This order of management for glaucoma applies to all four of the topical beta blockers.

Timolol tends to show a slightly larger decrease in IOP than Levobunolol or Betaxolol. [23] The mechanism of Timolol in the eye is known to be a decrease in aqueous production at the ciliary body. It does not have any effect on outflow facility, anterior chamber

volume, or endothelial permeability. The decrease in aqueous production varies widely from 13% to 48% with a mean and standard deviation of 34%±9%.[7] Timolol's topical application acts fairly quickly with an onset of 1/2 hour, its maximum effect is at about 1-2 hours, and it has a duration of up to 24 hours. Timolol has a good balance of lipophilicity and hydrophilicity with a log P value of 1.91. A big advantage that all the topical beta blockers possess is that they do not affect the pupils or accommodation like miotics and propine. This can be a very valuable factor in dealing with patient compliance to the prescribed therapy and proper patient management.

Timolol is also attractive for systemic use as well. It comes in 5,10, and 20mg tablets. Normally Timolol is started at 10mg twice a day with a maintainence dose between 20-40mg total a day. It displays no first-pass metabolism or plasma accumulation in renal disease. Some liver metabolism does take place which makes it susceptible to accumulation in hepatic dysfunction. One advantage though is that little blood plasma protein binding takes place. Timolol does not possess any intrinsic sympathomimetic activity and therefore should not be abruptly withdrawn. There are two reasons for this: The first is that chronic beta blockage can cause some patients to develop a hypersensitivity to catecholamines and secondly, a beta blocker that has no ISA causes complete beta blockage and does not allow the body to maintain very much sympathetic tone. In either case, an abrupt withdrawal can cause a major influx of sympathetic input which could possibly cause cardiac failure in a patient with a weak heart. The systemic mechanism of

Timolol is not known but several theories, which will be covered under Propranolol, have been hypothesized.

Timolol is used clinically in managing chronic open angle glaucoma, aphakic glaucoma, secondary glaucoma, ocular hypertension, and short-term management of angle closure. It also finds systemic use in managing hypertension and in reducing the risks of mortality in patients that have survived a myocardial infarct. Some serious side effects have been documented with the use of Timolol. Because of its non-selective beta receptor characteristics, it has caused pulmonary distress in patients with chronic obstructive pulmonary disease. Care should be used in patients with weak hearts because of the decrease in cardiac output and in diabetic patients as Timolol can block the signs of acute hypoglycemia. It can also mask the signs of hyperthyroidism. When Timolol is used in conjunction with catecholamine-depleting drugs, the patient should be observed closely for possible additive effects that could occur. Timolol is secreted in the milk of nursing mothers and is not recommended for them because of the adverse affects a beta blocker could have on an infant. Timolol has also been reported to occasionally cause systemic side effects such as muscle weakness, fatigue, headaches, nausea, dizziness, depression, skin rash, and impotence. Ocular side effects include conjunctivitis, blepharitis, keratitis, and decreased corneal sensitivity.

There are instances when Timolol is contraindicated instead of just being used with precaution. These include patients with any severe chronic obstructive pulmonary disease or a history thereof, sinus bradycardia, second and third degree atrioventricular heart block, overt cardiac failure, or cardiogenic shock.

Betaxolol

(Betoptic, Kerlone)

The pharmacology of Betaxolol has several differences from Timolol. It comes in 0.50% ophthalmic solution and in a 0.25% ophthalmic suspension that has been shown to be significantly more comfortable than the solution.[2] It is normally administered one drop twice a day for the solution or the suspension. For systemic use it comes in 10 and 20mg tablets, is usually started at 10mg once a day, and is normally not administered more than 20mg once a day. It is $beta_1$ selective in nature which is a distinct advantage in that it has shown very little effect in decreasing lung capacity or in lowering blood pressure when topically applied.[2] Since it is only approved for the management of glaucoma, its main administration is topically. Betaxolol has also shown an additive effect when used in conjunction with epinephrine.[17] An additional decrease in IOP was achieved when epinephrine was added to Betaxolol therapy; This additional decrease was attributed to an increase in outflow facility caused by the epinephrine. With a log P value of 2.73, Betaxolol is very lipophilic but still manages to penetrate the cornea sufficiently to be effective when topically applied. Being lipophilic also makes it prone

to causing corneal anesthesia by stabilizing the membranes of the unmylenated nerves in the cornea but this has been reported only rarely. The mechanism of Betaxolol has been shown to be a decrease in aqueous humor production with no effect on outflow facility.[8] It decreased aqueous humor production between 7% and 51% with a mean and standard deviation of 32%±13%. It has an onset of 1/2 hour, a maximum effect at about 2 hours, and lasts only around 12 hours. Betaxolol's duration is only about half of Timolol's. This may be due to Betaxolol's much higher lipophilicity which makes it more prone to liver metabolism.

Clinically, Betaxolol is limited in use because it is only FDA approved for topical administration. Therefore, it is only used in managing glaucoma and ocular hypertension.

Ocular side effects to watch for include keratitis, decreased corneal sensitivity, and photophobia. Systemic side effects that have been reported in rare instances include dyspnea, bradycardia, impotence, headache, insomnia, and depression. Caution should be used in patients taking catecholamine-depleting drugs because of possible additive effects and in nursing mother and children.

Betaxolol is contraindicated when the patient has sinus bradycardia, greater than first degree atrioventricular heart block, cardiogenic shock, overt cardiac failure, or severe chronic obstructive pulmonary disease.

Levobunolol

(Betagan, Bunorit, Gotensin, Vistagan)

Levobunolol is another beta blocker that has only been FDA approved for ocular use in the US. It comes in ophthalmic solutions of 0.25% and 0.50%. The 0.50% solution is normally started out once a day while the 0.25% solution is started out twice a day. The 0.50% can be used twice a day but more frequent administration than this is generally not effective. Levobunolol shows no beta receptor selectivity, is between Timolol and Betaxolol in lipophilicity with a log P value of 2.4 and possesses no intrinsic sympathomimetic activity. As with other beta blockers, Levobunolol decreases aqueous humor production at the ciliary body but does not increase outflow facility at the trabecular meshwork.[19] It has also displayed the longest time to onset at about 1 hour with a maximum effect between 2-6 hours. A significant decrease in IOP can be maintained for up to 24 hours. This can be a big advantage in certain cases where patient compliance is a problem since Levobunolol can actually be used once a day with relatively good results in some patients.

Levobunolol, like Timolol, has been shown to cause significant systemic beta blockage in the heart and lungs. An average 4-5 beat per minute decrease in heart rate was observed.[9] Occasional reports of pulmonary distress and corneal anesthesia have also occurred. Other systemic side effects that have been observed include , headache, impotence, dizziness, heart block, congestive heart failure,

nausea, depression, and skin rash. Ocular side effects that have been observed are a burning sensation upon corneal application and hyperemia of the eyelids and conjunctivia. Caution should be exercised in nursing mothers, in children, and in patients who are taking catecholamine-depleting drugs because of possible additive effects.

The clinical uses of Levobunolol are very limited as it is only FDA approved for ocular use. Accordingly, it is only used in the management of glaucoma and ocular hypertension to lower IOP.

Situations where Levobunolol is contraindicated include patients with any severe chronic obstructive pulmonary disease, sinus bradycardia, second and third degree atrioventricular heart block, cardiogenic shock, and overt cardiac failure.

METIPRANOLOL
(OPTIPRANOLOL)

Metipranolol is the most recent addition to the topical beta blockers that are approved for glaucoma therapy in the U.S.. It is a non-selective beta blocker that has been shown to be as effective as Timolol in lowering IOP of the eye. It works by decreasing aqueous production at the ciliary body, but in addition may also slightly increase outflow facility. Metipranolol does tend to burn more upon topical application than the other three beta blockers but not enough to warrant discontinuing its use in most cases. Its onset of action for topical administration is one half hour, with a maximum effect at two

hours, and a duration of 24 hours. The mechanism of Metipranolol is not known but is felt to be similar to the three main theories of beta blocker action covered under Propanolol.

Clinically, Metipranolol is used for managing primary open-angle glaucoma, the secondary glaucomas, ocular hypertension and short-term management of angle closure. It comes in a concentration of 0.3% and is normally administered twice a day with good results. Caution must be used in patients with cerebrovascular insufficiency, chronic obstructive pulmonary disease, in patients receiving any catecholamine-depleting drugs, and in nursing mothers and children. It can also cause problems in diabetes and hyperthyroidism by masking some of the signs and symptoms of these two diseases. Ocular side effects include conjunctivitis, blepharitis, tearing, blurred vision, and photophobia. In addition, Metipranolol has been reported, in rare cases, to cause headaches, bradycardia, dyspnea, dizziness, anxiety, depression, impotence,and nausea.

Patients in which Metipranolol is contraindicated include those with COPD, symptomatic sinus bradycardia, second or third degree atrioventricular heart block, cardiogenic shock, and overt cardiac failure.

Propranolol

(Inderal, Dociton)

Propranolol is the most popular beta blocker for treating systemic hypertension, angina, and arrhythmia. It comes in several different forms including 10,20,40,60,80mg tablets, in 1mg/ml intravenous solution, and in 60,80,120,160mg Long Acting tablets that last up to 24 hours. A normal starting dose is 40mg(regular tablets) twice a day with a maintanence dose of 120-240mg total per day. It also comes in various combinations with hydrochlorothiazide called Inderide. It has displayed no beta receptor selectivity or intrinsic sympathomimetic activity. Propranolol is very lipophilic with a log P value of 3.2 which means it will be largely metabolized by the liver and in fact, does show a large first-pass metabolism. This leads to a larger dose requirement to obtain sufficient blood plasma concentrations so beta blockade can be achieved. It must be used with caution in patients with hepatic dysfunction because slower liver metabolism of Propranolol can greatly increase its blood plasma levels. There have been three theories proposed as to the mechanism by which Propranolol works: these are a decrease in cardiac output, an inhibition of renin release by the kidneys, or a decrease of the tonic sympathetic nerve outflow from the vasomotor centers in the brain.[2] The mechanism could be one or a combination of any of these theories. Propranolol's maximum effect occurs around 1-1/2 to 2 hours and because of extensive liver metabolism

only lasts about 12 hours. The long acting type of Propranolol lasts up to 24 hours.

There are a wide range of clinical uses for Propranolol. As mentioned earlier, its main areas of use are in managing hypertension, angina, and arrhythmias of the heart. It is also used in patients who have stabilized after a myocardial infarct to lessen the risk of another, in managing hypertrophic subaortic stenosis, and occasionally in preventative treatment of migraine headaches.

Propranolol has some potentially serious sides effects. Due to its high lipophilicity, it is better able to penetrate the brain tissues and cause psychological problems such as mental depression, lassitude, hallucinations, short-term memory loss, and disorientation. It has been shown to cause a decrease in pulmonary capacity like most of the other beta blockers. There are also reported cases of insomnia, muscle weakness, fatigue, visual disturbances, dry eyes, nausea, abdominal cramps, skin rash from allergic reactions, agranulocytosis, male impotence, and drug induced deafness. One of the big advantages of Propranolol is that it reduces high density lipoproteins and therefore, the cholesterol ratio. This helps in preventing plaque build-up in the blood vessels and thus helps decrease the risk of myocardial infarct. Propranolol, in general, reduces the oxygen requirements of the heart at any given level of effort. This is an advantage in treating angina. Propranolol also causes a significant decrease in IOP of the eye.

Contraindications for Propranolol are cardiogenic shock, sinus bradycardia, second or third degree atrioventricular heart block, and

severe chronic obstructive pulmonary disease or any history thereof, and congestive heart failure.

Acebutolol

(Sectral)

Acebutolol's pharmocology is fairly colorful. It comes in 200 and 400mg tablets. Normally 400mg once a day is the initial dose with a maintanence dose of 400-800mg total per day. In some patients twice a day dosing may be required to control blood pressure. It possesses both $beta_1$ receptor selectivity and intrinsic sympathomimetic activity. The $beta_1$ selectivity produces less problems in decreased pulmonary capacity and the ISA allows for some sympathetic tone to be maintained which can be important in patients with weak hearts. It displays only moderate lipophilicity but enough that liver metabolism does occur and the active metabolites that are produced in this instance must be considered when prescribing it. On the other hand, it is hydrophilic enough that it, along with the active metabolites, are eliminated mainly through the renal system. In patients with kidney dysfunction, Acebutolol can accumulate in the blood plasma leading to a possible overdose. Protein binding in the blood plasma occurs significantly enough to also be considered. In geriatric patients, a larger proportion of the dosage reaches the blood plasma probably because of less hepatic metabolism and renal ability. The mechanism of Acebutolol is not known for sure but it is felt to be similar to that of Propranolol's.

Maximum effect of Acebutolol is realized in about 2-1/2 to 3 hours and can last for up to 24 hours.

Clinically, Acebutolol is somewhat limited in use, finding its main administration in two cases: treatment of premature ventricular beats and in systemic hypertension.

Some of the side effects that have been observed in the use of Acebutolol include bradycardia, hypotension, heart failure, decreased pulmonary capacity, nausea, anxiety, conjunctivitis, and dry eyes. One disadvantage of Acebutolol is that its liver metabolism produces an active metabolite. This causes large differences in blood plasma concentrations from patient to patient because of differing degrees of hepatic function. Boundaries to be crossed with caution are patients with hepatic or renal dysfunction and in pregnant or nursing females. An additive effect should be watched for in patients receiving catecholamine-depleting drugs. Signs of thyrotoxicosis can be masked by Acebutolol's use. It has also been shown that a decrease of IOP in the eye occurs.

In patients with bradycardia, second or third degree atrioventricular heart block, cardiogenic shock, or overt cardiac failure, the use of Acebutolol is contraindicated.

Metoprolol

(Lopressor, Beloc)

Metoprolol is another of the beta blockers that exhibits extensive $beta_1$ selectivity which, as with the other $beta_1$ selective beta blockers, lends itself to use in patients with chronic obstructive

pulmonary disease. It comes in 100 and 200mg tablets, in 5ml ampuls for intravenous administration, and in combination with hydrochlorothiazide called Lopressor HCT. It is usually started at a dose of 100mg total once or twice a day with a usual maintanence dose of between 100-450mg. It possesses no intrinsic sympathomimetic activity. With a log P value of 1.88, Metoprolol has about the same lipophilicity as Timolol. This characteristic makes the probability of liver metabolism more likely and, in fact, it proves to be a significant factor in the administration of Metoprolol. It displays only a small amount of first-pass metabolism though, and produces no active metabolites from the liver metabolism that does take place. Elimination occurs mainly through the liver. Metoprolol has shown minimal protein binding, it does not tend to accumulate in patients with renal dysfunction, and favorably affects blood lipid levels. The mechanism of Metoprolol, like all the other beta blockers, has not been determined for sure but one or a combination of the following are felt to be involved: decreased cardiac output by adrenergic beta blockage at the heart, reduced renin release by the kidneys, or a decrease in sympathetic outflow from the brain to the periphery. Onset of Metoprolol beta blockade occurs within an hour with maximum effect at 4-6 hours and a single dose lasting up to 24 hours. It is also FDA approved for intravenous administration for a quicker onset with maximum effect at about 20 minutes.

The use of Metoprolol is indicated in patients with angina, hypertension, and in reducing the risk of death after an acute heart attack. It is the only beta blocker approved for use during a heart attack.

Some of the advantages of Metoprolol are its $beta_1$ selectivity, its lack of active metabolites, and it reduces oxygen requirements of the heart. A major disadvantage is its significant penetration into the central nervous system which leads to many of the negative side effects of its use. Side effects that have been observed are dizziness, headaches, nightmares, insomnia, mental confusion, short-term memory loss, nausea, fatigue, cold extremities, and dry eyes. It has also been shown to lower IOP in the eye.

Contraindications for Metoprolol are as follows: sinus bradycardia, heart block greater than first degree, overt cardiac failure, and cardiogenic shock.

Pindolol

(Visken, Durapindol)

Pindolol is an adrenergic beta blocker that displays no beta receptor selectivity but does exhibit considerable intrinsic sympathomimetic activity. The ISA of Pindolol allows it to maintain some sympathetic tone which is important in patients with a history of cardiac failure. Beta blockers with ISA also tend to cause less of a disturbance in some metabolic processes such as lipid metabolism.[27] It comes in 5 and 10mg tablets, with an initial dose of 5mg twice a day, and a maintanence dose of 10-60mg total per day. The mechanism of Pindolol has not been discovered. A reduced sympathetic outflow from the brain, a decrease in renin release, and

a decrease in cardiac output are the main-line theories of beta blocker action but they seem less likely in Pindolol's case because of its modest affect on cardiac output and renin release. It has been shown to be as effective as Propranolol in reducing both systolic and diastolic blood pressure.[2] Pindolol does not exhibit any first-pass metabolism, produces no active metabolites, and shows no accumulation in kidney disease. An accumulation in the blood plasma does occur in patients with decreased hepatic function though. Pindolol does possess considerable protein binding ability that must be considered when prescribing it. Pindolol has an onset of about 1 hour, a maximum effect at 2-3 hours, and lasts only about 12 hours with a single dose.

Clinically, Pindolol is used only for the management of hypertension. It works well though because its ISA maintains a degree of sympathetic tone while also causing a vasodilation which decreases peripheral resistance. This is the opposite of nearly all other beta blockers which normally cause an increase in peripheral resistance. It does have the disadvantage of causing some edema though.

Pindolol has various side effects that are common to most beta blockers. These include pulmonary distress, heart block, diarrhea, nausea, male impotence, and burning eyes. Precautions must be exercised in diabetic patients as it can mask the signs of hypoglycemia, in patients with decreased hepatic function because of possible plasma accumulation, and in patients with a history of cardiac failure. Pindolol should not be abruptly withdrawn after chronic use as a hypersensitivity to catecholamines has developed in

some patients. Thus, abrupt withdrawal can lead to excessive sympathetic input and consequent heart failure. Pindolol has exhibited an ocular effect by reducing IOP.

In patient who show signs of severe bradycardia, chronic obstructive pulmonary disease, cardiogenic shock, second or third degree atrioventricular heart block, or overt cardiac failure Pindolol is contraindicated.

Nadolol

(Corgard)

Nadolol is a beta blocker that is similar to Timolol. It comes in 20,40,80,120,160mg tablets. An initial dose is usually 40mg once a day with a maintanence dose of 40-80mg total per day. It displays very weak lipophilicity with a log P value of only .93. This means elimination through the renal system is predominate. Accumulation of Nadolol in the blood plasma must therefore be watch for closely in patients with any decreased kidney function. Nadolol does maintain renal blood flow and the glomerular filtration rate though, unlike most other beta blockers.[11] It has shown no evidence of any beta receptor selectivity or intrinsic sympathomimetic activity. Liver metabolism does occur to a sufficient degree that it must be considered in prescribing Nadolol but no active metabolites of consequence are produced. There is no major first-pass metabolism that occurs and, in fact, Nadolol is only one of two beta blockers that are excreted by the kidneys unchanged.[11] Protein binding occurs to

a considerable extent and can affect availability of Nadolol. The mechanism of Nadolol has not been determined but is thought to be similar to the other beta blocker mechanism theories. Onset of action is about 1 hour, with peak effect at 3-4 hours, and a duration of up to 24 hours.

Nadolol finds two main areas of use. The first being the management of angina as Nadolol tends to reduce oxygen requirements of the heart. Management of hypertension is its second clinical application. Nadolol does not have a direct depressant effect on the heart like most of the other beta blockers which is an advantage in treating hypertension.

Side effects of Nadolol, like the other beta blockers, are numerous but uncommon. They include dizziness, fatigue, depression, hallucinations, disorientation, visual disturbances, short-term memory loss, insomnia, bradycardia, hypotension, weight gain, skin rash, headaches, and respiratory distress. Nadolol should be used cautiously in pregnant and nursing females.

Contraindications of Nadolol include the following: bronchial asthma, sinus bradycardia, second or third degree atrioventricular heart block, cardiogenic shock, and overt cardiac failure.

Labetalol

(Normodyne, Trandate)

Labetalol is a unique, non-selective beta blocker in that it also selectively blocks alpha receptors. The ratio of alpha to beta blockade has been estimated to be about 1:3 for oral administration and 1:7 for intravenous administration.[2] The additional alpha blockade results in less peripheral resistance and, unlike most of the other beta blockers, cardiac output is not decreased.[28] It comes in 100,200,300mg tablets and in 5mg/ml intravenous solution. An initial dose of 100mg twice a day is recommended with a maintanence dose of 200-400mg twice a day. Labetalol is metabolized by the liver and exhibits major first-pass metabolism but does not produce any active metabolites of concern. Being eliminated by the liver, Labetalol does not show any accumulation in renal disease but hepatic disease can cause a decreased breakdown of it and thus an accumulation. It has also exhibited considerable protein binding ability that must be taken into account. Labetalol has displayed some intrinsic sympathominetic activity by causing slight beta agonistic activity but it is minimal. This could be a possible explanation of why Labetalol does not cause a decrease in heart rate. Onset of action depends on the type of administration. For intravenous administration, onset is nearly immediate with maximum effect within 5 minutes and a duration of about 12 hours. When administered orally, onset is within an hour, 2-4 hours for peak effect, and a duration of about 12 hours.

In the clinical setting, Labetalol is used in managing hypertension and hypertensive emergencies. The immediate action of Labetalol in IV, along with the advantage of no decrease in cardiac output, is important in managing hypertensive emergencies when the condition of the patient's heart is not known. Other advantages of Labetalol are its vasodilatory effect that decreases peripheral resistance, a lack of effect on kidney function, and less pulmonary problems. Disadvantages include its large first-pass metabolism and extensive protein binding that causes major variations in the amount of Labetalol that is actually available for blockade from patient to patient. It has not shown a positive effect on blood lipid levels like nearly all the other beta blocker. This is a major disadvantage when managing patients with hypertension and atherosclerosis.

Labetalol has shown side effects similar to the other beta blockers such as fatigue, nausea, edema, depression, bradycardia, pulmonary distress, skin rash, and visual disturbances, In addition, there have been reports of muscle cramps, jaundice, and difficulty in urinating. A decrease of IOP in the eye has also be documented.

Contraindications for Labetalol include chronic obstructive pulmonary disease, bradycardia, overt cardiac failure, cardiogenic shock, and second or third degree atrioventricular heart block.

Atenolol

(Tenermin)

Atenolol is a beta blocker that has several interesting pharmacological aspects. It is supplied in 50 and 100mg tablets, in a 1/2 mg/ml intravenous solution, and in tablet form in combination with chlorthalidone called Tenoretic. It is usually started at a dose of 50mg once a day with a maintanence dose of 50-100mg once a day. It has the least lipophilicity of any of the beta blockers with a log P value of only .16. This causes the drug to show very little central nervous system penetration which is useful in treating patients with mental disorders and in lessening many of the potentially harmful side effects of beta blockers caused by CNS penetration. Being more hydrophilic also means less liver metabolism which alleviates any major first-pass metabolism. Along with very low protein binding in the plasma, this helps Atenolol achieve a less variable bioavailability from patient to patient. Atenolol also exhibits high $beta_1$ receptor selectivity which lends itself to less peripheral vascular resistance along with less of a reduction in pulmonary capacity. As with other renally excreted drugs, an accumulation of Atenolol can occur in patients with impaired kidney function. The onset of Atenolol takes about 1 hour, with peak effect from 2-4 hours, and a duration of up to 24 hours.

Clinically, Atenolol is used in the management of hypertension. Its beta selectivity is helpful in decreasing peripheral vascular resistance and pulmonary problems that may occur from administration. It is also a good pick for treating angina as it normally reduces the amount of oxygen needed by the heart.

Most of the side effects of Atenolol are quite rare. Some of the more serious ones include cardiac failure, pulmonary distress, agranulocytosis, and mental depression progressing to catatonia. Other less serious ones are fatigue, nausea, leg pain, bradycardia, and cold extremities. A reduction of IOP in the eye has been observed.

Atenolol is contraindicated in sinus bradycardia, cardiogenic shock, second or third degree atrioventricular heart block, and overt cardiac failure. Precautions should be exercised in patients with reduced renal function and steps must be taken to monitor possible additive effects if any catecholamine-depleting drugs are being taken in conjunction with Atenolol. In addition, Atenolol therapy should not be abruptly withdrawn as it can lead to cardiac failure caused by hypersensitivity to catecholamines that may have developed during extended beta blockade.

Beta blocker drugs, although all fairly similar, have subtly, yet important differences. Their lipophilicity, liver metabolism, active metabolites, beta receptor selectivity, and protein binding ability are some of the most important characteristics that must be considered in administration. Each patient has different health characteristics that must be considered to find the most effective beta blocker to achieve the safest possible beta blockage. In practice all beta blockers are not the same.

Recently several other beta blockers have met Federal approval for systemic use. These are Esmolol, an ultra-short acting beta blocker, and Oxprenolol. Some of the beta blockers, other than Timolol, Betaxolol, Levobunolol, and Metipranolol have also met foreign governments' approval for ocular use. These include Befunolol, Bupranolol, Carteolol, and Pindolol.

APPENDIX 1

	$Beta_1$ Selectivity	ISA	Lipid Soluability	First-pass Metabolism	Active Metabolites	Protein Binding
Acebutolol	X	X	Moderate		X	
Atenolol	X		logP=0.16			
Betaxolol	X		logP=2.73			
Labetalol		X	Weak	X		X
Levobunolol			logP=2.4			
Metipranolol			Moderate			
Metoprolol	X		logP=1.88			
Nadolol			logP=0.93			X
Pindolol		X	Moderate			X
Propranolol			logP=3.21	X	X	X
Timolol			logP=1.91			

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