Medical Committee
The University of Jordan

PHARMACOLOGY

Lecture No.: 23

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SHEET

SLIDES

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Beta Adrenoceptor Antagonists

Beta receptors are distributed in many sites in the human body like those of ; heart, bronchial tree and juxtaglomerular apparatus of the kidney…etc. Beta receptors are blocked by beta antagonists –beta blockers- which are of a clinical importance, they occupy β receptors and competitively inhibit occupation of these receptors by catecholamines.

Beta blockers are of two types:

1) Pure/full Antagonists, they cause no activation or agonist activity at all.
2) Partial Agonists (or Partial Antagonists): they cause either activation or inactivation depending on the presence of the endogenous ligand that occupies the receptor.

A Closer Look

1) The full antagonists:
They include many drugs and you are required to memorize them. Notice that most of them end with (OLOL).
The drugs are:
Atenolol, Bisoprolol, Carvedilol, Esmolol, Metoprolol, Nadolol, Propranolol, Sotalol and Timolol.

The prototype of these drugs is Propranolol. A prototype means: the 1st drug of the group (1st beta adrenoceptor) which is NONselective it blocks all beta receptors 1, 2&3 and has no agonist activity, then the other drugs came later with different selectiveness toward beta receptors.

2) Partial Agonists**:**
As mentioned they either activate or inactivate depending on the presence of the endogenous ligand of the receptors. Examples of these drugs: Acebutolol, Labetolol, Pindolol.

They cause PARTIAL activation of the receptor (agonism) in the absence of the full agonist (absence of Epinephrine and NE here)
Inactivation: (antagonism) in the presence of Epi & NE because the drugs here occupy the receptors preventing the original endogenous ligand from binding to its receptors thus, decreasing its EFFICACY and the net result would be inhibition.

Beta receptors and their ligands serve many important physiological functions, for e.g: bronchodilation,vasodilation (decrease the diastolic pressure), in case of their blockage, all of those functions will be blocked, but this is not true for beta1 selective drugs , selectivity allows these drugs to block only one type of receptors therefore, results in the desired effect, examples of these drugs: Acebutolol, Atenolol, Bisoprolol, Esmolol, Metoprolol. As a matter of fact this selectivity is not absolute as it diminishes by increasing the dose. It's thought that increasing the dose results in a better response, but this is not always true and in case of beta1 selective drugs, the more the dose increases, the more the selectivity decreases and the drug becomes beta2 antagonist as well.

The prototype propranolol undergoes extensive hepatic 1st pass metabolism, consequently, low bioavailability. This actually explains the great difference between the oral and the IV dose; The IV dose is about 2mg while the oral dose is around 80 to 320 mg given 2 to 4 times a day, again due to the extensive hepatic metabolism in case of oral administration. The new medical trend is heading toward "personalized medicine" which considers the physiological variations among individuals: in our case here Because first-pass effect varies among individuals, there is great interindividual variability in the plasma concentration after oral administration of propranolol – *With drugs that undergo 1st pass effect, there will be interindividual variation in the amount of drug in the circulation, because of interindividual variation in the degree of metabolism, that*

was the answer to a Q in the exam, the answer was not linked to liver cirrhosis-.

Another important thing to consider is the liver condition, in case of liver cirrhosis, a shunt would cause the blood to bypass the hepatic metabolism and go directly to the systemic circulation with no 1st pass effect so the oral dose should be much less for those patients otherwise toxicity (overdose) would result.

Conclusion:

The elimination of high ER (extraction ratio) drugs - that undergo extensive 1st pass metabolism- is highly dependent on the hepatic blood flow (proportional) and on the enzyme inducers/inhibitors, in case of an enzyme inducer, the metabolism will increase and the drug plasma conc will decrease.

The doses you read in the books are the ones prescribed for normal individuals.

Most of these drugs are well absorbed after the oral administration except for the very hydrophilic drugs. Note that for a hydrophilic drug to be more absorbed by the intestine, the oral dose should be increased to overcome the effect of the metabolism.

General notes:

** Propranolol has some effects on the CNS because it is a lipid soluble drug that is able to cross the blood brain barrier (BBB), once the patients take Propranolol, nightmares start @_@ .

***Metoprolol** is also metabolized by CYP2D6 in the liver. The CYP2D6 genotype is the major determinant of the drug's clearance. (PMs* have 3-10 fold plasma concentration than EMs).
*PM: poor metabolizers. Any deficiency in this enzyme in (PMs) with inappropriate high dose will result in toxicity due to the negligible metabolic value.

***Nadolol** and **Atenolol** are water-soluble drugs therefore, not metabolized and excreted by the kidneys, any renal failure will increase the plasma conc of those drugs and their half-life will be prolonged. Atenolol is a selective drug; once its conc gets higher in the plasma it loses its selectivity.

According to slide number 23 there are many drugs that share similar half-life ranges but still there are some exceptions, for 3 drugs, *you are required to know them and for the other drugs, at least memorize their half-life range.*

The 3 drugs are:

Name	Half-life	Notes
Esmolol	Ten minutes	Rapidly hydrolyzed in the plasma and used in diagnosis or emergency. Also, it's used for differentiation between types of cardiac arrhythmia, can be used for a short time followed by the administration of another beta blocker.
Bisoprolol	9-12h	*The most common drug* used from one to two times a day.
Nadolol	14-24 h	Given one time/day only, due to its long half-life

Clinically Important drugs:

1- Propranolol:

A. Effects on the cardiovascular system

Pharmacodynamics:

It blocks beta1,beta2 & beta3 receptors. (not selective)

A clinical case: (try to understand the case well)

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A doctor prescribed Propranolol for a Hypertensive patient, the day after, the doctor measured the patient's blood pressure and he found that the **systolic blood pressure has decreased** while **the diastolic pressure increased**, the patient continued taking the same drug, five days later the measurement of the same patient's blood pressure again showed that the **diastolic pressure has decreased** as well. What explains the 1st increase and the 2nd decrease in the diastolic pressure?

Explanation:

That was not a manifestation of tolerance, because if tolerance occurs it would affect all the receptors.
The 1st increase in the diastolic pressure resulted from beta2 blocking effect, (the vasodilation mediated by catecholamines was blocked)**. The 2nd drop:** the diastolic pressure decreased despite the blockage of beta2 receptors, due to the beta1 receptors present in the juxtaglomerular apparatus. Further elucidation;

1) Beta1 receptors here are involved in Renin secretion**, Renin is an angiotensenogenase which** converts angiotensinogen to **angiotensin I** and by another enzyme angiotensin I is converted to **angiotensin II** which is a very potent vasoconstrictor (means it produces vasoconstriction at low conc).
2) Renin itself causes water and sodium retention by aldosterone stimulation, (aldosterone is a mineralocorticoid) which increases the blood pressure by increasing the blood volume. Once it is inhibited by beta blockers, the vasoconstriction caused by angiotensinII is inhibited and the water+sodium retention is inhibited as well, so blood pressure decreases and this is why the diastolic pressure will drop.
3) Conclusion: Beta blockers affect the renal system they remove the effect of angiotensin2.
4) Autoreceptors that provide +ve feedback and increase NE release are inhibited here by beta blockers-autoreceptros are beta1 receptors-. Therefore, the whole sympathetic outflow is reduced and NE release as well.

So Propranol drug was involved in the listed changes:

i. Negative inotropic effect on the heart → reduction of cardiac output.
ii. Suppression of renin-angiotensin system through beta1 receptors.
iii. A centrally-mediated effect due to reduction of sympathetic outflow from the CNS by the blockage of presynaptic beta1 receptor which originally mediates positive feedback (they are responsible for the whole sympathetic outflow from CNS so even alpha receptors are affected –inactivated-).

So Propranol does the following changes to the cardiovascular sys:
Negative chronotropic effect (reduction of heart rate)→ Bradycardia (abnormal)

3. Slowing of AV nodal conduction and prolonging its refractory period. This is useful for treating supraventricular arrhythmias (supraventricular arrhythmias: what comes from the atria (SA and peacemaker) or even from the AV nodes). Impul ses come to ventricles through the AV nodes so when we slow the conduction of AV node and make the refractory period longer some of these impulses will come to the AV refractory so they don't enter to the ventricles. So the ventricular rate is usually different from the atrial rate in the presence of beta blockers due to the changes in the refractory period.

4. Conventional doses do not usually produce hypotension in healthy individuals with normal blood pressure; so if they were given to a normal person with no hypertension nothing will happen, they may reduce the blood pressure **but** not to the hypotension extent. However, they are given for other reasons for e.g: migraine profilaxis –not the treatment-.

B. Effects on respiratory tract:

Increased airway resistance due to block of β2 receptors (bronchoconstriction). They are contraindicated for patients with bronchial asthma or obstructed pulmonary diseases. If these drugs -beta blockers- are needed for other conditions, it is preferable to use selective β1 receptor blockers AT SMALL DOSES because larger doses will diminish the selectivity and harm the patient.

C. Effects on the eye:

They reduce the intraocular pressure (useful for glaucoma) by reduction in aqueous humor production**.**
The drug used for glaucoma treatment here is Timolol as an eye drop.
The mechanism is reduction of aqueous humor production but not by vasoconstriction, remember that the production of the aqueous humor fluid is part of the beta receptors function and once you block them you reduce the fluid production from the cilliary epithelium (which contains the beta receptors).

We have studied that muscarinic agonists facilitate the outflow of the aqueous humor, alpha1 agonist reduces the production of the aqueous humor due to vasoconstriction which reduces the fluids that are produced from the ciliary epithelium.
So we can use: beta blockers, muscarinic agonists and alpha1 agonists to treat glaucoma

D. Metabolic and endocrine effects:

1. Inhibition of lipolysis (β3). There are beta3 receptors in the brain that have other functions. Any nonselective beta blocker would block beta3 receptors.
2. Partial inhibition of glycogen**olysis** (β2). It is partial not complete inhibition due to the other hormonal effects that control the glycoenolysis, so any component related to beta receptors regulation during the glycogenolysis would be blocked and results in reduction of glucose output but not full inhibition.

3. **Keep in mind** that the use of these drugs would impair recovery from hypoglycemia in **insulin-dependent** diabetic patients. **β1 receptor antagonists are less prone to do so (selective)**.

Further Elucidation:
During hypoglycemia the sympathetic sys is stimulated (manifested by sweating, tachycardia), this stimulation aims to recover this hypoglycemia by increasing the rates of gluconeogenesis and glycogenolysis –to give gluscose- . The drug here blocks the receptors → blocks the sympathetic stimulation → blocks the recovery and the glucose level will remain very low. So these drugs exacerbate the problem of hypoglycemia in insulin-dependent diabetic patients (those who take insulin, because it directly lowers glucose). Remember that the brain would be affected in case of hypoglycemia because it depends on glucose only and it tolerates glucose absence only for 10 minutes max. These drugs are safer (not safe completely) in type 2 diabetics who do not usually have frequent hypoglycemic episodes.

If the drug is necessary for diabetic patients, it is preferable to give them beta1 selective drugs with smaller doses. However, try to avoid giving them any beta blocker.

4. Chronic use has been associated with increased plasma concentrations of VLDL (makes atherosclerosis) and decreased concentration of HDL (protective) →atherosclerosis → increased risk of coronary artery disease. This is less common with partial agonists. Mechanism is unknown.

E. Effects not related to β-blockade: (clinically not important)

Local anesthetic action or membrane stabilizing action is a prominent effect of several β-blockers, due to sodium channel blockade but at concentrations higher than those achieved during therapy.

That was all about Propranolol and Betablockers for this Lec.

واذا كانت النفوس كبارا ... تعبت في مرادها الأجسام
Good Luck!