

Learning Pharmacology by Metaphors: A Tale of Beta-blockers

Sir,

Metaphors, similes, homologies, and analogies are used in day-to-day communication to enhance mutual understanding. The use of such instructional tools is shown to enhance pedagogic learning. Some classical examples are; resemblance of pus of amoebic liver abscess with “Anchovy sauce” and appearance of fibrinous pericarditis like “bread and butter”! Recently, a few workers have developed educational tools incorporating such metaphors and analogies that have shown to enhance understanding of complex topics in pathology and clinical medicine.^[1,2]

The metaphoric language keeps the learner engaged in finding an association between known to unknown and therefore, helps him understand the otherwise difficult areas of a topic. A well-constructed metaphor or analogy by an experienced and imaginative teacher can simplify learning of difficult medical topic such as thrombosis and embolism, or pharmacological differences among psychedelics in a delightful manner.^[3,4] The learner finds familiar association with phrases used in common parlance, and edibles and culinary items which breaks monotony, improves creative thinking, and promotes conceptualization. Students themselves can be involved in constructing such analogies with which they are familiar. Being an active learning, it enhances their interpersonal, and communicational skills, and ability to associate appropriately between two ideas or concepts. It is possible to prepare a metaphoric presentation to promote integrated learning in pharmacology and microbiology.^[5] An instrument, called improved metaphor analysis, is developed to improve the method of using metaphors for research in education.^[6]

Beta-blockers are drugs that exhibit diverse functional cardiovascular characteristics, because of unique ancillary properties in them – cardioselectivity, membrane stabilizing action, alpha blockade, lipid/water solubility, partial agonist activity (intrinsic sympathomimetic activity [ISA]), and direct vasodilatory actions.^[7] Often, it becomes difficult for a teacher to explain these functional diversities to students in a short class. A metaphoric construct of pharmacodynamic profile and therapeutic uses of beta-blockers (BBs) is presented here with an objective to facilitate learning of complex ancillary properties and uses of BBs.

There lived a family called as LOLs in a metro city. The members were only males staying together. Most of them had strong physique. Five of them named as Mr Atenolol, Mr Propranolol, Mr Carvedilol, Mr Betaxolol, and Mr Metoprolol were particularly mighty and known for their characteristic effects in resting and exercising (hearts) human beings. Mr Propranolol was the eldest and was born in

1964, followed by Mr Atenolol (1976), Mr Betaxolol (1985), and Mr Carvedilol (1995). Mr Metoprolol, although born in 1969, could not make much dent on human ailments, so he renounced himself in 1975 to requiem as metoprolol tartrate and as metoprolol succinate in 1990 to achieve greater prowess (bioavailability). The succinate avatar of Metoprolol thus became the blue-eyed boy of cardiologists.

The LOLs frequently mixed with the neighbors (Families such as Messrs Diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin-II receptor blocker) to add-in their humanitarian works. All met together once in a while and discussed their virtues and other contemporary issues. In one such meeting held at a boxing ring and outside gymnasium, these five LOLs boasted of their strengths and machismo. Miss Adrenaline, a pugilist, known for her proverbial (Adrenaline Rush) role to enthuse typical behavior of “fight or flight” when engaged or enraged, was also present.

Mr Metoprolol, the youngest of them preened while pointing at Miss Adrenaline, “Look Bros, I can mow down her strength extensively.”

“Alas, we could do it, Dear,” said Mr Propranolol, “I am here since 1965 and have never been able to cut her (Adrenaline) down completely because she is endowed with dual power (has the double action of exciting alpha and beta receptors in human beings).” You know, “we cannot humble (block) alpha-receptors.”

“Oh yes,” said Mr Betaxolol with a bated breath “I am endowed with the least power to block even β_1 receptors and people use me as eye drops for reducing their eye pressure only.”

“No no, the picture is not as gloomy as you paint” bragged Mr Carvedilol, “I have the power to subdue her alpha actions as well.”

All took a sigh of relief.

Mr Propranolol said, “Look guys, we all share common characteristics, which you may call as generic roles (actions) of LOLs. Under our influence, the human heart feels less tired and is strengthened to work for a longer time and more effectively by utilizing available oxygen (depressive actions on heart seen as reduced contractility, atrioventricular nodal conduction, and slowing of heart rate. All these actions lead to reduced work done by heart). This way we all allay human sufferings due to ischemic heart diseases and high blood pressure (BP) (hypertension).

“Don’t you think bros it to be a paradox that we reduce BP?” asked Mr Atenolol. “We spare alpha receptors to narrow (constrict) blood vessel (tubes) which may lead to

increased peripheral vascular resistance (PVR). That should cause rise in BP instead,” he Moaned.

“But that is not the way we reduce BP,” explained Mr Propranolol. “We reduce stress on heart and reduce work-load (cardiac output, heart rate, and contractility). In addition, on prolonged usage, we actually decrease vascular reactivity (Miss Adrenaline just can’t fully excite the blood vessels) and this reduces PVR.”

“That is quite interesting to know,” said Mr Atenolol, “I also know that many of us can inhibit renin release (by β_1 inhibition on JG cells) and thus also do not allow adrenal gland to produce aldosterone (a hormone that causes salt and water retention) which actually contributes to our antihypertensive strength!”

“And of course, I, Mr Carvedilol and Mr Metoprolol, also have special permission to traverse brain barrier to calm down BP controlling sites (reduce stress and sedation) which contribute to BP lowering actions,” said Mr Propranolol.

“Do you mean that we are not so effective in reducing BP?” said Mr Atenolol (a water-soluble agent unable to cross blood-brain barrier) with face turned toward Mr Propranolol.

“No, no it’s not like this,” said Mr Propranolol, “Actually we all reduce BP to similar extent, irrespective of different characteristics we have. In fact, you are the one used most commonly for this purpose because of longer action and less brain side effects.

Mr Atenolol smiled.

“I was informed that our cousins, Mr Pindolol and Miss Celiprolol, have unique characteristic called as ISA or Partial agonistic activity,” disclosed Mr Atenolol.

“Can anyone elaborate on this please?” he enquired.

“It is an interesting phenomenon,” explained Mr Propranolol, “During evolution of our LOL family many of the closer cousins were born (developed) having such properties as cardioselectivity, ISA, membrane stabilizing action, lipid solubility, alpha blocking action, antioxidant property, and direct vasodilating action. Another property was partial agonist activity that is their ability to nag and occupy the unstimulated beta receptors (When Miss Adrenaline does not occupy them) and behave like adrenaline (that is some β_1 receptor stimulation occurs, i.e., *less resting bradycardia*). But when the receptors are occupied by her, then they enjoy (have power) to displace her completely by occupying the receptors themselves. Since these blockers do not have ability to activate receptors (no intrinsic activity) but can block actions of adrenaline (Tachycardia) so cause typical beta-blocking effect during activities which increase adrenaline release such as exercise. Therefore, there is *attenuation of exercise tachycardia*.”

“Very intriguing indeed, signor,” said Mr Atenolol.

Mr Propranolol continued, “These guys with ISA have few more advantages over us.”

“Which advantages?” enquired Mr Metoprolol.

“They are less likely to cause fatigue by less reduction in skeletal muscle blood flow, less disturbance of blood lipids, less rebound rise in BP upon abrupt stoppage and less airway disturbance in asthma prone individuals.” explained Mr Propranolol.

“Hmm,” there was a period of silence and then Mr Propranolol spoke.

“See, cardioselectivity is understandably a distinct advantage with Mr Atenolol,” he said. “I have personally encountered a number of asthma cases; older people had cold limbs and fatigue.”

Mr Propranolol continued, “This can best be explained by giving an example of a poor diabetic chap who was on insulin (propranolol blocks hepatic β_2 receptors which are involved in increasing glucose output in the event of hypoglycaemia [as a counter regulatory back up] and thus causes prolongation/delayed recovery from hypoglycemia if insulin overdose occurs. Propranolol also blocks adrenergic manifestations of hypoglycemia such as palpitation, tachycardia, and tremulousness. This causes “Hypoglycemia unawareness”. Therefore, nonselective agents are avoided in diabetics.^[7]) and took me (propranolol). His attendant, a day when he missed meals but continued medications including insulin, found him unconscious in his house!”

“Can you further elaborate this irony?” asked Mr Carvedilol.

“See, when blood glucose decreases below normal, then to provide continuous supply of glucose to brain, the liver makes glucose by breakdown of fats and proteins (Neoglucogenesis). This effect is β_2 receptors mediated. I block this effect” Mr Propranolol said apologetically.

Mr Carvedilol enquired, “That means poor man remains with low blood glucose for a longer time” (delayed recovery from hypoglycemia by counter regulatory hepatic mechanism).

“Not only this, our big brother makes patients unaware about the symptoms of ongoing low blood glucose (hypoglycemia) such as palpitation, tachycardia and trembling by blocking adrenergic manifestation of hypoglycemia” said Mr Metoprolol.

“That is very cruel,” said Mr Timolol.

“But that is true”, surrendered Mr Propranolol.

Mr Atenolol said “Thank God, I am fortunate to be more selective on β_1 receptors only and thus many diabetic hypertensives are fond of me.”

“Tell us about yourself,” asked Mr Betaxolol to Mr Carvedilol.

“As such I am like you all but I am blessed with property of mowing the alpha receptors simultaneously. This makes me unique to boost the poorly performing hearts.”

“That is wonderful!” exclaimed Mr Betaxolol.

“And what about Mr Nebivolol, who has recently joined our clan?” enquired Mr Metoprolol.

“This powerful macho (Nebivolol (8 times) and Bisoprolol (4 times) are highly selective at β_1 receptors as compared to Atenolol, which in turn is 5 times more selective than Propranolol.^[7]) is endowed with ability to widen the arterioles as well and that makes it unique,” said Mr Propranolol.

He further elaborated, “Do you know how he causes widening of blood vessels (Vasodilatation)?”

“No,” all said.

“By release into blood vessel a widening molecule called as Nitric Oxide,” he said.

“That’s a new information to me,” said Betaxolol.

“For us all”, said others.

“Tell us about our cousin Mrs Labetalol,” asked Mr Carvedilol.

“She is as bad as you are on alpha receptors. The beauty of this young lady lies in its friendliness with pregnant hypertensives (common oral and parenteral agent for pregnancy associated hypertension and preeclampsia respectively),” said Mr Propranolol.

“Hmm,” muttered Mr Metoprolol.

Silence prevailed there for a short while, which was broken by Mr Propranolol.

He said, “Irrespective of the differing qualities among us, we have done a great service to mankind ever since our existence.”

He continued, “We all have reduced umpteen numbers of cardiovascular events in hypertensives such as strokes, heart attacks, nose bleeds, and have increased survival in heart failure with improvement in quality of life. In addition, we are still in use in chronic stable and unstable angina pectoris to reduce painful attacks, increase exercise tolerance and prevent occurrence of further attacks. I often read in literature that mankind is indebted to us.”

“Are we useful in cardiovascular diseases only?” asked Mr Metoprolol.

“Not at all,” said Mr Atenolol, “our big brother Propranolol (Metoprolol and Timolol also) is preferred to prevent migraine headaches, treat anxiety-related nervousness and tremor and alcohol withdrawal syndrome. He also has a unique distinction of reducing formation of T_3 from T_4 in human tissues. He effectively fights against Miss Adrenaline’s actions in thyrotoxicosis (Adrenergic manifestations such as tremor tachycardia, palpitation). Obviously, he is the clear choice among us for thyrotoxicosis. He, and our closer cousin Nadolol, also reduce pressure in portal circulation and reduce variceal bleeding.

Mr Metoprolol said “It is rightly said, Old is Gold!”

“But don’t forget us, bros, I and Mr Timolol are extremely useful medications in Glaucoma,” said Mr Betaxolol.

“True,” others said in affirmation.

“But, how is eye pressure reduced? Is it like BP reducing action?” asked Mr Metoprolol.

Mr Betaxolol explained, “About six of our closer cousins (Both, nonselective [Timolol, Levobunolol, Carteolol, and Metipranolol] and selective beta-blockers [Betaxolol and Levobetaxolol], reduce intraocular pressure when applied topically. Betaxolol and Levobetaxolol are highly selective for β_1 -receptors, and Levobunolol has a 140-fold selectivity for β_2 -receptors.

Aqueous humor production is mediated by the nonpigmented ciliary epithelial cells of the ciliary process and β_2 -receptors predominate in ciliary body and trabecular meshwork, although β_1 receptors are also present. Intraocular pressure is reduced by reduction in aqueous humor formation when beta-receptors are blocked. Beta-blockers act as neuroprotectives by reducing sodium influx into retinal ganglionic cells, and can also protect vulnerable neurones by reducing influx of calcium. Betaxolol and Levobetaxolol have greater neuroprotective action on ganglionic cells [prevent cell death] because of their great capacity to block sodium and calcium influx [blocking L-type of calcium channels])^[7] are useful in reducing eye pressure by decreasing formation of vital fluid from ciliary epithelium. In addition, we can prevent damage to retinal cells by reducing inward movement of Na^+/Ca^{++} in these cells. Thus, we protect eyes and prevent blindness.”

“Do you know I can transform myself in two shapes, L-form and D-form?” confided Mr Betaxolol.

“No, you never told us”, said Mr Timolol.

“OK, in my L-Avatar (called as Levobetaxolol), I am more effective in protection of neurones with less ill effects on airways. That is why ophthalmologists love me!” He confided.

“That’s a good human service, I suppose,” said Mr Timolol.

“Yes,” all nodded.

“We have heard enough sweet music in our ears, dear brothers; let us now depart with a vow that we shall continue to offer our services for the betterment of mankind. It fulfils our *raison d’etre*.”

They all wished goodbye to Miss Adrenaline and walked away.

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