

**Learning Pharmacology by metaphors: a tale of NSAIDs****Gurudas Khilnani<sup>1</sup>, Ajeet Kumar Khilnani<sup>2\*</sup>, Rekha Thaddanee<sup>3</sup>****Sir,****Prologue**

Metaphors are increasingly used for learning in medical education.<sup>1,2</sup> Learning can be facilitated by giving homologous/analogous examples and story-telling.<sup>3-5</sup> The undergraduate students are involved, and learning becomes enjoyable and stress-free. Here is a conversation between two NSAIDs while travelling in anthropomorphic forms (human beings) and discussing the detailed pharmacology and therapeutics of NSAIDs.

**Background**

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most frequently used drugs because of their analgesic, antipyretic and anti-inflammatory actions. The analgesic action is peripheral at the site of injury or inflammation. The mechanism of action is inhibition of formation of inflammatory prostaglandins (PG) of PGD, PGE and PGF series. In general, NSAIDs inhibit key enzyme of PG synthesis, the Cyclo-oxygenase (COX), which has two isoforms: COX-1 (Constitutive and protective) and COX-2 (Inducible by cytokines during inflammation). A splice of COX-1 is called as COX-3 (neuronal, pyretic) and is inhibited by paracetamol. The anti-inflammatory action is due to COX-2 inhibition, but COX-1 may also be involved. In addition to COX-inhibition, drugs like nimesulide have other effects; such as inhibition of superoxides and interleukins formation, and stabilization of lysosomal membrane of leukocytes. Aspirin is irreversible inhibitor and other NSAIDs are reversible inhibitors of COX enzymes. In low doses, aspirin (Lodoasp) inhibits selectively COX-1 of platelets. This results in inhibition of formation of pro-aggregatory and vasoconstrictor, thromboxane-A<sub>2</sub> (TxA<sub>2</sub>). There is continued production of vascular PGI<sub>2</sub> (anti-aggregatory and vasodilatory). This useful anti-aggregatory effect makes lodoasp a useful antithrombotic in cardiovascular disorders. Other NSAIDs also have mild to moderate antiplatelet action that is not useful clinically. Inhibition of prostaglandin synthesis results in adverse effects in the form of gastric erosions (gastric epithelial COX-1 inhibited), renal impairment (reduction in GFR due to COX-1 inhibition and inhibition of tubular sodium and chloride reabsorption due to COX-2 inhibition) and precipitation of asthma in susceptible children {COX-1 inhibition diverts arachidonate to lipoxygenase pathway with more formation of bronchoconstrictor leukotrienes

(LTC<sub>4</sub> and LTD<sub>4</sub>)}. Obviously, COX-2 inhibitors do not worsen asthma.

Mr Paracetamol (PC), a centenarian, boarded the train, kept the luggage safe and sat on the berth. He was amazed to find a graceful sexagenarian sitting across the berth. At the very first instance he sensed that there was something in common between them. As the train started crawling and all began to settle, he picked up a book on "Poppy war". As train gained speed all became busy in their chores, reading book, conversing with fellow passengers or glued to mobile screen. All of a sudden, train screeched to an abrupt halt, leaving little time for anyone to manage the jerk and thus she unwittingly fell down in front of Mr Paracetamol.

PC extended a helping hand.

"Oh, I am extremely sorry", She apologized and straightened herself to sit back to her seat.

"It's alright dear...er..."

"I am Ibuprofen, a member of NSAIDs that are used by humankind for pain relief."

"I am Paracetamol, people call me Acetaminophen also."

"Hi, you are famous as fever-pill, you may call me Ibu", She said.

"Oh! That's why I felt that there is something common between us", he exclaimed.

"We, the NSAIDs have done great human service for alleviating their pains and inflammation for over a century. Millions of people, young and old, have used us to get rid of body pains, menstrual spasms and joint ailments like gout and arthritis, apart from reducing fever due to a variety of causes." Mr PC elaborated.

"I agree with you sir and that is the real purpose of our existence." She said.

PC: "I am the lone survivor of para-aminophenols clan. My brother phenacetin died at the ripe age of 96 years (Born 1887 and banned 1980). He had no other offspring.

"Do you know how old I am?" he asked her.

“May be around 80 years, I suppose,” she said cautiously.

“I am afraid you are wrong, I was born in 1877 (discovered) and used for pain relief in 1893!”

She looked with eyes wide open, “you have defied your age, Mr PC”.

“If it pleases you, I may tell you more about me. I belong to a chemical class of anilines. Acetanilide (Antifebrin) was serendipitously found to possess fever and pain relieving properties in 1886, but it caused cyanosis due to methemoglobinemia. I was born well before antifebrin in 1877, but it was not until 1887 that I was used for pain relief. This was because my younger brother phenacetin conspired against me spreading rumours that I caused methaemoglobinemia. Thus, I was quickly discarded in favour of phenacetin. It remained popular over-the-counter "headache mixture" along with Aspirin and caffeine as APC Tablet and powder. However, truth always triumphs. Sooner, it was shown that phenacetin was converted into paracetamol (I was a real man behind phenacetin's effects) and I did not cause methaemoglobinemia as much. These analgesic mixtures caused analgesic nephropathy, haemolysis and bladder cancer. So, I became preferred fever reliever in 1950. Since then, I am the undisputed hero to relieve pain and fever. I am children friendly as well.”

“That's an interesting story!” she said.

“Do you know I am called acetaminophen in USA and Japan, whereas my International Non-proprietary Name (INN) is paracetamol?”

“And look at my virtues, Ibu”, the old man boasted further, “I am perhaps one of the few medicines available in all dosage forms such as tablet, dispersible tablet, syrup, injection, suppository and capsule. I can be used in all age groups and in wide dose ranges.”

He continued, “Perhaps you forgot, we have worked together for quite some times (Ibu-para is perhaps the commonest FDC used for pain relief in India). I am also pre-compounded in cough and cold medicines along with antihistaminics, for relief of severe pain of cancer and migraine along with codeine, nimesulide and tramadol and for skeletal muscle spasms along with muscle relaxants such as methocarbamol, chlorzoxazone, tizanidine.”

It appeared she was tired of his boastful narrations.

She retorted, “There are at least 10 other drugs with whom I am combined by the manufacturers of medicines. For me it becomes difficult to mind all these formulations.”

A brief silence prevailed and then Mr PC reiterated, “I would like to know more about you.”

Ms Ibuprofen said, “I was born in 1961 and put to use in 1969 in UK and 1974 in USA. I am considered as one of

the most important and commonly used pain relieving medicine which is safe to use!”

She further elaborated, “I am in WHO essential medicine list (and of course you too are) and people are happy with me because I do not harm their stomach, heart and blood, as much as other NSAIDs do. Those elderly who take many drugs are happy with my use because I am least likely to interfere with the effects of concurrent medications.”

“Dear Ibu, I provide perhaps the safest analgesia for common aches and pains without inflicting injury human body”, he said proudly.

“But you damage the livers of young children”, she surprised him.

“Not frequently, and only when children receive very large doses accidentally. Their tender livers do not have sufficient capacity to detoxify large doses because of limited supply of protective glutathione (needed for my inactivation - glucuronidation) and this allows a hepato-toxic intermediate, N-acetyl-para-benzquinone imine (NAPQI), to accumulate”, he said thoughtfully.<sup>6</sup>

“Then, what is the antidote for liver toxicity?” She asked.

“So far as I know, such children require close monitoring, gastric lavage, fluid and electrolyte balance and most importantly, use of N-acetyl cysteine intravenously to replenish depleted glutathione reserves in liver, provided the child should be brought for treatment as soon as possible for better recovery. Late treatment may not prevent liver cell damage due to liver cell necrosis.”

“Therefore, you are not as innocuous as you feel”, she said.

“Yes, see no drug is safe! The safety lies in the proper use of drugs by treating physician” he said.

“What about your family and closer cousins?” he asked.

“We belong to propionate family, and apart from me; three others in use are ketoprofen, flubiprofen and naproxen. Ketoprofen works like me but has additional inhibitory action on another PG enzyme, the lipoxigenase. Naproxen is a robust anti-inflammatory drug which inhibits white cell migration to the site of injury and inflammation and is useful in rheumatoid arthritis. It is somewhat safer with lower risk of thrombosis. Flubiprofen eye drops are used in eye allergy. One of our close cousins, the enfenamic acid (Tromaril) was borne in India (developed by CSIR and RRL Hyderabad) but lived a short life only, whereas mefenamic acid, another closer cousin, is still used alone and along with dicyclomine in relief of painful menstruation (spasmodic dysmenorrhea).”

PC: “Do you know who our great grand-mother is?”

Ibu: "I am afraid...."

PC: "She is aspirin, borne in 1899 as acetylsalicylic acid, named Aspirin by Bayer. Do you know how was this name coined?"

Ibu: "That would be interesting to know."

PC: "The letter 'A' stands for acetyl, 'spir' is derived from the plant known as Spiraea ulmaria (meadowsweet), which yields salicin, and 'in' was a common suffix used for pain relieving drugs (analgin, antifebrin). She is still alive at a ripe age of 120 years. She has served humanity by alleviating joint pains and arthritis in millions of users. The use of aspirin declined in late twentieth century because large number of newer molecules began to appear in market and were considered safer than her on stomach and kidney. She was reincarnated as life-saver, mini or little aspirin (lodoasp), after the discovery of its anti-prostaglandin property by Noble Laureate John Vane in 1971. In her new avatar, she has prevented millions of heart attacks, strokes and kept blood thin and flowing freely in arteries of many organs."<sup>7</sup>

Ibu: "Perhaps, you are referring to lodoasp as anti-platelet agent", she asked?

PC: "Yes, and do you know how does it prevent coagulation?"

Ibu: "Not exactly, please explain", she requested.

PC: "Platelets initiate thrombosis in the event of vascular injury. In low doses (75-150mg), aspirin prevents formation of potent platelet aggregator chemical, thromboxane-A<sub>2</sub>, by irreversibly acetylating (inactivating) cyclooxygenase enzyme in platelets circulating particularly in portal and arterial blood. The antiplatelet action remains for the life span of the platelets (7-10 days). In addition, it affects platelet - neutrophil interaction in blood."

He continued, "I may share a secret with you. Aspirin is so possessive that it does not allow other NSAIDs to share the seat of action (COX-1 enzyme binding) on platelets. Even if you try (Ibuprofen co-administered with aspirin), she gets annoyed and halts its anti-platelet activity. The patient is at the risk of thrombosis again. Therefore, my advice to you would be to be away from her for the sake of patient."

Ibu: "Surely, I shall do that."

PC: "Conversely, she is a good friend of another blood thinner-clopidogrel (used together)."

Ibu: "Oh! I suppose clopidogrel does not share the same site of action!"

He smiled in affirmation, "clopidogrel inhibits ADP induced platelet activation and increases platelet survival in blood vessels."

She continued, "Sometimes back, I heard about NSAIDs which were active having anti-inflammatory analgesic actions but not the anti-platelet action?"

PC: "These drugs are called as selective anti-inflammatory agents or COX-2 inhibitors agents because these agents inhibit COX-2 (major inflammatory PG). Two types of such agents are known. Type-1 are those which are relatively more selective inhibitors of COX-2 but also inhibit COX-1 (aceclofenac, diclofenac, meloxicam, etodolac and nimesulide), and type-2 are those which are highly selective inhibitors of COX-2 (Celecoxib, rofecoxib, etoricoxib, lumiracoxib, parecoxib and valdecoxib). These drugs have useful anti-arthritic and analgesic effects and are stomach friendly as well, i.e., less likely to cause gastric erosions and worsening of peptic ulcers. Of course, these agents are devoid of anti-platelet activity.

Ibu: "If it is so then why these agents are not used commonly?"

PC: "That is because COX-2 inhibitors reduce protective vascular PGI<sub>2</sub> formation (vide supra) and meta-analysis of several carefully controlled trials has shown that COX-2 inhibitors have pro-thrombotic actions. Rofecoxib and valdecoxib were withdrawn because there was several fold increase in risk of myocardial infarction compared to naproxen. Lumiracoxib causes liver damage. Others also carry a labelled warning against their use. Only etoricoxib is currently used in India, though celecoxib and parecoxib are also available."

Ibu: "I learnt that there are many potent anti-inflammatory agents in use since decades. Have they lost their relevance today?"

PC: "I shall briefly describe one by one.<sup>8</sup> Indomethacin has been a time-tested agent since 1963 and is still used in special clinical situations such as acute gout, ankylosing spondylitis, psoriatic arthritis, fever in malignancy, closure of PDA and Bartter's syndrome. It is a potent anti-inflammatory agent which causes gastro-toxicity. Amazingly, frontal headache is an adverse effect of it! Users are warned against working on machines as it causes dizziness and in-coordination.

Nabumetone: It is the only non-acidic NSAID which is a pro-drug and is activated in liver to inhibit COX-1 and COX-2 enzymes. It is useful in pain. It has hepato-toxic potential but causes less gastro-toxicity. Being long acting it is used once a day.

Piroxicam: It is another potent anti-inflammatory analgesic which is used as once a day for rheumatoid arthritis, gout and osteoarthritis. It prolongs bleeding time.

Pedal edema and renal damage may occur with its longer use. It is also available as intramuscular injection and local gel.

Nimesulide: It is a unique drug. It was first marketed in Italy in 1985 and since then it has seen rise and fall. This agent has a number of anti-inflammatory actions such as inhibition of superoxide generation from neutrophils, inhibition of platelet activating factor and TNF $\alpha$ . Despite its efficacy as good analgesic anti-inflammatory agent for short term use, its worrisome association with fulminant liver damage in children has deterred its frequent use in many countries. Unlike some NSAIDs, it does not precipitate asthma in children.

Diclofenac and aceclofenac (more COX-2 selective than diclofenac) have been in clinical use for over a decade. They work like naproxen. Gastric toxicity occurs less often with them but hepatic damage is also reported with diclofenac. Diclofenac is available as tablet, injection, local gel and eye drops. Some formulations have me as co-partner for pain relief!

Ketorolac: It is a potent analgesic (equal to that of morphine) but has anti-inflammatory activity also. It is used orally and parenterally for postoperative pain, renal colic, migraine, and dentistry. Ketorolac eye drops are used in ocular inflammatory conditions.

Nefopam: It is analgesic but does not inhibit COX enzymes. You may place it between opioids and NSAIDs. It is used to relieve pain due to musculoskeletal injuries and postoperatively. It worsens epilepsy and causes lot of nausea and dryness of mouth.”

Ibu: “I must thank you for providing me so much information about our cousins. It appears we all share some good and bad effects.”

PC: “Pain relief is our family business and motto. Unfortunately, some adverse effects occur on stomach, kidney liver and skin, which the man has to bear. Because, the genesis of pain is multi-factorial, research in selective molecules have not been as successful as expected. If you read about yet another super-family of pain relievers, the opiates, you would find that it has been possible for mankind to develop selective opiates due to limited number of sites of actions, particularly  $\mu$  and  $\kappa$  receptors, in cerebrospinal axis. Unlike this, the NSAIDs act peripherally mostly at the site of injury and inflammation due to multitude causes.”

Meanwhile, the train slowed down to a halt at her destination station.

Ibu: “It was so nice of you for a useful informative talk. I have to disembark here. Hope to see you again, take care and Goodbye.”

And Mr PC continued his journey onward.

Gurudas Khilnani, Ajeet Kumar Khilnani\*,  
Rekha Thaddanee

<sup>1</sup>Department of Pharmacology, <sup>2</sup>Department of Otorhinolaryngology, <sup>3</sup>Department of Pediatrics, Gujarat Adani Institute of Medical Sciences, Kutch, Gujarat, India

\*Correspondence to  
Dr. Ajeet Kumar Khilnani,  
Email: ajeetkhilnani@gmail.com

## REFERENCES

1. Kanthan R, Mills S. Using metaphors, analogies and similes as aids in teaching pathology to medical students. *J Int Assoc Med Sci Educ*. 2012;16:1-27.
2. Khilnani G, Khilnani AK, Thaddanee R. Learning pharmacology by metaphors: A tale of beta-blockers. *J Pharmacol Pharmacother*. 2017;8:172-5.
3. Khilnani G, Thaddanee R, Khilnani AK, Pathak RR. Psychopharmacological dinner: A metaphoric learning of psychedelics from gustatory revelations of a pillbox. *Indian J Psychiatry*. 2016;58:99-102.
4. Khilnani G, Khilnani AK, Thaddanee R. Learning pharmacology by metaphors: A tale of aminoglycosides. *Indian J Pharmacol*. 2016;48:S94-S97.
5. Khilnani G. Medical dinner. *J Assoc Physicians India*. 1990;38:375-6.
6. Guggenheimer J, Moore PA. The therapeutic applications of and risks associated with acetaminophen use: a review and update. *J Am Dent Assoc*. 2011;142(1):38-44.
7. Desborough MJR, Keeling DM. The aspirin story—from willow to wonder drug. *Br J Haematol*. 2017;177:674-83.
8. Grosser T, Smyth EM, FitzGerald GA. Pharmacotherapy of Inflammation, Fever, Pain and Gout. In: Bruton LL, Hilal-Dandan P, Knollman BC, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 13th ed. New York, NY: McGraw-Hill; 2018:685-709.

**Cite this article as:** Khilnani G, Khilnani AK, Thaddanee R. Learning Pharmacology by metaphors: a tale of NSAIDs. *Int J Basic Clin Pharmacol* 2019;8:610-3.