www.ijramr.com

ISSN : 2350-0743

International Journal of Recent Advances in Multidisciplinary Research

Vol. 06, Issue 11, pp. 5305-5307, November, 2019

RESEARCH ARTICLE

PARACETAMOL: THE SCIENCE OF A DRUG THAT IS COMMON BUT ESSENTIAL OVER THE YEARS

*** Dr. Omotayo, R.S.**

Consultant Obstetrician and Gynaecologist, University of Medical Sciences Teaching Hospital, Akure, Nigeria

ARTICLE INFO

Article History:
Received 28th August, 2019
Received in revised form
14th September, 2019
Accepted 04th October, 2019
Published online 21st November, 2019

Keywords
Paracetamol Discovery,
Acetaminophen,
Analgesic,
Antipyretic.

ABSTRACT

The name 'Paracetamol' is derived from a compound name PARA-ACETylAMinophenOL by taking the underlined alphabets together. It is also refered to as acetaminophen. In some contexts, it is simply abbreviated as APAP, for Acetyl-Para AminoPhenol. Also variously referred to by trade names like Tylenol, Panadol and others. It is used orally, rectally, intramuscularly and intravenously. It is metabolized predominantly in the liver and 85-90% is excreted in the urine. Paracetamol is the active metabolite of phenacetin, once popular as an analgesic and antipyretic in its own right. It was in 1950 that the first paracetamol product- a combination of Paracetamol, Aspirin and Caffeine was on the USA market under the name Triagesic but was later phased out because of its untoward haematological effects. When it was discovered that Paracetamol does not have blood damaging effects, in 1955 Paracetamol was back in USA market. For over a century, Paracetamol has been widely used as an effective antipyretic and analgesic medication with well-established tolerability. Certainly, the discovery of Paracetamol was a monumental one. Today, it is unarguably the commonest used drug across the world. It comes handy in the treatment of various conditions that have fever and or pain as part of their manifestation and even labour pains.

INTRODUCTION

Paracetamol refers to a compound with systematic (International Union of Pure and Applied Chemistry-IUPAC) name N-(4-hydroxyphenyl) acetamide and as a drug, has trade names such as Tylenol (USA), Panadol (Australia) and many others. It is used orally, rectally, intramuscularly and intravenously. Its bioavailabilty (Macintyre, 2010) is 63-89% and small protein binding capacity of 20-25% (Milligan, 1994) with half live of 1-4hrs. It is metabolized predominantly in the liver and 85-90% is excreted in the urine (Codapane Forte Paracetamol, 2014). Its molecular mass is 151.163g/mol and with density and melting point of 1.263g/cm^3 and 169^{o}c (336^{o}F) (Karthikeyan, 2005). It has solubility of 12.78mg/ml in water at temperature of 20^{o}c. Paracetamol is the International Non Proprietary name (INN), Australian Approved Name (AAN) and British Approved Name (BAN), while Acetaminophen is the United States Adopted Name (USAN) and Japanese Adopted Name (JAN) (International Non Proprietary Names, 2014). Paracetamol is the active metabolite of phenacetin, once popular as an analgesic and antipyretic in its own right. In ancient and medieval times, known antipyretic agents were compounds in white willow barks known as salicins, which led to the development of aspirin), and compounds contained in cinchona bark. Cinchona bark was also used to create the anti-malarial drug quinine. Quinine itself also has antipyretic effect.

Corresponding author: **Dr. Omotayo, R.S.,**
Consultant Obstetrician and Gynaecologist, University of Medical Sciences Teaching Hospital, Akure, Nigeria.

Efforts to refine salicin and salicylic acid took place throughout the middle and late 19th century and was accomplished by Bayer chemist Felix Hoffmann (this was also done by French chemist Charles Frederic Gerhardt 40 years earlier, but was abandoned after deciding it was too impractical). The cinchona bark became scarce in the 1880s and people began to look for alternatives, Acetanilide in 1886 and phenacetin in 1887. By this time, Paracetamol had been synthesized by Harmon Northrop Morse via the reduction of p-nitrophenol with tin in glacial acetic acid in 1873. Paracetamol was not used medically for another two decades. It was in 1893 that a white odorless crystalline compound with a bitter taste was discovered to be Paracetamol and was introduced as an antipyretic by Von Mering same year. At the university of Strasburg, Professor Adolf Kussmaul of the Department of Internal Medicine asked Arnold Cahn and Paul Hepp who are his assistants to treat patients with naphthalene hitherto used elsewhere as internal antiseptic. It was however discovered that Paracetamol was found in urine of these patients who had great reduction in fever temperature. It was not until 1948-1949 that Paracetamol experienced a resurgence of interest when Brodie and Axelrod discovered that Paracetamol was main metabolite of both acetanilide and phenacetin. It was in 1950 that the first paracetamol product- a combination of Paracetamol, Aspirin and Caffeine was on the USA market under the name Triagesic but was later phased out because of its untoward haematological effects. When it was discovered that Paracetamol does not have blood damaging effects, in 1955 Paracetamol was back in USA market. However, unlike phenacetin and its combinations, paracetamol is not carcinogenic at therapeutic doses (Bergman, 1996). Paracetamol is used for the relief of pains associated with many parts of the body. Paracetamol also known as

acetaminophen (Bradley, 1996) has analgesic properties comparable to those of aspirin, while its anti-inflammatory effects are weak. Its better tolerated than aspirin in patients in whom excessive gastric acid secretion or prolongation of bleeding time may be a concern. Available without prescription, it has in recent years become a common household drug (Medication and drugs, 2010). Regarding comparative efficacy, studies show conflicting results when compared to NSAIDS. A randomized controlled trial of chronic pain from osteoarthritis in adults found similar benefits from Paracetamol and Ibuprofen (Bradley et al., 1991). In recommended doses and for a limited course of treatment, the side effects of Paracetamol are mild to non existence (Hughes, 2008).

Paracetamol is part of the class of drugs known as 'aniline analgesics', it is the only such drug still in use today (Bertolini, 2006). To date, the mechanism of action of paracetamol is not completely understood. The main mechanism proposed is the inhibition of cyclooxygenase (COX) and recent findings suggest that it is highly selective for COX-2 (Hinz, 2008). In view of the selectivity of Paracetamol for COX-2 it does not significantly inhibit the production of the pro-clotting thromboxanes. The COX family of enzymes are responsible for the metabolism of arachidonic acid to prostaglandin H_2, an unstable molecule that is in turn, converted to numerous other pro-inflammatory compounds. Classically anti-inflammatories such as the NSAIDs block this step. Only when appropriately oxidized is the COX enzyme highly active (Ohki, 1979; Adv. Exp. Med.Biol).

Paracetamol reduces the oxidized form of the COX enzyme, preventing it from forming pro-inflammatory chemicals (Aronoff, 2006; Roberts, 2001). This leads to a reduced amount of prostaglandin E_2 in the Central Nervous System (CNS), thus lowering the hypothalamic set-point in the thermoregulatory centre. Researchers in London, United Kingdom (UK) and Lund, Sweden (Andersson et al., 2011) suggested possible analgesic mechanism of Paracetamol, being that the metabolites of paracetamol e.g NAPQI (N-acetyl-p-benzoquinone imine), act on TRPA1 (Transient receptor potential cation channel subfamily A member 1) receptors (sensor of irritants, pain, cold and stretch) in the spinal cord to suppress the signal transduction from the superficial layers of the dorsal horn, to alleviate pain. The team of researchers used a 'hot-plate' test to observe the effects of Paracetamol in mice. This involved measuring the number of seconds it takes for a mouse to withdraw its paw from a slightly hot surface. They found that paracetamol increased the time it took for mice to withdraw their paw, showing that the drug reduced the heat-induced pain.

Paracetamol also modulates the endogenous cannabinoid system (Hogestatt, 2005). It is metabolized to AM404 (N-arachidonoylaminophenol) an active metabolite of Paracetamol responsible for its analgesic action (Ottani, 2006), a compound with several actions, what is most important is that it inhibits the uptake of the endogenous cannabinoid/vanilloid anandamide by neurons. Anandamide reuptake would result in lower synaptic levels and less activation of the main pain receptor (nociceptor) of the body, the TRPV1 (older name: vanilloid receptor 1). By inhibiting anandamide reuptake, levels in the synapse remain high and are able to desensitize the TRPV1 (Transient Receptor Potential Cation subfamily V member 1) receptor much like capsaicin. Furthermore, AM404 inhibits sodium channels, as do the anaesthetics lidocaine and procaine (Kofalvi, 2008). Either of these actions by themselves has been shown to reduce pain, and are a possible mechanism for paracetamol. However, it has been demonstrated that, after blocking cannabinoid receptors with synthetic antagonists, Paracetamol's analgesic effects are prevented, suggesting its pain relieving action involves the endogenous cannabinoid system. Spinal TRPA1 receptors have also been demonstrated to mediate antinociceptive effects of Paracetamol and 9-tetrahydrocannabinol in mice (David, 2011). For over a century, Paracetamol has been widely used as an effective antipyretic and analgesic medication (Malaise, 2007) with well-established tolerability (Graham, 2005). Paracetamol comes handy in the treatment of various conditions that have fever and or pain as part of their manifestation and even management of labour pains (Omotayo, 2018). As compared with other analgesics, opioids, and nonsteroidal anti-inflammatory drugs, it has a favorable safety profile (Hyllested, 2002). Recently, it has been reported not to be associated with an increased risk of congenital anomalies (Rebordosa, 2008).

While it has virtually non existing side effects when used as prescribed and at therapeutic range. Rarely, its side effects could include rash, hypotension when given in the hospital by infusion, liver and kidney damage when taken at higher-than-recommended doses. It is advised that doses should not exceed 4g in 24 hours. In extreme cases the liver damage that can result from a Paracetamol overdose can be fatal. In case of overdose, N-Acetylcysteine has long been recognized as an effective antidote, via oral or intravenous administration protects against acute liver injury. (Acharya and Lau-Cam, 2010)

Conclusion

Certainly, the discovery of Paracetamol was a monumental one. Today, it is unarguably one of the most used medications across the world. It comes handy in the treatment of various conditions that have fever and or pain as part of their manifestation. Therefore, the importance of Paracetamol in health care cannot be overemphasized.

REFERENCES

Acharya M, Lau-Cam C. 2010. Comparison of the protective actions of N-acetylcysteine, hypotaurine and taurine against acetaminophen-induced hepatotoxicity in the rat. J Biomed Sci 17(Suppl. 1):S35[PMC freee article][PubMed]

Adv. Exp. *Med.Biol. Advances in Experimental Medicine and Biology*197:739-47

Andersson DA., Gentry C., Alenmyr L., Killander D., Lewis SE., Andersson A. et al., 2011. TRAP1 mediates spinal antinociception induced by acetaminophen and the cannabinoid (9) tetrahydrocannabiorcol. *Nat Commun*., 2: 551

Aronoff DM., Oates JA., Boutaud O. 2006. New insights into the mechanism of action of acetaminophen: its clinical pharmacological characteristics reflects its inhibition of the two prostaglandin H2 synthases. Clin. Pharmcol. Ther., 79(1) 9-19.

Bergman K., Muller L., Teigen SW. 1996. The genotoxicity and carcinogenicity of paracetamol: a regulatory review. *Mutat Res.,* 349(2):263-88

Bertolini A., Ferrari A., Ottani A., Guerzoni S., Tacchi R., Leone S. 2006. Paracetamol: new vistas of an old drug. *CNS drug reviews.,* 12(3-4):250-75.

Bradley JD., Brandt KD., Katz BP., Kalasinski L.A., Ryan SI. 1991. Comparison of an anti-inflammatory dose of ibuprofen, an analgesic dose of ibuprofen, and acetaminophen in the treatment of patients with osteoarthritis of the knee" *N. Engl j Med.,* 325(2): 87-91.19.

Bradley N. 1996. BMJ should use "paracetamol" instead of "acetaminophen" in its index. BMJ 313 (7058):689.

Codapane Forte Paracetamol and codeine phosphate PRODUCT INFORMATION" (PDF). TGA eBusiness Services. Alpharpharm Pty Limited. 29 April 2013. Retrieved 10 May 2014.

David A., Clive G., Lisa A., Dan K., Lewis SE., Anders A. et al., 2011. TRPA1 mediates spinal antinociception induced by acetaminophen and the cannabinoid delta 9-tetrahydrocarnnabiorcol, Nature Communications 2.

Graham GG., Scott KF., Day RO. 2005. Tolerability of paracetamol. *Drug Saf*., 28(3): 227–40.

Hinz B., Cheramina O., Brune K. 2008. Acetaminophen (Paracetamol) is a selective cyclooxygenase-2 inhibitor in man. The FASEB journal: official publication of the *Federation of American Societies for Experimental Biology*, 22(2):383-390.

Hogestatt ED., Jonsson BA., Ermund A. 2005. Conversion of acetaminophen to the bioactive N-acylphenolamine AM404 via fatty acid conjugation in the nervous system. *J. Biol. Chem.,* 280 (36):31405-12

Hughes J. 2008. Pain Management: From Basics to Clinical Practice. *Elsvier Health Sciences*. ISBN 9780443103360.

Hyllested M., Jones S., Pedersen JL., Kehlet H. 2002. Comparative effect of paracetamol, NSAIDs or their combination in postoperative pain management: a qualitative review. *Br J Anaesth* 2002;88(2):199–214.

International Non Proprietary Names (INN) for Pharmaceutical Substances: List 1-96 of proposed IIN, cumulative list No12. *World Health Organisation*. 2007. P.v Retrieved 20 January 2014.

Karthikeyan M, Glen RC, Bender A. 2005. General Melting Point Prediction Based on a Diverse Compound Data Set and Artificial Neural Networks" Journal of Chemical Information and Modeling 45 (3): 581-590.

Kofalvi A. 2008. Alternative interacting sites and novel receptors for cannabinoid ligands. Cannabinoid and the brain. *Springer-Verlage.,* Pp. 131-160.

Macintyre PE, Schug SA, Scott DA, Visser EJ, Walker SM: working group of the AUSTRALIAN AND Faculty of Pain Medicine 2010. Acute Pain Management Scientific Evidence (PDF) 3rd ed. Melburn Australia National Research Council.

Malaise O., Bruyere O., Jean-Yves R. 2007. Intravenous paracetamol: a review of efficacy and safety in therapeutic use. *Future Neurol*., 2(6):673–88.

Medication and drugs" MedicineNet 1996-2010. Retrieved April 22, 2010.

Milligan TP, Morris HC, Hammond PM, Price CP. 1994. Studies on Paracetamol binding to protein. Ann. Clin Biochem. 31;492-496.

Ohki S., Ogino N., Yamamoto S., Hayaishi O. 1979. Prostaglandin hydroperoxidase, an integral part of prostaglandin endoperoxide synthetase from bovine vesicular gland microsomes. *J.Biol.Chem*., 254 (3):829-36.

Omotayo RS, Faturoti SO, Ehinmitan RR, Alao FO. Comparison of intramuscular paracetamol and intramuscular pethidine as analgesic in the first stage of labour. Tropical journal of obstetrics and gynaecology. 2018;35:3;348-357.

Ottani A., Leone S., Sandrini M., Ferrari A., Bertolini A. 2006. The analgesic activity of paracetamol is prevented by the blockade of cannabinoid CB1 receptors. *Eur. J. Pharmacol.*, 531 (1-3): 280-1.

Rebordosa C, Kogevinas M, Horváth-Puhó E, Nørgård B, Morales M, Czeizel AE. Acetaminophen use during pregnancy: effects on risk for congenital abnormalities. Am J Obstet Gynecol 2008;198(2):178.e1–7.

Roberts LJ. II, & Marrow JD. 2001. Analgesic-antipyretic and anti-inflammatory Agents and drugs employed in the Treatment of Gout, In: Goodman & Gilman's The Pharmacological Basis of Therapeutics 10th Edition, by Hardman JG & Limbird LE Published by McGraw Hill, pp. 687-731

****