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A Review: Why Aminopyrine Banned?

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Abstract **Review Article**

Aminopyrine is used as an antipyretic and analgesic drug. It belongs to the pyrazolone derivatives having a most toxic and most dangerous analgesic effect and it is a non-narcotic drug. It had been widely used in the clinical treatment of rheumatism because of its good efficacy. It was inexpensive drug and due to this reason, it was widely used in many countries. It causes agranulocytosis, aplastic anemia and blood dyscrasias in many patients. In this review, we are providing an overview of fatal side effects of aminopyrine drug such as neutropenia, acute renal failure, bone marrow depression and damage to stomach which are reported and make it banned in many countries. Because of its serious adverse effects, it has been withdrawn from most of the countries like France, Thailand and India. Aminopyrine is rarely used in the Europe like countries at present. In 1986, it was forbidden in Japan. The Committee on the Safety of Drugs of the Japanese Pharmaceutical Affairs Bureau has ordered for its withdrawal. Before that it was extensively used as analgesics, until its side effects were not reported. Even though it is in use at present time in some developing countries.

Keywords: Aminopyrine, agranulocytosis, myelosuppression.

INTRODUCTION

In 1884 aminopyrine (amidopyrine) was introduced as antipyretic and analgesic [1, 16]. Several observers had connected with prolonged consumption of aminopyrine at the end of 1930s, agranulocytosis or granulocytopenia (a rapid and often dangerous decline in the number of white blood cells in the marrow and the blood) had been observed. In 1949, Geigy tried to lessen the worrying side effects of aminopyrine by announcing a new intravenous formulation of equal mixture of aminopyrine and phenylbutazone, latter serving as a solvent, the company called "Irgapyrin". Though, trials showed that phenylbutazone is an effective analgesic and anti-inflammatory, in 1952 Geigy marketed it on its own under the trade name "Butazolidin" [2]. In the 1960s and 1970s, in many western countries aminopyrine has been withdrawn from the market [3]. It was a pyrazolone derivative which falls in the category of non-selective COX inhibitor (Celecoxib inhibitor), classification of NSAID's (Non-steroidal anti-inflammatory drugs) [1]. NSAID's such as salicylates and aminopyrine shows severe side effects such as renal failure, dependency and gastrointestinal tract disturbance [4]. Due to a hypersensitivity mechanism of aminopyrine in some patients which results in blood dyscrasias The Committee on the Safety of Drugs of the Japanese Pharmaceutical Affairs Bureau withdraw aminopyrine drug from the market [5]. Aminopyrine can cause irreversible agranulocytosis due to which is has been banned [6]. Aminopyrine has antipyretic, analgesic, anti-inflammatory and anti-rheumatic effects. Because of its low cost it had been widely used in the clinical treatment of rheumatism and good efficacy. Though, long-term uses of aminopyrine make patients addicted to aminopyrine and bring out many side effects such as neutropenia, myelosuppression and cancerous, damage to stomach, liver and intestines, [3]. Aminopyrine drug ($C_{13}H_{17}N_{3O}$) was commonly used probe substrates in experimental animals and humans for the determination of CYP-3A4 enzyme (major metabolizing enzyme in the liver and intestine) activity. In humans due to side effects of this drug its use was quit, before that it was used as an antipyretic and analgesic drug [7]. Side effects such as granulocytopenia (i.e., an unusual decrease in the overall number of granular leukocytes in the blood), myelosuppression (i.e., a decrease in the ability of the bone marrow to produce blood cells), and nitrosamine carcinogens formation develops on taking aminopyrine drug [1]. In Chinese patent medicine illegal drug dealer, add aminopyrine to receive heavy

profits to anti-rheumatic drugs because it shows quick response in rheumatic diseases with low cost treatment.

Due to large no. of side effects identification of aminopyrine in Chinese patent medicine become a very vital issue. Various identification techniques of aminopyrine components have been reported in anti-rheumatic Chinese patent medicines. One of them is terahertz spectroscopy which is used in finding of adulteration of aminopyrine in rheumatic Chinese patent medicines and the investigation of counterfeit medicines. In aroma rheumatism capsules, aminopyrine constituent is quantitatively detected by surface-enhanced Raman spectroscopy. Due to large no. of side effects, aminopyrine adulteration detection becomes a notable drug safety issue in traditional Chinese medicine [3]. Aminopyrine is a pyrazolone derivative [1]. Pyrazolone and its derivatives have several biological and pharmacological actions with anti-inflammatory, antifeedant, anticonvulsant, antidiabetic, herbicidal, antihypertensive, antiplatelet, antifungal, antibacterial, anticancer and antiviral actions. Some other side effects are also exposed by them such as bleeding, nephrotoxicity and gastrointestinal lesions [8]. An aminopyrine derivative, metamizole drug used in both human and veterinary medicine and one of the strongest analgesic. It has severe hematological adverse effects such as agranulocytosis and aplastic anemia. In some countries e.g. Sweden, USA, Japan, UK, Australia and Iran due to these side effects it also has been withdrawn from the marketplace [9].

Other names of aminopyrine

- Amino phenazone [5]
- Amidopyrine [5]

Trade name of aminopyrine is "Pyramidon" [2].

Aminopyrine drug was basically used as an antipyretic analgesic. Aminopyrine is a white powder, also named as 4- (dimethyl amino) antipyrine. Chemical molecular formula of aminopyrine is $C_{13}H_{17}N_{3O}$. Due to strong adverse effects, its single medicine preparation is gradually replaced by compound preparation [10].

Effect of Aminopyrine with Other Drugs & its Contraindications

In combination with Herbal Preparations

Currently in many herbal preparations, aminopyrine has been detected, which shows risks of allergies and drug interactions with prescribed medicines. Furthermore, there is a potential risk of consuming uncontrolled quantities of these drugs. There are reports of aplastic anemia with exposure to aminopyrine. To increase the superficial effectiveness these types of drugs are added to the herbal preparations, but they are not mentioned on the label [11].

With Mexazolam

Aminopyrine enhancing mexazolam effects such as drowsiness, vertigo, dizziness, headache, ataxia, dry mouth, weakness, an increase of aspartate amino-transferase, alanine aminotransferase, and gamma-glutamyl-transpeptidase, reported swollen tongue, hypotension, nausea, vomiting, and decreased libido [12].

Therapeutic Uses of Aminopyrine

Aminopyrine has analgesic, anti-inflammatory and antipyretic effects [3]. Aminopyrine gained favor amongst physician, due to analgesic and anti-inflammatory effects, it is useful for treating both rheumatoid arthritis and rheumatic fever [2].

Mechanism of Aminopyrine to protect neuronal cells from Aβ amyloid toxicity

Aminopyrine acts as 20S proteasome activator. Enzyme assays carried out on an "open gate" mutant (α3ΔN) proteasome demonstrated that aminopyrine stimulates proteasome by binding the α-ring surfaces and influencing gating dynamics. Experiments showed that H-bond and π-π stacking interactions between pyrazolone and enzyme show major role in connecting α1 to α2 and, α5 to α6 subunits of the outer αring. Aminopyrine exhibit neurotrophic property and protect differentiated human neuroblastoma SH-SY5Y cells from β-amyloid (Aβ) toxicity. Aminopyrine improves Aβ degradation by proteasome in a dose-dependent method. Aminopyrine is promising compound for the growth of proteasome activators for Alzheimer's treatment [8].

Metabolism of Aminopyrine

Aminopyrine is very slowly metabolized by normal neonate. In older infants, a higher amount of exhaled 13-CO_2 is observed [13]. In chicken aminopyrine-N-demethylase inhibits the activities of some important P-450 enzymes [14]. It is mostly metabolized through N-demethylation to form monomethyl-4-antipyrine and formaldehyde, which can be measured by colorimetry Nash. Aminopyrine N-demethylase is almost equal to isoform CYP-3A4 and closely linked to the methylation reaction of drugs [7].

Degradation

Chloramine could hardly degrade aminopyrine, while UV/chloramine greatly increased the observed first-order rate constant of aminopyrine degradation. The experiments illustrated that their active chlorine species contributed to the degradation of aminopyrine. The overall degradation rate of aminopyrine decreased as pH increased from 6.5 to 10. Aminopyrine general degradation pathways were proposed to be hydroxylation, deacetylation, and depenalization. In aminopyrine degradation, demethylation in tertiary amine group was only observed. Additionally, the results of the genetic toxicity according to the micronucleus test of Viciafaba root tip indicated that UV/chloramine treatment could partly decrease the genetic toxicity of aminopyrine [15].

Major Side Effects of aminopyrine

Aminopyrine causes Agranulocytosis [2]. Another symptoms are allergic reactions, strong spasmolytic effect on smooth muscle of peripheral blood vessels, irritability, palsy, copious sweating, dilated pupils, sharp drop then rise in body temperature, dysuria, dyspnea, anxiety, tenesmus, urinary frequency, intermittent fever, fatty infiltration of the liver, heart muscle degeneration and death due to circulatory failure following cardiovascular collapse. Ingestion may cause central nervous system stimulation, vomiting, convulsions, cyanosis, tinnitus, leukopenia, kidney damage and coma. Ingestion can also cause to nausea, mental disturbances, methemoglobinemia, chocolate-colored blood, dizziness, epigastric pain, difficulty in hearing, and liver damage. Some other symptoms are also noticed such as hemolytic anemia, porphyria and severe gastrointestinal bleeding, bone marrow depression, rare eye effects include acute transient myopia [3, 13].

Chronic Symptoms

Anorexia, edema, oliguria, urticaria, hypersensitivity, aplastic anemia, sore throat, fever, pharyngeal membrane, jaundice enlargement of the liver and spleen, exfoliative dermatitis, gastric or duodenal erosion with perforation or bleeding, adrenal necrosis, thrombocytopenic purpura and acute leukemia are some chronic side effects of aminopyrine.

ACUTE/CHRONIC HAZARDS OF AMINOPYRINE

When it is heated to decomposition, this drug substance emits poisonous fumes of nitrogen oxides [13].

Table-1: Side Effects of Aminopyrine

S. No	ORGANS AND SYSTEMS	SIDEEFFECTS OF AMINOPYRINE
1	Hematologic	Bone marrow depression is caused by aminopyrine, usually with a fulminant course and a high risk of death. Specific antibodies and leucoagglutinin are noted. By arrest of maturation, agranulocytosis caused at the metamyelocyte stage.After the administration of aminopyrine suppositories, thrombocytopenia has been reported in a breastfeeding infant.
2	Gastrointestinal	Gastrotoxicity is less common by aminopyrine with other analgesic/anti-inflammatory drugs, because of its poor anti-inflammatory effect.
3	Liver	Aminopyrine is not hepatotoxic, but due to general hypersensitivity reaction liver damage can occur.
4	Urinary tract	Aminopyrine causes direct renal damage, albuminuria, hematuria, and acute renal insufficiency even at therapeutic doses. It can also cause analgesic nephropathy.
5	Skin	Toxic epidermal necrolysis, exfoliative dermatitis, and Stevens–Johnson syndrome have been observed due to the usage aminopyrine.
6	Immunologic	In predisposed patients, many allergic skin reactions, acute anaphylactic shock, acute bronchospasm, and cross-sensitivity to aspirin have been noted.
7	Long-term effects-Tumorigenicity	Aminopyrine and its derivatives may be metabolized to carcinogenic nitrosamines. But the clinical importance of is not clear.
8	On Drug overdose	Aminopyrine mainly affects the central nervous system in overdose, such as coma and convulsions. Lethal intoxication has arisen in infants.

Side Effects of Aminopyrine on Environment

Large amounts of pyrazolone pharmaceuticals from households and hospitals have been discharged into natural water environments, which have brought worldwide concern due to their potential risks to human health and ecological systems. Aminopyrine have been frequently detected in surface waters (1.0-6.0 µg/L), sewage treatment plants (2.5-251.0 µg/L) and even drinking waters (1.0-36.0 ng/L). Previous research indicated that chlorine disinfection showed high efficiency for pyrazolone removal, while it might produce undesired chlorinated disinfection by-products resulting in higher water quality toxicity. Previous studies have shown that chlorine and chlorine dioxide could efficiently degrade pyrazolone pharmaceuticals because of their high reactivity, while the generated disinfection by-product has risks to the water quality safety. Compared to the acute toxicity, the genetic toxicity appears to be a more important index because of its practical significance to evaluate the potential effects on human health. The degradation products of aminopyrine were similarly produced from the reaction of hydroxylation, demethylation, deacetylation, and depenalization reaction of hydroxylation, demethylation, deacetylation, and depenalization. The genetic toxicities of aminopyrine were observed to be partially reduced by UV/chloramine treatment [15].

CONCLUSION

In Conclusion, this review provides the knowledge about the serious outcomes of aminopyrine which make it banned in the world. Patients receiving aminopyrines were reported with major adverse reaction like agranulocytosis, blood dyscrasia, and aplastic anemia with many other side effects. Due to this it has been banned or withdrawn from the market in most of the countries in the world. The risk of

agranulocytosis and aplastic anemia made it is unsuitable for use. Though, this drug is still available in many parts of the world.

REFRENCES

1. Cai MQ, Feng L, Zhang LQ. Transformation of aminopyrine in the presence of free available chlorine: Kinetics, products, and reaction pathways. Chemosphere. 2017 Mar 1;171:625-34.
2. Worboys M, Elizabeth T. Phenylbutazone: one drug across two species, History and Philosophy of the Life Sciences, 2018;40(2):P-3
3. Huang F, Liu M, Xie M, Liu W, Sun L. A combined study on the skeletal vibration of aminopyrine by terahertz time-domain spectroscopy and DFT simulation. Optik. 2020 Apr 1;208:163913.
4. Ibrahim ZYY. International journal of advances in pharmacy, biology and chemistry. IJAPBC. 2015; 4(4):838-839.
5. Aronson, J. Aminophenazone (amidopyrine), Meyler's Side Effects of Drugs; 16th ed.; Elsevier Science, 2016:239–240.
6. Eren, OT, Armagan R, Talmac MA. Nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids; Musculoskeletal research and basic science; Springer, Cham; 2016: 683-693.
7. Han CJ, Akowuah GA, Shukkoor MS, Biswas A. Modulation of rat hepatic CYP3A4 activity by Brassica oleracea, Hibiscus rosa sinensis, and Tradescantia zebrina. 2020; 11(1):7453-7459.
8. Santoro AM, Lanza V, Bellia F, Sbardella D, Tundo GR, Cannizzo A, Grasso G, Arizzi M, Nicoletti VG, Alcaro S, Costa G. Pyrazolones Activate the Proteasome by Gating Mechanisms and Protect Neuronal Cells from β- Amyloid Toxicity. ChemMedChem. 2020 Feb 5;15(3):302-16.
9. Onur O, Emrah D, Bahadir Y. Cellulitis Developing After Intramuscular Metamizole Injection A Case Report. International Journal of Medicine and Surgery. 2016;3(2):54-5.
10. Zhang L, Su W, Qian Y, Chen T, Fan S, Fu Q, Zhao Y, Zhu Z, Wang D. Analysis and treatment of a type of 110- kV transformer with insulation resistance decline defect. IEEJ Transactions on Electrical and Electronic Engineering. 2019 Nov;14(11):1602-8.
11. Byard RW, Musgrave I, Maker G, Bunce M. What risks do herbal products pose to the Australian community?. Medical Journal of Australia. 2017 Feb;206(2):86-90.
12. Da Costa IS, Moreira R, Fernandes H. Tranquilizer/Anxiolytics: Mexazolam, Springer Nature Switzerland AG. 2020: 5-8.
13. National Center for Biotechnology Information. "PubChem Compound Summary for CID 6009, Aminopyrine" PubChem, https://pubchem.ncbi.nlm.nih.gov/compound/Aminopyrine. Accessed 24 September, 2020.
14. Li Y, Mou Y, Thunders M, Wu Y, Ai X, Zhou X, Qiu J. Effects of enrofloxacin on antioxidant system, microsomal enzymatic activity, and proteomics in porcine liver. Journal of veterinary pharmacology and therapeutics. 2018 Aug;41(4):562-71.
15. Jiang B, Tian Y, Zhang Z, Yin Z, Feng L, Liu Y, Zhang L. Degradation behaviors of Isopropylphenazone and Aminopyrine and their genetic toxicity variations during UV/chloramine treatment. Water Research. 2020 Mar 1;170:115339.
16. Tripathi KD. Essentials of Medical Pharmacology, 8th ed.; Jaypee Brothers Medical Publisher, New Delhi (IND), 2019: 220.