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Azithromycin as an Immunomodulatory: Antibiotics Used In Primary Care

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Abstract – Azithromycin is an antibiotic that is commonly prescribed for upper and lower respiratory tract infections in children. While it has proven benefits, some concerns regarding azithromycin use have arisen in recent years. This practice point considers azithromycin therapy for acute respiratory infections in otherwise healthy children. Pharmacokinetics, spectrum of activity, the problem of resistant bacteria and clinical aspects are considered, along with recommendations for use and contraindications. Azithromycin should be avoided in patients with a significant risk of bacteremia. It is associated with pneumococcal resistance and, with stated exceptions, is generally not recommended for the treatment of acute pharyngitis, acute otitis media or pneumococcal community-acquired pneumonia in the pediatric population.

"The usage of modern medicine is associated with the risk of relapses and danger of side effects. There is a great need to develop the cost effective as well as harmless drugs for this liver disease. On the other hand, herbal drugs used in the liver diseases are claimed to be effective and safe. The phytochemicals derived from plant extracts possess multiple activities. It has been found that naturally formulated compound is more active than the isolated form. Recently green synthesis of silver and gold nanoparticles synthesis has been increasingly attempted worldwide and this noble metal of silver and gold has been used for medicinal application and as ornaments since ancient time.

Keywords - Azithromycin, Plants, Medicine

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1. INTRODUCTION

"Nature is god invisible and it bounds in good things. It has offered us countless varieties of useful medicinal plants. Traditional medicine is still tried in the primary treatment of many diseases in developing countries including India. India has a long history in the use of medicinal plants but the effort to develop the drug from medicinal plants is limited. The modern scientific medicine is available with great advancement even though the alternative medicine usage is increasing worldwide. As per the WHO report 80% of the people in the developing countries depend upon these herbal drugs for their therapeutic effectiveness. Herbal drug plays a major role in health care programmed; mainly it supposes that herbal drugs may not cause any side effects."

"These natural herbal products have the biochemical specificity, high chemical diversity besides molecular properties. These Characteristics favored the medicinal plant based drug discovery. Now the new drugs are mostly designed to mimic a plant compound or directly derived from plant sources. In U.S.A one out of three persons has tried to use alternative medicine. This response was increasing from 33.8% in 1990 and after seven years it increased to 42.71%. In developed countries the great interest towards the medicinal plant is increasing so as to meet the demand of the people and also Industrial needs. In the 21st century the trend has been towards the evaluation of traditional systems of medicine carefully carried out by evidence based medicinal evaluation, standardization and randomized placebo controlled by clinical trials. Recently these clinical trials have focused to screen biological active components and many researchers characterize pharmacological importance of these plants. This research paves a path for traditional medicine and also reduced side effects of the modern system. In practice the medicinal plants were used for the treatment of many diseases being started long time before. These plants are widely present in our environment and people are accepting them because of their cheaper cost and their effectiveness. The medicinal plants have the diverse pharmacological properties due to the presence of phytochemicals like flavonoids, terpenes and alkaloids. Mostly all plants have the phytochemicals and dietary nutrients. The non-nutritive antioxidant also lowers the risk of chronic

diseases because it contains the potent biological components. Plants produce these components to protect themselves against various oxidative stress induced damage. Plants contain many antioxidants which may be susceptible to protect the damage even when they are exposed to radiation, UV light etc.,. In recent research it has been proved that these phytochemicals protect the human pathological abnormalities and dangerous diseases like cancer, nervous disorders, cardiovascular diseases, genetic diseases, inflammation and its side effects. All the living beings naturally have the defense mechanism towards the oxidative stress. Liver disorder is one of the top priority diseases in the world for which an effective alternative therapy is needed. Because liver regulates many important metabolic functions, detoxification, and secretary functions in the body. Hepatic injury is associated with distortion of these metabolic functions. (European Medicines Agency, 2010) Thus, liver diseases remain one of the serious health problems and its disorders may create numerous side effects and it may not have any effective remedies. Despite considerable progress in the treatment of liver diseases by oral hepatic protective agents, search for newer drugs continues because the existing synthetic drugs have several limitations. The hepatic protective drugs mostly available in the market are so expensive."

2. REVIEW OF LITERATURE

"Toxicity of chemicals mostly affects all kinds of flora and fauna. Excess of any kind of compounds will be harmful to life and cause many abnormalities in our body (Paliwal et al 2009). (Goossens, *et. al.,* 2005). Treatment of diseases may lead to many implications in the liver cells." (Goossens, *et. al.,* 2007).

"Due to its increased selectivity and sensitivity compared to classical spectrophotometry, DS (Derivative spectrophotometry) is especially widely applied in analytical chemistry for the determination of pharmaceutical compounds and trace elements of similar chemical properties present in mixtures at different concentration levels. For the purpose, the first and the second order derivative are usually used, although in some cases higher-order derivatives provide more reliable results. Methods for the determination of organic substances by the DS technique have been developed mainly for application in the analysis of pharmaceuticals and/or clinically and biochemically interesting systems. The interference of the formulation excipients or other UV-absorbing components, such as co-formulated drugs and degradation products, usual in conventional UV-spectrophotometry can be successfully eliminated by the DS technique."

"A variety of procedures that render the DS determination of drugs more specific and sensitive, regardless of whether they are determined as single compounds or in mixtures, have been published. First- and second-order DS methods have been proposed for the assay of the anti-inflammatory drugs such as fentiazac, flufenamic acid, tiaprofenic acid and proquaone, matronidazole in tablets, Carboplaton, anthralin in ointments and paracetamol in blood sera."

"Aspirin, phenacetin and caffeine in analgesic tablets have been determined by zero crossing derivative spectrophotometry. Chlorpheniraminemaleate, codeine phosphate and ephedrine hydrochloride have been estimated without separation using second-order DS. For quality control of pharmaceutical preparations containing clozapine derivative spectrophotometric method is suitable for different levels of the drug. Simultaneous determination of atropine sulfate and morphine hydrochloride in their binary mixture using spectrophotomtric methods is proposed by Dinc et al. A method for the determination of cetrizine dihydrochloridein pharmaceuticals by first, second, third and fourth-order derivation spectrophotometry is described using "Peak-Peak" (P-P), and "Peak-Zero" (P-O) measurements. First and second derivative spectrophotometry is applied for the simultaneous determination of amoxycillin and clavulanic acid in pharmaceutical preparations. A simple and rapid derivative spectrophotometric assay procedure is described for the analysis of casteine, acetaminophen and propyphenazone in tablet formulations. Caffeine content is determined in cola, coffee and tea by second and third order derivative spectrophotometry without using any separation or background correction technique and reagent."

"Second derivative spectrophotometric determination of trimethoprime (TMP) and sulfamethoxazole (SM) in the presence of hydroxyl propyl-ß-cyclodextrin (HP-ß-CD) has been reported (McCaig, Hughes, 1995). A fast and accurate method for the determination of dropenidol in the presence of methylparaben and propylparaben is developed using derivative spectrophotometry (Uetrecht, 2007). Derivative spectrophotometry in the determination of phenyl-ß-naphthlaine (PBN) used as an antioxidant in rubber mixtures have been described (Zapater, *et. al.,* 2006). Simple, fast and reliable derivative spectrophotometric methods are developed for determination of indapamide (Kaplowitz, 2005). in bulk and pharmaceutical dosage forms. A derivative spectrophotometric method is developed for the three binary mixtures of pseudophedrine with fexofenadine (mix.I), cetrizine (mix.II) and loratidine (mix.III) (Andrade, *et. al.,* 2004). Derivative procedures reported for vitamin mixtures are concerned with pyridoxine hydrochloride and thiamine hydrochloride in tablets (first and third order) (Chang, Schiano, 2007), vitamins B (6) B1 and B triphosphate in injections (second order) (Bénichou, 1990), and sodium salicylate, thiamine hydrochloride and ascorbic acid in visalicyl tablets (first and second order). First-derivative measurements have been used to determine benzimidazole and cinnamate, as well as benzophenone derivatives in order to characterize sun-screens in cosmetic formulations (Danan, Benichou, 1993). First- and second-order DS

have been described for evaluating bilirubin, albumin and oxyhemoglobin in amnionic fluid (Farrell, 1994). First-order DS is used 12 uridine 5- for the determination of intact ceftazidime cefuroxime sodium and cefotaxime sodium in the presence of their degradation products (Björnsson, Olsson, 2005). For a simultaneous determination of acetaminophen and Phenobarbital after their extraction from the corresponding suppositories with borate buffer, pH 10, a first-order DS method is developed (Watkins, *et. al.,* 2008)."

"Simultaneous analysis of a ternary mixture containing etamizole, paracetamol and caffeine (Ferrajolo, *et. al.,* 2010) is carried out by derivative spectrophotometry. First DS methods for determination of triamterene and hydrochlorothiazide respectively in combined tablets have also been described. A first order DS method has been developed for the simultaneous determination of rifamycin SV sodium and lidocaine hydrochloride in injection solutions. The simultaneous determination of ethinyl estradiol and norgestrel in tablets utilizing first-order DS has been reported. A method for the simultaneous determination of melatoninpyridoxine combination in tablets by the zero-crossing technique of the first and second-order DS has been reported."

"This method is successfully applied for the determination of both drugs present in laboratory prepared mixtures and in tablets. For the evaluation of diclofenac and benzyl alcohol as an excipient in injectable formulations, the first- and second-order DS method using the zero-crossing technique has been described. Three new methods (first-order DS, ratio spectra DS and Vierordt's method) for the quantitative analysis of tablet formulations containing pseudoephedrine hydrochloride and triprolidine hydrochloride are developed and compared. A rapid, simple and direct assay procedure based on first-order DS using zero-crossing and peak-to-base measurements for the determination of dextromethorphan HBr and bromhexine HCl has also been developed. A simple and economical DS procedure is developed for the simultaneous determination of indomethacin and paracepamol in combined dosage forms. Applying the zero-crossing technique of the second-order DS a method for the determination of 1,4-benzodiazepin, midazolam and lorazepam in tablets is developed. A second-order derivative UV spectrophotometric method for determination of vitamin C content in a variety of natural samples is described. A second-order derivative spectrophotometric method for the determination of bifonazole in the presence of methyl- and propyl p-hydroxybenzoate as preservatives has been developed."

3. ANTIBIOTICS USED IN PRIMARY CARE

"Antibiotics are considered as a common cause of drug-induced liver injury (DILI).[1–3] Although the frequency of serious antibiotic-induced hepatotoxicity is low compared with the amounts prescribed each year—population-based estimates suggest that it occurs in <5 per 100000 population[4]—it remains a main reason for antibiotic withdrawal after product launch. Antibiotic-induced hepatotoxicity is usually asymptomatic, transient and associated with only mild hepatic impairment.[5] In rare cases, however, significant morbidity,[6,7] the need for liver transplantation[7,8] and death from acute liver failure[7–9] have been reported. In recent years, the European Medicines Agency (EMA) and the US FDA have addressed these issues by putting emphasis on both pre-clinical (to detect signals) and clinical studies.[10] Nonetheless, predicting what hepatotoxicity will be after approval based on data assembled during drug development remains a risky exercise."

"Public awareness of antibiotic-induced hepatotoxicity has, however, increased over recent years (following actions of regulatory bodies targeting specific antibiotics), making it essential for the primary care physician to better identify and minimize the risk of serious liver damage with existing agents. In the present review, we describe the adverse hepatic effects of antibiotics, including their frequency, severity and clinico-pathological features, and discuss these observations within the context of the primary care setting. Indeed, this is not only where antibiotic consumption is greatest but also where risks are highest, given the inherent difficulties of rapid access to in-depth biological investigations for prompt diagnosis. As a source of information, we first searched electronically the online version of the US National Library of Medicine (Bethesda, MD, USA; http://www.pubmed.com) for original research studys, case reports and reviews published until the end of February 2011. For antibiotics used primarily for non-tuberculosis indications, the search terms were 'hepatic adverse event OR hepatotoxicity AND <each of the following terms>': 'beta-lactam*'; 'macrolid*'; '(sulfonamide OR sulphonamide)'; 'tetracyclin*'; 'fluoroquinolon*'; 'amoxycillin*'; 'clavulanic'; 'telithromycin'; 'clarithromycin'; 'azithromycin'; 'erythromycin'; 'levofloxacin'; 'moxifloxacin'; 'gatifloxacin'; and 'trovafloxacin', with restriction to studys dealing with antibiotic-induced hepatotoxicity. For hepatotoxicity related to antibiotics used for the treatment of tuberculosis, the search terms were 'hepatotoxicity AND <each of the following terms>': 'anti-tuberculosis agents'; 'ethambutol'; 'isoniazid'; 'pyrazinamide'; '(rifampicin OR rifampin)'; and 'streptomycin', with focus on studys published within the last 10 years. Reference lists from review studys were examined for additional relevant articles. Current prescribing information and

regulatory documents from both the FDA and the EMA were also systematically retrieved and examined."

"Most cases of antibiotic-induced hepatotoxicity are idiosyncratic (the adverse reaction occurs in a very small proportion of patients, cannot be predicted either from the drug's pharmacology or from pre-clinical toxicology tests and is host dependent). It is thought to occur either via an immunological reaction, including concomitant liver inflammation associated with viral or bacterial infection of liver or inflammatory disease, in response to hepatotoxic metabolites, or, as more recently suggested, when the drug synergizes with lipopolysaccharide-induced inflammatory cytokine signalling to cause acute hepatocyte death. Symptoms are similar to those of other liver diseases, and include jaundice, malaise, abdominal pain, unexplained nausea and anorexia. Because antibiotic-induced hepatotoxicity mimics other liver diseases, diagnosis is necessarily one of elimination and is usually based on a high degree of clinical suspicion following exclusion of competing aetiologies, such as viral hepatitis or biliary disease. Clues suggestive of drug allergy include rash, fever or eosinophilia, duration of exposure of 1–5 weeks and an often rapid response following re-administration of the antibiotic."

4. AZITHROMYCIN AS AN IMMUNOMODULATORY

"In addition to their antimicrobial properties, there are in vitro and animal data on the Immunomodulatory or anti-inflammatory effects of macrolides.

Effects in humans were initially reported in the treatment of diffuse pan bronchiolitis, in which macrolides are associated with improved lung function and prognosis based largely on non-controlled trial data and retrospective studies.

In cystic fibrosis, treatment for six months is associated with improved respiratory function and reduced respiratory exacerbations.

Azithromycin produced a small increase in lung function (mean 8.8%) at seven months in patients treated for bronchiolitis obliterans syndrome after lung transplant, but was no different compared to placebo for bronchiolitis obliterans syndrome after haematopoetic stem cell transplant.

Azithromycin and other macrolides have also been 13proposed for use in sepsis and epidemic respiratory viral infections to prevent cytokine storm.

It has been used for various respiratory and non-respiratory inflammatory conditions. However, this use has been controversial due to limited direct clinical evidence for many conditions, and concerns about increased antimicrobial resistance."

New non-antibiotic macrolides may provide immunomodulatory benefits without contributing to antimicrobial resistance.

"In non-cystic fibrosis bronchiectasis, three randomized, double-blind, placebo-controlled trials found that azithromycin reduced the number of exacerbations. In adults with bronchiectasis on CT scanning and at least one pulmonary exacerbation treated with antibiotics in the past year, the EMBRACE trial found a reduction in the rate of exacerbations (0.59 vs 1.57) with azithromycin three times weekly for six months compared to placebo."

"The BAT trial found a reduced number of exacerbations (median 0 vs 2) in adults with radio logically confirmed bronchiectasis and at least three respiratory infections treated with antibiotics in the past year (daily azithromycin therapy over 12 months)

Finally, the Bronchiectasis Intervention Study investigated Australian and New Zealand indigenous children with non-cystic fibrosis bronchiectasis or chronic suppurative lung disease who had had at least one pulmonary exacerbation in the past 12 months. After once-weekly azithromycin for up to 24 months, the incidence of pulmonary exacerbations was half that observed in those given placebo. However, the authors noted a greater incidence of macrolide-resistant bacteria in children treated with azithromycin (46% vs 11%)."

"Trials in children and adults with asthma and chronic obstructive pulmonary disease (COPD) have been small with heterogeneous outcomes, and the optimal regimens and subgroups are not yet established. Patients with neutrophil asthma may benefit from macrolides, but further research is needed."

"A randomized controlled trial of daily azithromycin in 18patients with variable COPD severity, smoking status and medical management found that azithromycin prolonged time to exacerbation compared to placebo – median 266 days (95% CI* 227–313) versus 174 days (95% CI 143–215) ($p<0.001$). The rate of exacerbations was 1.48 per patient-year in the azithromycin group, compared with 1.83 in the placebo group ($p=0.01$). However, there was only a 7% increase in the proportion of people reporting clinically important improvements *Asthma and chronic obstructive pulmonary disease*

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"According to the most current Infectious Diseases Society of America (IDSA) guidelines, penicillin or amoxicillin remains the drug of choice for the treatment of group a streptococcal pharyngitis. A first-generation cephalosporin is recommended if a patient has a history of no anaphylactic allergy to penicillin. Alternatives include clindamycin, clarithromycin, and azithromycin."

"All recommended oral treatment courses extend for 10 days except for azithromycin, for which a 5-day treatment course is recommended.[1] this may lead clinicians to choose azithromycin for patients who have no clear contraindication to a penicillin or cephalosporin."

"Whereas the penicillin and cephalosporin recommendations are rated as being based on high-level strong evidence, the azithromycin recommendation is rated as based on moderate evidence.[1] The remainder of this discussion will examine the appropriate utilization of azithromycin for this indication."

CONCLUSION

"The proposed validated method for the estimation of AMX and CLV in human plasma is highly selective, accurate and precise. The method offers significant advantages over those previously reported, in terms of lower sample requirements, sensitivity and analysis time. The efficiency of solid phase extraction and a chromatographic run time of 2.0 min per sample make it an attractive procedure in high-throughput bioanalysis of this antibiotic combination. The linear dynamic range established was adequate to measure the plasma concentration of AMX and CLV in a clinical study involving healthy subjects. In addition, matrix effect and stability of analytes in plasma was extensively studied."

"Antibiotic-induced hepatotoxicity produces an array of hepatic lesions that are often clinically indistinguishable from those of hepatobiliary diseases, making causality difficult to establish. While the temporal relationship between drug administration and onset of hepatic symptoms and exclusion of competing aetiologies may help, in most cases diagnosis is largely circumstantial. Delayed onset of hepatic dysfunction after cessation of therapy, which has been reported with several antibiotics, complicates the picture further, especially in cases of fatal liver failure. It is also difficult to determine cause and effect when there are only a few isolated spontaneous reports. Amoxicillin/clavulanate (due to the clavulanic acid component), co-trimoxazole (due to the sulphonamide component) and flucloxacillin appear as the most frequently involved drugs among those in current clinical use by primary care physicians. Conversely, no other currently approved antibiotic that is in use in general practice, except for telithromycin, can be singled out to be overly hepatotoxic."

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