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Research Article

ERYTHROMYCIN: ITS GLYCEMIC EFFECT IN AN INFECTIOUS PATIENTS

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ABSTRACT

Background: In the present study, our objective is to determine the effect of erythromycin therapy on glycemic level in nondiabetic patients suffering from mild acute bacterial pharyngitis. Materials and Methods, Sixteen hypersensitive patients to penicillin therapy with mild acute bacterial pharyngitis followed up for 1 month, all patients had a normal glycemic profile, they were divided into two groups with regard to sex, the first group contains 8 male patients, while the other includes 8 female patients, erythromycin stearate 250 mg PO qid, was indicated for two weeks, to investigate its effect on glucose serum. Common blood count and glucose profile were performed before, upon completion of treatment, as well as two weeks following discontinuation of erythromycin therapy. Results, orally prescribed erythromycin (250 mg PO qid) for 2 weeks produces no effect on glycemic profile in the first group but exerted reversible hypoglycemic effect in in most patients (75%) of the second category in females above 47 years of age. Conclusion, Erythromycin therapy in non-diabetic middle-aged female patients, should be used with caution, and must be evaluated clinically and by laboratory analysis in the first 2 weeks of treatment in order to minimize its possible hypoglycemic effect.

Keywords: Erythromycin, Pharyngitis, Glycaemia, Penicillin.

INTRODUCTION

Upper respiratory tract infections (URTIs) are the most common infections in the population. Common URTIs include rhinitis, sinusitis, nasopharyngitis, pharyngitis, epiglottitis, laryngitis, laryngotracheitis and tracheitis, rhinoviruses and coronaviruses are the main pathogens involved in URTIs.

Bacterial microorganisms may also be nvolved in URTIs, up to 15% of diagnosed URTIs are caused by *Streptococcus pyogenes, a group A streptococcus, Streptococcus pneumoniae, Haemophilus influenzae, Corynebacterium diphtheriae,* and others.[1] Most of URTIs are mild and treated at home, by over-the-counter (OTC) drugs such as non-steroidal anti-inflammatory drugs (NSAIDs), antihistamines, selective α-1 adrenomimetics such as phenylephrine, opioids such as dextromethorphan and codeine are sometimes employed to relieve cough, which is associated with URTIs., but in some cases, when severe complications do occur, such as meningitis, pneumonia, endocarditis and glomerulonephritis, antibiotics should be prescribed[2, 3].

The antimicrobial therapy of respiratory tract infection depends not only on the microbial cause of infection but also on the primary site involved and the severity of disease. Penicillin is considered as the first line therapy in URTIs, in the state of either contraindication or hypersensitivity reactions to penicillin, erythromycin (250 mg and 500 mg) is indicated and depending on severity is usually given four times a day [4, 5].

The macrolides are group of closely related compounds characterized by a macro- cyclic lactone ring, usually containing 14 or 16 atomsto which deoxy sugars are attached, erythromycin consists of two sugar moieties, attached to a 14-atom lactone ring, obtained from *Steptomyces erythreus,* it is poorly water-soluble , but readily dissolves in organic solvents, erythromycin comes in 4 forms: Erythromycin A, B, C and D. Erythromycin A is known for being the most antibacterial, with B, C and D following respectively[2,6].

It remains one of the safest and most important broad-spectrum antibiotics available, even though it was nearly discovered 65 years ago. It was the first macrolide antibiotic to become available for clinical use and has served as the prototype for newer macrolides. Because of its equal efficacy to penicillin, it is widely employed as alternative antibacterial therapy in patients who had hypersensitivity reactions to penicillin [5,9,10].

Erythromycin is available in different oral and pharmaceutical forms including enteric-coated tablets, oral suspensions, ophthalmic solutions, ointments, gels and injections. The main oral erythromycin combinations are erythromycin base, erythromycin estolate (contraindicated during pregnancy), and erythromycin ethylsuccinate and erythromycin stearate, for injection the available combinations are erythromycin gluceptate and erythromycin lactobionate [11,12].

All orally erythromycin formulations are given as either enteric-coated or more-stable salts or esters, because it is destroyed by gastric juice, administered food usually decreases its absorption, Intravenous infusion of erythromycin is characterized by high incidence of thrombophlebitis, it is metabolized by demethylation in the liver, with the formation of estolate that can cause cholestatic hepatitis, so its use is restricted in liver impairments[5,6].

Erythromycin is widely distributed to all body tissues except the cerebrospinal fluid, crosses the placenta and excreted in the breast milk. The American Association of Pediatrics (AAP) determined

erythromycin is safe during lactation period[13].

Erythromycin is still the second choice following penicillin's contraindications or allergic reactions in infectious pregnant women, (assigned to pregnancy Category B by FDA). Pregnant women receiving erythromycin estolate may be more prone to hepatotoxicity. Erythromycin should only be given during pregnancy when need has been clearly established[14-17]. There have been reports of infantile hypertrophic pyloric stenosis (IHPS) occurring in infants following erythromycin therapy[18].

Erythromycin is metabolized in the liver, its major metabolites are the demethylated product at the dimethylamino group, the N-oxide of the desosamine, and des-cladinose erythromycin, all of which have much reduced antibacterial potency, elimination mainly occurs in the bile and partially in the urine [7].

Erythromycin is a potent inhibitor of the 3A isoform subfamily of CYP3A, more than 700 drugs interact with erythromycin; several reports and controlled studies have shown that erythromycin may interact with theophylline, carbamazepine, cyclosporin, tacrolimus, warfarin, digoxin, terfenadine, astemazole, cisapride, lovastatin, triazolam, and disopyramide [11,19,20].

Erythromycin is the prototype of macrolides that binds irreversibly on the 50S subunit of the bacterial ribosome, consequently inhibiting translocation step in protein synthesis, its activity is enhanced at alkaline pH, its action may be bactericidal or bacteriostatic, the effect depending on the concentration and on type of microorganisms. It should not be co-administered with lincomycin, clindamycin or chloramphenicol, because of pharmacodynamic antagonism, on 50S subunit[8, 10].

In addition to its antibacterial effect, erythromycin has immunomodulatory, anti-inflammatory and prokinetic activity, the exact underlying mechanism is not known, but possibly by decreasing the oxidative production of cytokines by neutrophils (IL-1, IL-6, IL-8 and TNF), in addition, production of IL-10 and platelet count are increased, the prokinetic activity of erythromycin refers to its ability to stimulate the release of motilin from endocrine M cells of enterocytes, and consequently sometimes erythromycin is employed for management of gastroparesis[24-27].

Orally administered erythromycin ethylsuccinate is readily and reliably absorbed, widely distributed into most body compartments, with a little concentration in the cerebrospinal fluid (CSF), that is increased in state of meningitis.

Erythromycin ethylsuccinate is indicated in the treatment of URTIs infections caused by *Streptococcus pyogenes, Streptococcus pneumoniae*, or *Haemophilus influenzae*.

It is also effective against lower respiratory tract infections caused by *Streptococcus pneumonia* or *Streptococcus pyogenes*. Listeriosis caused by *Listeria monocytogenes*, Pertussis caused by *Bordetella pertussis* and *Corynebacterium diphtheriae* infections[5,10,28,29].

Erythromycin is indicated when tetracyclines are contraindicated or not tolerated, the treatment of uncomplicated urethral, endocervical, or rectal infections in adults due to· *chlamydia trachomatis*[30].

American heart Association (AHA) suggested that erythromycin is no longer advised to be approved for prevention of respiratory or dental infections, because of its frequent gastrointestinal side effects, as well as its complicated formulations, nowadays, erythromycin is largely replaced by clarithromycin, azithromycin or clindamycin in patients who manifested allergic reactions to pencillins [4,8,28].

Penicillin or sulfonamides are considered by the AHA to be the drugs of choice in the prevention of recurrent attacks of rheumatic fever. In patients who are allergic to penicillin and sulfonamides, oral erythromycin is recommended by the AHA in the long-term prophylaxis of streptococcal pharyngitis (for the prevention of recurrent attacks of rheumatic fever [3,8,10,30,31].

The dosage of erythromycin is variable and depends on severity and species of invading microorganisms, Mild to moderate infection: 250 to 500 mg (base, estolate, stearate) or 400 to 800 mg (ethylsuccinate) orally every 6 hours, for severe infections: 1 to 4 g/day IV in divided doses every 6 hours or by continuous infusion. In children, the usual dosage is 30 to 50 mg/kg/day [2,3].

Resistance to erythromycin is usually plasmid-encoded. The main mechanisms of resistance include decreased its accumulation due to either inadequate uptake or increased drug efflux under the action of the pump efflux system of bacteria. Esterases produced by pathogens can also inactivate erythromycin by breakdown of its lactone ring, ribosomal protection is also an important mechanism of macrolides resistance, and it is associated with a change in a 23S ribosomal RNA (rRNA) residue or a mutation in ribosomal protein L4 or L22 [12,21,32,33].

GIT symptoms (in 5 to 30% of the cases) such as nausea, vomiting, abdominal cramps and diarrhea the most common adverse effects of erythromycin, that is linked to its ability to have a direct effect on gut motilin. Erythromycin estolate can produce choestatic hepatitis, as a hypersensitivity reaction, other allergic reactions include fever, maculopopular rash and eosinophilia, most allergic reactions are reversible, but hepatitis recurs if erythromycin is readministered. Ototoxic effects of erythromycin have been reported and seemed to be reversible.

Erythromycin is contraindicated in hepatitis, pancreatitis, and colitis. Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving erythromycin concomitantly with lovastatin[8,9,22].

Because of its broad-spectrum action, it can kill useful bacterial miroflora, that are involved in retarding overgrowth of fungi and other microorganisms, if superinfection develops, erythromycin therapy should be withdrawn, and metronidazole or vancomycin are indicated[4,6,20,28].

Several studies were performed to evaluate the action of erythromycin on glycemia in diabetic patients, since erythromycin is frequently employed for management of diabetic gastroparesis, because it triggers releasing of motilin that improves secretion of insulin [24,34-39].

The most important of these researches include the ability of erythromycin to improve glycaemic control in patients with type II diabetes mellitus; based on its ability to stimulate motilin release, which in its turn enhances insulin secretion, increases insulin's receptors sensitivity and reduces insulin requirements in diabetic patients[40].

The other study showed that erythromycin administration before sleep is effective in decreasing fasting hyperglycemia in type 2 diabetic patients, properly by increasing early phase of insulin secretion[41].

Until nowadays, there is no study that was carried to evaluate the

effect of erythromycin on glucose serum in nondiabetic infectious patients, since erythromycin is widely employed, as replacement therapy for patients who are either susceptible to penicillin therapy or have contraindications to its use, so we studied acute pharyngitis patients to determine the influence of erythromycin therapy of 2 weeks duration on glucose levels in nondiabetic patients.

MATERIALS AND METHODS

Sixteen adult patients of mild acute bacterial pharyngitis, age ranged 22-65 years, with no earnest cardiovascular, hepatic, endocrine, renal or GIT pathologies, participated in this study, all patients gave written informed consent.

In all subjects, complete blood count (CBC) and fasting glucose were measured before, upon completion of treatment, as well as, two weeks after discontinuation of erythromycin therapy.

Mild acute bacterial pharyngitis in all patients was confirmed by a throat culture that revealed streptococcus pyogenes (group A Streptococcus [GAS]) [3,4]. Patients were divided equally into two groups with regard to gender; the first category includes eight male patients; five of them aged 50-65 years, the remainder are younger, aged 22-50 years. The second contains eight female patients; six among them aged 47- 65 years, the other 2 patients of 22 years of age.

All subjects were medicated with erythromycin stearate 250 mg PO qid (orally four times a day) for 14 days. The patients were investigated for a possible glycemic effect of erythromycin in a 4- week period, at the end of treatment, CBC and glycemic tests were done to ensure the efficacy of antibiotics as well as to evaluate the effect of erythromycin on glucose levels.

RESULTS AND DISCUSSION

This research is carried out as per International conference of Harmonization-Good Clinical Practices Guidelines (ICH-GCP). It was undertaken to assess whether or not conventional doses of commonly used erythromycin causes clinically significant deviations in plasma glucose levels when was given to nondiabetic infectious patients who have had allergic reactions to penicillin. All patients experienced classic symptoms of acute bacterial pharyngitis (pharyngeal exudates, anterior cervical lymphadenitis, history of fever 38 C, and absence of cough),[2,4] and for this reason, erythromycin therapy was started before identification of the invading microorganism, in order to confirm diagnosis and to exclude viral pharyngitis which is manifested by rhinorrhea, hoarseness, cough, and conjunctivitis, that were absent in all patients, throat culture was taken, and streptococcal pharyngitis diagnosis was done[1,8,19].

All selected patients had a history of hypersensitivity reactions to traditional therapy of bacterial pharyngitis, clinically, it is well recognized that erythromycin is considered the first alternative for treatment of group A streptococcal pharyngitis in patients allergic to penicillin[6,8,19,30].

Analysis showed that all patients of both groups before their medication with erythromycin, (250 mg qid for 2 weeks) ibuprofen 400 mg, and acetaminophen 500 mg were supplied orally every 4 to 6 hours as needed, had inflammatory markers in their CBCs, the acute inflammatory reaction appeared in CBC by leukocytosis and increased erythrocyte sedimentation rate (ESR) values, the mean average of inflammatory markers for both categories respectively were 14,500-16,500 mcL and 13,000-15,000 mcL, compared to normal rangers of white blood cells count (4,000- 11,000 mcL). After a 2-weeks period of treatment, in both investigated groups, the signs of inflammation are decreased by normalization of laboratory values of the CBC and ESR. (Table 1)

Regarding glycemia, all patients of the first group had normal glucose levels, before and after treatment, respectively (70-97 mg/dl), (75-89 mg/dl).

All subjects of the second group showed lowered glucose serum, following treatment by erythromycin, compared to their normal sugar levels before management. A significant decrease was noted in six patients above 47 years of age, (48- 50 mg/dl), the glycemia of the other two patients was 61 mg/dl, no one of them had demonstrated any clinical symptoms of hypoglycemia at the moment of investigation, and thereby erythromycin-induced hypoglycemia could not be taken in consideration, because, in non-diabetics 61 mg/dL mg is not considered hypoglycemia, which is recognized when glucose levels under 55 mg/dL, as well as diagnosis is confirmed in the presence of acute symptoms of hypoglycemia[42,43].

Only six patients of the second group experienced signs of acute hypoglycemia, such as pallor skin, palpitations, sweating, headache, hunger, nausea, vomiting at the time of investigation, in all subjects, these symptoms were relieved, after consumption of sugar, which suggests the presence of hypoglycemia. In fact, hypoglycemia value is variable, in diabetics, it is diagnosed when glycemia is below 70 mg/d, on the other hand in non-diabetics, hypoglycemia is considered as glucose serum is below 55 mg/dL, symptoms are related to hypoglycemia; at the time of symptoms, and improvement when blood sugar is restored to normal confirm the diagnosis[34,36,44].

In order to exclude the possibility of hypoglycemia caused by either ibuprofen or acetaminophen, (which were also indicated for patients along with erythromycin), non-steroidal anti-inflammatory drugs (NSAIDs) have no significant effect on carbohydrate metabolism, if they are taken irregularly, even in diabetic patients. Multiple studies showed that taking ibuprofen and other NSAIDs regularly could alter glycemic levels in diabetic patients type II, in the form of hypoglycemia[19,24,27,31].

All investigated subjects in whom hypoglycemia was diagnosed, were asked to visit laboratory two week following discontinuation of erythromycin, glucose levels were around their normal limits, suggesting that erythromycin-induced hypoglycemia was reversible, the level of glucose was increased from 48-50mg/dL, at the end of treatment to 74-85 mg/dL 2 weeks following discontinuation of erythromycin treatment.

The results obtained by CBC and blood glucose serum of sixteen patients, aged 22-65 years, before taking erythromycin stearate 250 mg PO qid, after a period of 2-weeks treatment, and two weeks following erythromycin therapy were compared. In both groups, decreased infectious inflammatory process was noted by normalization of CBC values, compared to values before erythromycin's therapy. The first group had not any deviation from glycemic profile. Hypoglycemia was found in most patients of the second group, (75%), above in female patients 47 years of age. Low blood glucose level in all subjects was reversible, because levels of glucose in the second group were around their normal limits after 2 weeks of erythromycin withdrawal therapy.

Table 1: Laboratory values of both groups, before and after their medication with erythromycin

Hematologic Tests	Normal Values	I Group B/T ©	I Group A/T ©	II Group B/T ©	II Group A/T ©
Leukocytes	4,000 11,000 mcL	14,500-16,500 mcL	5,000-10,000 mcL	13,000-15,000 mcL	4,500-9,000 mcL
ESR	#	©: #: under 50y: 18 mm/hr. ©: #: over 50y: 25 mm/hr.	#: under 50y: 13 mm/hr. #: over 50y: 17 mm/hr	#: under 50y: 24 mm/hr. #: over 50y: 36 mm/hr.	#: under 50y: 16 mm/hr. #: over 50y: 27 mm/hr.
Fasting Glycemia mg/dl	70–99	©: 75-89	70-97	71-92	6 pts: 48- 5 2 pts: 61

N.B: Pts: Patients**,** B/T: Before treatment**,** A/T: After treatment

#: Normal erythrocyte sedimentation rate (ESR)

 Women under age 50 should have an ESR under 20 mm/hr.

 Women over age 50 should have an ESR under 30 mm/hr.

 Men under age 50 should have an ESR under 15 mm/hr.

 Men over age 50 should have an ESR under 20 mm/hr.

Mg/dl: milligram per deciliter, Mcl: microliter of blood, ©: Mean average of laboratory values.

Table 2: Glycemic Profile of The II group After Erythromycin Withdrawal

Patient's Group	**Normal Glycemia**	**At The End of Erythromycin Treatment** © mg/dL	**2 weeks Alter Erythromycin Withdrawal** © mg/dL
II group (6 patients)	70-99 mg/dL	48- 50	74-89
II Group (2 patients)		61	72-81

©: The symbol refers to mean average of glycemia.

The mechanism of hypoglycemia is not well understood, but it may be associated with the ability of erythromycin to increase secretion of motilin, which in its turn stimulates liberation of insulin, that inhibits glycogenolysis and maintains deposition of glycogen in hepatocytes, adipocytes as well as in skeletal muscle cells[35-37]. (Table 2)

CONCLUSION

Taking consideration that hypoglycemic patients of the second group were free from serious organic diseases, particularly (cardiovascular, endocrine, renal and hepatic), their analysis before, upon completion of management, and two weeks following erythromycin withdrawal therapy, as well as the negative effect of NSAIDs on carbohydrate metabolism, we can conclude that erythromycin 250 mg PO qid for a two-week period of therapy was the cause of reversible hypoglycemia, which occurred mostly in female patients aged above 47 years, compared to males of the first group in whom no one manifested signs of hypoglycemia.

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