The Effects of Some New Macrolides on Psychomotor Performance in Humans.

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Abstract:
Objective. The study was designed to show the effects of single oral doses of new macrolides (Clarithromycin, Roxithromycin and Azithromycin) on psychomotor performance by using the computerized Leeds psychomotor Tester...
Setting: Department of Pharmacology, College of Medicine, Al-Mustansiriya University, Baghdad- Iraq.
Design: double-blind, balanced and controlled study.
Main outcome measures: Choice reaction time (CRT), recognition reaction time (RRT) movement reaction time (MRT), and critical flicker fusion Frequency (CFF). These parameters were recorded before treatment and 2 hours interval taking 2 readings post treatment
Results: The results showed that the changes in the CRT,RRT ,MRT and CFF values following the three new macrolides treatments ,not significantly different between the four treated groups , nor across the two hours intervals of the study.
Conclusion: Single oral doses of the new macrolides Clarithromycin (500 mg) Roxithromycin (150 mg) and Azithromycin (250 mg)have no impairment effects on the sensorimotor and arousal states in . These findings increase the safely profile of the new macrolides.

Key wards: Macrolides, Psychomotor Performance, Clarithromycin, Azithromycin, Roxithromycin

Introduction:

Macrolides are a group of antibiotic with a macrocyclic lactone structure .They are composed of 14 (erythromycin and clarithromycin), 15 (azithromycin) or 16 (josamycin and spiramycin) – membered lactones to which are attached amino and / or neutral sugars via glycosidic antibiotic[1]. Macrolides were introduced to the field of anti – infective beginning with erythomycin in the early 1950s [2]. They are active against Gram- positive bacteria, Mycoplasma spp, Legionella spp, Chlamydia spp, and Haemophilus influenzae [3, 4]. Apart from their antibacterial activity , these agents exhibit a broad spectrum of pharmacological effects [5], including anti-inflammatory activity in humans and animals[6,7,8], prolong action potential duration of cardiac muscle and causing torsade de pointes dysarrhythmia[9], immunomodulatory activities [10], increasing nitric oxide synthetase activity, decreasing xanthin oxidase activity, and induction of apoptosis[11,12]. The newer macrolides, such as clarithomycin, azithromycin and roxithromycin, have improved intracellular and tissue penetration, are more stable, are better absorbed, have a lower incidence of gastrointestinal side effects, are less likely to interact with other drugs, and their pharmacokinetics provide for less frequent dosing than erythromycin [13,14] . As a result, the usage of the newer macrolides has increased dramatically over the last few years. Moreover, over the past 20 years a number of reports have incriminated macrolides as a potential source of clinically severe drug interactions.

However, differences have been found between the various macrolides in this regard and not all macrolides are responsible for drug interactions [15].

With the recent advent of many semisynthetic macrolide antibiotics it is now evident that they may be classified into 3 different groups in causing drug interactions; the first group (e,g. troleandomycin, erythromycin)are those prone to forming nitrosoalkanes and the consequent formation of inactive cytochrome P450 metabolite complexes [15], the second group (e.g. josamycin, flurithromycin, roxithromycin, clarithromycin, miocamycin and midecamycin) form complexes to a lesser extent and rarely produce drug interaction [16,17], the last group (e.g spiramycin ,rokitamycin, dirithromycin and azithromycin) do not inactivate cytochrome P450 and are unable to modify the pharmacokinetics of other compounds [15].

The aim of the present study was to investigate the effect of single oral doses of some new macrolides (clarithromycin, azithromycin, and roxithromycin) on sensori- motor performance in humans.

Subjects & Methods:

Thirty four healthy male subjects from the 3rd year students of the College of Medicine of Al-Mustansiriya University were enrolled in the study. Their mean age was 21.5 years (range 21-22 year) and mean weight was 68 kg (range 60-80 kg). The study design was double-blind, balanced and

controlled pattern and was performed between November to December 2004. Written informed consents were obtained from all subjects. Treatments used in the study included single oral doses of clarothrimycin 500 mg tab. (Clarithromycin-KANAWATI), roxithromycin 150 mg tab. (Roxithromycin-UMEDICA), azithromycin 250 mg tab. (Azithromycin-IBN HAYAN) and placebo. All treatments were presented to subjects in identical opaque gelatin capsules. Treatments were randomly allocated to subjects according to 2-Latin-square randomization and were prepared by an independent colleague not involved in the study.

Volunteers attended the department in the morning after a light breakfast. All were drug-free the day before and abstained from taking tea & coffee during the study hours. They were divided into four groups(each consists 9 subjects); group 1 took single oral dose of 500 mg tab. Clarithromycin, group 2 took single oral dose of 150 mg tab Roxithromycin, group 3 took single oral dose of 250 mg tab Azithromycin, and group 4 took single oral dose of placebo.

Psychomotor performance test [18] was recorded before treatments and at two hours interval afterwards for 2 readings using the computerized Leeds psychomotor tester. Parameters recorded included the choice reaction time (CRT is the whole time from start of the visual stimulus to the end of the motor response measured in msec), recognition reaction time (RRT is the time from start of the visual stimulus to the beginning of the motor response measured in msec) and the critical flicker fusion frequency (CFF is the lowest frequency at which a flickering light is perceived as a continues light, or the highest frequency at which flickering is perceived, measured in Hz). Movement reaction time (MRT is the time from start of motor response to its end measured in msec) was obtained by subtraction of RRT from CRT for each recording. CRT & RRT were measured as the means of 25 recording while the CFF was taken as the mean of 5 ascending & 5 descending readings. The CRT with its two components RRT and MRT are good indicators of the sensorimotor performance while the CFF is a reliable indicator of the overall integrative activity of the CNS or the arousal state [18].

Results were statistically analyzed by ANOVA test.

Results:

Are shown in table 1 as means ± SEM of the 9 subjects. ANOVA of the results showed statistically non-significant changes following single oral doses of Clarithromycin (500 mg), Roxithromycin (150 mg) and Azithromycin (250 mg) in comparison with placebo. Performance parameters CRT, RRT, MRT & CFF did not change significantly following the three Macrolides drugs in comparison with the placebo group.

Changes across the two hours intervals of the study also showed non-significant changes following the 3 Macrolides & placebo treatments

Also the results showed that The changes of the psychomotor performance parameters in relation to baseline values in the 2^{nd} & 4^{th} hours after treatments were non-significant statistically (table 2).

Table 1 – Effect of clarithromycin, Roxithroycin, Azithromycin and placebo on psychomotor performance parameters (CRT, RRT, MRT, and CFF). Values are mean ±SEM of 9 subjects. (P>0.05).

Drug	0hr	2hr	4hr
CRT(msec) Clarithromycin	569±20	523± 14	550±18
Roxithromycin	585 ± 25	562±25	549±22
Azithromycin	603±27	558±16	553±15
placebo	570± 18	552±35	511+15
RRT(msec) Clarithromycin	365 ±12	346±9.9	352±12
Roxithromycin	367±16	356±11	347±12
Azithromycin	375±11	373±11	363±8.6
placebo	340±13	341±28	323±10
MRT(msec) Clarithromycin	203±13	185±7.3	198±13
Roxithromycin	198±12	206±17	202±17
Azithromycin	227±22	185±13	189±12
placebo	230±16	210±18	188±13
CFF(Hz)Clarithromycin	30±1.2	32±1.1	31±0.5
Roxithromycin	28±0,9	29±0.9	29±0.4
Azithromycin	28±1.2	29±1.3	28±1.3
placebo	31±1.8	33±1.5	30±1.3

Table 2: The changes in CRT, RRT, MRT (msec) & CFF (Hz) in the second, and forth hour after treatment (values are means of percent difference).

	azithromycin		clarithromycin		roxithromycin		placebo	
	2h	4h	2h	4h	2h	4h	2h	4h
CRT	6.5	6.8	7.8	2.9	2.7	4.9	4.0	10.2
RRT	0.3	2.5	5.0	3.5	6.9	9.7	-0.2	4.7
MRT	15.7	12.4	11.8	0.8	-7.6	-4.9	7.6	17
CFF	-4.1	-3.5	-6.5	-5.7	-5.7	-4.2	-4.3	-3.7

*Difference between different groups was not significant (P>0.05)

Discussion:

In this study, the use of single oral doses of clarithromycin (500 mg), roxithromycin (150 mg) and azithromycin (250 mg) showed no statistically significant impairment in the sensori-motor state and the arousal condition of healthy subjects. In the early nineties, erythromycin was the most common only used macrolide antibiotic in the united states, since 1998, azithromycin has taken the place of erythromycin with more than 30 million prescription in the year 2000[19]. Erythromycin is produced by saccharopolyspora erythraca, while the newer macrolides are semisynthetic molecules with substitutions on the lactone. Macrolides inhibit protein synthesis by stimulating dissociation of the peptidy1± RNA molecule from the ribosome during elongation [20, 21] this result in chain termination and a reversible stoppage of protein synthesis. The binding site in the 50S ribosomal subunit for erythromycin overlaps the binding site of the newer macrolides.

Their action may be bactericidal or bacteriostatic, the effect depending on the concentration and on the type of microorganism [22].In addition , macrolide have been shown to affect several pathways of inflammatory process, such as the migration of neutrophils, the oxidative burst in phagocytes, and the production of pro- inflammatory cytokines[7,23,24]. Although the precise mechanisms of these effects are not clear, it has been suggested that the interaction between macrolides and leukocytes may be important. However some have suggested that the antioxidant properties, shared by several macrolides [25], may play a role in the anti- inflammatory activity of these agents [26].Data indicate that macrolides may have immunomodulatory activities through affecting cytokine production by several cell types and altering polymorphonuclear cell function which may serve as one explanation for the beneficial effects of macrolides in patients with chronic pulmonary inflammation [10]. Moreover, various macrolide antibiotics have different electro physiological properties, as it has been noted that erythromycin, clarithromycin, and azithromycin prolong myocardial repolorization. Compared with erythromycin and Clarithromycin, the torsadagenic potential of azithromycin seems to be remarkably low [27]. Additionally, macrolide antibiotics (clarithromycin, Azithromycin, Roxithromycin and erythromycin) increase nitric oxide synthetase activity, decrease xanthin oxidase activity and malondialdehyde level which are an important markers of oxidative stress [12].It is well known that macrolide antibiotics can

interact adversely with commonly used drugs resulting in enhanced pharmacological effects and the potential for increased adverse reactions as it has been found that erythromycin prolongs the clearance of digoxin by altering the flora in the distal portion of the intestine that metabolizes digoxin to various inactive compounds and leading serum digoxin concentration to be increased substantially[28]. Clarithromycin may have similar effect on the metabolism of digoxin [29]; interaction has not been reported with azithromycin [30].

Also macrolides antibiotics inhibit the CYP3A4 isoenzyme that is responsible for most drug metabolism that enhancing more drug interaction which does not occur with non-inhibitory macrolides like Azithromycin [31].

Review of literature and Medline data survey showed no studies of these new drugs on psychomotor performance. Therefore, and because of their wide future applications as antibiotics, and anti-inflammatory this study was designed to throw some light on effects of these macrolides on some CNS function studied by the psychomotor performance test. In the doses used, they lacked any impairment effects on the sensory and motor functions and on the arousal state. These findings increase their safety profile.

In conclusion, the doses of Macrolides used in this study were free from impairment effects on the sensorimotor performance and the arousal states. Therefore, these are suitable as initial starting doses even when patients are doing heavy duties. Effects of higher doses and repeated chronic dosing are to be investigated later.

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