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Research Article

EFFECT OF ERYTHROMYCINE IN ALTERED GASTRIC MOTILITY AND PH IN WISTAR RATS

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ABSTRACT
Drug absorption through the gastrointestinal tract plays a major role in determining the systemic exposure of the drugs when administered by oral route. The physicochemical properties of the drug like particle size, polymorphism, salt forms, lipophilicity and dosage form characteristics like disintegration time, dissolution time, manufacturing variables, pharmaceutical ingredients, nature and type of dosage form are known to impact drug absorption. Apart from physicochemical properties of drug various patient related factors like gastric emptying, gastric pH, intestinal transit, disease state and GI blood flow can affect the drug absorption to a huge extent. The change in the gastric emptying, intestinal transit and gastric pH in this study was accomplished by using Metoclopramide, Atropine, Neostigmine and Omeprazole. Metoclopramide also significantly increases the blood flow by about 67.3 and 29.7% at the duodenum and jejunum.

In the present study, Patient related parameters were conducted for erythromycin in presence of metoclopromide, atropine, neostigmine and omeprazole in rats. Charcoal meal test were performed in rats to confirm the effect of above drugs on gastrointestinal motility.

KEYWORDS: Erythromycin, Intestinal transit, Gastric emptying

INTRODUCTION
Erythromycin is a 14 member macrolide antibiotic produced from a strain of the actinomyces saccaropolyspora erythraea, formerly known as Streptomyces erythraeus. It possesses broad spectrum antimicrobial activity. It is used in treatment of respiratory tract infections; it has better coverage of atypical organisms, including mycoplasma. Erythromycin is also used to treat outbreaks of Chlamydia, syphilis, and gonorrhea. It possesses spectrum similar to or slightly wider than that of penicillin, and is often used for people who have an allergy to penicillin[1].

Erythromycin displays bactericidal activity, particularly at higher concentrations, but the mechanism is not fully elucidated. By binding to the 50s subunit of the bacterial 70s r RNA complex, protein synthesis and subsequently structure/function processes critical for bacterial life or replication are inhibited. It interferes with the production of functionally useful proteins and is therefore the basis of antimicrobial action.

Various salt forms of erythromycin are available which are known to show enhance oral bioavailability. To be therapeutically active, the drug should have good serum and target selective tissue exposure. Generally speaking, rapid gastric emptying increases bioavailability of the drugs. Gastric emptying is the passage of drug from stomach to the small intestine. It is the rate-limiting step in drug absorption because the major site of drug absorption is intestine. For better drug dissolution and absorption, the gastric emptying can be promoted by taking the drug on empty stomach. Drugs are also known to alter gastric emptying rate. Drugs that retard gastric emptying include poorly soluble antacids (Aluminum hydroxide), anticholinergics (Atropine, Propantheline), and narcotic analgesics (Morphine)

and tricyclic antidepressants (Imipramine, Amitriptylene). Metoclopramide, Domperidone and Cisapride (antiemetic) stimulates gastric emptying. Taking all these factors into consideration, the present study was planned to evaluate the pharmacokinetic of erythromycin in rat by modifying the gastric motility, pH and intestinal transit. The change in the gastric emptying, intestinal transit and gastric pH in this study was accomplished by using Metoclopramide, Atropine, Neostigmine and Omeprazole[2].

MATERIAL AND METHODS

Drugs and Chemicals

1. Erythromycin base
2 Neostigmine (Batch No-101673 from neon lab. Ltd.
3. Atropine Sulfate A-0257 (Lot No.114H0645) From Sigma-Aldrich Chemical
4. Metoclopramid (Batch No.GF-9009D) From Ipca Lab. Ltd.
5. Omeprazole
6. Activated Charcoal
7. Gum Acacia(2.5%)
8. Tween 80 (1%)

Preparation of solution

1. Erythromycine suspension: Erythromycin was suspended in 1% tween 80.
2. Metoclopramid: Metoclopramid was made with Mili Q water
3. Omeprazole: Omeprazole was made with Mili Q water
4. Atropine Sulfate: Atropine Sulfate was made with Mili Q water
5. Charcoal meal: Charcoal meal was prepared with 10% of gum acacia and 10% of activated charcoal.

Experimental Animals

Adult male Wistar rats weighing 200-250 g were used. The animals were placed in an air-conditioned (18-22 ° C) animal house kept at relative humidity between 40% and 70% (except during the cleaning slot) in which non-recycled filtered air was changed approximately 10 times per hour. The artificial day/night cycle involved 12 hours light and 12 hours darkness with light on at 7.30 a.m.

Animals had free access to standard pellet diet (Amrut laboratory animal feed, Sangali - Maharashtra) and water *ad libitum*. The experimental protocol was approved by the Institutional Animal Ethics Committee IAEC and CPCSEA.

Experimental procedure of Intestinal transit

The day prior to the study, animals were kept on a water-only fast in cages with grid floors in order to minimize coprophagia. On the study day, animals were dosed as defined by the randomization plan. 15 minutes after treatment of enhancer drug, animals were given orally a suspension (with 1% Tween 80) of Erythromycin, 15 minutes after the 10 % Charcoal in 2.5 %Gum acacia (kept at 37 ° C ± 1 ° C) in a volume of 2 mL/animal administration of charcoal, animals were euthanized by cervical dislocation. Following midline la-parotomy, the stomach was ligatured at the level of the cardiac and pylorus, and then the stomach and the intestines, from the pylorus to the extremity of the caecum were rapidly removed. The intestines were spread out on a glass plate and the total length of intestine and the distance covered by the charcoal were measured immediately[3].

Experimental Procedure of Gastric Emptying

The stomach was weighed full, then it was opened, contents were washed out with water and the weight was recorded again (empty stomach weight)[3].

Presentation of results

The total length of intestine and distance covered by charcoal were expressed in cm. Results wereexpressed as percentage of the distance covered by charcoal calculated in relation to the total length of the intestine. The weight of full and empty stomach, and the weight of the stomach contents were expressed in grams. Results of gastric emptying were expressed as the amount of charcoal meal emptied.

Analysis of results

Erythromycin, Atropine, Neostigmine, metoclopromide and omeprazole treated groups were compared with control using non parametric Mann-Whitney test. Erythromycin + Neostigmine, Erythromycin

+Atropine, Erythromycin+ Metoclopromide and Erythromycin+ Omeprazole treated group were compared with Neostigmine, Atropine, Metoclopromide and Omeprazole per se treated groups respectively using the same Statistical test.
Statistical test was applied using Graph Pad prism 4

RESULTS

Intestinal transit

Small intestine transit was about 50% in the control study, showing that the front of a charcoal meal had reached the middle of the small intestine in 20 minutes Erythromycin (50mg/kg p.o.) showed highest small intestinal transit with Neostigmine(40ug/kg s.c.) as compared to others as shown in the figure 4.1.The figure also shows that small intestinal transit was significantly increased by Metoclpramide(12.5mg/kg i.v.) and Omeprazole(50mg/kg p.o.). The increase in small intestinal transit shown by Erythromycin was completely abolished by atropine(10mg/kg s.c.)[4].

Gastric Emptying

As shown in the figure the gastric emptying in the control study was over 70%, suggesting that most of the stomach contents were emptied within 15 min. Erythromycin treated animal shows delayed in gastric emptying were as erythromycin in combination with Omeprazole and Metoclpramide showed significant increased in the gastric emptying[5].

DISCUSSION

Our focus of the current topic is mainly on the patient related factors affecting bioavailability. These factors include gastric emptying, intestinal transit, gastric blood flow and gastric pH. Taking these factors into consideration our investigation was directed. Gastric emptying and Intestinal transit of erythromycin (50 mg/ kg) were studied and its interaction with atropine (10 mg/ kg, i.p.), neostigmine (40 µg/ kg i.p.), metoclopramide (12.5 mg/ kg, i.v.), omeprazole (50 mg/ kg, p.o.) was examined. From the charcoal meal study, effects of various drugs known to alter the gastrointestinal motility were assessed. Atropine being an antimuscarinic agent caused significant reduction in both gastric and intestinal motility[6].

Metoclopromide caused significant increase in both gastric and intestinal transit. Metoclopromide is also known to increase the intestinal blood flow. When erythromycin is administered along with metoclopromide no significant change in rate and extent of absorption was observed[7].

Neostigmine demonstrated increase in intestinal transit without affecting the gastric emptying[8].

Omeprazole, an antiulcer drug, not only increased the gastric pH but also facilitated the intestinal transit. Thus we can say that Erythromycin when given along with omeprazole caused significantly improvement in rate and extent of oral absorption. This could be because of mainly gastric pH neutralization[10].

Erythromycin did not affect the gastrointestinal motility of any of the above drug treatments. It possesses very poor oral bioavailability of 14% which improved with omeprazole to 30%.

Thus at the end we can conclude that alteration in gastric and intestinal transit i.e. reduction in gastrointestinal motility with atropine and increase in gastrointestinal motility with metoclopromide, neostigmine did not change the serum exposure of erythromycin.

However change in gastric pH with omeprazole significantly improved oral pharmacokinetics of erythromycin. This improvement in Pharmacokinetics is only because of pH or some other mechanism is involved needs to be further evaluated.

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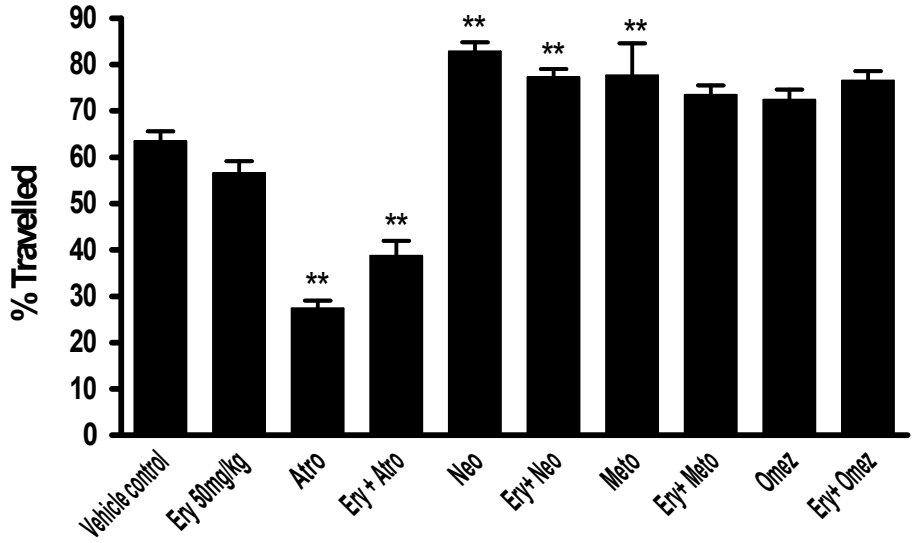
Table 1: Effect of Erythromycin 50mg/kg and Ery 50mg/kg with combination of Neostigmine, Atropine, Metoclopramide and Omeprazole on Gastrointestinal transit time in wistar rats

Sr.No	Groups	% Traveled by Charcoal
1	Vehicle control	63.50±2.058
2	Erythromycin	56.60±2.52
3	Neostigmine	82.85±1.94
4	Erythromycin+ Neostigmine	77.26±1.74
5	Metoclopramide	77.63±6.92
6	Erythromycin+ Metoclopramide	73.49±1.99
7	Atropine	27.42±1.61
8	Erythromycin+ Atropine	38.71±3.26
9	Omeprazole	72.43±2.17
10	Erythromycin+ Omeprazole	76.50±1.90

Table 2: Effect of Erythromycin 50mg/kg and Ery 50mg/kg with combination of Neostigmine, Atropine, Metoclopramide and Omeprazole on Gastric emptying in wistar rats

Sr.No	Groups	Gastric Emptying(gm)
1	Vehicle control	0.71 ± 0.074
2	Erythromycin	0.81 ± 0.203
3	Neostigmine	0.72 ± 0.088
4	Erythromycin+ Neostigmine	0.60 ± 0.082
5	Metoclopramide	0.37 ± 0.210
6	Erythromycin+ Metoclopramide	0.42 ± 0.081
7	Atropine	1.38 ± 0.24
8	Erythromycin+ Atropine	1.37 ± 0.214
9	Omeprazole	0.68 ± 0.24
10	Erythromycin+ Omeprazole	0.64 ± 0.241



Results are expressed as mean ± SEM (n = 8)
* P< 0.05 when compared with Vehicle control

Figure 1: Comparison of vehicle control group with combination of Ery 50mg/kg + Drug treated groups in Intestinal transit of wistar rats.

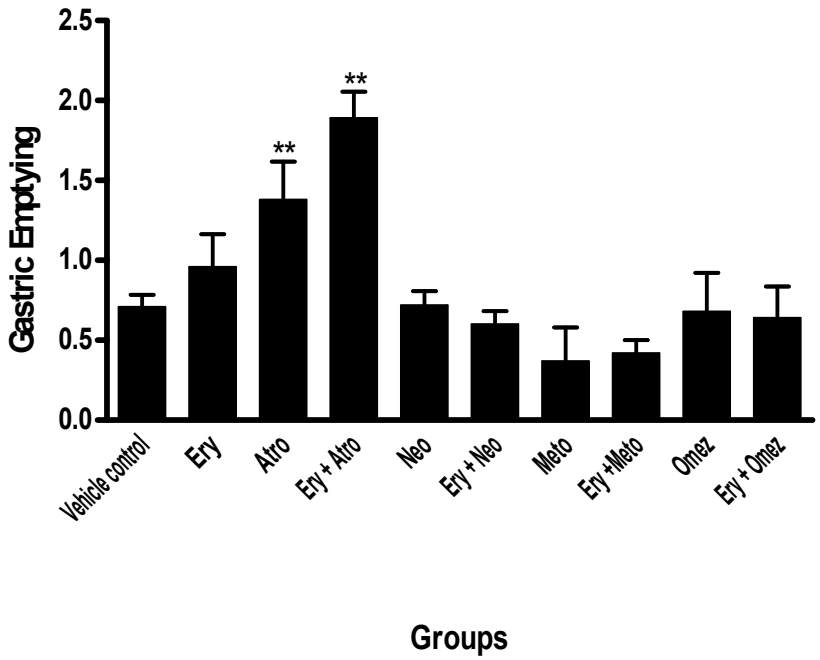


Figure 2: Comparison of vehicle control group with combination of Ery 50mg/kg +Drug treated groups in Gastric emptying of wistar rats.

Results are expressed as mean ± SEM (n = 8)
* P< 0.05 when compared with Vehicle control

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