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Research Article

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Rationale of Ornidazole and Ofloxacin in Management of Diarrhoea

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Abstract

Diarrhoea a commonest food and water born disease affecting equally from neonates to geriatrics due to varied causative pathogens, commonly presents with loose motion may be watery or varied natured stool, principally due to altered water and electrolyte absorption as a result of altered sodium potassium ATPase pump caused by altered mechanism of normally secreted bio molecules Enkephalin.

For diarrheal disease control the common prescription these days is combination of broad spectrum anti protozoal and broad spectrum anti-bacterial, among them are tinidazole–norfloxacin and ornidazole-ofloxacin, and tinidazole and co trimoxazole but unusual presentation observed and reported by patients or parent with ofloxacin and ornidazole consumption, necessitate the present evaluation which affirm superiority of Tinidazole-norfloxacin and tinidazole and co trimoxazole as compared to Ofloxacin and ornidazole in both therapeutic outcome, safety profile and drug adversity as–Ofloxacin -Ornidazole both acts on DNA and alters DNA function, possess high volume distribution thus both remain in GIT for very short duration thus fails to ensure sustained availability to sterilize the GIT while other anti-diarrhoeal composite Norfloxacin never binds with DNA but to DNA substrate, possess very low volume distribution, thus remain in GIT for comparatively longer duration, ensure gut sterility, Co trimoxazole inhibit dihydrofolate enzyme inhibiting synthesis of folinic acid, possess low volume distribution and stay longer in GIT thus check post diarrheal sequel i.e- mucous colitis and Urinary tract infection. All the three anti-diarrheal combination proved safe for haematological, hepatic and renal parameter. Thus Ofloxacin-Ornidazole remain no longer choice for Diarrheal management considering its hazards and outcome.

Key words: *Diarrhoea; Enkephalin; Sodium potassium ATPase pump volume distribution; DNA substrate; Dihydrofolate; Folinic acid; Diarrheal sequel; Mucous colitis*

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Introduction

Based on the characteristics of characteristic feature of stool, diarrhoea is classified as [3] – Acute Diarrhoea is the 3rd leading cause of childhood morbidity in India and responsible for 13% of all death among children of age < 5 yrs and decrease in diarrheal death in India is very slow. [1,2]

Watery diarrhoea	:	lasts for several days
Acute diarrhoea with blood	:	also known as dysentery
Persistent diarrhoea	:	lasts for 14 days or more

Diarrhoea, a commonest GIT problem causing encumbrance to both patients and parent. Considering a synergistic pathogenesis of diarrhoea due to [4-6] protozoa and bacterial super infection, a combination of antiprotozoal and broad spectrum quinolones are quite in vogue. Commonest among them is Norfloxacin, a quinolone with least volume distribution and plasma binding capacity i.e.- Norfloxacin was quite in use, but these days an isomer of 5 fluoroquinolone having high volume distribution and plasma binding capacity.

i.e Ofloxacin is in rampant use. Considering the pharmacokinetics of Ofloxacin and Norfloxacin, ofloxacin is more toxic than norfloxacin and due to high volume distribution and common toxicity i.e- cartilaginous osteoarthropathy, ofloxacin is never a choice at least in paediatrics. [7-9]

For diarrhoeal disease management, the composite must ensure

- Potent effect against intestinal micro organisms
- Must have low absorption and low volume distribution to have maximum effect to counter intestinal infection
- Must get excreted through kidney as migration of intestinal commensal through systemic circulation may cause post diarrhoeal urinary tract infection which in turn results in suppression of erythropoietin and erythropoiesis leading to chronic anaemia
- Amoebicidal must be potent and active against both local and extra intestinal protozoal infection
- It should not pose any toxic or untoward effect

Objective of the study

Evaluate the rationality of ofloxacin use in diarrhoea management

Duration of study

Study was conducted during January 2014 to December 2016 and cases were followed for 6 months post therapy for drug related or disease related untoward effects.

Ethical status

Ethical committee of the National Institute of Health & Research duly permitted the study, based on case data.

Material and Method

Material

Patients attending Centre For Research in Diarrhoeal Disease, National Institute of Health & Research, Warisaliganj (Nawada) Bihar and Aarogyam Punarjeevan, Ara Garden Road Jagdeo path, Baily Road, Patna 14 suffering with lose motion were selected for the evaluation and justification for use of Ofloxacin in management of diarrhoea. Patients of diarrhoea with septicaemia or any other complication were excluded from the study.

Method

Data sheet of patient of diarrhoea attended for treatment at RA Hospital & Research Centre are analysed for the clinical presentation, duration of illness, therapeutics taken, their response and were duly investigated for basic bio parameters, stool examination, urine routine and culture to asses clinical effect, disease sequel and drug adversity.

Based on clinical presentation as per data sheet selected patients were graded for the disease severity as per following index –

Degree of severity	Characteristic features
Mild	Lose motion with mucous without fowl smell Frequency of motion 5/day Mild dehydration
Moderate	lose motion with mucous with fowl smell Frequency up to 10 /day Moderate dehydration
Severe	Watery fowl smelling stool Frequency >12/day Severe dehydration

State of dehydration was adjudged as per following [10,11]

Dehydration status	Characteristics
Mild	irritable, thirsty
Moderate	irritable, weak pulse, reduced urine output Anterior fontanelle depressed, eye ball sunken, face dry and parched lips and buccal mucosa dry, skin turgor lost thirsty
Severe	moribund, apathetic, pulse weak, thread Marked reduced in the urine volume Fontanelle depressed, eye ball markedly sunken Lips parched, face markedly dried and pinched Buccal mucosa dry, loss of skin turgor and thirsty

Cases of diarrhoea were classified as per therapeutic regime -
Ornidazol and Ofloxacin: Group A
Tinidazol and Norfloxacin: Group B
Tinidazole and Co trimoxazole: Group C
Dose Schedule:
Children: 2.5-5 ml every 12 hours
Adult: 1 tab every 12 hours

Patients of either group were also taking Racecadotril to monitor Sodium Potassium ATPase pump to bioregulate absorption of fluid and electrolyte in following dose schedule -
Children: 10-15mg sachet every 8 hours
Adult: 100mg Cap every 8 hours

Patients were analysed for outcome of therapy i.e.- decrease in frequency of stool and water loss, change in faecal matter consistency, total duration in achieving formed stool, post diarrhoeal sequel i.e. urinary tract infection, mucous colitis and nephritis.

Post therapy status of stool, urine, haematological, hepatic and renal bio parameters were analysed to ascertain the clinical outcome and safety profile.

In addition any unusual presentation were duly recorded in either group of patients. Clinical response achieved was graded as per following index of achievement

Clinical grades	Characteristics
Grade I (Excellent)	Decline in frequency and change in consistency of Stool, formed stool in 12 hrs. Recovery with minimal Water and electrolyte supplementation, reduced Duration of illness and ultimately cost of therapy Without any drug or diseases related untoward effect No reversal, No post therapy sequel
Grade II (Good)	Decline in frequency and change in consistency of stool in 48 hours, recovery on fluid and electrolyte intravenous Supplementation, persistence of 2-4 lose mition daily with post therapy sequel
Grade III (Poor)	No response, worsening of diarrhoea

Observations

Selected patients were of age group 5-50 years and 572 were male and 468 female (T-1, figure 1). Out of all majority patients 436 (42%) were presenting with 5 motions per day while 210(20.2%) were with >12 motions per day (Figure 2) 508(48%) patients were presenting with watery fowl smelling stool, 344 (33%) with mucous and fowl smell while 188(18.1%) were with non-fowl smelling stool presenting since long duration (figure -3). Out of all 488 patients presented within 24 hours of illness while 198 after 5 days (figure -4). Stool examination reveals 276 (26.5%) viral, 504 (48.5%) bacterial, 140(13.5%) protozoal and 120 (11.5%) parasitic. (T-2). 59.6% patients are on Ofloxacin-Ornidazol, 27% Norfloxacin-Tinidazole and 13.4% on Co trimoxazole-Tinidazole combination (T-3)

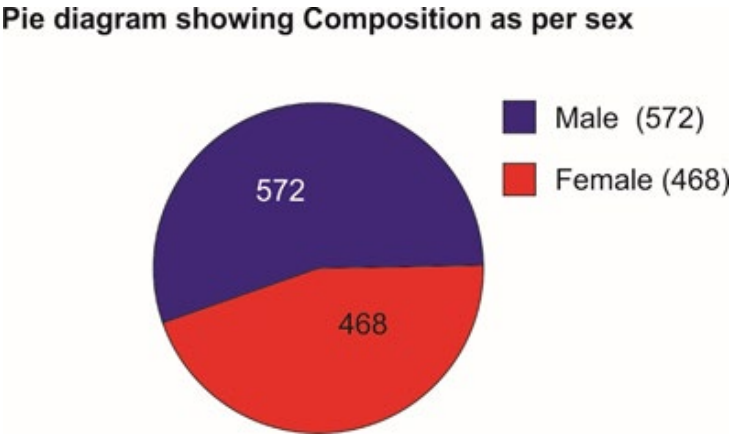


Figure 1:

Age group (In years)	Number of patients		
	Male	Female	Total
5-10	28	32	60
10-15	32	24	56
15-20	74	65	139
20-25	64	57	121
25-30	70	64	134

30-35	68	49	117
35-40	105	78	183
40-45	86	62	148
45-50	44	37	81

Table 1: *Distribution of patients as per age and sex.*

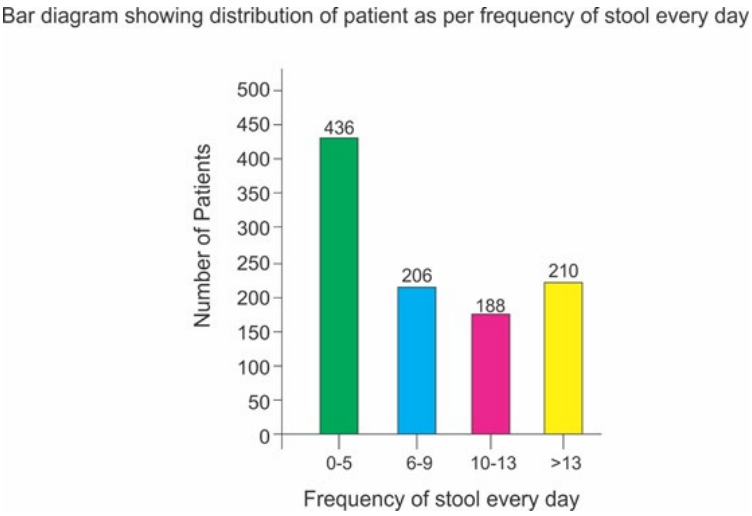


Figure 2:

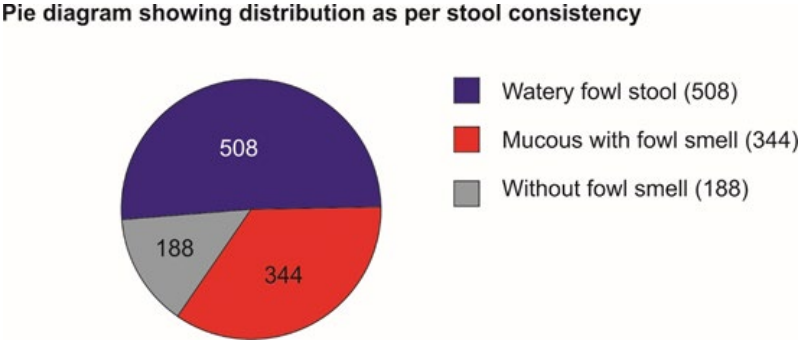


Figure 3:

Isolated organism	Number of patients	Percentage
Viruses	276	26.5
Bacteria	504	48.5
Protozoa	140	13.5
Helminthes	120	11.5

Table 2: *Showing distribution of patients as per causative pathogens.*

Therapeutic group	Number of patients	Percentage
Ofloxacin -Ornidazole (A)	620	59.6
Norfloxacin-tinidazole (B)	280	27.0
Cotrimexazole-tinidazole (C)	140	13.4

Table 3: *Showing distribution of patients as per their therapeutic status.*

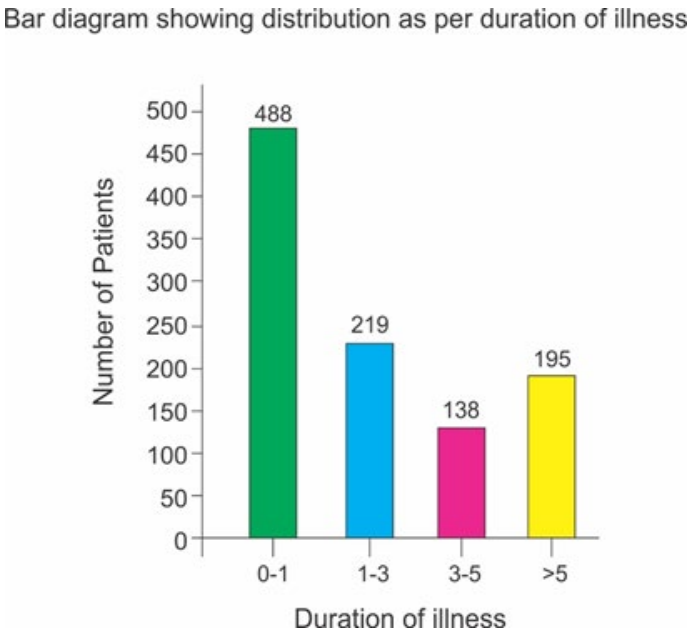


Figure 4:

Patients taking Ofloxacin and Ornidazole though achieves changes in faecal matter consistency in 24 hours of therapy but lose motion persist for more than 3-4 days with pain in abdomen. Heaviness in the abdomen recurrent fever, mucous in the stool, lethargy and in some cases (30%) agonizing leg cramps. 46% patients needed fluid and electrolyte intravenous supplementation. (T-4, Figure -5)

Clinical presentation	Number of patients		
	Group A	Group B	Group C
Nausea	510	12	8
Vomiting	210	10	2
Abdominal pain	385	6	-
Abdominal distension/heaviness	402	7	-
Uneasiness	600	7	02
Dryness of mouth	578	3	01
Headache	108	2	-
Dizziness	103	-	-
Vertigo	103	-	-
Rash	84	8	-
Pruritis	84	8	-

Insomnia	128	-	-
Visual disturbances	34	-	-
Leg cramps	398	-	-

Table 4: *Showing presentation during therapy.*

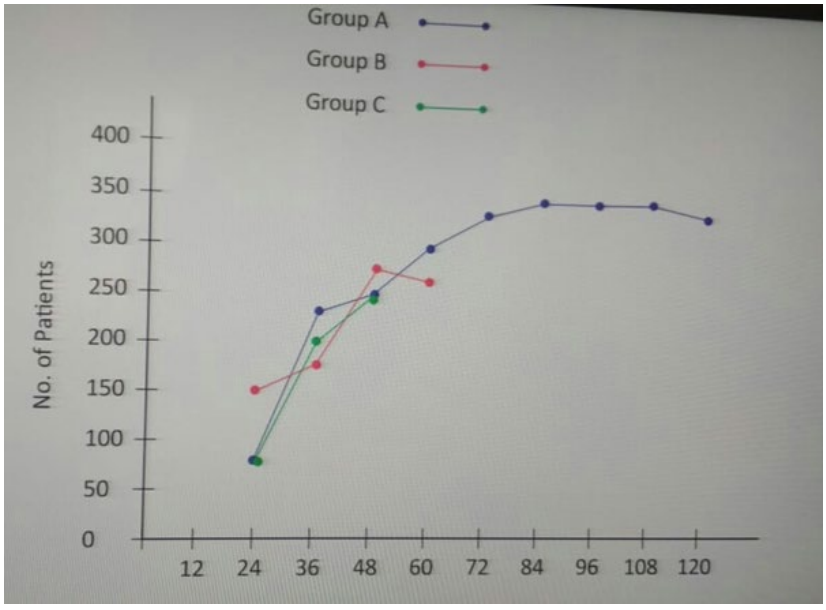


Figure 5: *Graph showing status of achievement of formed stool in various therapeutic group.*

Characteristics	Number of patients		
	Group A	Group B	Group C
Duration required for			
Change in faecal matter Consistency	24 Hrs	30 Hrs	36 Hrs
Diarrhoea persistence	3-4 days	-	-
Post therapy stool status			
Positive for pathogen	40%	-	-
Sterile	60%	98%	94%
Needed fluid & electrolyte			
Replacement	46%	None	None
Post diarrheal mucous colitis	30%	None	None
Post therapy Urine status			
Sterile	All	All	All
Status of bio parameter:			
Haemopoietic	Unaltered	Unaltered	Unaltered
Hepatic	Unaltered	Unaltered	Unaltered
Renal	Unaltered	Unaltered	Unaltered

Clinical Grade:			
Grade I	-	98%	94%
Grade II	80%	02%	06%
Grade III	20%	-	-

Table 5: *Showing outcome of therapy.*

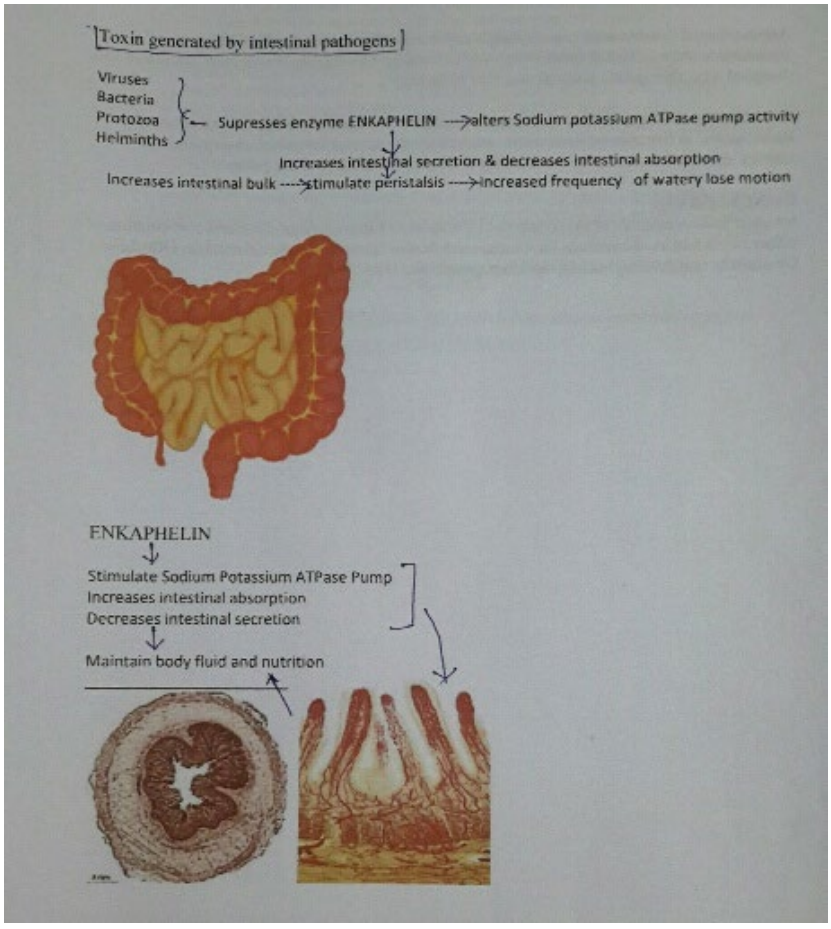
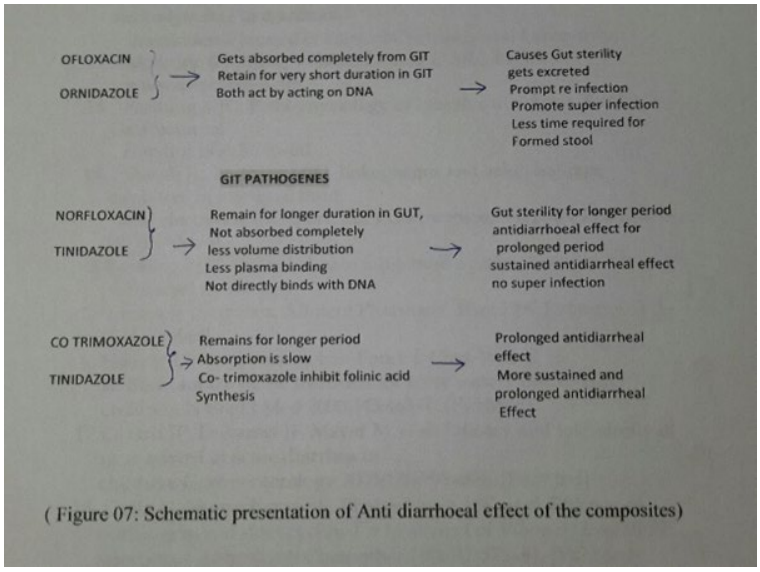


Table 6: *Showing schematic presentation normal intestinal mechanism.*

Patients taking norfloxacin with tinidazole and co trimoxazole with tinidazole achieved formed stool in 30 hours without any untoward effect like pain in abdomen, mucous colitis, heaviness in abdomen, nausea vomiting and fever. No patients required any fluid and electrolyte replacement.

Post therapy stool examination reveals – 40% patients taking Ornidazole -Ofloxacin, positive for causative pathogen while others taking norfloxacin-tinidazole and Cotrimoxazole-tinidazole shows complete absence of causative pathogen, in addition mucous was predominant in 30% cases on Ornidazole -ofloxacin therapy.

On completion of therapy clinical response grading reveals grade I response in 98% cases of both taking Norfloxacin-Tinidazole and Cotrimoxazole -Tinidazole, 80% cases on ofloxacin- ornidazole shows grade II response in 86% while rest shows grade III response. No patients of either group show any alteration in haematological, hepatic and renal parameters. (Table-5)



(Figure 07: Schematic presentation of Anti diarrhoeal effect of the composites)

Table 7: *Schematic presentation of antidiarrheal effect.*

Discussions

Diarrhoea ,usually a symptom of intestinal tract infection or intoxication is a second leading cause of death in children i.e.- 1.7-5 millions death per year common in developing country and usually infection is caused by virus, bacteria ,protozoa and parasites. [12,13]

Commonly prescribed antidiarrheals consist of potent antiprotozoal and antibacterial combination irrespective of age considering protozoal infection a common associate but considering diarrhoea etiopathogenesis i.e- [14-16]

Alteration in Sodium potassium ATPase activity decreases intestinal absorption and increases intestinal mucosal secretion resulting in increased intestinal bulk and irritation of intestinal mucosal nerve ends causing hyperperistalsis presenting as lose motion and electrolyte and water loss.

Thus in present analysis a common composite prescription i.e.- Racecadotril to every patient irrespective of anti-diarrhoeal regime ,which activate the enzyme modulated Sodium Potassium ATPase pump i.e.- Enkephalin ,secreted by the intestinal gland which stimulate Sodium Potassium ATPase pump and promote intestinal absorption and restrict intestinal secretion of intracellular fluid, thus help achieve formed stool. [17-20]

Antiprotozoal and antibacterial are prescribed to combat infection and super infection, as normal commensal become pathogenic due to migration from its normal site. The prescribed composites are Ofloxacin-Ornidazole. Norfloxacin Tinidazole and Co- trimoxazole – Tinidazole.

Clinical superiority of two combinations i.e- Tinidazole – Norfloxacin and Tinidazole – cotrimoxazole over commonly prescribed Ofloxacin-Ornidazole, can be explained as [21-29]. Ornidazole, a nitro group of drug reduced by redox protein to reactive nitro radicals, which produces cytocidal action by destabilizing DNA helix and posses high volume distribution. Ofloxacin, a rapidly and completely absorbed after oral ingestion, widely distributed in the body due to its high volume distribution and acts as bactericidal by acting on DNA (DNA gyrase and topoisomerase II & IV), prevent DNA transcription to RNA and subsequent protein synthesis. While in other two combination, antimicrobial absorbs very slowly and posses low volume distribution thus remain longer in the GIT, facilitate longer action on intestinal pathogen ensuring early recovery and cure without any untoward effects.

Thus still Norfloxacin -Tinidazole combination remains best option as antidiarrheal than Ofloxacin-Ornidazole. Hence prescription of Ofloxacin -Ornidazole be restricted for diarrhoea management, considering the therapeutic effect and observed hazards.

Norfloxacin never binds with DNA but binds with substrate DNA, while Ornidazole and Ofloxacin both acts on DNA, poses combined toxicity and hazards commonly observed by patients of either age.

Tinidazole is nitro imidazole which has broad spectrum cidal activity against Protozoa and some anaerobic bacteria. Its selective toxicity to anaerobic microbes enters the cell by diffusion .Nitro group of drug is reduced by redox proteins present only in anaerobic organisms to reactive nitro radical which exerts cytotoxic action by DNA helix destabilization &strand breakage. Co trimoxazole inhibit successive steps in the folate synthesis pathway by its effect on enzyme dehydrofolate reductase (Figure 6, Figure 7)

Result

Antidiarrheal combination constituting Norfloxacin -Tinidazole and Tinidazole -Co trimoxazole shows clinical superiority over Ofloxacin -Ornidazole in outcome, quality of life, hospital stay, therapeutic hazards and cost of therapy.

In addition to bio regulate most cumbersome fluid and electrolyte loss prescription of Racecadotril in therapeutic dose seems mandatory to increase intestinal absorption and restrict intestinal secretion by modulating Sodium potassium ATPase pump.

Conclusion

For diarrhoea management prescription of Racecadotril in prescribed dose and combination of either Norfloxacin -Tinidazole or Cotrimoxazole-tinidazole to be preferred than Ofloxacin -Ornidazole considering toxicity and therapeutic outcome.

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