

STUDY OF EFFECT OF THE DOSE AND DURATION OF METRONIDAZOLE ON AMEBIC COLITIS AND PLATELETS

Dr. Adnan Muhsin CABP , FICMSP , DCH*,
Dr. Tariq Khudair CABP , FICMSP*,
Dr. Amin Turki CABP , DCH

ABSTRACT :

Background and Objective : Amebiasis caused by Entamoeba Histolytica (E.H) is a common problem in areas with poor hygiene . Metronidazole is abroad antiprotoza agent used in symptomatic or asymptomatic infection .

Aim of Study : To findout which idial course duration 7 or 10 days and which logical effective dose 30 mg / kg or 50 mg / kg for treatment of amebiasis beside effect the dose on platelets .

Method : Prospective study was conducted on (171) hospitalized patient at Bint – Al-Huda hospital during the period from the 1st of May 2010 to the 1st of May 2011 , suffering from amebic colitis .

The patients divided for four groups . Group A (45) patient treated by 30 mg/kg and group B (47) patient treated by 50 mg/ kg for 7 days . Group C (38) patient treated by 30 mg/ kg and group D (41) treated by 50 mg / Kg for 10 days .

The diagnosis of amebiasis depend on positive fresh stool sample for E.H trophozoites and followed more than once . Platelets count performed for all patient at the end of each course .

Result : The 7 days treatment course cure (86.6 %) of patient from group A and (89.4%) for group B, while 10 days treatment course cure (94.4%) of group C and (96 %) for group D. Duration of bloody diarrhea in group A was (89. ± 14 hrs), group B (86.± 21.98hrs) , group C (85.2 ± 17.76 hrs) and group D was (83. ± 14.97) . So the dose difference 30 mg/ kg or 50 mg / kg not affect the duration of bloody diarrhea significantly . P value > 0.05 .

One patient from group D develop thrombocytopenia , four patients develop dark urine in presence of normal heamostasis .

Conclusion : Amebiasis is a great problem in our locality and 30 mg / kg for 10 days of metronidazole course so effective equally to that 50 mg/kg , therefore the former course looked more logical unless the infection so severe , because the less dose administration the least side effects . Effect the dose and duration of metronidazole on platelets need to be investigated more .

* Department of Paediatric . Thi-Qar College of Medicine .

INTRODUCTION

Infection with *Entamoeba Histolytica* (E . H) affects much as 10% of the worldwide population with the highest prevalence seen under developed countries , and low sanitary standard ^{(1), (2)} . In most infected individuals E. H. parasites enter the lumen of the gastro-intestinal tract and causes few or no symptoms or sequelae ⁽³⁾ . Amebiasis is the 3rd leading parasite cause of death worldwide . It is estimated that infection with E. H. leads to 50 million cases of symptomatic disease and 40000 – 110000 death annually ^{(4), (5), (6)} . Infection is established by ingestion of parasite cysts which measure 10 – 18 mm in diameter and contain 4 nuclei and can resist unfeverable condition including gastric acidity . After ingestion the cyst excyst in small intestine to form trophozoite which then colonize the lumen of large bowel and may invade the mucosa ^{(2), (7)} . Invasion is accomplished by lytic enzymes secreted by trophozoites which result in tissue necrosis and erosion of blood vessels . The colonic lesions may vary from small pinched erosion confined to the cecum and recto sigmoid to extensive , deep confluent ulcers extending throughout the colon . Similarly to the bowel liver abscess is characterized by localized necrosis without much inflammatory response ^{(3), (8)} . Clinical features range from asymptomatic cyst passage to amebic colitis , amebic dysentery which may occur within 2 weeks of infection , the onset is usually gradual with colicky abdominal pain and frequent bowel motion , stool are blood stained . Fever accompany in only one third of patients severe fulminating dysentery is associated with watery blood stained , mucoid stool , fever , chills resulting in dehydration , electrolyte disturbance , toxemia , abdominal pain , tenesmus and

tenderness , and rarely to be perforated ^{(9),(10),(11), (12)} . Enlargement of the liver may occur without evidence of an abscess presumably the result of toxic product transported in the portal vein from the diseased bowel ⁽¹³⁾ .

Diagnosis : In patient with clinical features , microscopical demonstration of E.H trophozoites is probably sufficient for diagnosis ^{(3), (11), (14)} . Enzyme-linked immunosorbent assays is sensitive and specific in more than 90% ⁽¹⁵⁾ . Polymerase chain reaction (PCR) testing of stool is highly sensitive and specific ⁽¹⁶⁾ . Serological test are useful for diagnosis of extra-intestinal amebiasis including abscess or severe invasive infection ^{(3), (15)} . Imaging study very helpful in diagnosis liver abscess ⁽¹³⁾ .

Treatment : Invasive disease should be treated by metronidazole in a dose 30 – 50 mg/kg / day in 3 divided doses for 7 – 10 days or Tinidazole 50 mg/kg / day once daily for 3 days followed by paramomycin 30 mg/kg/day in 3 divided doses for 7 days . Or Diloxinide furate 20 mg / kg / day in 3 divided doses for 10 days ^{(2), (3), (8), (11)} . Chloroquine may be used in liver abscess beside metronidazole . For asymptomatic patient should be treated by diloxinide furate 20 mg / kg / day for 10 days ^{(3), (8), (17)} . Paramomycin can be used for eradication of cyst carrier ⁽¹⁸⁾ .

PATIENTS & METHODS :

Prospective study carried out in Bint Al-Huda Maternity and Pediatric Teaching Hospital in Al-Nassiriyah city were admitted to the hospital and studied during the period from the 1st of May 2010 to the 1st of May 2011 . Four different groups of patients suffering from bloody diarrhea due to amebiasis and fulfilling the following finding .

1. Bloody diarrhea diagnosed macroscopically and microscopically for presence of E.H. trophozoites .
2. Colicky abdominal pain .
3. All patient not suffering from any chronic health problems and exclude any other cause for bloody diarrhea .

All patients received routine care with correction of dehydration beside that all patients send initially for stool examination microscopically of fresh sampling that reveal positive for E . H . Trophozoites . Preschool patients in this present study divided for Four groups . Group A consist of (45) patients , group B consist of (47) patients , treated for 7 days course of metronidazole by a dose of 30 mg/kg and 50 mg/kg respectively . Group C consist of (38) patients and group D consist of (41)patients , treated for 10 days course of metronidazole by a dose 30 mg/ kg and 50 mg / kg respectively . The stool sampling repeated again at 3rd and 5th days of treatment , for all patients , another stool sample done at the end of each course for presence or absence of trophozoites or cyst . Many patients out of our cases excluded from the study due to loss of the attachment at the end of the courses . All the patient send at the end of each course for complete blood count including platelets . One patient from group D develop thrombocytopenia , therefore he send for bleeding time test , however the platelets return to normal after 3 weeks of metronidazole cessation . All the patients above 2 years received diloxinide furate for 10 days after metronidazole course . The result were analyzed statistically using mean standard deviation and P. value .

RESULTS :

A total (171) preschool patient presented in this study divided for four groups .

Table (1) shows the patients that treated for 7 days metronidazole course in a dose 30 mg/kg for group A , and 50 mg / kg for group B , to assess the effectiveness of the 7 days course for eradications of amebiasis . Both groups looks similar regarding the mean age ($5. \pm 0.79$ for A and 4.75 ± 0.99) which is statistically not significant . P. value > 0.05 . Duration of bloody diarrhea in group A was $89. \pm 14$ hrs while in group B was $86. \pm 21.98$ hrs . This difference statistically not important . P value > 0.05 . After 5 days of treatment 15 patient (33 %) of group A were positive for trophozoties or cysts of H . E . compared to that of group B with 15 patients (31.92) . So there is no any superiority of the dose at this stage of treatment . P. value > 0.05 . At the end of 7 days course , 6 patients (13.3 %) of group A and 5 patients (10.6%) of group B positive for presence of E.H. cyst . This indicate 7 days course in present study failed to eradicate amebiasis in both 30 mg/kg or 50 mg/kg and this the critical point .

Table (2) shows the patients that treated for 10 days course of metronidazole in a dose of 30 mg / kg for group C and 50 mg / kg for group D for assessment the effectiveness of this course for eradication of amebiasis . Both groups C and D relatively similar mean age $5. \pm .6$ for C and $5. \pm . 38$ for D and the result not statistically significant . The duration of bloody diarrhea in group C was 85.2 ± 17.76 hrs while in group D was 85.6 ± 14.97 and the result not significant statistically , so the dose deference not affect the duration of bloody diarrhea as in group A and B . After 5 days 13 patients (34.2 %) of group C positive for trophozoites or cysts of E . H. versus 12 patients (29.3 %) for group D . At the end of 10 days course 2 patients (5.3 %) of

group C and 2 patients (4.87%) of group D were positive for E. H. The difference taken together, these results indicate that 10 days course in both doses can cure more patient than 7 days course as shown in figure (1). The figure shows metronidazole cure rates 86.6% for group A, 89.4% for group B, while 94.7% for group C and 96% for group D. At the end of 2 courses all of patients with normal platelets count except one male patient from group D with account 125,000, however the bleeding time was normal and the platelets return to normal at 3 wks after cessation of metronidazole course. Four patient (2.3%), one from group B, one from group C and two from group D develop dark urine during the treatment, all of them with normal platelets count and bleeding time and only one patient positive for urine R.B.C.

DISCUSSION :

According to the conditions of our locality and presence of unsanitary media like bad sewage system drainage, contamination of most water supplied for drinking, cleaning and dishwashing, therefore amebiasis so common in our society and according to this fact, metronidazole became the most famous drug that prescribed by specialist and even by general population without doctors consultation. This study primarily was performed to determine which is the best course of study medication (Metronidazole) for treatment of amebiasis, regarding the duration of the course (7, or 10 day) and which effective dose (30 mg/kg or 50 mg/kg). So the aim of study to reach the best effective course with least side effects of the dose. This study deal with preschool patients because complications like dehydration, electrolyte disturbance and malnutrition occur mostly at this age group. In present

study group A and group B treated with metronidazole by 30 mg/kg and 50 mg/kg respectively. Bloody diarrhea stop after $89. \pm 14$ hrs for group A and $86. \pm 21.98$ for group B, and so on duration of bloody diarrhea at group C (85.2 ± 17.76) and ($85. \pm 14.97$) for group D. These differences statistically not significant. These finding little bit higher than that reported by Mansour - Ghanaie⁽¹⁹⁾. So this part of study tell us there is no significant difference for shorting the duration of bloody diarrhea by increasing the dose up to 50 mg/kg rather than 30 mg/kg. P. value > 0.05. The study medication metronidazole was administered as (30 mg/kg) for group A and (50 mg/kg) for group B, 3 times daily for (7) days. Cure rates, were (86.6%) for group A and (89.4%) for group B. These finding similar to that fined by A bid M et al (20). So according to this finding 7 days course with 30 mg/kg or 50 mg/kg leave some patient suffering from the infection, so the study considered the course not ideal for treatment of amebiasis. Metronidazole again was administered as 30 mg/kg for group C and 50 Mg/kg for group D, but for 10 days course duration. Cure rates for group C were (94.4%) and (96%) for group D. The difference between the 2 doses not significant statistically regarding the cure rate P. value > 0.05. This finding higher than that reported by Powell SJ⁽²¹⁾. So both doses for 10 days course give relatively similar high cure rates, therefore this course (10 days) consider ideal for treatment of amebiasis, but which dose (30 mg/kg or 50 mg/kg) can be chosen, therefore to minimize the multiple side effect of metronidazole, we can choose the least dose that give more care rate. So 30 mg/kg for 10 days duration consider a logical course for treatment of amebic colitis. Severe infection may need 50

mg/kg for 10 days . One male patient receive 50 mg / kg from group D develop thrombocytopenia . Is this finding related to the high dose of metronidazole especially the reading return to normal after cessation of treatment , this need to be investigated more . Presence of dark urine occur more at patients that received 50 mg/kg . It is related to the dose or not need to be investigated again and again .

CONCLUSION :

Amebiasis still so common in our society need to be treated by metronidazole . The dose 30 mg/kg or 50 mg/kg course treatment for 10 days so effective , and the former dose appear to be more logical and the cause related to less side effects . Effect the dose on platelets in need to be evaluated more many times .

TABLES

Table 1 : Seven days course of Metronidazole .

	Group A 30 mg/kg No. = 45	Group B 50 mg/kg No. = 47
Age (Yrs)	5. ± 0.79	4.75 ± 0.99*
Duration of bloody diarrhea (hrs)	89. ± 14	86. ± 21.98*
positive stool result at 5 days of treatment for E . H	15 (33 %)	15 (31.9 %)*
positive stool result at end the course for E . H	6 (13.3 %)	5 (10.6 %)*

* P. value > 0.05

Table (2) 10 days course of Metronidazole

	Group C 30 mg/kg No. = 38	Group D 50 mg/kg No. = 41
Age (Yrs)	5. ± 0.60	5. ± 0.38*
Duration of bloody diarrhea (hrs)	85.2 ± 17.76	85. ± 14.97*
positive stool result at 5 days of treatment for E . H	13 (34.2 %)	12 (29.3 %)*
positive stool result at end the course for E . H	2 (5.3 %)	2 (4.87 %)*

* P. value > 0.05

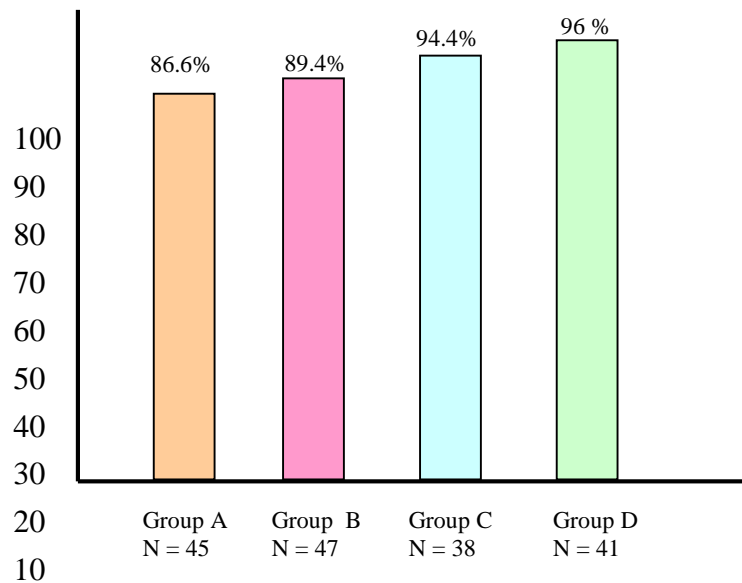


Figure (1) Percentage of patients that cured by Metronidozole

REFERENCES :

1. Bradly Haward Kessler : Entamoeba Histolytica . In : Oski's Essential paediatrics . Michael Crocetti , Michael A. Barone 2nd ed . 2004 : 351 – 2 .
2. Adriana Werinberg, MD, Myron J Levin, MD: Parasitic Infection. In: Current Diagnosis and Treatment in Pediatrics . William W. Hay , JR , Myron J. Levin , Judith M. Sondheimer . 18th ed . 2007 : 1225 – 7 .
3. Chandy C. John and Robert A. Salata : Amebiasis . In : Nelson textbook of Pediatrics . Robert M. Kliegman MD , Richard E. Behrman MD , Hal . B. Jenson , MD . 18th ed . 2007 : 1460 – 2 .
4. Trol , H. , H. Marti and N. Weiss : Simple differential detection of Entamoeba Histolytica and Entamaeba Dispar in Fresh stool specimens by Sodium acetate-acetic acid – formalin concentration and PCR. J. Clin . Microbiology 1997 . 35 ; 1701 – 1705 .
5. Stanley , S. L. , Amobeiasis . The Lancet . 2003 . 36 : 1025 – 1034 .
6. Voigot H , Olivo JC , Sansonetip , Guillen N. Mysin IB From Entamaeba Histolytica involved in phagocytosis of human erythrocytes . 1999 . J cell science 112 : 1191 – 1201 .
7. Nahed Abdel-Hag, MD: Pimparada chearskul MD , Yaseen Rafee ; Parasitic infections : In American Academy of pediatrics Textbook of pediatrics care. Thomas K. McInerny , Hery M. Adam , Dehorah E. Campbell . 2009 : 2372 – 73 .
8. A. G. M. Campbell : Infection . In : Forfar and Arneil's textbook of pediatrics . A G. M Campbell , Neil McIntosh . 5th ed . 1998 : 1467 – 69 .
9. Brain Coulter . Tropical Paediatrics Medication . In : Practical paediatric problems . Jim Beattie , Robert Carachi . 5th ed . 2005 : 635 – 6 .
10. Bradly . Howard Kessler : Entamoeba Histoytica . In : Oski's pediatrics . Julia A. McMillan , Ralph D. Feigin , Catherine D. Angelis . 4th ed 2006 : 1321 – 135 .

11. Hal B . Jenson and Robert B. Baltimore : Infections Disease . In : Nelson Essential of pediatrics . Robert M. Kliegman , Karen J . Marcadante , Hal . B. Jenson . 5th ed . 2006 : 513 – 18 .
12. Artizabal H , Acevedo J , Batero M ; Clinical Features Fulminant Amebic Colitis . World J Surg . 1991 ; 15 : 216 – 221.
13. Kat Zenstein D, Rickerson V , Braude A. Liver abscess . New Concepts of amebic liver abscess derived from hepatic imaging . Serodiagnosis , San Diago , 1982 ; 243 – 246 .
14. Tanyaskel , M. , and W. A. Petri Jr., Diagnosis Laboratory Diagnosis of Amebiasis . Clin . Microbiol Rev, 2003 , 16 ; 713 – 729 .
15. Pillai, D. R. and K. C. Kain ; Immunchromatographic strip-based detection of Entameba Histolytica , Entamoeba Dispar and Giardia lamblia coproantigen . J. Clin . Rev. , 2003 : 37 ; 3017 – 3019 .
16. Heckendron F , N'Goran EK , Felger I , Vounatson P , Yapi A , et al Species – specific testing of Entamoeba Histolytica . Spp . in an area of endemicity . Trans R Soc. Trop Med Hyg . 2007 . 96 ; 521 – 528 .
17. Dupony – Camet : New drugs for the treatment for human parasitic protozaa . parasitology . 2004 . 46 ; 81 – 84 .
18. Blassmann J . Tannich E. Treatment of asymptomatic intestinal Entamoeba Histolytica infection . N Engl J Med . 2002 ; 15 : 335 – 337 .
19. ManSour – Ghanaei F, Dehbashi N Yazdan Parast K , Sh'afaghi A , . Efficacy of succharomyces boulardii with antibiotics in acute amebiasis . World Gastroenterol . 2003 . 9 ; 1832 – 1833 .
20. Abid M. et al , European Journal of Medicinal Chemistry 43 (2008) 2035 – 2039 .
21. Powell SJ, Macleod I , Wilmot AL , Elson- Dew E . Metronidazole in amebic dysentery and amebic liver abscess .

تأثير الجرعة وفترة المعالجة لعقار المترونيدازول على التهاب القولون الاميبى والصفائح الدموية

د. عدنان محسن* ، د. طارق خضير* ، د. أمين تركي*

الخلاصة :

الزحار الاميبى مشكلة شائعة في المناطق قليلة النظافة العامة والتي تستوجب دائما استخدام عقار المترونيدازول . هدف الدراسة ايجاد الفترة الزمنية المثالية للعلاج من ناحية فترة العلاج اما ٧ يوم او ١٠ أيام مع ايجاد الجرعة المناسبة ٣٠ ملغم /كغم أو ٥٠ ملغم /كغم . مع تأثير الجرعة على الصفائح الدموية . اجريت الدراسة على (١٧١) طفلا دون سن الدراسة الابتدائية رقدوا في مستشفى بنت الهدى التعليمي من الفترة آيار ٢٠١٠ الى آيار ٢٠١١ وكانوا يعانون من الزحار الاميبى . تم توزيع المرضى الراقدين الى أربع مجاميع . المجموعة (أ) تتألف من (٤٥) مريضا تناولوا جرعة ٣٠ ملغم/كغم والمجموعة (ب) تتألف من (٤٧) مريض تناولوا جرعة ٥٠ ملغم /كغم وذلك لفترة ٧ أيام معالجة . المجموعة (ج) تتألف من (٣٨) مريض تناولوا جرعة ٣٠ ملغم/كغم والمجموعة (د) تتألف من (٤١) مريض تناولوا جرعة ٥٠ ملغم/كغم وذلك لفترة ١٠ أيام . تشخيص العدوى اعتمد على الاعراض السريرية ووجود الطفيلي داخل عينة البراز المأخوذة حديثا واعد لأكثر من مرة . فحص الصفائح الدموية اجري لكل حالات الدراسة في نهاية فترة العلاج .

النتائج :

في فترة العلاج الممتدة لسبعة أيام تم شفاء (86.6%) للمجموعة (أ) و (89.4%) للمجموعة (ب) بينما في فترة العلاج الممتدة لعشرة أيام كانت نسبة الشفاء للمجموعة (ج) (94.4%) و (96%) للمجموعة (د) . فترة وجود الاسهال الدموي للمجموعة (أ) كانت (14 ± 89) ساعة ، المجموعة (ب) (21.98 ± 86) ساعة ، المجموعة (ج) (17.76 ± 85.2) ساعة والمجموعة (د) (14.67 ± 85) ساعة ، لذلك هناك وضوح عدم تأثير زيادة الجرعة من ٣٠ الى ٥٠ ملغم/كغم على فترة الاسهال الدموي من الناحية الاحصائية . مريض واحد من المجموعة (د) اظهر نقصا في الصفائح الدموية . أربعة مرضى عانوا من انصبغ الادرار بلون داكن ثلاثة من هؤلاء تناولوا جرعة 50 ملغم /كغم .

الاستنتاج :

الزحار الاميبى ما زال يشكل مشكلة في بيئتنا . جرعة العلاج سواء كانت ٣٠ ملغم/كغم او ٥٠ ملغم/كغم ولفترة ١٠ أيام جدا فعالة في القضاء على المرض وبالتساوي تقريبا لذلك ٣٠ ملغم/كغم لفترة ١٠ أيام تبدو اكثر منطقية للعلاج وذلك لقلة الجرعة وهذا يعني بالتأكيد قلة الاعراض الجانبية . تأثير فترة وجرعة المترونيدازول على الصفائح الدموية تحتاج الى دراسة أكثر للاثبات .

* د. عدنان محسن ، د. طارق خضير ، د. أمين تركي / كلية الطب / جامعة ذي قار .