The Incidence (Extent) of Crystalluria, following Co-Trimoxazole or Trimethoprim Administration in Children with (4-10) years old age in Bint Al- Huda teaching hospital in Thi-Qar

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ABSTRACT

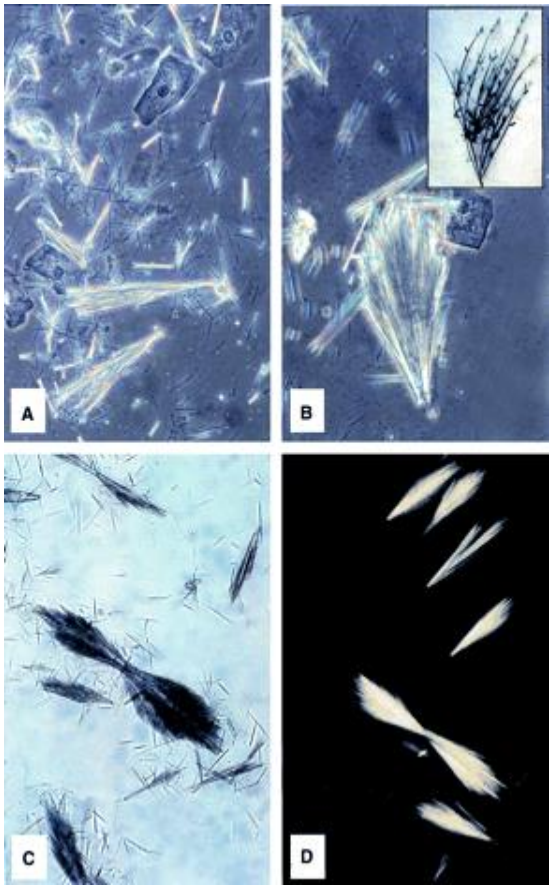
This present study, reflect the incidence of crystalluria among children (4-10) years old, in which the extent of crystalluria were more in patients who were suffered from G.I.T. infections 65(56.52%), more than those patients who were suffered from R.T.I. and were treated by co-trimoxazole. Also this study showing as, that the patients who were treated by only co-trimoxazole, were highly exposed to crystalluria 88(76.52%), more than those patients who were treated by both co-trimoxazole and I.V. fluid 27(23.43%). Also we found that crystalluria were developed more in female patients 74(64.34%), than male patients 41(35.62%).

Key words: Co-trimoxazole or Trimethoprim, crystalluria

INTRODUCTION

Co-trimoxazole (sulfamethoxazole plus trimethoprim), the optimum synergistic in vitro effect against most susceptible bacteria is achieved with 5:1 ratio of sulfamethoxazole to trimethoprim, although concentrations achieved in tissues vary considerably**(1)**. Co-trimoxazole the , at least first very largely replaced the use of a sulphonamide alone, in which trimethoprim on its own is now used in many conditions for which the combination was originally recommended, and it may cause fewer adverse reaction than co-trimoxazole in which the kidney is the principal route of the drug and acetylates, that crystalluria may occur in patients mainly those who were dehydrated, and in children**(1&2)**. Crystallurea may be caused due to genetic disorder that Primary hyperoxaluria type I (PH I) is a congenital error of metabolism that can be manifested by an increased oxalate production, and ultimately result in kidney failure. After a combined liver/kidney transplantation, children with PH I have persistent excretion of oxalate that causes crystal formation in the urinary tract, and could result in systemic oxalosis and eventual graft failure**(3)**. We speculated that crystalluria may be predictive of this nephrolithogenic tendency and thus investigated the effect of an intensive therapeutic strategy to prevent crystal formation in a hospital.(Daudon M, Marfisi C, Lacour B *et al.* Investigation of urinary crystals by Fourier transformed infrared microscopy. Clin Chem1991; 37: 83–87)**(4)**.Other

causes of crystalluria in children are drugs adverse effect as cotrimoxazole, some of antiepileptic drugs, rarely metronidazole and amoxicillin may causing crystalluria in young children**(5).** The description of the following pictures is for one of crystalluria due to co-trimoxazole adverse effects:- (**A**) Large numbers of needle-shaped co-'bunches' (phase-contrast microscopy, original magnification 400×). (**B**) A co-trimoxazole crystals resembling the branch of a broom magnification 400×). (**C**) A co-trimoxazole 'sheaf' as seen under bright-field microscopy (original magnification 400×). (**D**) The birefringence of 'bunches' and 'sheaves' under polarized light (original magnification 400×).Picture "No1"**(6).**Co-trimoxazole should be adjusted in newborns babies and young children, because of its side effects which are involved nausea or vomiting, skin rash and crystalluria**(7).** Co-trimoxazole may be ontraindicated in newborn babies and young children, who were complaining from renal impairment, or it may be indicated with caution doses, that crystalluria may develop and more injuries to the renal system may occurred**(8).** The doses of co-trimoxazole is 8-10mg kg(based on trimethoprim component), I.V. 9,8, or 12 hours for up to 10 days, depending on the case susceptible organisms**(9)**.



Picture (No.1): Different shape of crystalluria due to Co-trimoxazole adverse effect "original magnification × 400"**(6)**.

PATIENTS and METHODS

All the patients were investigated and managed in Bent Al-Huda Teaching Hospital of Pediatric and Gynecology in Thi-Qar Province. The majority of those patients had a history of upper and lower bacterial respiratory tract infections(R.T.I.), and bacterial gastroenteritis (G.I.T.infections).Clinical examinations and full history taking as well as a general urine examinations(G.U.E.), were done. The G.U.E. reflects, either the present of crystalluria in the urine of patients, or not, after exclusion any other causes of crystalluria with exception for that which were due to administration of co-trimoxazole, by the following: (All the patients with gastroenteritis "G.I." or with urinary tract infection" U.T.I.", treated with cotrimoxazole or sulfonamide were evaluated at baseline and at 10 days and 15 days after consuming the drug.

Evaluation for crystalluria were done for most of the patients after 10 days and little were evaluated after 15 days, if crystalluria not clear visualized in their urine by the way of G.U.E.**(5)** The ages of the children patients were ranging from (4-10years), as shown in table (No.1, 2 and 3). After exclusion of any other causes of crystalluria, those patients grouped into: those who were suffering from G.I.T.infections, and those who were suffering from R.T.I. and were treated by cotrimoxazole table (No.1). Also they grouped into: those patients who were treated by both cotrimoxazole and I.V. fluid, and those who were treated by only cotrimoxazole (i.e. without I.V. fluid) table (No. 2). And the third group: were those patients who were females, and those who were males table (No.3).

RESULTS

A total of 115 patients with ages ranged from (4-10) years old were suffered from crystalluria, the peak frequency of distributions of crystalluria following cotrimoxazole were found in the age (9.1-10) years, in which the number of the patients were 32(27.82%), while the lower level of frequency of distributions of crystalluria, were found in the age ranged from(4-5) years, no. 13(11.30%); out of the total of 115 patients, table (No.1) shows this frequency of distributions of the age data . Also, we found the peak frequency of distributions of crystalluria of those patients suffered from G.I.T. infections 65(56.52%), more than those patients who were suffering from R.T.I. 50(43.34%), table (No.1) .Table (No.2); showing as that, the peak frequency of distributions of crystalluria for those patients who were not received I.V. fluid(administered only cotrimoxazole) 88(76.52), while those patients who were treated by both cotrimoxazole and I.V. fluid, had low level of frequency of distributions of crystalluria 27(23.48),table (No.2). In this study also, we found that the frequency of distributions of crystalluria were differ according to the sex variations, that the higher (peak) frequency of distributions of crystalluria found in the in the ages ranged from (4-5) years old, for both sex, i.e. males and females, who were administered cotrimoxazole drug, number 34(29.56%) out of the total 115 patients, while the lower value of the frequency of distributions of crystalluria following administration of cotrimoxazole, present in the ages ranged (7.1-8) years for both sex number 10(8.70%) out of the total 115 patients . And the peak frequency of distributions of crystalluria following cotrimoxazole administration for females ,were found in the ages (6.1-7)years old, number 17(22.97%) out the total of 74(64.34%) patients, while the peak frequency of distributions of crystalluria following cotrimoxazole administration in males group found in the ages ranged (4-5) years old, number 18(43.90%) out of the total 41(35.62%) male patents, table (No. 3).

DISCUSSION

All the patients which were studied, were complaining from either gastroenteritis (G.I.T.) infections, or upper and lower respiratory tract infections (R.T.I.). The cotrimoxazole is one of the drug(s) of choice for the treatment of 1-Acute gastroenteritis in children involving vibrio cholera. 2-All, or most types of respiratory tract infections**(1,10)**. So this study showing as, that the higher percentage of frequency of distribution of crystalluria were found in those patients who were younger(older), in which 32(27.82%) of younger patients developed crystalluria following cotrimoxazole administration due to both G.I.T. infections and R.T.I..And this percentages do not affected by the type of the disease. This means that, younger (older) patients 18(27.96%) for G.I.T infections, and 14(28%) for R.T.I. were developed crystalluria following cotrimoxazole administration more than the small babies patients 7(10.76%) for G.I.T infections and 5(10%) for R.T.I., this is accepted by U.S. Fogazzi, that Crystalluria caused by co-trimoxazole is a rare event that may be asymptomatic or may have severe renal implications. In January 2002 a urine sample from a 1-14-years-old children which contained a large amount of unusual crystals was referred to different types of diseases with same range and different shapes

In general that, the percentage of frequency of distribution of crystalluria following cotrimoxazole administration were more in patient with G.I.T. infections 65(56.52%), than those who were complaining from R.T.I. 50(43.34%), this is accepted by the study that said: "crystalluria" is more frequent in dehydrated, diseased, malnourished children, mainly fluid loss as in severe diarrhea**(12)** And this study reflect that there were higher values of frequency of distributions were presented in older (younger) children 32(27.82%), than small age babies 13(11.30%), for both patients who were treated or not by I.V. fluid, in which this percentage of frequency of distribution of crystalluria following cotrimoxazole administration, were more in patients who were treated with only cotrimoxazole 29(32.95%), than those which were treated by both cotrimoxazole and I.V. fluid 6(22.22%), that in some studies they found drinking a lot of water and/or other fluids well reduce the formation of crystalluria in children**(13)** Also from table(No.2), we found that the treated by both cotrimoxazole and I.V. fluid had low percentage of frequency of distribution of crystalluria following cotrimoxazole27(23.48), while those children who received only

cotrimoxazole had high percentage of frequency of distribution of crystalluria following cotrimoxazole 88(76.52%), that some study found that the frequency of formation and secretion of crystalluria may be less frequently for I.V. admitted patients who were managed by different type of drugs like some antiepileptic drugs, paraldehyde, cotrimoxazole, and others**(14).**Also Leonard G. Gomella, Steen H. Haist et. al, said, that cotrimoxazole must be taken with plenty of water, to avoid crystals formation**(15) .**We found that the frequency of formation and secretion of crystalluria had sex difference(sexually variation), that the frequency of crystalluria in females 74(64.34%),were more than males 41(35.62%), following cotrimoxazole administration, this is accepted with Varoquaux O, Lajoie D, Gobert C, et al, that Co-trimoxazole should be used with caution in patients receiving pyrimethamine or immuno-suppressive therapy or dehydrated patients or malnourished children, that crystalluria may develops, with some sexual variations**(16)**. Also some studies found that anatomical difference between males and females may affect the formation of crystalluria from any source**(17)**.

So we concluded that crystalluria were more extent in female patients, who were suffered from G.I.T. infections, and who were treated by only by co-trimoxazole.

Table (No.1) Frequency of distributions of crystalluria following cotrimoxazole according to the type of the disease which they were suffered.

No.	Age	***Suffering from G.I.T.infections***	%	***Suffering from R.T.I.***	%	Total	%
1	4-5	7	10.76	6	12	13	11.30
2	5.1-6	8	12.30	6	12	14	12.17
3	6.1-7	7	10.76	8	16	15	13.04
4	7.1-8	10	15.38	5	10	15	13.04
5	8.1-9	15	23.07	11	22	26	22.60
6	9.1-10	18	27.69	28	28	32	27.82
Total	4-110	65(56.52%)	100	50(43.34%)	100	155	100

Table (No.2) frequency of distributions of crystalluria following cotrimoxazole according to the type of drugs administration.

No.	Age	***Treated by both I.V. fluid & cotrimoxazole***	%	***Treated by only cotrimoxazole***	%	Total	%
1	4-5	4	14.81	9	10.22	13	11.30
2	5.1-6	6	22.22	8	9.10	14	12.17
3	6.1-7	6	22.22	9	10.23	15	13.04
4	7.1-8	4	14.81	11	12.50	15	13.04
5	8.1-9	4	14.18	22	25.00	26	22.60
6	9.1-10	3	11.11	29	32.95	32	27.82
Total		27(23.43%)	100	88(76.52%)	100	115	100

Table (No.3) Frequency of distributions of crystalluria following cotrimoxazole, according to the sex variation.

No.	Age	***Females***.	%	***Males***	%	Total	%
1	4-5	9	12.16	3	7.32	12	10.43
2	5.1-6	13	17.56	2	4.88	15	13.04
3	6.1-7	11	14.84	6	14.63	17	14.78
4	7.1-8	8	10.81	2	4.88	10	8.70
5	8.1-9	17	22.97	10	24.39	27	23.47
6	9.1-10	16	21.62	18	43.90	34	29.56
Total	4-10	74(64.34%)	100	41(35.62%)	100	115	100

REFRRENCE

1-Laurence D.R., Bennett P.N. et al, Clinical Pharmacology,"Sulphonamide and sulphonamide combination" (Churchill Lingstone), 9th Ed. 2003, 231-32.

2- Jick H and Derby LE, "A Large Population-Based Follow-Up Study of Trimethoprim-Sulfamethoxazole, Trimethoprim, and Cephalexin for Uncommon Serious Drug Toxicity," Pharmacotherapy, 1995, 15(4):428-32.

3- Jick H and Derby LE, "Is Co-Trimoxazole Safe?" Lancet, 1995, 345(8957):1118-9.

4- Dawkins B, Albury D, and Olsen TE, "Trimethoprim/Sulfamethoxazole-Induced renal injury - A Case Report Supported by the Laboratory Diagnosis," Aust N Z J Med, 1995, 25:83.

5- Brumfitt W, Hamilton-Miller JM (December 1993). "Reassessment of the rationale for the combinations of sulphonamides with diaminopyrimidines". J Chemother **5** (6): 465–9. PMID 8195839.

6- Dawkins B, Albury D, and Olsen TE, "Trimethoprim/Sulfamethoxazole-Induced renal injury and crystallizations- A Case Report Supported by the Laboratory Diagnosis," *Aust N Z J Med*, 1995, 25:83.

7- Cockerill FR and Edson RS, "Trimethoprim-Sulfamethoxazole in Pediatrics," Mayo Clin *Proc*, 1991, 66(12):1260-9.

8- Domingo P, Ferrer S, Cruz J, et al, "Trimethoprim-Sulfamethoxazole-Induced Renal Tubular Acidosis in a Patient With AIDS," Clin Infect Dis, 1995, 20(5):143, 45-7.

9-"Co-trimoxazole use restricted". Drug Ther Bull 33 (12): 92–3. December 1995. doi:10.1136/dtb.1995.331292. PMID 8777892.

10-"Co-Trimoxazole and Infectious Diseases". ScienceOfInfec.com. 2011-09-20. Retrieved 2012-08-07.

11- Fogazzi GB. Crystalluria: a neglected aspect of urinary sediment analysis.Nephrol Dial Transplant1996; 11: 379–83.

12- Noto H, Kaneko Y, Takano T, et al, "Severe Hyponatremia and Hyperkalemia Induced by Trimethoprim-Sulfamethoxazole in Patients With Severe Gastroenteritis ," Intern Med, 1995, 34(2):96-9.

13- Naber K, Vergin H, and Weigand W, "Pharmacokinetics of Co-trimoxazole and Co-tetroxazine in pediatric Patients," Infection, 1981, 9(5):239-43.

14- Hennessy S, Strom BL, Berlin JA, et al, "Crystalluria following antiepileptic agents," J Gen Inter Med, 1995, 10(7):380-6.

15- Leonard G. Gomella, Steen H. Haist, Armee G. Adams, Kelly M. Smith "Clinician Pocket Reference" (Side Effect of Trimethoprim and Cotrimoxazole)-Copyright Ed.-2007, 192.

16- Varoquaux O, Lajoie D, Gobert C, et al, Sexual variation of drugs-induced crystalluria" : A Randomized Trial," Br J Clin Pharmacol, 1985, 20:575-81.

17 - Böhni E (1969). "Chemotherapeutic activity of the combination of trimethoprim and sulfamethoxazole in infections of mice". Postgrad Med J45 (Suppl): Suppl:18–21. PMID 4902845.

الخلاصة

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مدى انتشار البلورات المهجرية (بيلة البلورات) عند المرضى الأطفال الذين يتراوح أعمارهم بين 4-10 سنوات

تبين هذه الدراسة انتشار البلورات المجهرية الناتجة من التداوي بعقار(cotrimoxazole) عند الأطفال الذين يعانون من التهابات الجهاز الهضمي وكذلك التهابات الجهاز التنفسي والذين كانت تتراوح أعمارهم بين (4-10) سنوات وقد تبن انتشار هذه البلورات بنسبة كبيرة عند الأطفال الذين يعانون من التهاب الجهاز الهضمي أكثر انتشارا من مرضى التهابات الجهاز التنفسي . وأشارت هذه الدراسة على أن هذه البلورات أقل انتشارا لدى المرضى الذين خضعوا للعلاج بواسطة أعطاء السوائل الوريدية (المغذيات الوريديه) سوية مع عقار(cotrimoxazole) مقارنة بالمرضى الذين عولجوا بواسطة عقار (cotrimoxazole) فقط.

وأيضا بينت هذه الدراسة على ان انتشار البلورات الناتجة من تناول عقار (cotrimoxazole) تكون بنسبة كبيرة عند الإناث مقارنة بالذكور من المرضى.