Adverse Drug Reactions and Outcome of Short Course Anti-Tuberculosis Drugs between Single Daily Dose and Split Drug Dose (BID) in Pulmonary Tuberculosis

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Background: *Standard six months short course regimen for treatment of pulmonary tuberculosis is very effective and is recommended as standard treatment. But this regimen composes of many drugs and causes high adverse drug reactions especially gastrointestinal irritation. Spitted administration of drugs to two times a day may reduce adverse drug reactions.*
Objective: *To study adverse drug reactions and outcome of single daily versus split drug (two times a day) administration of standard six month short course regimen in newly diagnosed pulmonary tuberculosis.*
Material and Method: *Newly diagnosed pulmonary tuberculosis patients of the Central Chest Institute of Thailand were randomized to receive standard six months regimen once daily or two times a day (split drug). Patients were followed-up every two weeks and a questionnaire was used to detect adverse drug reactions. Outcome of treatment was evaluated according to national tuberculosis treatment guideline.*
Results: *122 pulmonary tuberculosis were eligible for the present study and 61 patients were enrolled to each group of once daily or split drug regimen. Pulmonary tuberculosis patients who received split drug regimen had a higher cure rate but not statistical significance because of lower transfer out rate. Adverse drug reactions were similar in both groups of patients who received once daily and split drug regimen. Although split drug group had lower gastrointestinal adverse drug reactions.*
Conclusion: *Split drug regimen has the same cure rate of treatment as single daily regimen and same adverse drug reactions.*

Keywords: *Single daily, Split drug, Short course regimen, Pulmonary tuberculosis*

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Pulmonary tuberculosis is still a public health problem in Thailand. Each year approximately 60,000 new cases of pulmonary tuberculosis are diagnosed in Thailand. One of the most effective strategy to control pulmonary tuberculosis is to treat the patient with the six month standard short course regimen. Regimen composes of two phases of treatment. In the first 2 months, four drugs of Isoniazid (INH), Rifampicin (RMP), Pyrazinamide (PZA) and Ethambutol (EMB) are used. And two drugs with INH and RMP are used for another 4 months[1-4]. Cure rate of treatment with this short course regimen is as high as 98% with relapse rate of 1-3%. Many potent drugs are used to treat patients so it is likely to cause more adverse drug reactions. Adverse drug reactions (ADR) from anti-tuberculosis drugs are very common. In many clinical studies had shown ADR rate of around 21-50%[5-10].

These ADRs may compromised patient compliance to the treatment especially in the old age patients. Gastrointestinal ADRs are the most common ADR in patients who take anti-tuberculosis drugs because of number and size of pills. Most of the guideline recommended to modify the treatment regimen when patients experienced with ADRs. But modification of treatment regimen will make duration of treatment to be prolonged. In order to reduce the gastrointestinal ADRs, the present study is designed to split the dose of anti-tuberculosis to two times instead of single daily. The objectives of the present study were to evaluate ADR rate and outcome of single daily dose compared to split drug dose (two times a day) of anti-tuberculosis

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drug for the treatment of tuberculosis.

Material and Method

The present study was a prospective, open-label, randomized study. The study was conducted at the TB clinic, the Central Chest Institute of Thailand. The present study was approved by the Central Chest Institute of Thailand Ethical Committee for Research on 30th March 2008. Newly diagnosed tuberculosis patients who had never received or received anti-tuberculosis treatment less than one month were screened for eligibility to the study and informed of the present study details. Inclusion criteria were chest x-ray compatible with pulmonary tuberculosis, sputum smear positive for acid fast bacilli at least one specimen, age over 20 years old, no pregnancy and willing to participate in the present study. Exclusion criteria were chronic cardiac or lung disease, hepatitis with liver enzymes more than 3 times upper normal limit, renal disease with serum creatinine > 2.0 mg%, neurological disease that will effect compliance of patients such as dementia, HIV infection, relapsed tuberculosis and not willing to participate in the present study. The patients were requested to sign the informed consent. Patients were randomized to two study groups, Group A or B. Group A was given the anti-tuberculosis drug once daily at bed time. Group two B was given the anti-tuberculosis drug two times a day. INH and RMP were given in the morning before breakfast and PZA and EMB were given at bed time. Dosage of INH, RMP, PZA and EMB were 300 mg, 450 mg, 1,000 mg and 800 mg respectively for patient's body weight 45 kilograms or less. And INH 300 mg, RMP 600 mg, PZA 1,500 mg, EMB 1,000 mg for patient's body weight more than 45 kilograms. Treatment was given under direct observation by a family member. Patients were followed-up every two weeks and ADRs were asked by a study nurse with the questionnaire for the first eight weeks. Sixty-one patients were enrolled into each Group of treatment. Number of patients were calculated by Epicalc 2,000 program using ADRs rate of 10-29%, significant level of 0.05 and power of 80%. Patients were treated for six months with standard short course regimen and outcome of treatment was analyzed at the end of treatment according to standard national guideline[3].

Results

There were 122 patients enrolled into the present study. 61 patients were enrolled to group A (single) and 61 patients were enrolled to group B (BID). Both group had the same demographic characteristics as shown in Table 1. Laboratory findings before anti-tuberculosis treatment was started in both groups were similar as shown in Table 2. Outcome of treatment in group B (BID) was not different to group A (single) as shown in Table 3. Reason for higher cure rate in group B (BID) because of lower transfer out and default rate. The transfer out rate in group A was higher. Outcome of treatment from transfer in health services was not known even tried to contact the health services. There was no case of death in group B (BID) but two patients died in group A (single). One patient died after 7 weeks of treatment in District Hospital near his home town which is 700 kilometers from Bangkok and cause of death was not known. Another patient died after 5 months of treatment because of hepatoma. According to national guideline, any patient who died during anti-tuberuclosis treatment was considered as died from tuberculosis. Adverse drug reactions in both groups were the same in terms of rate (Table 4). Group B (BID) had more patients without any ADRs but not statistical significance. ADRs of nausea, anorexia, skin reactions and arthralgia were seen more in Group A (single) than Group B (BID) but not significant. Only ADR of blurred vision was seen more in Group B (BID) than Group A (single). No patient in the present study died from ADR.

Discussion

ADRs from anti-tuberculosis treatment are very common. From well designed, randomized, case-control study of tuberculosis treatment showed the ADR rate of 14-60%[5-11]. ADR from anti-tuberculosis treatment compromised patient's compliance to treatment. Patients may default from treatment by themself because of ADRs or clinician has to change or stop some drugs in the treatment regimen. Treatment would be prolonged more than six months. Modification of administration may reduce ADR and improve compliance. Santha reported a study which modified administration method of anti-tuberculosis drugs in order to reduce ADRs. The present study was used INH and EMB in one day and alternated to RMP and PZA in the next day. Santha had also showed that split drug regimen in newly diagnosed pulmonary tuberculosis patients was effective and lower ADRs[11]. The present study was designed to modify administration of anti-tuberculosis drugs in order to reduce ADRs. This is the first study to modify administration of anti-tuberculosis drugs to two times a day instead of once daily as recommended in national guideline[3]. INH and RMP were chosen to take in the morning

Table 1. Demographic characteristics of tuberculosis patients in both group

	Group A (single) (n = 61)	Group B (BID) (n = 61)	p-value
Male (%)	44 (72.1)	41 (67.2)	0.575
Female (%)	17 (27.9)	20 (32.8)	0.562
Age (yr)	37.1 ± 11.4	37.2 ± 10.9	0.968
Body weight	51.8 ± 9.1	51.9 ± 9.9	0.961
Diabetes mellitus	11 (18.2)	9 (14.8)	0.617

Table 2. Base line laboratory characters of patients in both group

	Group A (single) (n = 61)	Group B (BID) (n = 61)	p-value
Hemoglobin (gm%)	13.4 ± 7.4	13.2 ± 5.9	0.795
White blood cell count (cells/cu.mm.)	9,849 ± 3,305	10,174 ± 3,410	0.597
Fasting blood sugar (mg%)	92.2 ± 20.5	98.2 ± 18.1	0.088
Blood Urea Nitrogen (mg%)	11.2 ± 4.2	10.7 ± 3.4	0.472
Serum creatinine (mg%)	0.9 ± 0.2	0.9 ± 0.2	1.000
AST (IU/cu.mm.)	26.6 ± 20.5	33.4 ± 27.1	0.119
ALT (IU/cu.mm.)	21.5 ± 14.2	25.1 ± 19.9	0.308

Data were presented as mean ± SD

Table 3. Demonstrate outcome of treatment in Group A (single) and Group B (BID)

	Group A (single) n (%)	Group B (BID) n (%)	p-value
Cure (%)	44 (72.9)	53 (84.6)	0.115
Transferred out (%)	8 (13.1)	2 (3.3)	0.049
Defaulted (%)	5 (8.2)	4 (6.5)	0.264
Failure (%)	2 (3.3)	2 (3.0)	0.929
Died (%)	2 (3.3)	0 (0.0)	0.110

Table 4. Adverse drug reaction after treatment in both Group A (single) and Group B (BID)

	Group A (single) n (%)	Group B (BID) n (%)	p-value
No any reaction	23 (37.7)	29 (47.5)	0.276
Adverse drug reaction			
Nausea, anorexia	16 (26.2)	14 (22.9)	0.675
Skin rash	19 (31.1)	16 (26.2)	0.555
Numbness of hands	5 (8.2)	2 (3.3)	0.246
Myalgia	1 (1.6)	1 (1.6)	1.000
Arthralgia	1 (1,6)	0 (0.0)	0.322
Blurred visison	1 (1.6)	3 (4.9)	0.308
Blood stained sputum	2 (3.3)	0 (0.0)	0.153

because of food interference of absorption[12]. The number of tablets were reduced in each administration. In the present study, patients who took medication two times a day (Group B) had same cure rate as patients who took medication once daily. Even though the cure rate of Group B was higher than Group A but not statistical significance. Transfer out and default rate in a single daily dose were higher that were the reasons of lower cure rate in single daily dose. Regarding to national guideline for evaluation of treatment outcome

of tuberculosis, if the outcome of transfer out was known from transfer in health service, it could be used to evaluate outcome as cure.

The most common ADR was gastrointestinal disturbance of nausea, anorexia and vomiting after treatment with anti-tuberculosis drugs[7-11]. Udonpanich had reported ADRs in Thai tuberculosis patients who received DOTS in King Chulalongkorn Memorial Hospital of 29%. The most common ADR was skin reaction (17%) and gastrointestinal disturbance was 10%[6]. Saipan had reported gastrointestinal disturbance of 60% in pulmonary tuberculosis patients who received DOTS in Central Chest Institute of Thailand. In the present study, number of patients who did not have any ADR was more in two times a day (split drug) group but not significance. Patients who took medication two times a day had lower gastrointestinal ADRs but not statistical significance. Skin rash in the present study was mild grade and anti-histamine was prescribed to control symptom. No patient developed serious skin ADR such Steven-Johnson syndrome or toxic epidermal necrolysis. Patients who developed numbness of hands were supplemented with vitamin B_6 and improvement of symptom. Myalgia was a mild symptom and relieved with analgesics. One patient developed arthralgia with mild symptom and relieved with analgesics as recommended in national guideline. One concerned ADR was blurred vision. Blurred vision was more often seen in group B (BID) but no patient stopped the medication permanently. Two patients complained of blurred vision after anti-tuberuclosis treatment for a few days and then disappeared. They did not have any symptoms at the time of visit so medication was continued. One patient had blurred vision at the end of week 8 visit of treatment which EMB had to be stopped in order to enter continuation phase. Another patient complained of mild blurred vision and EMB treatment was interrupted for a few days. After symptom disappeared, EMB was resumed and no blurred vision was seen any more. Result of the present study will be applied to any pulmonary tuberculosis patient who had ADRs after taking anti-tuberculosis medication be able to change taking medication to two times a day (split drug) in order to reduce ADRs.

Conclusion

Tuberculosis patients who received anti-tuberculosis drugs two times a day had same cure rate as patients who received once daily drugs as standard recommendation. ADRs rate was lower in patients who received drugs two times a day but not statistical difference.

Potential conflicts of interest

None.

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อาการไม่พึงประสงค์และผลของการรักษาวัณโรคสูตรยาระยะสั้นเปรียบเทียบระหว่างการให้ยารักษาวันละครั้ง และการให้ยาแยกวันละสองครั้ง

เจริญ ชูโชติถาวร, เบญจวรรณ สายพันธุ์, โฉมนภา กิตติศัพท์, กฤษณา ชีวะกุล

วัตถุประสงค์*: เพื่อศึกษาอัตราการเกิดอาการไม่พึงประสงค์และผลของการรักษาผู้ป่วยวัณโรคด้วยสูตรยามาตรฐานระยะสั้นหกเดือนเปรียบเทียบระหว่างการให้ยาวันละครั้ง และการให้ยาวันละสองครั้ง-เช้าและเย็น*

วัสดุและวิธีการ*: ผู้ป่วยวัณโรครายใหม่ของคลินิกรักษาวัณโรคแบบมีพี่เลี้ยง สถาบันโรคทรวงอก จะได้รับการสุ่มเพื่อรับยารักษาวัณโรคสูตรยามาตรฐานวันละครั้ง หรือ เช้า-เย็น โดยให้ไอโซนัยอะซิดร่วมกับไรแฟมปิซินตอนเช้า และพัยราซินามัยด์ร่วมกับอีแธมบิวตอลตอนเย็น ในระยะรักษาเข้มข้น 2 เดือน ผู้ป่วยจะได้รับการติดตามอาการไม่พึงประสงค์ทุก 2 สัปดาห์ และประเมินผลการรักษาเมื่อสิ้นสุดการรักษา 6 เดือน*

ผลการศึกษา*: ผู้ป่วยวัณโรคปอดรายใหม่จำนวน 122 ราย เข้าร่วมในการศึกษาโดยมีผู้ป่วยที่ได้รับในแต่ละกลุ่มจำนวน 61 ราย 'ผู้ป่วยวัณโรคกลุ่มที่ได้รับยาแยกเช้าและเย็นมีอัตราการรักษาหายร้อยละ 84.6 ซึ่งสูงกว่ากลุ่มป่วยที่ได้รับยาวันละครั้ง (หายร้อยละ 72.9) อย่างไม่มีนัยสำคัญ เนื่องจากอัตราการย้ายการรักษาสูงถึงร้อยละ 13.1 ในผู้ป่วยกลุ่มที่ได้รับยาวันละครั้ง ผู้ป่วยกลุ่มที่ได้รับยาเช้าและเย็นมีอาการไม่พึงประสงค์ต่ำกว่ากลุ่มที่ได้รับยาวันละครั้ง โดยเฉพาะอาการทางระบบทางเดินอาหารและผื่นแต่ไม่มีนัยสำคัญทางสถิติ*

สรุป*: การรักษาวัณโรคด้วยสูตรยาระยะสั้นแบบให้ยาเช้าและเย็นมีผลการรักษาเทียบเท่าการรักษาแบบให้ยาวันละครั้ง และอาการไม่พึงประสงค์ไม่แตกต่างจากการให้ยาวันละครั้ง*