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The development of a standard drug use evaluation criteria form for Cefoperazone use at a regional hospital in Northeastern Thailand

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Objective : *The study was aimed to develop a standard drug use evaluation (DUE) criteria form for Cefoperazone, and to evaluate the effectiveness of the standard criteria form.*

Design : *A retrospective-descriptive study.*

Setting : *Sapasithiprasong Hospital, Ubon Ratchathani, Thailand.*

Participants : *In-patients treated with Cefoperazone from June 2003 to March 2004.*

Method : *The study involved the development of a DUE criteria form, and the evaluation of the effectiveness of the standard criteria form. The content validation of the criteria form was performed by two physicians and one pharmacist. Forty-two cases were enrolled in the study. Their history of Cefoperazone use was entered on the criteria forms. The aspects of DUE of Cefoperazone included: indications, dosage regimens, drug awareness, disease etiologies, durations of treatment, adverse drug reactions & monitoring, and medical outcomes. The study was conducted from June 2003 to March 2004.*

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Results : *Forty-two patients were involved in the study. Some patients were treated with Cefoperazone as empirical therapy (11.9 %) mainly for multiple infections. There were no patient data regarding their weights prior to the Cefoperazone dosage given, nor were there any history of drug allergy recorded in the medical charts. However, the given dosage in the regimens were generally appropriate, except for children due to the lack of information on their body weights. The most common diseases treated with Cefoperazone included: septicemia (50.58 %), respiratory tract infections (28 %), and neutropenic infections (21.42 %). Interestingly, there were no adverse drug reactions documented in the study. Only twenty-five patients completed treatment with Cefoperazone.*

Conclusion : *Generally, the use of Cefoperazone at Sapasithiprasong Hospital was appropriate. However, some crucial data related to the decisions made to prescribe Cefoperazone were missing. Limitations of the study need to be stated and actions taken to rectify them. Changes to the criteria forms based on the practical uses were required.*

Keywords : *Drug use evaluation, Cefoperazone.*

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เหตุผลของการทำวิจัย : *เนื่องจากมีการสั่งใช้ยา Cefoperazone ค่อนข้างมาก ซึ่งอาจส่งผลกระทบตามมาคือ การดื้อยาตัวนี้ เนื่องจากยากลุ่มนี้เป็น 3rd generation ของ Cephalosporins ซึ่งควรที่จะมีมาตรการการสั่งใช้ยาอย่างรอบคอบ นอกจากนี้ ยาดังกล่าวยังมีราคาค่อนข้างแพงและเป็นยาในบัญชียา ง. ซึ่งต้องได้รับการควบคุมดูแลในเรื่องของการสั่งใช้ อย่างไรก็ตาม ที่ผ่านมา ยังไม่มีการประเมินความเหมาะสมในการสั่งใช้ยา Cefoperazone และไม่มีแบบประเมินที่ให้กับบุคลากรในโรงพยาบาลใช้เพื่อประเมินการใช้ยาตัวนี้ ผู้วิจัยจึงทำการศึกษาเรื่องการสร้างแบบประเมินความเหมาะสมในการใช้ยา Cefoperazone ขึ้นพร้อมกับนำไปทดลองใช้ในผู้ป่วยในโรงพยาบาลสรรพสิทธิประสงค์*

วัตถุประสงค์ : *เพื่อพัฒนาแบบประเมินการใช้ยา Cefoperazone ที่ได้มาตรฐาน เพื่อทดสอบประสิทธิภาพการใช้งานของแบบประเมิน*

รูปแบบการวิจัย : *การศึกษาแบบย้อนหลัง (Retrospective Study)*

สถานที่ทำการศึกษา : *โรงพยาบาลสรรพสิทธิประสงค์*

วิธีการศึกษา : *ประกอบด้วย 2 ขั้นตอนดังนี้คือ 1. การสร้างแบบประเมินความเหมาะสมในการใช้ยา Cefoperazone, 2. การประเมินความเหมาะสมในการสั่งใช้ยา Cefoperazone ในโรงพยาบาลสรรพสิทธิประสงค์ในขั้นตอนการออกแบบประเมินนั้น เนื้อหาที่บรรจุในแบบประเมินต้องได้รับการตรวจสอบความถูกต้องจากผู้เชี่ยวชาญสาขาแพทยศาสตร์และเภสัชศาสตร์ (Content Validation) ก่อนนำไปใช้จริง การศึกษาครั้งนี้มีจำนวนผู้ป่วยทั้งสิ้น 42 ราย ซึ่งมีประวัติการใช้ยา Cefoperazone ในช่วงเวลาที่ทำการศึกษา ทั้งนี้ได้รับความร่วมมือจากเวชระเบียนโรงพยาบาลสรรพสิทธิประสงค์ ในการเก็บข้อมูล องค์ประกอบของการประเมินการใช้ยา Cefoperazone มีดังนี้คือ ข้อบ่งใช้, ขนาดยาที่ใช้, ข้อปฏิบัติระหว่างการใช้ยา, กลุ่มโรคที่ทำการรักษา, ระยะเวลาในการรักษา, อาการไม่พึงประสงค์, และผลการรักษา การศึกษาครั้งนี้ทำในช่วงเดือนมิถุนายน 2546 – มีนาคม 2547*

ผลการศึกษา : *ผู้ป่วยทั้งสิ้น 42 รายที่นำมาศึกษาในครั้งนี้ ส่วนใหญ่ใช้ยา Cefoperazone แบบ empirical therapy (11.9 %) ซึ่งมีภาวะ Multiple infections อย่างไรก็ตามข้อมูลในเรื่องของน้ำหนักตัวผู้ป่วยไม่ได้แสดงไว้ในเวชระเบียน ทำให้การประเมินขนาดยาที่ผู้ป่วยควรได้รับไม่สามารถประเมินได้ ไม่มีการระบุประวัติการแพ้ยาของผู้ป่วยในเวชระเบียน ทำให้การประเมินไม่สามารถทำได้ ในส่วนของขนาดยานั้น พบว่าผู้ป่วยส่วนใหญ่ได้รับขนาดยาเหมาะสม ยกเว้นในรายผู้ป่วยเด็ก ที่ไม่มีข้อมูลเรื่องน้ำหนักทำให้ไม่สามารถประเมินความเหมาะสมได้ โรคที่มีการสั่งใช้ยา Cefoperazone มากที่สุดได้แก่ Septicemia (50.58 %), respiratory tract infections (28 %), และ neutropenic infections (21.42 %) ตามลำดับ ซึ่งในกลุ่มผู้ป่วยทั้งหมดที่ทำการศึกษานั้น ไม่พบข้อมูลในเรื่องของอาการไม่พึงประสงค์ อย่างไรก็ตาม จากผู้ป่วยทั้งสิ้น 42 ราย มีเพียง 25 ราย ที่ได้รับการรักษาด้วยยา Cefoperazone จนครบระยะเวลาของการรักษา*

วิจารณ์และสรุป : *โดยรวม การสั่งใช้ยา Cefoperazone ในโรงพยาบาลสรพสิทธิประสงค์อยู่ในเกณฑ์ที่ยอมรับได้ อย่างไรก็ตามข้อมูลที่สำคัญที่ใช้ในการประเมินการใช้ยานั้น ไม่ได้มีการบันทึกให้ชัดเจนในเวชระเบียนผู้ป่วย ทำให้ไม่สามารถที่จะประเมินได้ และการศึกษาในครั้งนี้ยังคงมีข้อจำกัดในการวิจัยหลายประการที่ยังคงต้องได้รับการปรับปรุงแก้ไขต่อไป รวมทั้งแบบประเมินที่สร้างขึ้น ยังคงต้องได้รับการปรับปรุงให้มีคุณภาพดีขึ้น ก่อนที่จะมีการนำไปใช้ต่อไป*

คำสำคัญ : *การพัฒนาแบบประเมินการใช้ยา, ยา Cefoperazone.*

Drugs Use Evaluation (DUE) is a standard procedure in hospitals to limit unnecessary drug use, control spending and reduce casualties. It is also used by hospital administrations as a strategy of quality assurance. DUE usually occurs, especially with the use of antibiotics, when medications are expensive, having high toxicity, narrow therapeutic index and/or high resistance to the drugs. Such drugs need to be monitored closely when being used with patients. [1,2]

Cefoperazone is a third-generation of Cephalosporin. It inhibits gram positive and gram negative bacteria, and anaerobic bacteria.[3,4] It has been used to treat bacterial infections, such as urinary tract infection (UTI), lower respiratory tract infection (LRI), abdominal infections and septicemia. [5-7] A normal dosage regimen is 2-4 G/day q 12 for adults, and 25-50 mg/kg/day q 6-12 for children. The common side effects include: rash, nausea, vomiting, diarrhea and hepatotoxicity. Pregnant and breast-feeding women should avoid using Cefoperazone due to its teratogenic effects. [8] Because of its limitations such as high cost, drug resistance and adverse effects, Cefoperazone is required to undergo Drug Use Evaluation (DUE) . [9,10]

Sapasithiprasong Hospital in Ubon Ratchathani is a regional hospital of less than 1,000 beds serving seven provinces in Northeastern Thailand. Since 2000, the hospital has spent approximately 10 million baht on Cefoperazone. [11] The increased use of Cefoperazone has raised serious concerns regarding its safety and efficacy. Additionally, there have been no standard criteria of DUE of Cefoperazone. [12]

As a result, this study is aimed to develop a standard DUE form for Cefoperazone, and to evaluate the appropriate use of Cefoperazone at Sapasithiprasong Hospital, Ubon Ratchathani.

Method

The study was of a retrospective-descriptive design. Patients enrolled in the project were in-patients treated with Cefoperazone at Sapasithiprasong Hospital from June 2003 to March 2004. It involved two steps : development of a DUE form and evaluation of the appropriate use of Cefoperazone :

1. A DUE form was developed based on Cefoperazone drug monograph, including indications, dosage regimens, drug awareness, disease etiologies, durations of treatment, adverse drug reactions and monitoring, and medical outcomes. Additionally, the drug monograph was collected via clinical database resources that were standard, reliable, appropriate and correctable, such as Medline, Micromedex, USP DI and Pub-Med. [13-17] Primary resources, for example, randomized controlled trials, meta-analysis and a cohort study, related to the use of Cefoperazone were also implemented to develop a standard criteria form. A final DUE form was sent to three clinical experts (two doctors and one pharmacist) for content validation. The contents were modified based on their comments prior to a study.

2. Sapasithiprasong Hospital Administrative Committees allowed the authors to access the patient medical charts and collect patient data related to Cefoperazone use. The inclusion criteria of the patients involved all patients hospitalized and treated with Cefoperazone (either IV, IM) from June 2003 to March 2004. Three clinical pharmacists routinely involved with DUE of antibiotics use at Sapasithiprasong Hospital filled out a DUE form for Cefoperazone. If the patient

medical charts were not available at the time of the study, those cases were automatically excluded. The data were analyzed by descriptive analysis, such as frequencies and percentages.

Results

1. Demographic data

There were forty-two patients from the Patient Chart Unit who were treated with Cefoperazone from June 2003 to March 2004. Sixty percent were males and 40.5 % were above forty-nine years of age. Nineteen percent were admitted to the ICU Neuro Unit, 19 % to the ICU Surgery Unit and 9.5 % to the General Medicine Unit.

2. The appropriate use of Cefoperazone

DUE of Cefoperazone was divided into seven different aspects:

2.1 Indications

Patients were prescribed Cefoperazone as empirical therapy in five cases (11.9 %) and as specific therapy in 37 cases (88.1 %). The main indications for empirical included severe infections and septicemia. The specific therapies of Cefoperazone also included acinitobactor infections (59.5 %) followed by gm(-)ve bacterial infection (24.3 %) (see table 1)

2.2 Dosage Regimens

Cefoperazone was prescribed for thirty-six adult patients (85.7 %), four adult patients with renal impairment (9.5 %) and two children (4.8 %). Thirty-three adults were given an appropriate normal dose of between 1-2 G IV q 12. However, three adult patients were given a higher dose of 4 G Cefoperazone IV q 12 for severe infections. Four patients with renal impairment were treated with a full dose of Cefoperazone 1-2 G IV q 12, as it mainly excreted via bile duct rather than the kidneys. Thus, dose adjustments in renal impairment patients were not necessary. Two children were not evaluated due to the lack of body weight data.

2.3 Drug awareness

The results of drug awareness are shown in Table 2:

Table 1. Indications for specific therapy of Cefoperazone (n=37).

Indications	Results	
	Frequency	Percentage
Culture and Sensitivity		
1. Gm(+)ve aerobic bacterial infection	1	2.4
2. Gm(-)ve bacterial infection	9	24.3
3. Anaerobic and mixed aerobic bacterial infection	0	0
4. Acinitobactor sp. infection	25	59.5
5. Miscellaneous	2	5.4
Total	37	88.1

Table 2. Drug awareness of Cefoperazone (n=42).

Items	Outcomes [frequency, (%)]		
	Yes*	No	N/A
1. Weighed patient prior to drug administration	0 (0)	35 (83.3)	7 (16.7)
2. Checked CBC differential within 48 hours of drug administration	12 (28.6)	27 (64.3)	3 (7.1)
3. Checked drug allergy, especially *B*-lactam antibiotic allergies	1(2.4)	4(9.5)	37(88)
4. Checked Scr or Clcr within 48 hours of administration	16(38.1)	23(54.8)	3(7.1)
5. For specific therapy, administered Cefoperazone within 48 hours of c/s being reported (n=37)	19(51.4)	17(45.5)	1(2.7)
6. For empirical therapy, c/s is routinely ordered (n=5)	2 (40)	0 (0)	3 (60)
7. For empirical therapy, when c/s is reported, drug of choice is considered appropriate within 24 hours (n=5)	2 (40)	0 (0)	3 (60)

* Yes = performed No= not performed N/A = not applicable due to lack of data
c/s = culture and sensitivity

2.4 Disease etiologies

The common diseases treated with Cefoperazone included miscellaneous etiologies (16 cases), respiratory tract infections (RTI) (11 cases), neutropenic infections (9 cases) (Figure 1). Interestingly, septicemia was the most common miscellaneous etiology treated with Cefoperazone (8 out of 16 cases). Pneumonia was the most common RTI treated with Cefoperazone (5 out of 11) (Figures 1, 2 and 3).

2.5 Durations of Cefoperazone treatment

Fifteen patients (35.7 %) were treated with Cefoperazone for less than fourteen days and ten patients (23.8 %) for more than fourteen days. Thirteen cases (31 %) died due to disease complications (see Table 3).

2.6 Adverse drug reactions

There were no available data regarding adverse drug reactions to Cefoperazone in the patient medical charts. As a result, it was not appropriate to evaluate the incidence of such reactions in the study.

2.7 Medical outcomes

Twenty out of forty-five patients were stopped treatment for reasons such as death, treatment refusal and treatment changes. Thus, only twenty-five patients completed treatment with Cefoperazone. There was an improvement shown in 59.5 % of the patients by a drop in body temperature. However, they were all considered to be clinically better when the full course of Cefoperazone was completed. Interestingly, no culture and sensitivity data were collected after the completion of the courses of Cefoperazone.

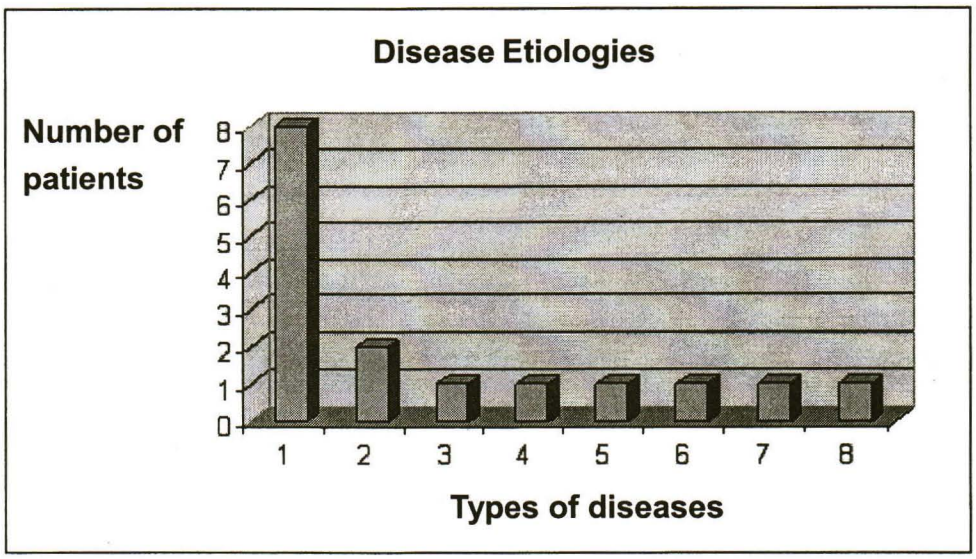

Figure 1. The most common diseases treated with Cefoperazone (n=42).

1 = Abdominal infection 2 = Biliary tract infection 3 = Gonorrhea
4 = Gynecologic infection 5 = Neutropenic infection 6 = Osteomyelitis
7 = Respiratory tract infection 8 = Urinary tract infection 9 = Miscellaneous infections

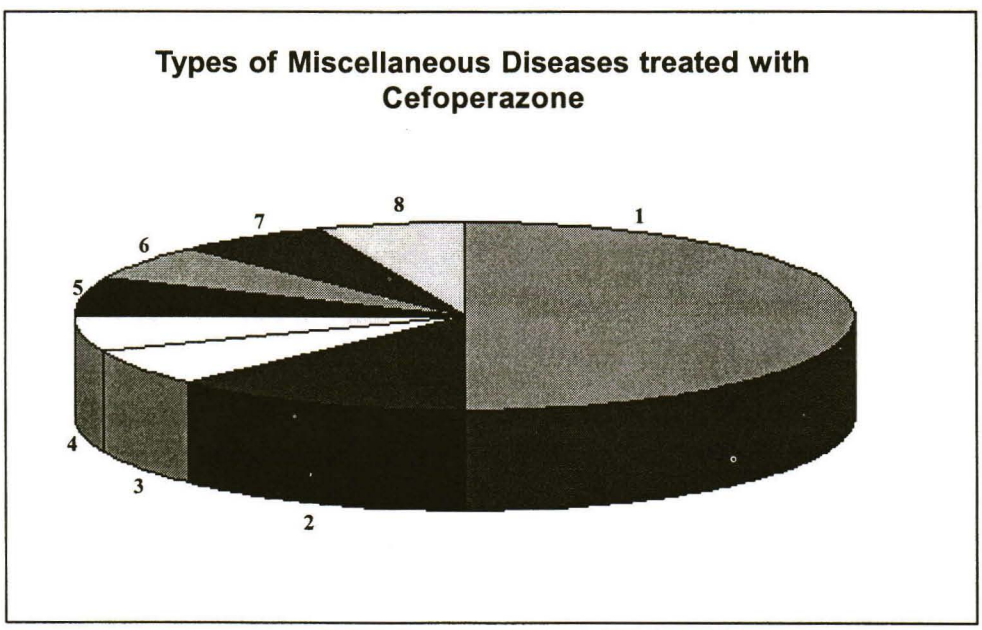

Figure 2. Miscellaneous Infections treated with Cefoperazone (n=16).

1 = Septicemia (8) 2 = Multiple infections (2) 3 = Fungal infection (1)
4 = Cornial pullo (1) 5 = SDM gm (-)ve (1) 6 = Head injury (1)
7 = ASD (1) 8 = Severe infection (1)

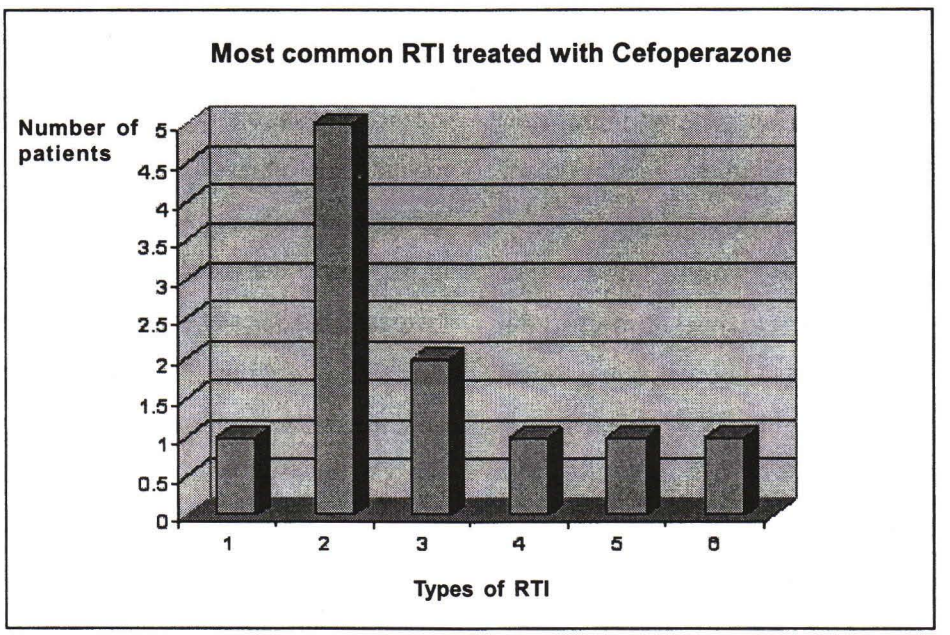

Figure 3. The most common Respiratory Tract Infections (RTI) treated with Cefoperazone (n=11).

1 = Pracheotomy 2 = Pneumonia 3 = CA lung

4 = Laryngeal injury 5 = Upper chest injury 6 = COPD

Table 3. Durations of Cefoperazone treatment (n=42).

Items	Outcomes	
	Frequency	Percentage
1. Less than 14 days	15	35.7
2. More than 14 days	10	23.8
3. Miscellaneous		
3.1 Death from medical complications	13	31
3.2 Lack of medications	1	2.4
3.3 Refusal of treatment	1	2.4
3.4 Changed treatment	2	4.8
Total	42	100

Discussion

Thirty-seven of the patients in the study were treated with Cefoperazone as specific therapies. However, two of them were reported to have rejected the treatment or culture/sensitivity data were lost.

Most patients received appropriate dosage regimens of Cefoperazone. However, two children received 500 mg IV q 12 without body weight data. As a result, it was difficult to evaluate the appropriateness of this dosage and it may be dangerous to initiate a dose of antibiotics in children without such information. Three severe infected patients were given inappropriate doses of Cefoperazone (1-2 G IV q 12). These patients should have been given higher doses (4 G IV q 12) to treat severe infection.

Regarding drug awareness, there was no body weight data recorded in the patients' medical charts. The reasons for this may be that healthcare practitioners forgot to record the weights or the patients were unable to measure their weights due to being unconscious and/or the severity of the disease did not allow them to.

Additionally, CBC data were not collected in most cases. It is important that CBC data must be collected prior to the initiation of Cefoperazone as it may cause bleeding and toxicity of medications. In one study, a case of hypoprothrombinemia was reported in a patient receiving 2 G Cefoperazone IV q 8 for seven days. [18]

Furthermore, allergy history data were not available in the medical charts. It is important to know whether the patient has a history of drug/substance allergies. Cefoperazone has a *B*-lactam ring structure similar to penicillin. Thus, if patients have a history of penicillin allergy, there may also be a chance of a cross-allergic reaction to cephalosporins. [19]

Results also showed that Cefoperazone was mainly given within 48 hours of culture and sensitivity being reported via specific therapy. The reason was it decreased the incidence of drug resistance and increased the efficacy of therapy. However, seventeen cases were reported to have not reached the criteria. This might be because of time spent in pathogen growth.

Thirty percent of the patients died during Cefoperazone treatment due to medical complications. Of these, only 35 percent of them were completely treated with Cefoperazone. It is possible that the longer the treatment with Cefoperazone, the more serious an adverse drug reaction could be. Unfortunately, data relating to adverse drug reactions to Cefoperazone were not available to the study. Some adverse drug reaction cases may not have been recorded in the medical charts due to healthcare practitioners forgot to state patients' adverse events or adverse events ceasing after stopping Cefoperazone. The authors, hereby, suggest a completion of the concurrent designed study to evaluate adverse drug reactions to Cefoperazone.

Only twenty-five patients completed the full course of treatment with a favorable medical outcome, including reduction in temperature. Significant information on the failure of Cefoperazone was not available, not to mention unclear records of deaths, refusals and changes of the treatment.

Limitations

1. As it was a retrospective-designed study, the evaluation depends upon the medical charts

available at the time. Such charts may not contain all required information. Therefore, it is recommended to perform a concurrent DUE study to gather updated sufficient data.

2. The number of cases is small due to such factors as patient deaths, medication changes and treatment rejection. As a result, the reliability of the outcomes in some particular areas is limited.

3. The use of a standard DUE criteria form was confined to one hospital. It is necessary to involve other hospitals to gain more feedback and evaluation.

4. There is no drug cost evaluation in the study. It might be useful to focus on price and the use of Cefoperazone in the hospital. It would be more beneficial to the committees to consider the hospital budget.

5. Drug allergies and adverse drug reaction data were not made available for evaluation in the study. This information is key to drug safety. Thus, a prospective study might be an alternative way.

6. There are a number of uncontrollable factors that may interfere with the results of this study. For example, there were some patients to whom Cefoperazone was not administered within 48 hours of culture and sensitivity being reported. The reasons behind this might have been the variation of time spent in pathogen growth, and the hospital had so serve a large number of patients daily, this could have been another cause of culture and sensitivity delay.

Suggestions

- The DUE form still needs to be modified prior to public use. More evaluation of the appropriateness and reliability of the form should be performed.
- More DUE of Cefoperazone should be conducted in different locations for comparison of the results.
- DUE process should be made available to the public.
- The effects of the use of Cefoperazone after the completion of DUE should be considered to assist in the assessment of the appropriate use of other medications.
- More DUE should be conducted for antibiotics that have high toxicity, narrow therapeutic index and/or high risk of resistance to the drugs.

Conclusion

This study is aimed both to develop a criteria form for DUE of Cefoperazone and to evaluate the use of Cefoperazone at Sapasithiprasong Hospital, a regional hospital in Northeastern Thailand. The drug monograph criteria of Cefoperazone included indications, dosage regimens, drug awareness, disease etiologies, durations of treatment, adverse drug reactions and monitoring, and medical outcomes. The results of DUE of Cefoperazone showed that both indications and dosage regimens of Cefoperazone used for in-patients were appropriate. However, the drug awareness was not satisfactory due to some limitations including the lack of data of body weights, absence of allergy histories, and no CBC differential checking. These limitations might have caused a number of drug-related problems. Moreover, adverse drug reaction records could not be evaluated in the study due to the lack of the data. Cefoperazone is normally a first-line drug used for septicemia,

respiratory tract infections and other infectious diseases.

Overall, the use of Cefoperazone at Sapasithiprasong Hospital was satisfactory, but there was a need to address certain issues. Further evaluations in other local hospitals are needed for more precise and reliable results.

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