

Incidence of Antibiotic-Associated Diarrhea in a Pediatric Ambulatory Care Setting

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Background: Although antibiotic-associated diarrhea (AAD) is a common adverse event in children receiving oral antibiotics, few epidemiological studies have investigated this issue.

Objective: To determine the incidence of AAD in children who received oral antibiotics at the Pediatric Outpatient Department, Chiang Mai University Hospital.

Material and Method: Children who were prescribed oral antibiotics between September 2004 and June 2005 were randomly enrolled. Subjects with immunodeficiencies, acute/chronic diarrhea, and a history of having taken antibiotics within two weeks prior to this visit were excluded. Patients' characteristics including age, gender, principal diagnosis, and type of antibiotics were recorded. Parents were asked to observe stool frequency and consistency until one week after discontinuing antimicrobial agents and fill out an appropriate questionnaire. AAD was defined if there were at least three loose or liquid stools per day for two consecutive days. Risk factors including age, type, and dosage of the antibiotics used, were analyzed.

Results: Two hundred and twenty-five children were eligible for data analysis. The mean age was 4.1 years (0.3-14.5 years). Pharyngotonsillitis was the most common diagnosis (53.8%), and amoxicillin and cloxacillin comprised the most common antibiotics prescribed in the present cohort. The incidence of AAD was 6.2%. All episodes were presented while the patients were taking antibiotics with a mean (+/- SD) onset and duration of occurrence of 2.28 +/- 1.13 and 2.64 +/- 1.15 days, respectively. Premature discontinuation of antimicrobial agents was reported in nine patients (64.3%). There was a trend towards a higher incidence of AAD in the amoxicillin/clavulanate group (16.7%) compared to amoxicillin (6.9%) and erythromycin (11.1%) groups, although it was not statistically significant. In addition, the present study could not demonstrate an association between younger age or the high dosage of antibiotics used, and the development of AAD.

Conclusion: AAD was not uncommon in a pediatric ambulatory care setting. It tended to occur in younger children receiving amoxicillin/clavulanate.

Keywords: Antibiotic-associated diarrhea, Incidence, Child, Adverse drug reaction

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Adverse drug reaction (ADR) is one of the major concerns in pediatric ambulatory care. Kramer *et al* reported an overall incidence of 11.1%⁽¹⁾, of which most commonly caused by oral antibiotics that was prescribed for the treatment of respiratory tract, skin, and urinary tract infections. Although tremendous benefits are noted, various side effects related to anti-

microbial agents have been continuously reported. One of the most common adverse events is gastrointestinal involvement including nausea, vomiting, abdominal pain, and diarrhea⁽²⁾. Among these, antibiotic-associated diarrhea (AAD) is well recognized and considered to be the most common adverse effect. It frequently led physicians to prematurely discontinuing the medicine or changing the medication to cover for possible super-imposed gastrointestinal infection. The aim of the present study was to determine the incidence of AAD in children who received oral antibiotics at the Pediatric

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Material and Method

Patients under 15 years of age, who were visiting the Pediatric Outpatient Department at Chiang Mai University Hospital and being prescribed oral antibiotics, were randomly invited to participate in the present study protocol between September 2004 and June 2005. With an estimated AAD prevalence of 20% (+/- 25%) and the confidence level of 95%, a sample size of 225 patients was calculated. Subjects with immunodeficiencies, acute/chronic diarrhea, and a history of taking antibiotics within two weeks were excluded. A written, informed consent was obtained from the parents. Patients' baseline characteristics including age, sex, principal diagnosis, type, dosage, and duration of antibiotics were recorded. The parents were asked to fill out a questionnaire regarding possible adverse drug reactions such as nausea, vomiting, abdominal pain, diarrhea, and rash. Stool frequency and consistency were recorded daily. Antibiotic-associated diarrhea (AAD) was defined as a presence of three or more loose/liquid stools per day for at least two consecutive days starting from initiation of antibiotic to one week after discontinuation of antibiotic. If the questionnaire was not returned by regular mail one-week after stopping the medication, the parents would be contacted by telephone in order to monitor the ADRs. Incidence, characteristics, and risk factors including age, type, and dosage of the antibiotics used were collected and analyzed using the SPSS program. Mean and standard deviation, number and percent were presented. A p -value < 0.05 was considered statistically significant. The present study was approved by the Research Ethic Committee of the Faculty of Medicine, Chiang Mai University.

Results

During a 10-month period, 225 patients were randomly enrolled, which accounted for 20.7 per cent of all children receiving oral antibiotics. One hundred and fifteen were male. The mean age was 4.1 years (0.3-14.5 years). Eighty-four (37%) cases returned the questionnaire, whereas the others were called directly to complete the data. The most common principal diagnoses comprised acute pharyngotonsillitis (53.8%), skin infection (13.8%), URI/rhinitis (7.6%), acute otitis media (6.7%), sinusitis (5.3%), and pneumonia (4.4%). Amoxicillin was most commonly prescribed (70.1%), followed by cloxacillin (15.1%), and amoxicillin/clavulanate (5.3%), respectively.

Besides antibiotics, common co-prescriptions included acetaminophen, decongestant, antihistamine, mucolytic/expectorant, and bronchodilator.

Fourteen (6.2%) patients developed antibiotic-associated diarrhea, 11 associated with amoxicillin, 2 with amoxicillin/clavulanate, and 1 with erythromycin. The mean (+/- SD) onset of AAD was 2.28 +/- 1.13 days (1-5 days) after oral antibiotics were taken and the condition lasted for the mean (+/- SD) duration of 2.64 +/- 1.15 days (2-5 days). Among children with AAD, the mean stool frequency was 4.42 +/- 1.22 times/day. Nine of fourteen cases (64%) discontinued antimicrobial agents prematurely. Three patients with AAD previously had a history of diarrhea after taking an antibiotic; however, they could not recall what medication was used at the time. Clinical presentations were generally mild with no need for hospitalization. The diarrhea improved in one day after discontinuing antibiotics in all cases.

There was a trend towards a higher incidence of AAD in the amoxicillin/clavulanate group (2/12; 16.7%) compared with amoxicillin (11/159; 6.9%), and erythromycin (1/9; 11.1%) groups, although it was not statistically significant. There was no association between AAD and younger age or the high dosage of antibiotics used. Although duration of treatment was inversely associated with AAD, this should be cautiously interpreted. Since most of AAD patients in the present study discontinued the medication shortly after the development of diarrhea (Table 1). Moreover, two patients reported nausea and rash following the administration of erythromycin and amoxicillin, respectively.

Discussion

Antibiotic-associated diarrhea is one of the most common gastrointestinal adverse drug reactions noted in pediatric ambulatory settings. The incidence varies between 5% and 25%, depending on case enrollment, definition of AAD, type, and protocol/guideline of the antibiotics used⁽³⁾. In an adult study, Wistrom *et al*⁽⁴⁾ reported a frequency of AAD in 4.9% of 2,462 hospitalized antibiotic-treated patients. The incidence of AAD in pediatric outpatients reported was 3.5% and 11%, by Kramer⁽²⁾ and Turck *et al*⁽⁵⁾. One of the factors that may influence the difference in study results between Kramer and Turck was the availability of amoxicillin/clavulanate in the latter study. Although there were racial differences, the clinical characteristics and incidence of AAD in the present study were

Table 1. Potential risk factors of antibiotic-associated diarrhea in a pediatric ambulatory care setting (n = 225)

Risk factors	Occurrence of Diarrhea		p-value
	Yes (n = 14)	No (n = 211)	
Gender, male:female	1:1	1.05:1	0.57
Age (y)*	1.94 ± 0.24	4.1 ± 3.4	0.27
High dose antibiotic (n)	0	14	0.39
Type of antibiotic (n)			0.68
Amoxicillin	11	148	
Amoxicillin/clavulanate	2	10	
Cloxacillin	0	34	
Penicillin	0	1	
Co-trimoxazole	0	2	
Erythromycin	1	8	
Cephalexin	0	5	
Cefaclor	0	2	
Cefixime	0	1	
Duration of treatment (day)*	5.9 ± 2.2	7.8 ± 2.1	<0.001

* Presented as mean +/- SD

comparable to these previous studies. Most studies, including the authors, demonstrated that the symptoms started within 5-7 days after commencing antibiotic treatment and lasted for approximately 3-4 days^(5,6). Similar to other reports, the present study found the clinical presentation was mild and no child was hospitalized due to AAD^(2,5-7). The diarrhea usually improved after discontinuing the medication.

The mechanisms by which antibiotics result in AAD have remained unclear. Although *Clostridium difficile*-associated diarrhea (CDAD) has been postulated and widely studied recently, only 10%-20% of all AAD patients are positive for toxicogenic *C. difficile* strain⁽³⁾. CDAD is primarily acquired from the hospital environment, which leads to the higher incidence noted in hospitalized patients who are treated with antibiotics, compared with those in outpatient settings. Beaugerie *et al*⁽⁸⁾ reported a 17.6% incidence of AAD from a community based study in adults, in which 3.8% of the cases were diagnosed as CDAD. Other infective agents, such as *C. perfringens*, *Candida* spp., *Staphylococcus aureus*, and drug-resistant *Salmonella* species, have been sporadically reported to associate with AAD^(3,9).

Another potential underlying mechanism of AAD is disturbances in the function of normal intestinal flora, which are involved in colonic carbohydrate metabolism. Under normal circumstances, unabsorbed carbohydrates and dietary fibers are metabolized further by colonic bacteria into short-chain fatty acid, in

which they can be reabsorbed to salvage energy and induce additional fluid and electrolyte absorption at the colonic mucosa. As a result, this group of patients is vulnerable for development of osmotic diarrhea after intestinal loading of cow's milk, poorly absorbable carbohydrates such as fructose and sorbitol, and metabolizable dietary fibers for instance carrots, cabbage, and peas⁽¹⁰⁾. Direct effects of antibiotics on intestinal motility have also been linked to the development of AAD, particularly those of erythromycin and amoxicillin/clavulanate⁽³⁾.

In earlier reports, younger age, longer duration of treatment, multiple drug therapy, and type and dosage of antibiotics used were found to associate with AAD^(2,4,5,7,8). Unfortunately, these risk factors were not found to associate with AAD in the present study. However, there was a trend towards a higher incidence of AAD in the amoxicillin/clavulanate group compared to amoxicillin and erythromycin groups. One of the important health impacts learned from the present study was that approximately two-thirds of the AAD patients stopped taking the medication prematurely without physician supervision. This action may lead to inadequate treatment of underlying diseases. To avoid this, careful counseling on expected AAD is strongly advised. Antibiotics may be continued if the symptoms are mild.

Major limitations in the present study were the small number of subjects enrolled and possibility of inter-current acute viral gastroenteritis, which is a

common problem in children. A study by Talbot-Smith and Heyworth showed that the incidence of AAD was 32.3%, of this 8.8% associated with a viral respiratory illness⁽¹¹⁾.

In conclusion, antibiotic-associated diarrhea was not uncommon in pediatric ambulatory care setting. It tended to occur in younger children receiving amoxicillin/clavulanate.

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อุบัติการณ์การเกิดภาวะอุจจาระร่วงจากยาปฏิชีวนะในผู้ป่วยเด็กที่คลินิกผู้ป่วยนอก

อลิสรา ดำรงมณี, ณัฐพงษ์ อัครผล

ภูมิหลัง: ถึงแม้ว่าภาวะอุจจาระร่วงจากการได้รับยาปฏิชีวนะชนิดรับประทานจะเป็นภาวะแทรกซ้อนที่พบได้บ่อยในผู้ป่วยเด็ก แต่ปัจจุบันยังมีการศึกษาถึงอุบัติการณ์การเกิดภาวะนี้ค่อนข้างน้อย

วัตถุประสงค์: เพื่อศึกษาหาอุบัติการณ์การเกิดภาวะอุจจาระร่วงจากยาปฏิชีวนะคลินิกผู้ป่วยนอก ภาควิชากุมารเวชศาสตร์ มหาวิทยาลัยเชียงใหม่

วัสดุและวิธีการ: ผู้ป่วยเด็กที่ได้รับการส่งจ่ายยาปฏิชีวนะชนิดรับประทานระหว่างเดือนกันยายน พ.ศ. 2547 ถึง ตุลาคม พ.ศ. 2548 ได้ถูกสุ่มเข้าร่วมการศึกษาวิจัย การศึกษานี้จะไม่รวมผู้ป่วยที่มีภูมิคุ้มกันบกพร่อง มีประวัติอุจจาระร่วงเฉียบพลันเรื้อรัง และได้รับยาปฏิชีวนะภายใน 2 สัปดาห์ก่อนเข้าร่วมงานวิจัย ข้อมูลทั่วไป เช่น อายุ เพศ การวินิจฉัย และชนิดของยาปฏิชีวนะ จะถูกบันทึกโดยแพทย์ ในขณะที่ ความถี่ และลักษณะของอุจจาระ จะถูกบันทึกโดยพ่อแม่ นับตั้งแต่วันที่เข้าร่วมงานวิจัยจนถึง 1 สัปดาห์หลังยาปฏิชีวนะหมด ภาวะอุจจาระร่วงจากยาปฏิชีวนะ หมายถึงการมีอุจจาระเหลวมากกว่า 3 ครั้งต่อวัน ติดต่อกัน 2 วัน บั๊จจัยเสี่ยงเช่น อายุ ชนิดและขนาดของยาปฏิชีวนะที่ใช้ ได้ถูกศึกษาในงานวิจัยนี้เช่นกัน

ผลการศึกษา: มีผู้ป่วยในงานวิจัยนี้ 225 ราย อายุเฉลี่ย 4.1 ปี (0.3-14.5 ปี) ได้รับการวินิจฉัยเป็น pharyngotonsillitis บ่อยที่สุด (ร้อยละ 53.8) ยาปฏิชีวนะที่ใช้บ่อยคือ amoxicillin และ cloxacillin อุบัติการณ์การเกิดภาวะอุจจาระร่วงจากยาปฏิชีวนะเท่ากับร้อยละ 6.2 โดยเกิดขึ้นหลังจากกินยาไปประมาณ 2.28 ± 1.13 วัน และเป็นอยู่นานเฉลี่ย 2.64 ± 1.15 วัน ร้อยละ 64.3 ของผู้ป่วยที่มีอุจจาระร่วงได้หยุดยาปฏิชีวนะ การศึกษานี้พบว่าผู้ป่วยที่ได้รับ amoxicillin/clavulanate มีแนวโน้มการเกิดอุจจาระร่วง (ร้อยละ 16.7) ได้มากกว่าผู้ป่วยที่ได้รับ amoxicillin (ร้อยละ 6.9) และ erythromycin (ร้อยละ 11.1) แต่ไม่มีความแตกต่างทางสถิติ อายุ และขนาดของยาปฏิชีวนะที่ใช้ไม่เป็นปัจจัยเสี่ยงสำคัญในการศึกษานี้

สรุป: ภาวะอุจจาระร่วงจากยาปฏิชีวนะพบได้ค่อนข้างบ่อยที่คลินิกผู้ป่วยนอกแผนกกุมารเวชกรรม และมีแนวโน้มที่จะเกิดในผู้ป่วยอายุน้อยที่ได้รับยา amoxicillin/clavulanate
