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Formulation of ciprofloxacin ear drop in Paholpolpayuhasena Hospital

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- Objective** : *To formulate an effective ear drop treatment that can reduce costs and shorten the duration of treatment for acute diffuse otitis externa, acute otitis media and chronic otitis media.*
- Design** : *Experimental*
- Setting** : *Pharmaceutical Department, Paholpolpayuhasena Hospital, Kanchanaburi Province.*
- Material and Method** : *The 3 % ciprofloxacin ear drop was formulated in 3 steps and was prepared by aseptic technique in sterile container under laminar air flow hood.*
- Result** : *The ciprofloxacin ear drop prepared is a sterile, clear solution and has a stability for up to six months in room temperature storage. Assay results of the two products revealed the 97 %, 99.334 % labeled amount, sterile, and pH 5.6, 5.67 respectively. Tests for efficiency and safety in 402 patients with acute diffuse otitis externa, acute otitis media and chronic otitis media were carried out and results were satisfactory. The patients showed no signs of irritation or drug allergy. The cost of preparation is lower than other antibiotic ear drops on the market (15 Baht per 10 milliliter bottle). The detail of clinical trial will be reported separately.*

Conclusion : *Ciprofloxacin ear drops were formulated at Paholpolpayuhasena Hospital in order to be used as an alternative for traditional ear drops. This formulation can reduce the hospital expenses for oral and topical antibiotic treatments in acute diffuse otitis externa, acute otitis media and chronic otitis media.*

Key words : *Ciprofloxacin, Ear drop, Acute otitis externa, Acute otitis media, Chronic otitis media.*

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นิตยา คณาวงษ์. การพัฒนายาหยอดหู ciprofloxacin ในโรงพยาบาลพหลพลพยุหเสนา.
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- วัตถุประสงค์** : เพื่อผลิตยาหยอดหูที่มีประสิทธิภาพ ปลอดภัย และราคาถูก ในการรักษา
การอักเสบเฉียบพลันของหูชั้นกลาง-ชั้นนอก และการอักเสบเรื้อรังของ
หูชั้นกลาง
- ชนิดของการวิจัย** : การศึกษาแบบทดลอง
- ประเภทของโรงพยาบาล** : แผนกเภสัชกรรม โรงพยาบาลพหลพลพยุหเสนา จังหวัดกาญจนบุรี
- วัสดุและวิธีการ** : ยาหยอดหูไซโปรฟลอกซาซินขนาดความเข้มข้นร้อยละ 0.3 ได้รับการ
พัฒนาและเตรียมโดยใช้ 3 ขั้นตอน ด้วยวิธีปราศจากเชื้อ
- ผลการศึกษา** : ยาหยอดหูไซโปรฟลอกซาซินที่ผลิตขึ้น มีลักษณะใสปราศจากเชื้อ มี
ปริมาณไซโปรฟลอกซาซินร้อยละ 97 และ 99.334 ของปริมาณที่แจ้งมี
ความเป็นกรดต่าง 5.6 และ 5.67 และมีความคงตัวนาน 6 เดือนใน
อุณหภูมิห้อง การทดสอบประสิทธิภาพและความปลอดภัยในการรักษา
ผู้ป่วยที่มีการอักเสบเฉียบพลันของหูชั้นกลาง ชั้นนอก และการอักเสบ
เรื้อรังของหูชั้นกลาง จำนวน 402 ราย ได้ผลเป็นที่น่าพอใจ โดยที่
ผู้ป่วยไม่มีอาการระคายเคืองหรือมีอาการแพ้ ราคาของยาที่ผลิตขึ้น ถูก
กว่ายาหยอดหูที่มีส่วนประกอบเป็นยาปฏิชีวนะอื่น ๆ รายละเอียดการ
ทดลองในทางคลินิกจะได้รายงานแยกต่างหากไปอีกรายงานหนึ่ง
- สรุป** : ยาหยอดหูไซโปรฟลอกซาซินได้รับการผลิตในโรงพยาบาลพหลพล
พยุหเสนา เพื่อให้ทดแทนยาหยอดหูที่มีส่วนประกอบเป็นยาปฏิชีวนะ
อื่น ๆ การพัฒนานี้สามารถลดค่าใช้จ่ายของโรงพยาบาลในการให้ยา
ปฏิชีวนะรักษาผู้ป่วยที่มีการอักเสบเฉียบพลันของหูชั้นกลาง ชั้นนอก
และการอักเสบเรื้อรังของหูชั้นกลาง

Acute diffuse external otitis is usually caused by *Pseudomonas aeruginosa*; although *Proteus mirabilis* and other gram - negative bacilli (*klebsiella*, *E.coli*) are also isolated from cultures. Staphylococcal and streptococcal species are also frequently encountered. Most chronic otitis media with or without cholesteatoma are caused by both aerobic and anaerobic organisms. Those aerobic bacteria isolated include *Pseudomonas aeruginosa*, *Staph.*

ciprofloxacin ear drops as an alternative for traditional ear drops. Data provided by Infopharma Media Services Limited in Thailand for recent years revealed that the estimated cost of traditional ear drops used yearly in governmental and private hospitals in Thailand was about 2,165,000/552,000 Baht, in 1996, 2,397,000/938,000 Baht in 1997, and 2,089,000/1,040,000 Baht in 1998. (Table1)

Table 1. Estimated cost of traditional ear drops used yearly in Thailand.

Year	Governmental Hospital (Baht)	Private Hospital (Baht)	Total (Baht)
1996	2,165,000	552,000	2,717,000
1997	2,397,000	938,000	3,335,000
1998	2,089,000	1,040,000	3,130,000

aureus, *proteus* species, *klebsiella* species and *E.coli*. Various anaerobes are isolated especially *Bacteroides fragilis*. The organisms encountered in acute diffuse otitis externa and chronic otitis media are usually sensitive to topical neomycin, polymyxin and gentamicin.⁽¹⁻⁴⁾ Recently ofloxacin ear drop have been used with satisfactory results. However, ciprofloxacin ear drops have never been marketed even though favorable results have been obtained by using 0.35% ciprofloxacin solution. They were more effective than oral ciprofloxacin or other topical ear drops including gentamicin; combination of oxytetracycline, polymyxin B, and hydrocortisone or polymyxin B - neomycin - hydrocortisone. There were no adverse effects or worsening of the audiometric and vestibular function observed after local therapy.⁽⁶⁻⁹⁾ The purpose of this project was to develop

Materials and Methods

Materials

The ciprofloxacin ear drops were composed of ciprofloxacin hydrochloride U.S.P. batch No: CPII 0997138, Mfd 09.97, Exp date 08.2002 made in India by Neuland Lab., benzalkonium chloride 50 % solution B.P. batch No: 151, made in United Kingdom by Henley Chemicals Ltd., propylene glycol B.P. made in Thailand by Thai-MC Company Limited., and sterile water U.S.P. made at Pharmaceutical Department, Paholpolpayuhasena Hospital, Kanchanaburi Province, Membrane filter 0.2 μ Minisart NML[®] was made by Sartorius AG.Germany, batch No. 165 34 951751, date of sterilization 06. 95, expiration date 06.98., and the laminar air flow hood was made from Holten Lamin Air model TLK-2472 serial No. 94603000 J.

Methods

There were three steps of study involved in formulation, and the solution was prepared by aseptic technique under a laminar air flow hood.

Step I Formulation of 0.35 % ciprofloxacin hydrochloride ear drop equivalent to 0.3 % ciprofloxacin base ear drop, This concentration of solution is the concentration of ciprofloxacin hydrochloride ophthalmic solution.⁽¹⁰⁾

Dissolve ciprofloxacin hydrochloride 3.5 g in 300 ml. sterile water. Preserve the solution by adding 10.0 ml. of 1% benzalkonium chloride solution in ciprofloxacin hydrochloride solution. Sterilize the solution by filtering the whole solution through 0.2 μ membrane filter. Mix the solution with 688.25 ml. of sterile propylene glycol and store the end product in a 10 ml. sterile ambered bottle under horizontal laminar air flow. The solution obtained can be stored at room temperature and preserved in a tight, light resistant container and should be used within six months after preparation.

Step II The standard requirement for 0.3% ciprofloxacin base ear drop were tested at the Department of Science, Ministry of Public Health. They included the percent labeled amount of active ingredient by HPLC under official monograph of ciprofloxacin (raw material) and sterility of the product as directed in the section *Test Procedures Using Membrane Filtration* under official monograph of ciprofloxacin injection or ciprofloxacin ophthalmic solution according to USP 23.⁽¹⁰⁾

Step III Treated the patients with acute diffuse otitis externa, acute otitis media and chronic otitis media in the Department of Otolaryngology, Paholpolpayuhasena Hospital, Kanchanaburi province during the period Feb. 1998 to Feb. 1999. Four hundred and two patients were enrolled in the study. There were 196 male and 206 female, between <1-92 years old; 236 (58.71%) with acute diffuse otitis externa, 79 cases (19.65%) with chronic otitis media and 87 cases (21.64%) with acute otitis media with tympanic membrane perforation. (Table 2)

Table 2. Diagnosis of 402 out - patients treated with ciprofloxacin ear drop at Paholpolpayuhasena Hospital, Kanchanaburi Province during the period Feb.1998 to Feb.1999.

Diagnosis	Children (1 month -15 years)		Adults		Total
	Male	Female	Male (16-80 years)	Female (16-92 years)	
Chronic otitis media	11	3	18	47	79
Acute otitis media	15	14	29	29	87
Acute otitis externa	31	22	92	91	236
Total	57	39	139	167	402

Results

The ciprofloxacin ear drop prepared is a sterile, clear solution containing 3.5% W/V ciprofloxacin hydrochloride (equivalent to 0.3 % ciprofloxacin base) in sterile water, propylene glycol with benzalkonium chloride 0.01%W/V as a preservative. Assay results of the product manufactured on Feb. 12, and Mar.5, 1998 by the Division of Drug Analysis, Department of Medical Science, Ministry of Public Health on Jun.12, and Jul.7, 1998 respectively revealed 97 % and 99.334% labeled amount sterile solution with pH of 5.6, and 5.67. Follow up assessment by clinical examination in 402 patients showed good results; inflammation had subsided and granulation tissue had regressed. There were no signs of irritation or drug allergy. The detail of clinical trial will be reported separately.

Discussion

Ciprofloxacin is active in vitro against a wide range of gram-negative and gram-positive organisms. The bactericidal action of ciprofloxacin results from interference with the enzyme DNA gyrase, which is needed for synthesis of bacterial DNA. Ciprofloxacin has been shown to be active against most strains of the following organisms both in vitro and in clinical infections. These organisms include *staphylococcus species including methicillin - resistant strains and streptococcus species, Pseudomonas aeruginosa, Proteus mirabilis, H.influenzae and M.catarrhalis*. It has been used orally for treatment of acute diffuse otitis externa and chronic otitis media and with favourable results.⁽¹⁻³⁾

The standard requirements for ciprofloxacin ear drop preparation had never been officially

published in pharmacopoeia ; while the ciprofloxacin (raw material), ciprofloxacin hydrochloride, ciprofloxacin injection, ciprofloxacin ophthalmic solution and ciprofloxacin tablets had their standard requirements.⁽¹⁰⁾ The percent labeled amount, sterility and pH of the products prepared were respectively assayed by HPLC under official monograph of raw material of ciprofloxacin, and sterility as directed in the section *Test Procedures Using Membrane Filtration* under official monograph of ciprofloxacin injection or ciprofloxacin ophthalmic solution according to USP 23.⁽¹⁰⁾

Conclusion

Ciprofloxacin ear drops were developed in order to be used as an alternative for traditional ear drops. It was proved to be effective, safe and less expensive than the currently used ear drops. This development would reduce the medical expenses for oral and topical antibiotic treatment in acute diffuse otitis externa, acute otitis media and chronic otitis media. Excellent results have been obtained by using this solution four times daily for a week. Because of low cost, high efficiency and lack of side effects or complication; it is recommended for wide use as an alternative for traditional ear drops for treatment of acute diffuse bacterial otitis externa, acute otitis media with perforation of tympanic membrane and chronic otitis media. We also believe that this preliminary report will be helpful for further development of ciprofloxacin ear drops in Thailand.

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