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December 1, 2000

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Proposed Rule: Labeling Requirements for Systemic Antibacterial Drug Products Intended for Human Use, *Federal Register*, September 19, 2000 [Docket No. 00N-1463] RIN 0910-AB78

We applaud the FDA for addressing the important issue of antibiotic resistance through the requirements in the proposed rule. We believe that the proposed rule to require additional information on antibiotic resistance will be another step in building public awareness and improving antibiotic use before we have a public health emergency. The following are suggestions to strengthen the FDA's intent and clarify several provisions.

1. We urge that all antibiotics be subject to the labeling requirement. Topicals are sometimes used as an alternative to systemic antibiotics to prevent the emergence of resistance, but resistance can still develop with the use of topicals; likewise for eye and ear infections. See Attachment A for abstracts of eight studies demonstrating this evidence.
2. The proposed rule exempts antibiotics such as Clarithromycin and Rifampin. However, these are used for both mycobacterial and other bacterial infections. Since antibiotics such as these have two purposes, one covered by the proposed rule and the other not, will the pharmaceutical companies be required to put the label in the package insert for these antibiotics? We are concerned that there is some loophole here in which Clarithromycin and Rifampin may not be required to have the additional labeling information. We urge the FDA to clarify how a label will apply in these circumstances.

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3. The proposed rule indicates that its purposes are to encourage physicians to use antibiotics more judiciously and for them to counsel their patients to comply with the directions given. It is questionable whether or not prescribers read package inserts thoroughly, due to the length and small type used. We strongly suggest that the FDA, in addition to adopting this rule, send periodic physician advisories to all physicians and other prescribers of medications discussing updates on antibiotic resistance and urging them to use antibiotics prudently.

4. Since patient demand (for antibiotics) often results in physicians prescribing unnecessarily, it is important for patients to learn more about antibiotic resistance. When patients receive the package inserts or a summary of them, we urge that pharmacists include the entire message, not a summary of what is in the package insert, when giving an antibiotic to a patient.

We would be happy to discuss these issues with you.

Sincerely,



Kathleen T. Young
Executive Director

Cc: Stuart B. Levy, M.D.
Barbara A. Souder, Ph.D.

Attachment A

Attachment A: Studies supporting evidence that topical antibiotics and ones used for ear and eye infections can lead to antibiotic resistance.

Study 1: Bertino JS Jr. Intranasal mupirocin for outbr...[PMID:9331438]
Related Articles, LinkOut

UI - 97472479
AU - Bertino JS Jr
TI - Intranasal mupirocin for outbreaks of methicillin-resistant Staphylococcus aureus.
LA - Eng
MH - Administration, Intranasal
MH - Adult
MH - Antibiotics/pharmacokinetics/*therapeutic use
MH - Cross Infection/*drug therapy
MH - Human
MH - Infection Control
MH - Methicillin Resistance
MH - Mupirocin/adverse effects/pharmacokinetics/*therapeutic use
MH - Rhinitis/chemically induced
MH - Staphylococcal Infections/*drug therapy
MH - *Staphylococcus aureus
MH - Support, Non-U.S. Gov't
RN - 0 (Antibiotics)
RN - 12650-69-0 (Mupirocin)
PT - JOURNAL ARTICLE
PT - REVIEW
PT - REVIEW, TUTORIAL
DA - 19971114
DP - 1997 Oct 1
IS - 1079-2082
TA - Am J Health Syst Pharm
PG - 2185-91
SB - M
CY - UNITED STATES
IP - 19

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VI - 54

JC - CBH

AA - Author

EM - 199801

AB - The pharmacology, pharmacokinetics, clinical efficacy, adverse effects, and dosage and administration of mupirocin are reviewed. Mupirocin is a naturally occurring antibiotic produced by submerged fermentation of *Pseudomonas fluorescens*. It inhibits bacterial protein synthesis by binding reversibly and specifically to isoleucyl-tRNA synthetase. Organisms resistant to other antimicrobials are not simultaneously resistant to mupirocin. Mupirocin is highly active against *Staphylococcus aureus* and other staphylococci and streptococci. When mupirocin ointment is applied topically, local concentrations exceed the inhibitory concentrations for staphylococci and remain detectable for up to 72 hours. Placebo-controlled studies demonstrate the ability of mupirocin to eliminate nasal carriage of *S. aureus* in health care workers.

Observational studies suggest that mupirocin is efficacious in treating methicillin-resistant *S. aureus* (MRSA) outbreaks. Preliminary studies show that mupirocin might have a role in preventing infections in high-risk patients. Although mupirocin seems to be well tolerated, mild to moderate adverse events have been reported, including respiratory problems and effects confined to the nose--erythema, swelling, burning or stinging, pruritus, and dryness. Mupirocin calcium ointment has FDA-approved labeling for the eradication of nasal MRSA colonization in adult patients and health care workers as part of comprehensive infection-control programs to reduce the risk of infection during institutional outbreaks.

The recommended dosage is 0.5 g inserted into each nostril twice daily for five days. Intranasal mupirocin ointment appears to be a useful addition to infection-control programs designed to reduce the risk of infection among patients during MRSA outbreaks.

AD - Clinical Pharmacology Research Center, Cooperstown, NY, USA.

jbertino@usa.net

RF - 45

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PMID- 0009331438

EDAT- 1997/10/23 22:23

MHDA- 1997/10/23 22:23

SO - Am J Health Syst Pharm 1997 Oct 1;54(19):2185-91

Study 2

UI - 20243903

TI - Assessment of the potential for microbial resistance to topical use of multiple antimicrobial agents.

SO - Wound Repair Regen 1999 Jul-Aug;7(4):238-43

TA - Wound Repair Regen

VI - 7

IP - 4

PG - 238-43

DP - 1999

AU - Holder IA

AU - Boyce ST

AD - Shriners Hospitals for Children, Cincinnati, OH 45229, USA.

AB - The goal of this study was to reduce the likelihood of the generation and/or persistence of bacterial resistance to some antimicrobial components contained in a topical antimicrobial mixture (neomycin, polymyxin B, mupirocin and ciprofloxacin) for use with cultured skin grafts, by

substitution of alternative antimicrobials, specifically fusidic acid for mupirocin and ofloxacin for ciprofloxacin. The alternative agents failed to serve that purpose. However, with the exception of specific genera of bacteria, *Proteus* sp. and *Providencia stuartii*, 90% or more of all other bacteria

tested were susceptible to the action of one or more of the individual antimicrobial agents contained in the original mixture. This was true when bacteria were highly susceptible to the antimicrobials, generally, or when bacteria resistant to specific antimicrobials such as penicillin-class antibiotics and ciprofloxacin, were tested. These results suggest that the redundancy of antimicrobials contained in this mixture reduces the chance that resistant bacteria generated by the use of this mixture or already present on wounds would persist when the mixture is used clinically.

IS - 1067-1927

MJ - Antibiotics, Combined [administration & dosage]

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MJ - Drug Resistance, Microbial

MN - Administration, Topical

MN - Antibiotics, Combined [pharmacology]

MN - Fusidic Acid [administration & dosage] [pharmacology]

MN - Microbial Sensitivity Tests

MN - Mupirocin [administration & dosage] [pharmacology]

MN - Neomycin [administration & dosage] [pharmacology]

MN - Polymyxin B [administration & dosage] [pharmacology]

RN - 0 (Antibiotics, Combined); 12650-69-0 (Mupirocin); 1404-04-2 (Neomycin); 1404-26-8 (Polymyxin B); 6990-06-3 (Fusidic Acid)

MT - Support, Non-U.S. Gov't

LA - English

PT - JOURNAL ARTICLE

EM - 200007

Study 3

UI - 95281275

TI - New antimicrobial agents.

SO - *Pediatr Clin North Am* 1995 Jun;42(3):717-35

TA - *Pediatr Clin North Am*

VI - 42

IP - 3

PG - 717-35

DP - 1995

AU - Goldfarb J

AD - Department of Infectious Diseases, Cleveland Clinic Foundation, Ohio, USA.

AB - In any discussion of new antimicrobial agents in the 1990s, a warning and a plea are necessary. The spreading emergence of resistance among bacteria raises concerns for the effectiveness of antimicrobial therapy. Penicillin-resistant pneumococci are probably of most significance in pediatrics and are increasing in frequency, in part related to the use of antimicrobial therapy in young children to treat such infections as otitis media. New practice guidelines have suggested the more limited use of antimicrobial agents in treating serious otitis media. When pediatricians do treat, they

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should select effective agents. Limiting therapy to brief courses with effective and narrow-spectrum agents may be helpful also. Treating long enough to ensure eradication in serious infections is equally important. Methicillin-resistant *S aureus* are also increasing and are increasingly a concern in community-acquired infections and nosocomial infections. Using topical agents, such as mupirocin, to treat impetigo and other superficial skin infections can limit exposure to systemic agents and may delay the spread of resistance. Vancomycin-resistant enterococcal infections, an infrequent pediatric problem, are most frightening because no alternative therapies are available. Their occurrence is directly related to use of vancomycin in the communities that are affected. Containing the spread of drug-resistant bacteria will likely require a concerted effort by both physicians and the public. The indiscriminate use of antimicrobial agents to treat non-bacterial infections should be contained. The public must be educated to understand that antimicrobial agents are ineffective against viral infections. In the setting of managed care, educating administrators who make practice decisions that cheaper is not always better will be crucial. The issues of day-care infections and spread of potential pathogens must take on increasing attention and methods to decrease infection sought. Curbing inappropriate use of antimicrobial agents will be as important as learning the nuances between new agents.

IS - 0031-3955

MJ - Antibiotics [therapeutic use]

MJ - Bacterial Infections [drug therapy]

MN - Anti-Infective Agents, Fluoroquinolone [therapeutic use]

MN - Antibiotics, Lactam [therapeutic use]

MN - Antibiotics, Macrolide [therapeutic use]

MN - Child

MN - Pediatrics

MN - United States

RN - 0 (Anti-Infective Agents, Fluoroquinolone); 0 (Antibiotics); 0 (Antibiotics, Lactam); 0 (Antibiotics, Macrolide)

MT - Comparative Study; Human

LA - English

PT - JOURNAL ARTICLE; REVIEW (52 references); REVIEW LITERATURE

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EM - 199509

Study 4

UI - 98172022

TI - The emergence of mupirocin resistance: a challenge to infection control and antibiotic prescribing practice.

SO - J Antimicrob Chemother 1998 Jan;41(1):11-8

TA - J Antimicrob Chemother

VI - 41

IP - 1

PG - 11-8

DP - 1998

AU - Cookson BD

AD - Laboratory of Hospital Infection, PHLS Central Public Health Laboratory, London, UK.

AB - Mupirocin was introduced into clinical practice in the UK in 1985, and has proved to be an extremely effective treatment of skin infections and one of the most successful topical antibiotics for the clearance of nasal Staphylococcus aureus isolates including those resistant to methicillin. It

is currently registered for use in more than 90 countries worldwide. Unfortunately resistance was described shortly after its initial use. Many of the issues regarding its use are reviewed here, together with the mechanisms, genetics, surveillance and epidemiology of resistance, particularly in staphylococci. The various factors that increase resistance and how they might be controlled are also discussed.

IS - 0305-7453

MJ - Antibiotics [therapeutic use]

MJ - Mupirocin [therapeutic use]

MJ - Skin Diseases [drug therapy]

MN - Drug Resistance, Microbial [genetics] [physiology]

MN - Drug Utilization

MN - Methicillin Resistance

MN - Physician's Practice Patterns

MN - Skin Diseases [microbiology]

MN - Staphylococcal Infections [drug therapy] [therapy]

MN - Staphylococcus aureus [drug effects]

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RN - 0 (Antibiotics); 12650-69-0 (Mupirocin)

MT - Human

LA - English

PT - JOURNAL ARTICLE; REVIEW (62 references); REVIEW, TUTORIAL

EM - 199806

Study 5

UI - 98218000

TI - An overview of topical antibiotics for acne treatment.

SO - Dermatology 1998;196(1):130-4

TA - Dermatology

VI - 196

IP - 1

PG - 130-4

DP - 1998

AU - Toyoda M

AU - Morohashi M

AD - Department of Dermatology, Faculty of Medicine, Toyama Medical and Pharmaceutical University, Japan. toyodam@toyama-mpu.ac.jp.

AB - Topical use of antibiotics is currently a widely accepted effective and safe treatment for acne. A review of the articles published in the past 30 years revealed that topical application of antibiotics such as erythromycin, clindamycin or tetracycline showed clinical effectiveness for mild to moderate inflammatory acne, especially when they are combined with zinc, tretinoin or benzoyl peroxide, while they showed little influence on noninflammatory acne. The main mechanism of action of topical antibiotics for acne treatment is inhibition of inflammation caused by bacteria rather than a direct bactericidal effect. The adverse reactions of topical antibiotics are mostly minor and negligible, while special attention should be given to the risk of development of resistant strains of *Propionibacterium* acnes. The development of new antibiotics is promising and will provide a wider range of therapeutic options for refractory cases.

IS - 1018-8665

MJ - Acne Vulgaris [drug therapy]

MJ - Antibiotics [administration & dosage]

MN - Acne Vulgaris [microbiology]

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MN - Administration, Topical

MN - Antibiotics [adverse effects]

MN - Drug Resistance, Microbial

MN - Propionibacterium acnes [drug effects]

RN - 0 (Antibiotics)

MT - Human

LA - English

PT - JOURNAL ARTICLE; REVIEW (31 references); REVIEW, TUTORIAL

EM - 199808

Study 6

UI - 97070546

TI - Effects of topical erythromycin on ecology of aerobic cutaneous bacterial flora.

SO - Antimicrob Agents Chemother 1996 Nov;40(11):2598-604

TA - Antimicrob Agents Chemother

VI - 40

IP - 11

PG - 2598-604

DP - 1996

AU - Vowels BR

AU - Feingold DS

AU - Sloughfy C

AU - Foglia AN

AU - Konnikov N

AU - Ordoukhanian E

AU - Starkey P

AU - Leyden JJ

AD - Department of Dermatology, School of Medicine, University of Pennsylvania, Philadelphia 19104-6142, USA.

AB - We have demonstrated previously that application of topical erythromycin, an antibiotic commonly used for the treatment of acne, results in an increased density of cutaneous erythromycin-resistant (Emr) coagulase-negative staphylococci; however, it is unknown if this increase results in an overall higher density of total cutaneous staphylococci or if upon cessation of

erythromycin use, Emr coagulase-negative staphylococci remain at an increased density compared with the pretreatment density. To investigate this, 2% erythromycin or vehicle was applied to each subject's forehead (n = 225) twice a day by laboratory personnel for a period of 6 weeks. Samples were obtained for culture from the forehead, anterior nares, and back of the subjects at baseline and at weeks 6, 9, and 12 of the study. Cultures were performed on differential media. Plates into which erythromycin was incorporated (8 micrograms/ml) were used to identify Emr coagulase-negative staphylococci. The species of all Emr coagulase-negative staphylococci were determined, and an antibiogram for 16 antibiotics was obtained. The baseline prevalence of Emr coagulase-negative staphylococci on the forehead and nose was about 80% at the two study sites, whereas that on the back was 50%. The baseline density of Emr coagulase-negative staphylococci on the forehead, nose, and back was approximately 20% of the total flora. Following 6 weeks of erythromycin treatment, the prevalence of Emr coagulase-negative staphylococci on the forehead and nose was nearly 100% and the densities were 73 and 62%, respectively; the prevalence and density for the back were 78 and 42%, respectively. The most prevalent erythromycin resistance gene expressed by the Emr coagulase-negative staphylococci was ermC. There was no increase in the numbers of *Staphylococcus aureus*, gram-negative rods, or yeasts, nor was there increased resistance to any other antibiotic except clindamycin. The density of total aerobic organisms also remained static. There were no changes in the prevalence or density of Emr coagulase-negative staphylococci in the vehicle group. A statistically significant decrease in the prevalence and density of Emr coagulase-negative staphylococci in the erythromycin group was observed within 3 weeks posttreatment and by 6 weeks posttreatment, the prevalence and density returned to baseline values. These data demonstrate that the increased prevalence and density of Emr coagulase-negative staphylococci as a result of topical 2% erythromycin use are transient on both population and individual levels.

IS - 0066-4804

MJ - Antibiotics, Macrolide [pharmacology]

MJ - Erythromycin [pharmacology]

MJ - Skin [microbiology]

MN - Administration, Topical

MN - Adolescence

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MN - Adult

MN - Antibiotics, Macrolide [administration & dosage]

MN - Bacteria, Aerobic [drug effects]

MN - Coagulase [metabolism]

MN - Double-Blind Method

MN - Drug Resistance, Microbial

MN - Drug Resistance, Multiple

MN - Erythromycin [administration & dosage]

MN - Genes, Bacterial

MN - Middle Age

MN - Skin [drug effects]

MN - Staphylococcus [drug effects] [enzymology]

RN - 0 (Antibiotics, Macrolide); 0 (Coagulase); 114-07-8 (Erythromycin)

MT - Female; Human; Male

LA - English

PT - CLINICAL TRIAL; JOURNAL ARTICLE; RANDOMIZED CONTROLLED TRIAL

EM - 199705

Study 7

UI - 99266734

TI - Antibiotics in chronic suppurative otitis media: a bacteriologic study.

SO - Ann Otol Rhinol Laryngol 1999 May;108(5):440-5

TA - Ann Otol Rhinol Laryngol

VI - 108

IP - 5

PG - 440-5

DP - 1999

AU - Indudharan R

AU - Haq JA

AU - Aiyar S

AD - Department of Otorhinolaryngology, School of Medical Sciences, University Sains
Malaysia, Kota Bharu.

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AB - Conservative medical management of chronic suppurative otitis media (CSOM) is an important step in achieving a dry ear. Topical antibiotic ear drops and aural toilet form the mainstay of medical management of noncholesteatomatous CSOM. This study analyzes the causal organisms and their sensitivity to various antibiotics. Out of 382 swabs examined, the major organisms isolated were *Pseudomonas aeruginosa* (27.2%), followed by *Staphylococcus aureus* (23.6%). The sensitivity of *P. aeruginosa* was 100% to ceftazidime, 98.9% to ciprofloxacin, 96.3% to gentamicin, and 95.4% to polymyxin B, whereas the sensitivity of *S. aureus* was 98.6% to ciprofloxacin, 97.4% to cloxacillin sodium, 96.5% to cotrimoxazole, and 90.7% to gentamicin. *Pseudomonas aeruginosa* was almost completely resistant to ampicillin (97.6%) and chloramphenicol (96.6%), whereas *S. aureus* was almost completely resistant to ampicillin (73.8%) and polymyxin B (98.3%). Among the available topical antibiotic preparations for use in the ear, we found that ciprofloxacin and gentamicin are the best choices.

IS - 0003-4894

MJ - Antibiotics [therapeutic use]

MJ - Microbial Sensitivity Tests

MJ - Otitis Media, Suppurative [microbiology]

MN - Adolescence

MN - Adult

MN - Aged

MN - Bacteria [isolation & purification]

MN - Child, Preschool

MN - Child

MN - Chronic Disease

MN - Infant

MN - Middle Age

MN - Otitis Media, Suppurative [drug therapy]

RN - 0 (Antibiotics)

MT - Human; Support, Non-U.S. Gov't

LA - English

PT - JOURNAL ARTICLE

EM - 199908

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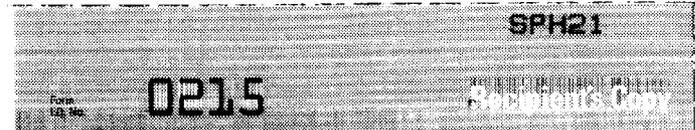
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