December 1, 2000

Documents Management Branch
(HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

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.
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,

[Signature]

Kathleen T. Young
Executive Director

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

Attachment A
December 4, 2000

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Addendum to Page 2, Letter from APUA (the Alliance for the Prudent Use of Antibiotics), dated and transmitted via Fed Ex on December 1, 2000

We would be grateful to the FDA if this Addendum could be added to Page 2 — Letter from APUA (the Alliance for the Prudent Use of Antibiotics), dated December 1 and sent via Fed ex to arrive on December 4th.

In the typing of this letter, one point was inadvertently omitted on Page 2. Please add:

"5. We urge the FDA to require that the additional information required on the label be highlighted in a black box to make it stand-out (for all areas – product name, clinical pharmacology, indications and usage, and in both precautions sections – ‘general’ and ‘information for patients’). We further encourage FDA to require in the final rule a print size in the package insert that can be ready by all.”

We apologize for any inconvenience and thank you in advance for adding this point.

Sincerely,

[Signature]
Kathleen T. Young
Executive Director
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. Intransal mupirocin for outbr...[PMID:9331438]

Related Articles, LinkOut
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.
bernino@usa.net
RF - 45
PMID- 0009331438
EDAT- 1997/10/23 22:23
MHDA- 1997/10/23 22:23

Study 2
UI - 20243903
TI - Assessment of the potential for microbial resistance to topical use of multiple antimicrobial agents.
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]
Study 3
UI - 95281275
TI - New antimicrobial agents.
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
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 Staphylococcus 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
Study 4
UI - 98172022
TI - The emergence of mupirocin resistance: a challenge to infection control and antibiotic prescribing practice.
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 staphyloococi. 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]
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]
Study 6
UI - 97070546
TI - Effects of topical erythromycin on ecology of aerobic cutaneous bacterial flora.
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
Study 7
UI - 99266734
TI - Antibiotics in chronic suppurative otitis media: a bacteriologic study.
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.
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 (73.8%) 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.