

Cefotetan: a second-generation cephalosporin active against anaerobic bacteria

Committee on Antimicrobial Agents,* Canadian Infectious Disease Society; Marie J. Gribble, MB, ChB, FRCPC

Objective: To offer guidelines for the use of cefotetan, a cephamycin antibiotic, in order to minimize its overprescription.

Options: Clinical practice options considered were treatment of infections with the use of second- and third-generation cephalosporins, carbapenems such as imipenem as well as combination regimens of agents active against anaerobic bacteria, such as metronidazole or clindamycin with an aminoglycoside.

Outcomes: In order of importance: efficacy, side effects and cost.

Evidence: A MEDLINE search of articles published between January 1982 and December 1993. In-vitro and pharmacokinetic studies published in recognized peer-reviewed journals that used recognized standard methods with appropriate controls were reviewed. For results of clinical trials, the reviewers emphasized randomized double-blind trials with appropriate controls.

Values: The Antimicrobial Agents Committee of the Canadian Infectious Disease Society (CIDS) and a recognized expert (M.J.G.) recommended use of cefotetan to prevent and treat infections against which it has proved effective in randomized controlled trials.

Benefits, harms and costs: These guidelines should lead to less inappropriate prescribing of cefotetan, with its attendant costs and risk of development of resistant bacteria.

Recommendations: Cefotetan could be considered an alternative single agent for prophylaxis of infection in patients undergoing elective bowel surgery. It may be used to treat patients with acute pelvic inflammatory disease and endometritis.

Validation: This article was prepared, reviewed and revised by the Committee on Antimicrobial Agents of the CIDS. It was then reviewed by the Council of the CIDS, and any further necessary revisions were made by the chairman of the committee.

Sponsor: The CIDS was solely responsible for developing, funding and endorsing these guidelines.

Objectif : Présenter des lignes directrices sur l'utilisation du céfotétane, antibiotique de la famille des céphamycines, afin d'en réduire au minimum la surprescription.

Options : Options d'interventions cliniques : Traitement d'infections à l'aide de céphalosporines de deuxième et de troisième génération, de carbapénèmes comme l'imipénème, ainsi que d'une combinaison d'agents actifs contre les bactéries anaérobies, comme le métronidazole ou la clindamycine jumelée à un aminoglycoside.

Résultats : Par ordre d'importance : efficacité, effets secondaires et coût.

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Preuve : Recherche dans MEDLINE d'articles publiés entre janvier 1982 et décembre 1993. Études in-vitro et pharmacocinétiques publiées dans des journaux reconnus critiqués par les pairs, au cours desquelles on a utilisé des méthodes standard reconnues et des témoins appropriés. Au sujet des résultats de ces essais cliniques, les examinateurs ont recherché surtout les essais randomisés à double insu et l'utilisation de témoins appropriés.

Valeurs : Le Comité d'agents antimicrobiens de la Société canadienne des maladies infectieuses (SCMI) et un expert reconnu (M.J.G.) ont recommandé d'utiliser le céfotétane pour prévenir et traiter les infections contre lesquelles il s'est révélé efficace au cours d'essais contrôlés randomisés.

Avantages, préjudices et coûts : Ces lignes directrices devraient réduire les ordonnances inappropriées de céfotétane, ainsi que les coûts connexes et le risque d'apparition de bactéries résistantes.

Recommandations : Il faudrait considérer le céfotétane comme un agent de rechange pour le traitement des infections chez les patients qui subissent une chirurgie électorale des intestins. On peut l'utiliser pour traiter des patientes atteintes d'inflammation pelvienne aiguë et d'endométrite.

Validation : Cet article a été rédigé, examiné et révisé par le Comité d'agents antimicrobiens de la SCMI. Il a été examiné ensuite par le Conseil de la SCMI, et le président du comité a fait quelques autres révisions nécessaires.

Commanditaire : La SCMI est le seul intervenant qui a élaboré, financé et appuyé ces lignes directrices.

Cefotetan is a semisynthetic cephamycin antibiotic. Compared with cefoxitin it is similar in antibacterial effectiveness against aerobic gram-positive cocci and *Bacteroides fragilis* (although less effective against other species in the *B. fragilis* group). It is more effective than cefoxitin against enteric gram-negative bacilli (although inferior to third-generation cephalosporins) and has a longer half-life, which permits twice-daily dosage. Cefotetan has been promoted as an effective, less costly substitute for cefoxitin in the treatment of intra-abdominal and gynecologic infections. We critically review evidence supporting or refuting this claim.

We hope that guidelines for the use of antimicrobials such as cefotetan will enable clinicians to avoid inappropriate prescribing, with its attendant costs and risk of development of resistant bacteria.

Methods

This article was prepared in a number of stages designed to ensure an unbiased and critical approach. A recognized expert identified by the Committee on Antimicrobial Agents of the Canadian Infectious Disease Society (CIDS) prepared a first draft, which followed a standardized format for articles concerning a specific drug, using the following headings: mechanism of action, in-vitro activity, pharmacokinetic features, clinical trials, side effects, dosage and recommendations.

Appropriate published sources of evidence were identified by a MEDLINE search. For the section dealing with clinical trial data we paid particular attention to study design and gave greatest credence to randomized, controlled, double-blind studies. Consideration was also given to position papers, consensus statements and reviews concerning cefotetan.

The first draft was reviewed by committee members, revised and reviewed again. After a second revision the article was reviewed by the Council of the CIDS. The committee chairman made any further necessary revisions.

Mechanism of action and resistance

Cefotetan inhibits synthesis of the bacterial cell wall. In gram-negative bacteria its greatest binding affinity is to penicillin-binding proteins 3 and 1A; it does not bind to penicillin-binding protein 2. Cefotetan is rapidly bactericidal. Its activity is little affected by bacterial inoculum concentrations, susceptibility-testing techniques, pH levels or media changes.^{1,2} Resistance to cefotetan is thought to be caused by permeability changes rather than alterations in penicillin-binding proteins.¹ The 7- α -methoxy configuration of cefotetan confers excellent β -lactamase stability, similar to that of cefoxitin, ceftizoxime and cefotaxime. However, cefotetan is also a potent inducer of certain β -lactamases.¹

In-vitro activity

Cefotetan is active against the gram-positive aerobic organisms *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus agalactiae* and methicillin-susceptible strains of *Staphylococcus aureus*.¹⁻³ Cefoxitin is two to four times more potent than cefotetan against these organisms, but first-generation cephalosporins are superior to both agents against staphylococci.³ Group D streptococci and enterococci are resistant to cefotetan, as are methicillin-resistant strains of staphylococci, *Corynebacterium* species and *Listeria monocytogenes*.^{1,2}

Against the commonly isolated Enterobacteriaceae (*Escherichia coli*, *Klebsiella* species and *Proteus* spe-

cies), cefotetan is 4 to 32 times more potent than cefoxitin.¹ Cefotetan is also generally active against *Serratia marcescens*, *Salmonella* species, *Shigella* species, *Providencia* species and *Morganella morganii*. Results of studies showing cefotetan's activity against *Citrobacter* and *Enterobacter* species vary widely, but these organisms are consistently the Enterobacteriaceae least sensitive to cefotetan.¹ Cefotetan is not active against pseudomonads, *Achromobacter* species or *Alcaligenes* species.¹ Like cefoxitin, cefotetan is effective against ampicillin-susceptible and most strains of ampicillin-resistant *Haemophilus influenzae*, but both drugs are appreciably less potent against *H. influenzae* than third-generation agents.² Pathogenic *Neisseria* species are susceptible to cefotetan.¹

Cefotetan and cefoxitin have similar activity against *B. fragilis*. Among strains isolated in eight centres in the United States, rates of resistance to cefotetan were, on average, 8% in 1985,⁴ 15% in 1986⁵ and 14% in 1987.⁶ There was substantial geographic variation in these rates. Cefotetan is less active than cefoxitin against other species of the *B. fragilis* group; rates of resistance to cefotetan among these organisms in 1987 were 71% for *B. distasonis*, 82% for *B. ovatus*, 52% for *B. thetaiotaomicron* and 17% for *B. vulgatus*.⁶ These species account for 37% of all clinical isolates and 28% of blood isolates that are in the *B. fragilis* group.⁴ In an animal model of abscesses caused by *E. coli* and species in the *B. fragilis* group, cefotetan was effective against *B. fragilis* but not against *B. thetaiotaomicron*, *B. vulgatus* and *B. ovatus*.⁷ However, some have questioned the clinical significance of the lack of in-vitro activity of cefotetan against *B. fragilis*-group species other than *B. fragilis*.⁸⁻¹⁰ As well, factors such as surgical drainage may contribute to the clinical outcome of anaerobic and polymicrobial infections.

Other anaerobic organisms susceptible to cefotetan and cefoxitin include *Clostridium*, *Peptostreptococcus*, *Peptococcus*, *Veillonella*, *Lactobacillus*, *Propionibacterium* and *Actinomyces* species.^{1,2,11} Most strains of *Clostridium difficile* are moderately susceptible to cefotetan but resistant to cefoxitin.^{1,12}

Pharmacokinetic features

Cefotetan may be administered intramuscularly or intravenously. Immediately after intravenous administration of a 1 g dose to a healthy adult, peak plasma concentrations of cefotetan are 140 to 250 mg/L,¹³ 3 times higher than concentrations achieved with a 1 g dose of cefoxitin¹⁴ and 1.6 times higher than those achieved with a 1 g dose of cefotaxime.¹³ Plasma concentrations are 52 mg/L after 3 hours.¹⁵ The apparent volume of distribution after intravenous or intramuscular administration of a 1 g dose is about 13 L. Therapeutic levels are reached in most body tissues and fluids except prostatic fluid, cerebrospinal fluid and sputum. There are low concen-

trations (0.34 to 0.50 mg/L) in breast milk.¹³ The serum-protein binding of cefotetan is concentration-dependent and varies from 76% to 91%.^{1,13}

In adults with normal renal function the elimination half-life of cefotetan is 3 to 4.5 hours. Renal elimination and biliary excretion account for 64% to 84% and 12% of plasma clearance respectively.¹³ Renal impairment results in a longer half-life.¹⁶ The drug is removed by hemodialysis; however, peritoneal dialysis has little effect on cefotetan clearance.¹⁷

Clinical trials

Trials have shown that cefotetan is effective against infections caused by susceptible organisms involving the urinary tract, the upper and lower respiratory tracts, the skin and soft tissues. It has also proved effective against intra-abdominal, obstetric and gynecologic infections and against *Neisseria gonorrhoeae*.

Agents that have been compared with cefotetan in clinical trials include cefoxitin, cefmetazole, cefotaxime, ceftriaxone and moxalactam. Many of these studies were reviewed in 1985 by Ward and Richards.¹³ They showed that cefotetan was as effective as the agents compared with it, although the sample sizes were generally too small to demonstrate statistically significant differences between the study and control groups. Recent trials have focused on the use of cefotetan in the treatment of intra-abdominal, obstetric and gynecologic infections.

In two large, multicentre trials that were randomized but nonblinded, cefotetan was compared with cefoxitin and moxalactam in the treatment of intra-abdominal infections.^{10,18} Most subjects had community-acquired infections that were mild or moderately severe. Rates of response to treatment were greater than 90% for all study groups, and no statistically significant differences in rates of response to the various drugs were observed. However, the probability of detecting a 15% difference in response rates was only 0.65 in one of these studies¹⁰ and was not calculated in the other.

In recently reported trials of cefotetan for acute obstetric and gynecologic infections, most subjects had acute pelvic inflammatory disease or endometritis. No differences in rates of response between subjects receiving cefotetan, cefoxitin or moxalactam were observed.¹⁹⁻²¹ In one of these trials, a multicentre study by Hemsell and associates, the probability of detecting a 15% difference in response rates was high, at 0.85.¹⁹

For perioperative prophylaxis cefotetan has been compared with cefazolin for elective upper gastrointestinal surgery,²² elective cholecystectomy²³ and cesarean section.^{24,25} No differences between cefotetan and cefazolin in rates of wound infection or endometritis were demonstrated in these studies. Faro and collaborators²⁶ examined 10 prophylactic regimens given to 1580 patients who had cesarean sections. Their results showed that a single 1 g dose of cefotetan, a 4 g dose of piper-

cillin, a 2 g dose of ampicillin or a 2 g dose of cefazolin was superior to three 1 g doses of cefazolin and that a single dose of cefotetan was superior to a single 1 g or 2 g dose of cefoxitin. However, the investigators did not make a statistical adjustment for multiple comparisons in the analysis. In another multicentre, randomized but nonblinded study, a single 1 gram dose of cefotetan was compared with three 2 g doses every 4 hours of cefoxitin in the prophylaxis of infection resulting from cesarean section. Results showed a significantly higher success rate for cefotetan.²⁷ Other large, multicentre trials of prophylaxis of infection resulting from abdominal or vaginal hysterectomy²⁸ and colorectal surgery^{29,30} showed that a single dose of cefotetan was as effective as several doses of cefoxitin.

Side effects

Data gathered from North American studies by the manufacturer showed side effects in 4% of patients.³ Hypersensitivity reactions (in 1.2%), gastrointestinal effects (in 1.5%) and reactions at the injection site (in less than 1%) were the most frequent side effects reported. Anaphylaxis³¹ and acute interstitial nephritis³² have been reported.

Cefotetan (like moxalactam, cefamandole, cefoperazone, cefmetazole and cefmenoxime) contains the N-methylthiotetrazole (NMTT) side group, which has been associated with disulfiram-like reactions and with hypoprothrombinemia. There have been several case reports of hypoprothrombinemia and bleeding associated with use of cefotetan.³³⁻³⁶

McCloskey³⁷ analysed postmarketing reports of adverse reactions received by the US Food and Drug Administration and compared the frequency of reports of hypoprothrombinemia and hemorrhage in patients treated with cephalosporins that contain NMTT and in those treated with cephalosporins that do not contain this side group. The drugs containing NMTT generated many more reports: the comparative frequency of hypoprothrombinemia with cefotetan versus drugs without the NMTT side group was 21:1 and that of both hypoprothrombinemia and hemorrhage, 44:1. These frequencies were exceeded only by those with moxalactam (hypoprothrombinemia, 97:1; hypoprothrombinemia and hemorrhage, 73:1). The data were based on voluntary reports and were uncontrolled.

Shevchuk and Conly³⁸ analysed prospective studies in which investigators measured serial prothrombin times; they concluded that risk factors such as malnutrition, hepatic and renal dysfunction, greater age and greater severity of illness may be the main determinants of hypoprothrombinemia. They noted, however, that most case reports and studies have identified agents containing the NMTT side group as being a high-risk factor for hypoprothrombinemia.

Cefotetan is active in vitro against *C. difficile*; none

the less, the product monograph states that pseudomembranous colitis has been reported. In a study of healthy volunteers who received single doses of various cephalosporins *C. difficile* appeared in the fecal flora of four of the six recipients of cefotetan.³⁹ Cefotetan may cause a false-positive result for glucose in the urine with Benedict's test or with Fehling's solution. High concentrations of cefotetan may cause a false elevation of the serum creatinine level measured by picric-acid methods.⁴⁰

Dosage

Mild to moderately severe infections should be treated with 1 to 2 g of cefotetan administered intravenously or intramuscularly every 12 hours. The maximum daily dose should not exceed 6 g. If the patient's renal function is impaired, the dosage should be modified. For patients with a creatinine clearance of 10 to 30 mL/min $\times$ 1.73 m², the interval between doses should be prolonged to 24 hours, and for those with a creatinine clearance below 10 mL/min $\times$ 1.73 m², every 48 hours.¹⁶ Patients undergoing hemodialysis may be treated with a quarter of the usual dose on days between dialysis and half the usual dose directly after dialysis.¹⁷ Cefotetan is not approved for use in children.

Recommendations

The position of cefotetan in the hospital formulary should be considered mainly in relation to that of cefoxitin. Both drugs have been used for single-agent therapy in mixed aerobic and anaerobic infections. However, other single agents (e.g., imipenem-cilastatin) or drug combinations (e.g., an aminoglycoside or a quinolone or a third-generation cephalosporin plus metronidazole or clindamycin) are superior to cefotetan or cefoxitin in their activity against species in the *B. fragilis* group, *Pseudomonas aeruginosa*, enteric gram-negative bacilli and enterococci and are preferred for treatment of life-threatening or hospital-acquired infections. Potential advantages of cefotetan over cefoxitin include its superior activity against some Enterobacteriaceae and its long half-life, which permits twice-daily dosage rather than dosage every 6 to 8 hours, as with cefoxitin. At current prices, this difference in dosages may result in substantial cost savings. Disadvantages of cefotetan compared with cefoxitin are the risk of hypoprothrombinemia and disulfiram-like reactions associated with the NMTT side group, and the lesser activity against the species of the *B. fragilis* group other than *B. fragilis*. The latter is potentially problematic, particularly in the many hospitals that lack services to identify species and test the susceptibility of anaerobic bacteria.

Prophylaxis

For prophylaxis of infections in patients undergoing

obstetric and gynecologic surgery, cefazolin, 1 g, administered intravenously, is preferred to cefotetan or cefoxitin, since no clear advantage of these more expensive, broad-spectrum agents has been shown in results of double-blind trials with adequate sample sizes. For patients undergoing elective bowel surgery, the regimen of choice is (a) erythromycin and neomycin (1 g of each administered orally or parenterally at 1300, 1400 and 2300 the day before surgery), (b) metronidazole (500 mg intravenously) plus gentamicin (1.5 mg/kg intravenously) or (c) clindamycin (300 mg intravenously) plus gentamicin (1.5 mg/kg intravenously).⁴¹ However, one could also consider single-agent prophylaxis of infection with cefoxitin (2 g administered intravenously) or cefotetan (2 g intravenously).⁴²

Treatment

For treatment of acute pelvic inflammatory disease and endometritis, cefotetan (1 to 2 g administered intravenously every 12 hours) is a reasonable replacement for cefoxitin. For treatment of intra-abdominal infections that are not life-threatening, evidence suggests that cefotetan could replace cefoxitin; however, observations from clinical trials are too limited to make a definitive recommendation at present. Although use of cefotetan has cost advantages, these should not override safety and efficacy considerations. Further well-designed clinical trials comparing cefotetan treatment with control regimens such as an aminoglycoside plus metronidazole or clindamycin are desirable.

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Oct. 2-7, 1994: World Congresses of Gastroenterology (includes 10th Congress of Gastroenterology, 8th Congress of Digestive Endoscopy, 5th Congress of Coloproctology; organized by the American Association for the Study of Liver Diseases, the American College of Gastroenterology, the American Gastroenterological Association, the American Society for Gastrointestinal Endoscopy, the American Society of Colon and Rectal Surgeons and the Society for Surgery of the Alimentary Tract)

Los Angeles

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Oct. 6-7, 1994: 4th Canadian Coordinating Office for Health Technology Assessment Regional Symposium: Reuse of Disposable Medical Devices (in collaboration with the Conseil d'évaluation des technologies de la santé du Québec and the Hôpital du Sacré-cœur de Montréal)

Montreal

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Les 6 et 7 oct. 1994 : 4^e Symposium régional de l'Office canadien de coordination de l'évaluation des technologies de la santé (en collaboration avec le Conseil d'évaluation des technologies de la santé du Québec et l'Hôpital du Sacré-cœur de Montréal)

Montréal

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Oct. 6-8, 1994: Modified Lipoproteins and Atherosclerosis (satellite symposium of the 10th International Symposium on Atherosclerosis)

Whistler, BC

Dr. Urs P. Steinbrecher, chairman, Division of Gastroenterology, Department of Medicine, University Hospital, University of British Columbia, 2211 Wesbrook Mall, Vancouver, BC V6T 1W5; tel (604) 822-7727, fax (604) 822-7897

Oct. 6-8, 1994: Nutrition and Atherosclerosis (satellite symposium of the 10th International Symposium on Atherosclerosis)

Quebec

Dr. Kenneth Carroll, chairman, Centre for Human Nutrition, Department of Biochemistry, University of Western Ontario, London, ON N6A 5C1; tel (519) 661-3097, fax (519) 661-3175

Oct. 6-9, 1994: 7th Annual Conference on Professional Well-Being

Dearborn, Mich.

Dr. Marge Harrison, Society for Professional Well-Being, 150-21 West Colony Pl., Durham, NC 27705; tel (919) 489-9167

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General Secretariat, Gerry Lou et associés, 211-1224 Stanley St., Montreal, PQ H3B 2S7; tel (514) 878-2530, fax (514) 878-2532

Du 10 au 14 oct. 1994 : 9^e conférence mondiale sur le tabac et la santé

Paris, France

Langues officielles : le français et l'anglais

SOCFI/Le tabac et la santé, 14, rue Mandar, 75002 Paris, France; tél 011-33-1-42338994, fax 011-33-1-40260444

Oct. 10-14, 1994: 9th World Conference on Tobacco and Health

Paris, France

Official languages: English and French

SOCFI/Tobacco and Health, 14, rue Mandar, 75002 Paris, France; tel 011-33-1-42338994, fax 011-33-1-40260444

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