Effect of Antibiotic Therapy on the Sensitivity of Indium-111-Labeled Leukocyte Scans

Frederick L. Datz and David A. Thorne

Division of Nuclear Medicine, Department of Radiology, University of Utah School of Medicine

Although ^{111}In-labeled leukocytes have been shown to be a useful technique for detecting infection, it has been postulated that antibiotic therapy may reduce the sensitivity of the leukocyte scan. Many patients with suspected bacterial infections are placed on antibiotics before a definite site of infection has been identified. Three hundred twelve leukocyte scans on 271 patients were retrospectively reviewed and classified as positive or negative, and as to whether or not they were being treated with antibiotics at the time the leukocyte scan was performed. The overall sensitivity, considering all 312 studies, was 90%. One hundred sixty-nine patient studies were on patients receiving antibiotics; 143 studies were on patients not on antibiotics. The sensitivity of the leukocyte scan was 88.7% in patients on antibiotic therapy; it was 92.1% in those who were not receiving antibiotics. The differences in sensitivity between the two groups were not significantly different ($p < 0.05$). We conclude that antibiotic therapy does not affect the sensitivity of the ^{111}In-labeled leukocyte scan.

J Nucl Med 27:1849–1853, 1986

Indium-111- (^{111}In) labeled leukocyte scans have been shown to be an excellent test for diagnosing intra-abdominal abscesses and other sites of infection (*1–4*). The overall sensitivity of the leukocyte scan for infection has ranged from 85-96% (*1–7*). Summarizing the results of three large clinical series, Coleman found the sensitivity to be 90% (*8*).

Some investigators have questioned if specific factors reduce the sensitivity of the leukocyte scan (*4,8–12*). One area that has been examined is the effect of the chronicity of infection on the sensitivity of leukocyte imaging (*10*). In a study by Sfakianakis et al. the sensitivity of the ^{111}In leukocyte scan was found to be significantly less in patients with infections >2 wk in duration compared with patients with more acute infection. This was presumed to be due to a reduced number of leukocytes infiltrating the more chronic inflammatory lesions.

It has been speculated that antibiotic therapy may also decrease the sensitivity of leukocyte scans (*4,8,9, 11,12*). Antibiotics could reduce leukocyte chemotaxis in two ways. By killing bacteria, they decrease the amount of chemoattractants directly released by bacteria and those produced by the interaction of bacteria with host serum (*13*). Second, they can decrease leukocyte chemotaxis by a direct effect on the leukocyte itself (*14*).

Many patients with suspected bacterial infections are placed on antibiotics before a definite site of infection has been identified. If antibiotics do decrease the sensitivity of the leukocyte scan, other imaging modalities, such as ultrasound and CT, would be more appropriate when searching for a source of infection in these patients. Since, to our knowledge, there has been no systematic study of the effect of antibiotic therapy on the sensitivity of the ^{111}In-labeled leukocyte scan, we undertook such a study.

MATERIALS AND METHODS

Three hundred twelve leukocyte scans on 271 patients (some patients underwent several exams) were retrospectively reviewed. The scans were classified as positive or negative. The patients' charts were then reviewed to determine if (a) the patients were infected or not, and (b) they were currently on antibiotic therapy. Culture results, in conjunction with the white count, other laboratory data, radiographic studies such as CT and ultrasound, surgical findings, necropsy and clinical course were used to determine if infection was present.

Patients on antibiotics had the following recorded:

Received Mar. 24, 1986; revision accepted June 11, 1986.

For reprints contact: Frederick L. Datz, M.D., Clinical Director of Nuclear Medicine, University of Utah School of Medicine, 50 North Medical Dr., Salt Lake City, UT 84132.

(a) the duration of therapy at the time of the scan, (b) the mode of administration (i.v. or oral), and (c) the type of antibiotics administered.

The overall sensitivity of the leukocyte scan for all patients (i.e., both those receiving antibiotics and those that were not), was determined. The sensitivity of the leukocyte scan in the group receiving antibiotic therapy and the group that was not was then calculated. The sensitivities of the antibiotic and no antibiotic groups were compared using the chi-square test.

The leukocyte labeling technique was a modification of that originally described by Thakur et al. (*6,15,16*). Specifically, 40 cc of whole blood were collected in a syringe containing 5 cc of ACD solution and the cells sedimented for 60 min in the inverted syringe. The leukocyte-rich supernatant was removed and centrifuged at 300-350 *g* for 5 min. The white-cell button obtained was resuspended in 5 cc of sterile saline. One millicurie of [^{111}In]oxine was added to this suspension and incubated for 30-40 min. During incubation, the suspension was gently agitated every 10 min. Five to eight cubic centimeters of leukocyte-poor plasma were added to the suspension of leukocytes, and the mixture centrifuged at 450 *g* for 5 min. Five to eight milliliters of the previously obtained leukocyte-poor plasma were gently added to the labeled white-cell button and agitated to resuspend the labeled cells. Five hundred microcuries of the leukocyte preparation were drawn into a syringe and reinjected into the patient.

Imaging was done at 24 hr postinjection using a large field-of-view gamma camera equipped with a medium-energy, parallel hole collimator using 20% windows set on the 173- and 247-keV photopeaks of ^{111}In.

TABLE 1
Antibiotics Patients Received at Time of Imaging

Penicillins		108
Ampicillin	39	
Dicloxicillin	2	
Mezlocillin	10	
Nafcillin	31	
Pen G	4	
Pen V	1	
Piperacillin	7	
Ticarcillin	14	
Cephalosporins		48
Cefaclor	3	
Cefazolin	9	
Cefotaxime	8	
Cefoxitin	17	
Cephalexin	2	
Cephamandalole	1	
Cephapirin	4	
Moxalactam	4	
Aminoglycosides		100
Amikacin	24	
Gentamicin	55	
Tobramycin	21	
Antifungal		8
Amphotericin	8	
Other		47
Chloramphenicol	3	
Clindamycin	20	
Doxycycline	1	
Erythromycin	2	
INH	2	
Metronidazole	3	
Nitrofurantoin	2	
Rifampin	4	
Trimethoprin and Sulfamethoxazole	2	
Vancomycin	8	

RESULTS

One hundred sixty-nine studies were performed while patients (90 M, 79 F) were on antibiotic therapy. Their mean age was 48.1 yr (range 3–83 yr). Of the 169 patients on antibiotics, the mean duration of therapy at the time of scanning was 11.2 days (range 1–52 days). One hundred forty-eight received i.v. antibiotics, 21 oral (seven patients were receiving both). Fifty-one patients received a single antibiotic, 118 multiple. The antibiotics the patients received are shown in Table 1.

There were 143 studies done on patients not receiving antibiotics. In this group 77 were males and 66 were females. Their mean age was 46.3 yr (range 5–79 yr).

Overall, 143 patients of the 312 were infected; 129 were true positives and 14 false-negatives. One hundred twenty-eight patients had soft-tissue infections, 15 had bone infection. This yields an overall sensitivity for all 312 studies of 90%.

In the group receiving antibiotics, there were 71 true positives and nine false negatives. The sensitivity for the group receiving antibiotics was 88.7%. In the group *not* receiving antibiotics, there were 58 true positives and five false negatives. The sensitivity of the group *not* being treated with antibiotics was 92.1%. The sensitivity of each of these two groups was not significantly different ($p > 0.05$).

DISCUSSION

The ^{111}In-labeled leukocyte scan has been widely used to diagnose intra-abdominal abscesses and other sites of infection (*1–4*). The overall sensitivity of ^{111}In-labeled leukocytes has ranged from 85–96% (*1–7*). Coleman combined the results of three large clinical series and calculated the sensitivity to be 90% (*8*).

In an attempt to explain false-negative scans, some investigators have wondered if there were certain, identifiable patient populations in whom the sensitivity of the labeled leukocyte scan is diminished. One population group that has been studied are those with chronic infections. Sfakianakis et al. correlated the sensitivity of ^{111}In-labeled leukocytes with the duration of infection

(*10*). They found that the sensitivity of the ^{111}In-labeled leukocyte scan fell from 100% for infections <2 wk in duration, to 73% for those greater than 2 wk in duration. Presumably this was due to the predominantly mononuclear cell infiltration of macrophages, lymphocytes and plasma cells, rather that leukocytes, in the chronically infected sites.

Some investigators have speculated that antibiotic therapy may also decrease the sensitivity of leukocyte scans by decreasing chemotaxis to the site of infection (*4,8,9,11,12*). They have felt that some of their false-negative leukocyte scans were due to antibiotic therapy. Many patients with suspected bacterial infections are placed on antibiotics before a definite site of infection has been identified. If antibiotics do decrease the sensitivity of the leukocyte scan, other imaging modalities, such as ultrasound and CT, would be more appropriate when searching for a source of infection in these patients.

Chemotaxis is the directed movement of cells in response to substances in their environment. It involves (a) the generation and diffusion of chemoattractants, (b) the binding of these factors to the receptors on the cell membrane, (c) microtubule formation and contraction, (d) cytoplasmic streaming to the advancing edge of the cell, and (e) energy generation (glycolysis) (*13, 14*). The ^{111}In-labeled leukocyte scan is based upon this directed migration of polymorphonuclear leukocytes to sites of infection.

Chemoattractants are generated in several ways. Bacteria undergoing replication synthesize elaborate small polypeptides that are chemotactic (*13,17*). Interaction of bacteria with host serum causes complement activation, generating the potent chemotactic factor C_{5a} from C_5. Bacteria can also directly generate C_{5a} without obligatory complement activation by elaborating proteases (*13*). Finally, host-derived chemotactic lipids may be generated (*17*).

Antibiotics can affect leukocyte chemotaxis through several mechanisms. By destroying bacteria, the elaboration of bacteria-derived chemotactic factors is diminished (*13*). Interestingly, this effect is somewhat counterbalanced by also preventing bacteria from elaborating chemotactic inhibitors that inactivate chemotaxins such as C_{5a} and bacteria-derived chemotactic factors. These bacteria-produced inhibitors act by destroying chemotactic factor or by combining with the factors rendering them inactive (*13*).

Some antibiotics may alter chemotaxis through a direct effect on the leukocyte itself. For example, polyene antibiotics (amphotericin B, nystatin) bind leukocyte membrane cholesterol, decreasing the affinity of the chemotactic receptor on the leukocyte cell membrane (*14*).

Studies of the direct effects of antibiotics on leukocyte chemotaxis, however, have primarily been performed in vitro and have often given conflicting results. Some studies of tetracyclines, the class of antibiotics best studied, have indicated tetracycline and related compounds can cause significant depression of leukocyte chemotaxis in vitro and even in vivo (*18–22*). In fact, some feel that the therapeutic effect of tetracyclines on acne vulgaris is partially mediated by an anti-inflammatory effect of the drug independent of its anti-microbial effects (*20*). Although the mechanism by which tetracycline affects chemotaxis is unknown, it may be related to chelation of divalent cations (*20*).

Other authors, however, have reported that the effect of tetracyclines on chemotaxis is not significant (*23–26*). These conflicting results are due to differences in methodology used to measure chemotaxis and to the doses of antibiotics employed (*26*). Many studies have used supertherapeutic concentrations of 10–20 times above normal therapeutic levels (*26*). Back and Norberg et al. feel that the inhibitory effect of the usual therapeutic concentrations of tetracycline on polymorphonuclear leukocyte migration if any, is slight (*26*).

Studies of the direct effects of other antibiotics on leukocyte chemotaxis have yielded conflicting results, as well (*19,23,25,27–30*). Most agree that penicillin (Pen G, carbenicillin, piperacillin) (*19,23,25,29*) has no direct effect on chemotaxis. Erythromycin and clindomycin, on the other hand, have been shown to significantly decrease chemotaxis by some (*19*) but to have only a slight effect by others (*23*). Aminoglycosides (gentamycin, amikacin) have been described as significantly decreasing chemotaxis by some (*28*), to have a minimal effect by others (*27*) and no effect by still others (*29*). Some cephalosporins (cephazolin, cephalothin, cefotetan, ceftazinimide, and moxalactam) have been shown to have no effect on chemotaxis (*22*) whereas other cephalosporins (cefoperazone) have had a significant effect, even at therapeutic levels (*29*). Rifampin and chloramphenicol have been described as decreasing chemotaxis whereas streptomycin and sulfonamides have no effect (*23–28*). Griseofulvin has little effect, as well (*30*). Interestingly, amoxycillin has actually been shown to slightly stimulate leukocyte chemotaxis (*22*).

Peters et al. and Eckelman feel that in vitro studies do not necessarily reflect the in vivo function of leukocytes (*31,32*). They, as well as others, feel that in vivo studies are the ultimate test of leukocyte function (*31–33*). The high sensitivity of the leukocytes in our series, both on and off antibiotics, is a sign of excellent in vivo function in most patients. This sensitivity is in line with the sensitivities reported by others (1–8).

Our results indicate that antibiotic therapy has no demonstrable effect on the sensitivity of the ^{111}In-labeled leukocyte scan. Supporting evidence for our findings can be found in cancer patients receiving chemotherapeutic agents. In vitro studies indicate that some

chemotherapeutic agents decrease leukocyte chemotaxis (*34,35*). Clinical studies of ^{111}In-labeled leukocytes in cancer patients, however, show no significant decrease of sensitivity (*36*).

Our findings are indirect evidence that, in vivo, most antibiotics do not significantly decrease leukocyte chemotaxis. Although we would have liked to determine the effect of individual antibiotics on the sensitivity of the scan, this was not possible since most patients were on multiple antibiotics.

We conclude that antibiotic therapy does not significantly decrease the sensitivity of the ^{111}In-labeled leukocyte scan. Therefore, there is no reason to substitute other imaging modalities for the leukocyte scan when searching for the source of infection in patients already on antibiotic therapy.

REFERENCES

1. McDougall IR, Baumert JR, Lantieri RL: Evaluation of ^{111}In leukocyte whole body scanning. *Am J Roentgenol* 133:849–854, 1979
2. Coleman RE, Welch DM, Baker WJ, et al: Clinical experience using indium-111-labeled leukocytes. In *Indium-111 Labeled Neutrophils, Platelets, and Lymphocytes*, Thakur ML, Gottschalk A, eds. New York, Trivirum Publishing Co., 1980, pp 103–118
3. Goodwin DA, Doherty PW, McDougall IR: Clinical use of indium-111-labeled white cells: An analysis of 312 cases. In *Indium-111 Labeled Neutrophils, Platelets, and Lymphocytes*, Thakur ML, Gottschalk A, eds. New York, Trivirum Publishing Co., 1980, pp 131–150
4. Ascher NL, Forstrom L, Simmons RL: Radiolabeled autologous leukocyte scanning in abscess detection. *World J Surg* 4:395–402, 1980
5. Forstrom LA, Weiblen BJ, Gomez L, et al: Indium-111-oxine-labeled leukocytes in the diagnosis of occult inflammatory disease. In *Indium-111 Labeled Neutrophils, Platelets, and Lymphocytes*, Thakur ML, Gottschalk A, eds. New York, Trivirum Publishing Co., 1980, pp 123–130
6. Datz FL, Jacobs J, Baker W, et al: Decreased sensitivity of early imaging with In-111 oxine-labeled leukocytes in detection of occult infection: Concise communication. *J Nucl Med* 25:303–306, 1984
7. Datz FL, Bedont RA, Baker WJ, et al: No difference in sensitivity for occult infection between tropolone- and oxine-labeled indium-111 leukocytes. *J Nucl Med* 26:469–473, 1985
8. Coleman RE: Radiolabeled leukocytes. In: *Nuclear Medicine Annual 1982*, Freeman LM, Weissmann HS, eds. New York, Raven Press, 1982, pp 119–141
9. Knochel JQ, Koehler PR, Lee TG, et al: Diagnosis of abdominal abscesses with computed tomography, ultrasound, and ^{111}In leukocyte scans. *Radiology* 137:425–432, 1980
10. Sfakianakis GN, Al-Sheikh W, Heal A, et al: Comparisons of scintigraphy with In-111 luekocytes and Ga-67 in the diagnosis of occult sepsis. *J Nucl Med* 23:618–626, 1982
11. Kipper MS, Williams RJ: Indium-111 white blood cell imaging. *Clin Nucl Med* 8:449–455, 1983
12. McAfee JG, Samin A: In-111 labeled leukocytes: A review of problems in image interpretation. *Radiology* 155:221–229, 1985
13. Dahl MV: Chemotaxis: Death march of the phagocyte. *Arch Dermatol* 115:1407–1408, 1979
14. Snyderman R: Pharmacologic manipulation of leukocyte chemotaxis: Present knowledge and future trends. *Am J Med*:10–18, 1983
15. Thakur ML, Coleman RE, Welch MJ: Indium-111-labeled leukocytes for the localization of abscesses: Preparation, analysis, tissue distribution and comparison with gallium-67 citrate in dogs. *J Lab Clin Med* 89:217–228, 1977
16. Beightol RW, Baker WJ: Labeling autologous leukocytes with indium-111 oxine. *Am J Hosp Pharm* 37:847–850, 1980
17. Klempner MS: Interactions of polymorphonuclear leukocytes with anaerobic bacteria. *Rev Infect Dis* 6:S40–S44, 1984
18. Majeski JA, Alexander JW: Evaluation of tetracycline in the neutrophil chemotactic response. *J Lab Clin Med* 90:259–165, 1977
19. Esterly NB, Furey NL, Flanagan LE: The effect of antimicrobial agents on leukocyte chemotaxis. *J Invest Derm* 70:51–55, 1978
20. Elewski BE, Lamb BAJ, Sams WM, et al: In vivo suppression of neutrophil chemotaxis by systemically and topically administered tetracycline. *J Am Acad Derm* 8:807–812, 1983
21. Esterly NB, Koransky JS, Furey NL, et al: Neutrophil chemotaxis in patients with acne receiving oral tetracycline therapy. *Arch Dermatol* 120:1308–1313, 1984
22. Grec V, Frei PC: Effect of amoxycillin and doxycycline on function of human granulocytes tested in vitro and on chemotaxis of granulocytes from rabbits given the two antibiotics. *Inflammation* 8:417–427, 1984
23. Forsgren A, Schmeling D: Effect of antibiotics on chemotaxis of human leukocytes antimicrobial agents and chemotherapy. *Antimicrob Agents Chemother* 11:580–584, 1977
24. Back O, Norberg B: The effect of a therapeutic doxycycline concentration on polymorphonuclear leukocyte migration in vitro. *Scand J Infect Dis* 16:369–372, 1984
25. Jayappa HG, Loken KI: Effect of antimicrobial agents and corticosteroids on bovine polymorphonuclear leukocyte chemotaxis. *Am J Vet Res* 44:2155–2159, 1983
26. Back O and Norberg B: Effect of a single oral dose of doxycycline on polymorphonuclear leukocyte migration in a casein gradient. *Eur J Clin Pharmacol* 28:193–195, 1985
27. Goodhart GL: Effect of aminoglycosides on the chemotactic response of human polymorphonuclear leukocytes. *Antimicrob Agents Chemother* 12:540–542, 1977
28. Khan AJ, Evans HE, Glass L, et al: Abnormal neutrophil chemotaxis and random migration induced by aminoglycoside antibiotics. *J Lab Clin Med* 93:295–300, 1979
29. Fietta A, Sacchi F, Bersani C, et al: Effect of B-Lactam antibiotics on migration and bactericidal activity of human phagocytes. *Antimicrob Agents Chemother* 23:930–931, 1983
30. Bandmann U, Back O, Norberg B: The effect of an oral therapeutical single-dose of griseofulvin on polymorphonuclear leukocyte migration in a casein gradient. *Arch Dermatol Res* 276:41–44, 1984

31. Peters AM, Saverymuttu SH, Reavy HJ, et al: Imaging of inflammation with indium-111 tropolonate labeled leukocytes. *J Nucl Med* 24:39–44, 1983
32. Eckelman WC: Technical considerations of labeling of blood elements. *Semin Nucl Med* 5:3–10, 1975
33. Datz FL and Taylor A Jr: Cell Labeling: Techniques and Clinical Utility. Section I: Radiolabeled Leukocytes. In *Freeman and Johnson's Clinical Radionuclide Imaging*, Third Edition, Update, Freeman ML, ed. Orlando, FL, Grune & Stratton, 1986, pp 1785–1913
34. Turner RA, Johnson JA, Mountz JD, et al: Neutrophil migration in response to chemotactic factors: Effects of generation conditions and chemotherapeutic agents. *Inflammation* 7:57–65, 1983
35. MacFadden DK, Saito S, Pruzanski W: The effect of chemotherapeutic agents on chemotaxis and random migration of human leukocytes. *J Clin Oncol* 3:415–419, 1985
36. Schell-Frederick E, Fruhling J, Van der Auwera P, et al: ^{111}Indium-oxine-labeled leukocytes in the diagnosis of localized infection in patients with neoplastic disease. *Cancer* 54:817–824, 1984