

ANTIPIRETTIC EFFECT OF INDOMETHACIN IN PATIENTS WITH MALIGNANCY

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The antipyretic effect of indomethacin in 30 febrile patients with malignancy was evaluated. Effective antipyresis was observed in 20 of the 30 patients. Responses were usually prompt and complete and side effects were reported infrequently. Defervescence was obtained much more frequently in those patients whose fever seemed related primarily to the neoplastic process rather than to a complicating infection. In eight patients indomethacin effected a defervescence after another antipyretic had failed to do so. The authors conclude that indomethacin should be considered as an alternate antipyretic in patients with malignancy complicated by fever.

THE DEVELOPMENT OF FEVER IS A COMMON complication in the clinical course of the patient with cancer. In the study of Boggs and Frei² fever occurred on 24% of the hospital days of 127 consecutive patients admitted to the National Cancer Institute. In that group of patients adults with acute leukemia were febrile on 60% of their hospital days while children with acute leukemia had fever on 42% of their hospital days. Fever was next most frequent in Hodgkin's disease (26%), followed by a variety of other malignancies.

The appearance of fever in a patient with cancer is generally thought to be related either to activity of the malignancy itself or to the presence of some complicating infection. In about half of the cases it is due to an infectious process and in the rest no infectious agent can be demonstrated.^{2, 9}

The manner in which the neoplastic process may produce fever remains unexplained. Results obtained in two recent studies suggest that fever in Hodgkin's disease may be due to an endogenous protein pyrogen, possibly produced by the neoplastic cell,¹³ and detectable in the urine.⁷

The presence of fever is usually detrimental, whatever its cause; it frequently causes

decreased ambulation and appetite, malaise and depression. Therefore, after adequate cultures have been taken and other appropriate studies performed, fever in a patient with malignancy is usually treated with an antipyretic.

Response of fever to treatment with standard antipyretic agents is sometimes incomplete or absent in patients with malignancies. In the report of Spear¹⁰ only four of 35 patients with Hodgkin's disease experienced defervescence after treatment with aspirin. It is apparent that other antipyretics for the treatment of fever in patients with malignancy should be evaluated.

Indomethacin, 1-(p-chlorobenzoyl)-5-methoxy-2-methyl-indole-3-acetic acid, is a non-steroid anti-inflammatory agent with analgesic and antipyretic effects. Numerous laboratory and clinical studies^{1, 3-6} have been published with regard to its analgesic and anti-inflammatory properties but until recently its antipyretic effect has received little attention.

In 1963 Winter, Risley and Nuss¹² showed that indomethacin administered in both rabbits and rats inhibited the fever produced by the injection of a lipopolysaccharide endotoxin of *Escherichia coli*. In that study indomethacin was found to be a more potent antipyretic than aspirin, phenylbutazone or aminopyrine.

Two reports of the clinical use of indomethacin as an antipyretic have appeared since that time. In 1965 Silberman, McGinn and Kremer⁸ used the compound to treat fever in nine patients with Hodgkin's disease.

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In all nine cases the fever was thought to be due primarily to the malignant process rather than some complicating infection. Using an oral dose of 25 to 50 mg every 6 to 8 hours, they reported complete defervescence in seven of the nine patients and partial lysis of fever in the remaining two.

Their study was followed by that of Walker et al.¹¹ in 1966, in which 100 consecutive febrile pediatric inpatients experienced some defervescence following treatment with indomethacin. These patients were then randomized into three groups. One of these received indomethacin in a dose of 0.5 mg/kg, the second 1.0 mg/kg and the third aspirin, 1.25 gr/yr of age. The fever did not respond as rapidly or as completely in the aspirin-treated group. The same investigators also found indomethacin to be a more effective antipyretic than aspirin in a series of 167 children who developed fever following administration of attenuated measles virus vaccine.¹¹

These studies prompted a retrospective analysis of our patients with malignancy who received indomethacin as an antipyretic from January through December 1966.

MATERIALS AND METHODS

The hospital charts of all patients with proven malignancy who received indomethacin as an antipyretic during 1966 were reviewed. Thirty patients, 16 of whom had acute leukemia and eight of whom had Hodgkin's disease, received the compound for that purpose. The rest were patients suffering from a variety of other malignancies (Table 1). The group included 28 adults and two children. All patients selected for review had oral temperatures over 101°F at least once daily for three days preceding antipyretic therapy. Oral temperatures were recorded every four hours when a patient was febrile. Appropriate bacterial cultures of throat, sputum, urine and blood were performed. In a few patients fungal cultures were also available. No viral studies were obtained.

The adult dosage of indomethacin varied but was generally in the range of 25 to 50 mg every 4 to 6 hours. The drug was administered orally in capsule form in all cases except in the two children, to whom a liquid suspension was given. The clinical descriptions and responses to indomethacin are summarized in Table 1.

RESULTS AND DISCUSSION

Of 30 patients who received indomethacin 20 responded with a fall in temperature. In 16 of these the response was prompt and complete. The temperature reached the normal range within 4 hours and remained normal as long as indomethacin was continued. Two of the group of responders later developed fever which was unresponsive to indomethacin and other antipyretics.

Table 2 demonstrates the number of responses in each disease group. Partial responses are included in the tabulation of total responses. A striking difference in response between the patients who had documented infections and those who did not can be seen. Of 21 patients whose malignancy was uncomplicated by infection 16 (76%) had defervescence with indomethacin treatment. On the other hand, in the group of nine patients in whom the fever was considered to be due to infection, only three (33%) obtained a satisfactory defervescence with indomethacin. This difference in response between the infected and the noninfected group is significant at a *P* level of 0.1.

All eight patients with Hodgkin's disease responded to indomethacin. This is confirmatory of the report by Silberman, McGinn, and Kremer.⁸ Only one of the patients with Hodgkin's disease had a demonstrable infection when he was treated with the antipyretic. His response was the only incomplete one in the Hodgkin's group. In contrast, seven of the 16 patients with acute leukemia had serious infections at the time they received indomethacin. Only two of those seven responded to indomethacin and in one the defervescence could have been due to antibiotics. On the other hand, seven of the nine patients whose leukemia seemed uncomplicated by infection had complete defervescence similar to that observed in the group with Hodgkin's disease.

In the remaining group of six patients with miscellaneous other malignancies three patients had defervescence with indomethacin. Two of the three were considered free of bacterial infection at the time they were treated. The lack of response by the two patients with reticulum cell sarcoma is interesting in view of the impressive antipyretic effect in patients with Hodgkin's disease.

Ten of the 30 patients failed to respond to indomethacin when first treated. Two addi-

TABLE 1. Clinical Responses

Patient No. Age/Sex Diagnosis	Clinical status	Prior antipyretic and response	Antibiotic therapy	Indomethacin dose and schedule (hr)	Therapeutic effect and comments
251953 24/M Hodgkin's	Generalized (stage IV), no infection	Aspirin grains X q 4h X 5 days, no re- sponse	None	50 mg q 6	Complete defervescence from temps. of 104°F within 12 hr after indomethacin started; remained afebrile on indome- thacin for 24 days before che- motherapy started
242383 20/M Hodgkin's	Generalized (stage IV), no infection	Acetamino- phen 650/mg q 4h X 3 days, no response	None	25 mg q 4	Temps. to 103°F prior to in- domethacin; lysed to 98°F within 12 hr of institution; remained there for 7 days with continued therapy until chemotherapy started
232473 40/M Hodgkin's	Generalized (stage III), no infection	Aspirin grains X q 4h X 3 days, no re- sponse	None	50 mg q 4	Temps. to 103°F prior to in- domethacin; lysed to 95°F within 4 hr after indome- thacin started; remained nor- mal with continued therapy for 10 days until chemo- therapy started
209804 25/M Hodgkin's	Generalized (stage IV), no infection	None	None	25 mg q 4 prn	Indomethacin only adminis- tered for elevations above 101°F; each elevation treated was followed by complete def- ervescence one or twice/24 hr for 10 days until chemo- therapy started
245689 28/F Hodgkin's	Generalized (stage IV), no infection	None	None	25 mg q 4	Temps. to 102°F; lysed to 98°F 30 hr after indomethacin instituted; remained normal with continued therapy until chemotherapy started
252410 18/M Hodgkin's	Generalized (stage III), no infection	Aspirin grains X q 4h, par- tial suppres- sion to as low as 101°F	None	25 mg q 4	Temps. to 103°F after aspirin discontinued. Institution of indomethacin associated with fall in temp. from 103°F to 96°F within 4 hr; temp. normal for 4 days on in- domethacin until prednisone started
237428 22/F Hodgkin's	Generalized (stage IV), bilateral pneu- monia	None	Cephalothin, Kanamycin	25 mg q 4	Temps. reached 103-104°F before antibiotics and indome- thacin instituted; temp. then ranged from 100.2-102°F for 6 days until patient's death
243933 38/M Hodgkin's	Generalized (stage IV), no infection	None	None	25 mg q 6	Temps. of 102-103°F initially responded to indomethacin; normal temps. were main- tained on indomethacin for several days; 6 wk later fever of 104°F daily recurred and was unresponsive to indome- thacin, aspirin, acetamino- phen or aminopyrine
249173 13/F Acute myelocytic leukemia	Initially leukemia uncomplicated, later infection suspected	None	Cephalothin Sodium colis- timethate	25 mg q6 to 50 mg q 4	Leukemic relapses were char- acterized by fever to 104°F daily; early in course patient had defervescence with 25 mg doses of indomethacin, re- maining afebrile with con- tinued treatment; later temp. rose while on indomethacin responding to antibiotic ther- apy although no infectious agent was isolated

TABLE 1. (Continued)

Patient No. Age/Sex Diagnosis	Clinical status	Prior antipyretic and response	Antibiotic therapy	Indomethacin dose and schedule (hr)	Therapeutic effect and comments
241557 35/F Acute Acute myelocytic leukemia	Leukemia in relapse, pneumonia (<i>A. aerogenes</i>)	Acetamino- phen 650 mg q 6h (given q 4h, no re- sponse	Kanamycin sulfate B sulfate,	50 mg q 6	Temps. to 103°F daily, re- ceived indomethacin for 48 hr ing 5-day period in which with no change in temp.; compound discontinued when generalized papular skin erup- tion developed
244507 36/M Acute myelocytic leukemia	Leukemia in relapse, no infection	None	None	50 mg q 6	Temps. to 102°F fell to nor- mal within 36 hr of institution of indomethacin; antipyretic continued for 3 days during which patient was afebrile, then stopped; 8 hr later temp. returned to 104.4°F
245890 25/M Acute myelocytic leukemia	Leukemia in relapse, no infection	None	None	25 mg qid	Fever of 102°F daily devel- oped while adrenal steroids were being withdrawn; In- domethacin administered for 3 days had no effect on fever
249639 37/M Acute myelocytic leukemia	Leukemia in relapse, meningitis of obscure etiology	None	Numerous antibiotics	25 mg q 6	Fever to 105°F daily; no re- sponse to indomethacin or antibiotics; died on fifth day of treatment
245527 23/F Acute promyelo- cytic leukemia	Leukemia in relapse, <i>Pseudomonas</i> <i>aeruginosa</i> septicemia	Acetamino- phen 650 mg q 6h (given concurrently)	Cephalothin, Polymyxin B sulfate, Methicillin	25 mg q 6	Temps. to 104°F daily gradu- ally decreased to 99.6°F during 5-day period in which patient received indomethacin, acetaminophen and anti- biotics; antipyretics then dis- continued and temp. gradually returned to 104°F, remain- ing elevated for several days despite re-institution of acetaminophen; indomethacin not reinstated because of gastrointestinal bleeding, cause undetermined
249079 27/M Acute myelocytic leukemia	Leukemia in relapse, bacterial pneumonitis	None	Cephalothin, Kanamycin sulfate, Sodium colistimethate	25 mg qid	Temps. to 104°F daily un- affected by indomethacin, which was discontinued after 10 days because of develop- ment of epigastric pain
252927 58/M Acute myelocytic leukemia	Leukemia in relapse, possible lung infection (not proven)	None	None	50 mg q 6	Temps. to 102°F partially suppressed to 100-100.6°F with indomethacin which was discontinued after 7 days, temp. remaining in 100°F range
247444 45/M Acute myelocytic leukemia	Critically ill, <i>Pseudomonas</i> <i>aeruginosa</i> septicemia, leukemia in relapse	None	Cephalothin, Kanamycin sulfate, Polymyxin B sulfate	50 mg q 4	Temps. to 103-104°F for 9 days until patient's death; no change in temp. chart after indomethacin started
247893 23/M Acute lymphatic leukemia	Leukemia in relapse, no infection	None	None	50 mg qid	Temps. to 102-103°F daily; indomethacin given for 5 days without response; fever re- sponded to antileukemic chemotherapy
248569 66/F Acute lymphatic leukemia	Leukemia in relapse, no infection	Aspirin grains X q 4h X 3 days, no response	None	50 mg q 6	Temps. of 104°F daily for 3 days on aspirin; indometha- cin instituted; temp. de- creased to normal in 8 hr; antibiotics and antileukemic chemotherapy started 4 hr later; temp. remained normal thereafter

TABLE 1. (Continued)

Patient No. Age/Sex Diagnosis	Clinical status	Prior antipyretic and response	Antibiotic therapy	Indomethacin dose and schedule (hr)	Therapeutic effect and comments
249432 9/M Acute lymphatic leukemia	Leukemia in relapse, initially no infection	Aspirin grains X one dose, no response	None	12.5 mg q 6	Received indomethacin 90 min after aspirin had failed to suppress temp. of 104°F; temp. fell to 100°F during next 2 hr and remained there during succeeding 3 days of indomethacin; later in course of disease, child developed daily fevers of 102–103°F which were completely un- responsive to indomethacin, aspirin or acetaminophen; fever eventually disappeared when chloramphenicol started despite negative cultures
250111 2/F Acute lymphatic leukemia	Leukemia in relapse, staphylococcal septicemia	None	Methicillin	5 mg q 4	Fever of 103–104°F for 7 days; no responses to in- domethacin
245530 4/F Acute lymphatic leukemia	Leukemia in relapse, no infection	None	None	10 mg q 4 prn	Indomethacin used for temps. above 101°F on 17 occasions and in each instance temp. fell to normal within 2 hr of institution; later in course of disease, fever to 104°F de- veloped while on prednisone in large doses and also re- sponded to indomethacin
253315 22/M Acute lymphatic leukemia	Leukemia in relapse, no infection	None	None	50 mg q 6	Temps. to 103–104°F prior to indomethacin; complete sup- pression of fever during 7 days of indomethacin treat- ment; antipyretic was dis- continued and fever of 103– 104°F returned within 12 hr
250029 53/F Chronic lymphatic leukemia	Leukemia in active phase, no infection	None	None	25 mg qid	Temps. to 102°F lysed slowly over 48 hr after indomethacin started, remaining normal un- til indomethacin was discon- tinued, then returned to 102°F
248350 30/F Reticulum cell sarcoma	Generalized disease, malignant lung infiltrates, no infection	Aspirin grains X q 4h X 3 days, no re- sponse	None	25 mg q 6	Temps. of 103–105°F with the lung infiltrates; after aspirin, indomethacin given for 5 days without antipyretic effect; patient died; no evidence of pulmonary or other infection found at autopsy
248679 52/M Reticulum cell sarcoma	Generalized disease, no infection	None	None	50 mg q 6	Temps. of 101–102°F during last 7 days of life; indometha- cin administered during that period without effect on temp. curve
255171 19/F Ganglio- neuro- blastoma	Widespread disease, no infection	Acetamino- phen 650 mg, good response	None	25 mg q 6	Acetaminophen suppressed temp. of 103.6°F to normal; temp. then returned to above 103°F and was promptly suppressed to normal by indomethacin, rising again 7 days later when indometha- cin was stopped
250017 35/M Embryonal carcinoma of testis	Diffuse metastases, bacterial pneumonia	None	Numerous antibiotics	25 mg q 4	Received indomethacin along with antibiotics for two sepa- rate episodes of bacterial pneumonitis with temps. to 104°F; no antipyretic effect noted
250135 54/M Renal cell carcinoma	Diffuse metastases, no infection	Aspirin grains X q 4h X 5 days, incom- plete antipy- resis	None	25 mg q 4	Temps. to 102°F suppressed to 101°F with aspirin, then to normal with indomethacin; 2 days after indomethacin was discontinued, fever re- turned to 102°F

TABLE 2. Summary of Responses

Diagnosis and infectious status	No. of patients	No. of responders
Hodkin's disease		
No infection	7	7*
Infected	1	1 ⁺
TOTAL	8	8
Acute myeloblastic leukemia		
No infection	4	3 ⁺
Infected	6	2 [‡]
Acute lymphatic leukemia		
No infection	5	4*
Infected	1	0
TOTAL	16	9
Reticulum cell sarcoma, no infection	2	0
Chronic lymphatic leukemia, no infection	1	1
Ganglioneuroblastoma, no infection	1	1
Embryonal cell testicular carcinoma, infected	1	1

* One patient responded initially to indomethacin but failed to respond later in the course of his illness.

⁺ One patient had only an incomplete response to indomethacin.

[‡] Response of one patient may have been due to antibiotics.

tional patients responded initially but failed to respond later in the course of their disease. Of these 12, three also failed to respond to at least one other antipyretic. In the remainder another antipyretic was not tried, usually because antibiotics or antineoplastic drugs were instituted.

In eight instances indomethacin effected a

defervescence after another antipyretic (aspirin in seven cases, acetaminophen in one) had caused no lysis or incomplete lysis of the fever. There were no cases in which patients responded to another antipyretic but failed to respond to indomethacin.

Side effects attributable to indomethacin were reported infrequently; but, in general, the period of administration required for antipyresis was less than is encountered in situations where it is used as an anti-inflammatory agent. Development of a skin rash in one patient and epigastric pain in another led to cessation of indomethacin treatment.

An initial fall in temperature to subnormal levels was noted in nearly a third of the responsive patients. This occurred less frequently on subsequent doses.

The separation of patients into "infected" and "noninfected" groups may be somewhat arbitrary in that it is based primarily on the results of bacterial and fungal cultures. A few patients may have had infections which were not diagnosed due to insufficiencies in culturing or to the presence of a viral infection. The latter possibility would seem unlikely, however, in view of the report of Boggs and Frei² which suggests that viral infections are probably responsible for only a very few of the febrile episodes seen in patients with cancer.

We believe that the results obtained in this study and in others^{8, 11} justify the consideration of indomethacin as an effective compound when the need for an antipyretic arises in a patient with malignancy.

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