Use of Indomethacin as an anti-pyretic agent in malignant reticulosis

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Introduction

FEVER IS A FAIRLY common symptom of malignant disease (Boggs et al, 1960). Although associable with any type of mitotic disease, fever has been noted to be more frequent in various haematopoietic, (Raab et al, 1960) lymphoreticular (Jackson and Parker, 1946) and renal (Kiely, 1960) malignancies. In most patients with such conditions, fever is due to some accompanying infection (Browder et al, 1961); however, in a considerable number of cases, and according to some workers, in as much as 50 per cent of cases, fever is directly related to the basic disease process (Boggs et al, 1960; Raab et al, 1960; Lobell et al, 1966). The fever thus found in malignant disease, which is due to the disease itself, has however no definite characteristic pattern and hence it has quite rightly been described as "typeless" (Boggs et al, 1960).

When present, whatever may be its cause or nature, fever can be very disquietening for the patient leading to malaise, anorexia, headache, debility and weakness and can be the major cause of the patient's incapacitation (Spear, 1962). Under such circumstances, every attempt should be made to bring the fever under control. If the pyrexia is proved to be due to infection, appropriate therapy is sufficient to combat it. However, in other situations where no proper evidence of infection can be established, suitable anti-pyretic therapy is indicated (Spear, 1962).

It is reasonable to assume that such pyrexial state will subside once the basic disease is brought under control by proper anti-neoplastic chemotherapy but there is always a considerable time interval before such therapy becomes clinically effective and although initially effective, the basic process may become "resistant" to the therapy. This has been shown quite definitely by Boggs and Frei (1960) and they concluded that anti-neoplastic chemotherapy or the duration of the illness may not have a complete effect on the fever associated with the disease. Hence anti-pyretic therapy may be required for a considerable number of patients with these conditions.

A number of anti-pyretic drugs have been used to control this kind of fever in various malignancies. However, in patients with malignant lymphomata, the fever is usually resistant to the commonly used anti-pyretics e.g. aspirin (Spear, 1962). Drugs like aminopyrine (Spear, 1962), phenylbutazone and adreno-cortical steroids (Ranney and Gellhorn, 1957), on the other hand, have been useful in lympho-reticular malignancies, but the incidence of toxicity, particularly of the two former agents, have limited their widespread use.

TABLE I

No.	Age	Sex	Histological Diagnosis	Bone Marrow	Duration of Illness	Main Features
1	36	M	Lympho-sarcoma	Marrow infiltrated with highly undifferentiated blast cells.	7 months	Irregular fever ranging from 37.2°-38.6°. Pallor. Mild icterus. Generalised enlargement of lymph nodes. Liver 4 cm. Spleen 17 cm. Raised Uric Acid. Low gamma globulin. Negative Coomb's Test.
2	12	M	Hodgkin's Disease	Bone marrow not done.	2 years	Irregular fever up to 39.6°C; Anaemia. Enlarged, hard and fixed lymph nodes at both groins a few nodes in cervical regions. Liver 5 cm. Spleen not palpable. E.S.R. raised.
3	43	M	Hodgkin's Disease	A few irregular lymphomonocytoid cells present, but on overt infiltration by Hodgkin's Disease apparent.	4 months	Progressive swelling of neck, axillae and groins. Loss of weight and appetite. Irregular pyrexia ranging from 37.2°-40°C. Pale. slightly icteric. Liver 4 cm. Spleen 6 cm. Generalised lymphadenopathy. Urine N.A.D. Chest X-ray: Infiltration right base. Left hilum slightly enlarged. Liver Function Tests normal. Serum Gamma Globulin low. Blood K.T. negative. Blood Cultures x 6: Negative.
4	52	M	Reticulum Cell Sarcoma	Bone marrow not done.	3½ months	Progressive swelling of neck and groins. Bouts of fever up to 38.6°C with chills and sweating at night. No pallor. Liver, spleen not palpable. Enlarged nodes in neck and inguinal regions. Uric Acid high. Liver functions normal. Gamma globulin high. ESR raised.
5	26	M	Reticulum Cell Sarcoma	No evidence of malignant or blast cell infiltration present	4 months	Hoarseness of voice. Progressive swelling of face and neck. Loss of weight. Bouts of irregular fever ranging 37.2°-39°C. Signs of superior vena cava obstruction due to cervical and mediastinal lymphadenopathy. Liver, spleen not palpable. Chest X-ray — huge tumour mass in antero-superior mediastinum. ESR elevated. Serum proteins normal. Blood cultures negative. Sputum Culture grew Strep. Viridans initially, sterile later.
6	14	M	Lympho-sarcoma	Marrow infiltrated with blast cells	18 months	Presented as a swelling of thyroid gland with respiratory distress. Cervical nodes were enlarged. Gross hepato-splenomegaly. Irregular pyrexia on and off ranging up to 38.4°C. Pale and poor general condition. Uric Acid raised.

TABLE I

Therapy	Response of Fever	Dosage of Indomethacin	Effects after Indomethacin
I.V. and Oral Cyclophosphamide Oral Prednisolone; Probenecid; Chlorambucil; Multiple blood transfusion. Soluble Aspirin (600 mg. 8 hrly.)	Slight initial response to steroids but that was temporary. No response to aspirin.	25 mg. t.d.s.	Patient became afebrile within 6 hours (Fig. 1) of the first dose and remained so during the duration of the therapy. Fever recurred when the drug was discontinued. There were some general signs of improvement e.g. reduction of spleen size, etc. but those could have been due to other coincidental therapy.
Cyclophosphamide Nitrogen Mustard Blood Transfusion. Paracetamol. Soluble Aspirin.	No response	50 mg. q.d.s.	Temperature down within 6 hours of the first dose. Rebound pyrexia on withdrawal, the same cycle repeated to confirm the effects of this drug (Fig. 2). General symptomatic improvement noticed. Slight macular rash during the second course, which cleared up within a day of cessation of therapy.
Nitrogen Mustard. Cyclophosphamide, Blood Transfusion Chlorambucil. Soluble Aspirin.	No response	50 mg. q.d.s.	Afebrile within 6 hours. Improvement in general state of health, increase in appetite. Fever returned when therapy discontinued. No appreciable change in signs.
I.V. Cyclophos-phamide. Paracetamol.	No response	50 mg. q.d.s.	Afebrile in 8 hours. General condition improved. But fever recurred and reached up to 37.6°C on two days during the therapy. On withdrawal, pyrexia was of higher degree.
Deep X-ray therapy for superior vena cava obstruction. Tetracycline. Paracetamol. Soluble Aspirin.	No response	50 mg. q.d.s.	Afebrile in 12 hours. General condition much improved. Although this patient had definite evidence of infection and was successfully treated with antibiotics to eradicate the infection his fever had containued even while on antibiotic. But there was a dramatic cessation of pyrexia when the antibiotic was replaced by Indomethacin. No change in lymph node enlargement.
Cyclophosphamide Prednisolone 6 Mercaptopurine. Methotrexate. Vincristine. Blood Transfusion. Soluble Aspirin. Paracetamol.	No response	50 mg. q.d.s.	Temperature normal in 8 hours, Great improvement in general condtion. Sense of well being and increase in appetite. Pyrexia returned on withdrawal. Lymph nodes slightly smaller during therapy.

Indomethacin, I-P-Chlorobinzoyl-5-Methoxy-2-Methylindole-3-acetic acid, a well-known non-steroid anti-inflammatory and analgesic agent (Hart and Boardman, 1963, Thompson & Percy, 1966) has also been noted to have strong anti-pyretic properties (Winter et al, 1963). But not until recently (Walker et al, 1966) has it been clinically tried with success for its latter effects and it has been effective in controlling fever promptly in a fair proportion of cases with malignant reticuloses and leukaemia who had not responded to other anti-pyretic agents (Silberman et al, 1965; Begemann et al, 1966; Lusch et al, 1968; Kiely, 1969). A small number of patients with such conditions was tried on Indomethacin to observe the latter's effect on the patients.

Materials and Methods

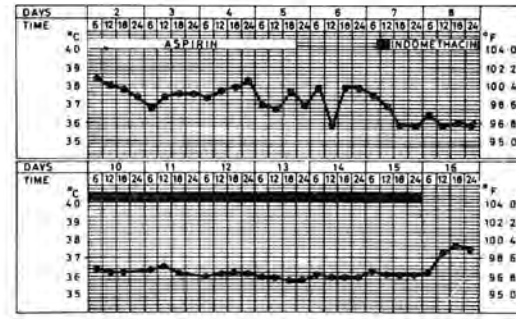
All patients with one of the malignant lymphomata, who were admitted at least once into the University Hospital between July 1969 and March 1970, were taken into consideration for the study. Age, sex or race of the patient were disregarded and so was the duration of the illness. The basic disease had been firmly diagnosed on the histology of lymph node biopsy material in each case. Patient's running fever, with at least one buccal temperature reading above 37.4°C (99°F) each day for three consecutive days, was closely studied for any secondary infection. Investigations, such as repeated cultures of blood, urine, sputum and radiological examination of chest, were carried out to exclude infection. Of course, these tests were carried out in addition to other haematological and biochemical tests. Finally, six patients were selected for anti-pyretic therapy as no definite evidence of infection could be elicited in them or they continued to remain febrile even after adequate therapy with appropriate antibiotics. Estimation of haemoglobin, total and differential leucocyte counts, platelet counts, EST, liver function test, serum protein, serum uric acid, urine microscopy, etc., were carried out on all patients. Bone marrow examination was done on four of them.

Almost all the patients had been on some form of cytotoxic therapy, the nature of the drug and the number of courses administered were dependent on the diagnosis and the duration of the disease. All the patients were kept on a 6-hourly temperature chart when 25-50 mg. of Indomethacin were administered orally three to four times a day. In most cases, the drug was discontinued after a few days and re-administered a few days later to substantiate its anti-pyretic effects. All patients were closely observed and repeatedly examined and interrogated to find out any undesirable effects of the drug and also to note whether this had any other beneficial effects on the basic disease manifestations.

Results

Short clinical descriptions and the effects of Indomethacin in all the six patients are summarised in Table I. Almost all the patients were given regular dosage of aspirin prior to Indomethacin therapy but had not responded. All six cases responded successfully to Indomethacin with prompt relief of fever within 6-8 hours. The fever, however, returned within 10-12 hours in each case when the drug was withdrawn. Only one patient (Case 4) did not manifest a complete response. Although his pyrexia had settled initially, he continued to have occasional spikes of temperature whilst on Indomethacin, but the temperature range was much lower than before. No undesirable or serious side effects were noted which could have been attributed to this drug. However, therapy in one patient (Case 2) had to be discontinued because of skin rash. No one had any difficulty in tolerating this drug by mouth. Although some reduction in the lymph node size were noted in two patients, it is doubtful whether this was due to this drug or due to concurrent cytotoxic therapy. Bone marrow was involved in two patients but did not seem to

CASE 1



CASE 2

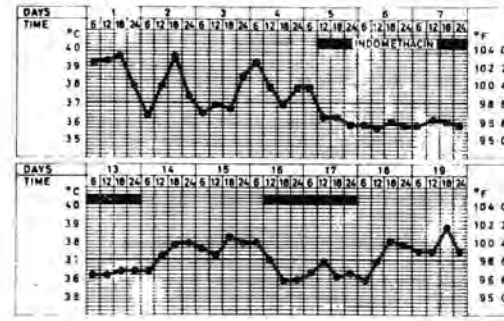


Table II. Results of Previously Published Trials.

Workers	Diagnosis Based on Lymph Node or from Marrow Biopsy					Total No. of Cases	Daily Dosage of Indomethacin	Response to Fever		Side Effects
	Hodgkin's Disease	Raticulum Cell Sarcoma	Lympho-Sarcoma	Acute Leukaemia	Other Malig. Tumour			Complete	Partial	
Silberman et al (1965)	9	—	—	—	—	9	25 mg. t.d.s. to 50 mg. q.d.s.	7	2	Nil
Begemann et al (1966)	8	—	—	—	—	8	25 mg. t.d.s. to 50 mg. q.d.s.	7	1	Nausea 2 Abdominal pain 2
Lusch et al (1968)	8	2	—	16	4	30	25 mg. t.d.s. to 50 mg. q.d.s.	14	6	Skin Rash 1 Abdominal pain 1
Kiely (1969)	3	—	—	1	1	5	50 mg. q.d.s.	5	—	Nil
Present Series	2	2	2	—	—	6	25 mg. t.d.s. to 50 mg. q.d.s.	5	1	Skin Rash 1

have influenced the anti-pyretic effect of this drug. There was no evidence, however, to suggest that Indomethacin had any effects on the primary disease or it exerted any synergistic or antagonistic influence on the cytotoxic agents.

Discussion

The pathogenesis of fever of non-infective origin seen in patients with malignant reticuloses is obscure and there is good reason to believe that the majority of these fevers are not due to "occult" infection, tissue necrosis, therapy, hypermetabolism or psychogenic factors (Boggs and Frei, 1960). However, in recent years the mechanism of this pyrexia is being more and more understood. It has been suggested that neoplastic cells may secrete pyrogen or interact with other normal tissues (Atkins and Snell, 1963) to enhance its relase in a similar way as injected endotoxins stimulate the release of endogenous pyrogen from granulocytes (Bennett and Beeson, 1953; Atkins and Wood, 1955). This pyrogen, presumably by its effect on the anterior hypothalamus and pre-optic areas, produces pyrexia (Cooper, Cranston and Honour, 1967). In fact, pyrogenic proteins have been shown to be produced by the neoplastic cells in Hodgkin's Disease and the activity of such pyrogen has been demonstrated in the urine of patients with Hodgkin's Disease (Shimaoka and Sokal, 1967). Anti-pyretic effects of Cycloheximide, an inhibitor of pyrogenic protein synthesis, in these conditions would also support the same pathogenesis (Young and Karnofsky, 1967). This latter agent, however, is not commercially available.

In 1963, Indomethacin was first shown to be a fairly potent anti-pyretic agent in pyrogen-induced fevers of experimental animals (Winter et al, 1963). Since then, this drug has been used in various febrile diseases of children and has been shown to be superior to aspirin (Walker et al, 1966). Its effects in pyrexia of malignant reticuloses were first noted in 1965. However, there has not been many published observations on this aspect in comparison with voluminous literature on Indomethacin's anti-inflammatory or analgesic effects on various rheumatic diseases. In Table II, the results of all the publications regarding this drug's anti-pyretic action on malignant lympho-reticular diseases are summarised.

From the published reports and the present study, it is quite evident that Indomethacin is a very effective anti-pyretic in controlling the fever of malignant lymphomata. Although its pharmacological mechanism of anti-pyresis is not definitely known, it may be suggested that it is due to its anti-pyrogenic (Winter et al, 1963) or anti-inflammatory effects (Begemann et al, 1966).

A number of side effects, especially its gastric ulcerogenic properties (Lovgren and Allander, 1964), have been noted with Indomethacin therapy

in rheumatic diseases. However, not many untoward effects were encountered when the drug was used in the present context. It might be that the relatively shorter duration of therapy could have been the cause of this paucity of side effects.

Summary and Conclusion

In six histologically confirmed cases of malignant reticuloses, the associated pyrexia of non-infective origin have been successfully treated with oral Indomethacin. No serious untoward effects were noted. It can be concluded, in agreement with previous workers, that Indomethacin may be used as a safe and useful anti-pyretic agent in these conditions. The pathogenesis of fever in malignant diseases and the effect of Indomethacin thereon are breifly discussed.

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