Tuberculosis and nonsteroidal anti-inflammatory drugs

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In 1980 and 1982 two case reports documented reactivation of pulmonary tuberculosis in patients who had used nonsteroidal anti-inflammatory drugs (NSAIDs). A case–control study was designed to test the hypothesis that such an association does exist. Data for 38 patients were obtained from the patients' family physicians, and each patient was matched with a control from the same practice for age, sex, race and length of time in that practice. A statistically significant relation was found between the reactivation of tuberculosis and the use of NSAIDs. However, further research is imperative to determine whether the association is direct, indirect or secondary to an unknown factor. Physicians should keep in mind that NSAIDs are potent anti-inflammatory agents and may thus activate, spread and mask infections.

Deux cas observés en 1980 et 1982 ont mis en évidence la réactivation d'une tuberculose pulmonaire chez des patients qui avaient reçu des anti-inflammatoires non stéroïdiens (AINS). Une enquête prospective sur sujets appariés a été mise sur pied afin de vérifier l'hypothèse d'une telle association. Des données portant sur 38 patients ont été obtenues de leur médecin de famille. Chaque patient a été apparié avec un témoin provenant de la même pratique médicale pour l'âge, le sexe, la race et la durée de son appartenance à cette pratique médicale. Un rapport statistiquement significatif a été retrouvé entre la réactivation de la tuberculose et l'emploi des AINS. Toutefois, il faudra mener de la recherche supplémentaire afin de déterminer si cette association est directe, indirecte ou secondaire à un facteur inconnu. Les médecins doivent garder à l'esprit que les AINS sont des anti-inflammatoires puissants et qu'ils peuvent, en conséquence, activer, propager et masquer l'infection.

The probability that there is an association between the reactivation of pulmonary tuberculosis and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) was suggested by one of us in 1980 and 1982.[1,2] Other investigators have also pointed to the activation, masking and spreading of infection with these agents.[3-6]

Tuberculous infection is controlled by a local cell-mediated immune response, including chronic granulomatous inflammation, that walls off the tubercle bacillus.[7] It appears that reactivation relates to the integrity of the cell-mediated immunity system. Specific cell-mediated immune defects can, however, only be shown in a few instances. Factors known to be associated with the activation of tuberculosis include low socioeconomic status, diabetes, alcoholism, malnutrition and prior use of corticosteroids.[8] In that context, an association between the activation of tuberculosis and the use of corticosteroids was recognized soon after the introduction of these drugs for clinical use.[9,10] While the exact cause is not known, the anti-inflammatory properties of corticosteroids are thought to be operative, since one of the physiological functions of inflammation in the body is to confine noxious substances.[11]

NSAIDs are extensively used for their anti-inflammatory and analgesic properties. In the past decade there has been a considerable increase in both their numbers and their use. For example, the number of patients taking these drugs in Saskatchewan increased by 84% between October 1975 and October 1979.[12] The mechanism for the anti-inflammatory action of NSAIDs has, however, only been partly elucidated, and it is not known whether their interference with prostaglandin synthesis is the principal aspect.[13]

We performed a study to test the hypothesis that there is an association between the activation of tuberculosis and the use of NSAIDS.

Method

A case–control study in London, Ont. was chosen because tuberculosis is uncommon in southwestern Ontario. The patient group included persons born before 1937 in whom active tuberculosis had been diagnosed between January 1975 and March 1982 and antituberculous therapy had been begun. Only those who had lived in Canada for 5 years before the date of diagnosis were included in the study; thus recent immigrants from areas with a high incidence of tuberculosis were excluded. As a result, most of the patients had had endogenous reactivation of dormant foci of infection.[14]

The age, sex and family physicians of the patients were identified from the Provincial Chest Clinic, pulmonary specialists in London and the Public Health Department. For each patient whose family physician agreed to participate in the study a control was chosen from the same practice who matched in age (± 3 years), sex, race and length of time in that practice. The first person meeting these criteria whose chart was encountered in a search forward through the chart rack from the patient's record was chosen. Because the ethical review committee of the University of Western Ontario would not permit a review of the patients' charts without signed consent from the patients the data were abstracted by the patients' physicians under the supervision of one of us (H.O.T.).

Data were gathered from the charts of the patient and control groups regarding sociodemographic factors, length of time in that practice, frequency of office visits and drug use. Although acetylsalicylic acid (ASA) is an

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NSAID, it was considered separately from the 13 other NSAIDs available in Canada in 1982 because of its history, marketing and chemical properties. Patients were considered to have previously used NSAIDs only if their use had been recorded in the chart in the 3 years before tuberculosis had been diagnosed. We sought information on other drug use as well as data on the factors known to predispose to tuberculosis — alcoholism, chronic chest disease, gastric surgery, a history of tuberculosis, malnutrition, diabetes, pneumoconiosis and debility. Conditions associated with NSAID prescription (e.g., arthritis, muscular pain and injury) were also noted. For the patient group, data on presentation, diagnosis and site of disease were gathered. The NSAIDs identified in the patient group included indomethacin, phenylbutazone, ibuprofen, fenoprofen and naproxen, and the dosages were all within the recommended range.

Because of the close matching for five variables, we used the McNemar chi-square test with continuity correction to test the significance of the difference in the proportions.[15] When the expected proportions were small we used a binomial test.[16]

Results

Of the 103 patients with tuberculosis diagnosed between 1975 and 1982 who were potentially eligible for inclusion in the study, 65 were excluded because a family physician could not be identified or because a suitable control could not be found. The mean ages of the 65 patients who were excluded and the 38 who were included in the study were similar (62.9 and 60.9 years respectively), but more of those in the first group were men (70.8% v. 55.3%). Four of the 38 study patients were native Canadian Indians.

In 36 cases the diagnosis was verified by culture and in 1 case by the chest x-ray films; in the remaining case the verification technique was unknown to the physician.

The average length of time in the practice, the frequency of use of ASA and corticosteroids, and the frequency of office visits were similar for the patients and controls (Table I).

Table II shows the association between tuberculosis and the use of NSAIDs for 1 week or more in the 3 years before tuberculosis was diagnosed. Each number represents a matched pair. We were primarily interested in discordant pairs. In only 1 of the 38 pairs had both the patient and the control used NSAIDs. In 12 pairs only the patient had used NSAIDs, whereas in 3 pairs only the controls had used NSAIDs, a statistically significant difference ($p < 0.05$). The relative risk of prior NSAID use among the patients was four times that among the controls. This relation was more striking when we examined long-term (more than 4 weeks') continual use of NSAIDs: only one of the controls, compared with eight of the patients, had been receiving long-term NSAID therapy (Table III).

The discordant pairs in Table III show that significantly more of the patients had been receiving long-term NSAID therapy. For seven of the eight patients the controls had not been receiving long-term NSAID therapy. In no instance had a control used NSAIDs when a patient had not. It was therefore impossible to calculate the relative risk, but it must have been between 8 and infinity. Long-term NSAID use preceded the onset of tuberculosis symptoms by an average of 17.9 months (standard deviation 15.2 months, extremes 2 and 48 months). Seven of the eight patients had been taking NSAIDs at the time of diagnosis.

The use of ASA was similar in the two groups. Although such use was likely under-reported, this would be true for both groups. Similar frequencies of long-term use of other drugs in both groups support that contention.

Three patients who had probably been taking NSAIDs were classified as nonusers since the treatment had not been recorded in their charts. One of these

Table I—Characteristics of 38 patients with tuberculosis and 38 controls

Characteristic	Patient group	Control group
Average length of time in the practice (yr)	6.3	7.9
White-collar worker (%)	36.1	28.9
Had used acetylsalicylic acid for more than 1 week (%)	5.3	10.5
Had used corticosteroids orally (%)	5.3	2.6
Long-term* medication had been prescribed (%)	36.8	44.7
Had visited office four times or more (%)	55.3	55.3

*Defined as documented use for more than 3 months.

Table II—Use of nonsteroidal anti-inflammatory drugs (NSAIDs)* before the diagnosis of tuberculosis

	No. of patients		
No. of controls	Who had used NSAIDs	Who had not used NSAIDs	Total
Who had used NSAIDs	1	3	4
Who had not used NSAIDs	12	22	34
Total	13	25	38

*Proportions significantly different at $\chi^2_c = 4.26$, $p < 0.05$; relative risk of NSAID use was 4 (3/12).

Table III—Long-term* use of NSAIDs† before the diagnosis of tuberculosis

	No. of patients		
No. of controls	Who had used NSAIDs	Who had not used NSAIDs	Total
Who had used NSAIDs	1	0	1
Who had not used NSAIDs	7	30	37
Total	8	30	38

*Defined as more than 4 weeks of continual use.
†Proportions significantly different at $p = 0.008$.

patients had been treated by an internist for several months for lumbar disc disease, one had had a hip replacement for osteoarthritis 1 year before tuberculosis was diagnosed, and one had moved to London from another city, where he had received analgesics for a whiplash injury.

We were concerned as to whether the strong association between tuberculosis and prior use of NSAIDs could be secondary to an untested factor. Examining all the recorded factors, we found two of interest. The patients were slightly more likely to have chronic lung disease ($\chi_c^2 = 2.72$, $p < 0.1$), a not unexpected finding since 18.4% had a history of tuberculosis and 26.3% had past evidence of the infection on chest x-ray films. The patients were also more likely to have had arthritis as diagnosed by the family physician (we did not verify the diagnosis) (Table IV). Arthritis was the main indication for long-term use of NSAIDs. However, there were too few patients receiving long-term NSAID therapy for other indications to explore this association further.

Discussion

The association between the long-term use of NSAIDs and the diagnosis of tuberculosis is compelling. The main reason for the long-term use of NSAIDs was arthritic symptoms, but it is extremely unlikely that these symptoms were the early presentation of latent tuberculosis, since arthritis has not been associated with tuberculosis.[17] Furthermore, none of our patients had tuberculous arthritis.

Our patients accounted for only 36.9% of all the patients who had fulfilled the criteria for inclusion in the study. Although the study patients were not different from the nonparticipants in terms of age and sex, it is likely that they did represent a selected group of patients with tuberculosis. There were no patients of Asian extraction, and the requirement for a family physician would likely have led to the under-representation of persons with chronic alcoholism and vagrants, groups that are known to contribute disproportionately to new cases of tuberculosis.[17] However, for the 38 patients studied, the matching with the controls, especially for care by the same family physician, ensured a similar approach to drug prescribing, medical charting and diagnostic labelling for both groups.

Our findings, however, need to be interpreted with caution. Case–control studies have been criticized because there are many potential biases that can distort the results.[18] Although we attempted to minimize any biases when we designed the study, the findings cannot be taken as proof of a causal relation between prior use of NSAIDs and tuberculosis. Nevertheless, strong arguments can be made for such a relation. Nine factors have previously been identified to be important in determining the cause of a disease.[19] Those that apply to our study include the strength of the association, the dose–response gradient, the sequence of events, the epidemiologic evidence, the biologic plausibility and the analogous effects of corticosteroids. We found the association between prior NSAID use and tuberculosis to be significant ($p < 0.05$), the patients being four times as likely as the controls to have used NSAIDs. A dose–response gradient was found: the association between NSAID use and tuberculosis became much stronger when only the patients who had received long-term NSAID therapy were included in the analysis.

A temporal relation between NSAID use and tuberculosis is often striking, as the following case reports illustrate.

Table IV—History of arthritis* as diagnosed by the family physician

No. of controls	No. of patients: With arthritis	Without arthritis	Total
With arthritis	3	5	8
Without arthritis	14	16	30
Total	17	21	38

*Proportions significantly different at $\chi_c^2 = 3.36$, $p < 0.1$.

Case reports

Case 1: In 1971 a 69-year-old woman underwent a left hip arthroplasty. In 1973 lymphoma was diagnosed and a partial gastrectomy performed. There was no recurrence of the lymphoma. She had been taking ASA for years for arthritis, but in May 1978 indomethacin, 100 to 200 mg every 4 hours in suppository form, was substituted. In September 1978 a pleural effusion was noted on the follow-up chest x-ray films. The patient was asymptomatic. Five months later *Mycobacterium tuberculosis* was cultured from the effusion.

Case 2: A 74-year-old woman presented to her current family physician in November 1980, at which time she was taking ibuprofen, 400 mg four times a day, for osteoarthritis. In June or July 1981 she had a cough but no fever. Chest x-ray films in August showed signs of tuberculosis, and the diagnosis was confirmed by culture. There were no other factors predisposing to tuberculosis.

Case 3: In 1971 tuberculosis was diagnosed in a 70-year-old woman, and she was treated at that time. In October 1975 naproxen, 250 mg twice a day, was prescribed for low back pain, and in June 1978 ASA, 650 mg four times a day, was added to the regimen. In September 1979 follow-up chest x-ray films showed a pleural effusion; subsequent culture of the effusion yielded *M. tuberculosis*. There were no other predisposing factors.

Epidemiologic evidence of a causal relation between NSAID use and tuberculosis is, on the whole, not strong, as the incidence of tuberculosis is low and has declined even further in the Western world in this century. There are, however, developments in selected groups of patients that support such an association. The 1980 tuberculosis report of the Ontario Ministry of Health[20] noted a steady increase, from 39% in 1977 to 50% in 1978 and 61% in 1980, in the proportion of patients with reactivated tuberculosis in whom the inactive interval was more than 20 years. At the same

time the absolute number of patients with reactivated tuberculosis in the province stayed relatively stable. It is the older patients who are most likely to have arthritic symptoms and to be treated with NSAIDs, the use of which has increased steadily in Canada since 1975.

Biologically the association makes sense. NSAIDs do have anti-inflammatory activity. Experiments with animals have shown that these agents suppress the acute edematous inflammatory response and inhibit granuloma formation.[21] However, experiments with animals relating to NSAIDs and susceptibility to infections have been few and far between. Furthermore, their results have been somewhat conflicting, as some have shown no effect or even enhanced resistance to infection with NSAID administration,[22,23] whereas others have shown increased susceptibility to infections.[4,24] It is also difficult to apply the results of experiments with animals to humans,[25] especially in the case of tuberculosis, for which a good model does not exist.[14]

Tuberculosis can fluctuate between exacerbation and remission without causing clinical disease.[26] It is conceivable that if NSAIDs were used during exacerbation the risk of the infection's becoming disseminated would be increased, since the integrity of the cell-mediated immunity system appears to be essential in controlling the infection.[8] This risk would increase further with the duration of NSAID use, as the dose–response gradient in our study shows.

We performed our study after one of us encountered two cases in which there seemed to be an association between the reactivation of tuberculosis and the use of NSAIDs.[1,2] The value of case reports of unexpected drug toxicity was underscored recently in *The Lancet* in an editorial titled "Lessons from the benoxaprofen affair", in which it was noted that clinical trials usually exclude the elderly and patients with pre-existing disease.[27] Yet these are the patients who are most likely to experience adverse effects of a new drug. Moreover, since calculated rates of adverse reactions to drugs depend on physicians' reports, the frequency of reactions that occur independently of the time of drug use tend to be underestimated, especially when the interval between drug use and diagnosis of the induced illness is great. Thus, it is only through physicians' alertness that infrequent, unexpected events will be associated with long-term drug use.

The results of our study confirm the association hypothesized in the original two case reports.[1,2] Further confirmation is needed to determine whether the association is direct, indirect or secondary to an unknown factor. Policy changes regarding treatment with NSAIDs will have to await the results of further studies. However, since many of the NSAIDs are potent anti-inflammatory agents and thus have the potential to activate, spread and mask infections, we recommend caution in the use of NSAIDs in patients who may be at risk of tuberculosis, particularly those with a history of tuberculous infection who have been treated with NSAIDs.

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