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USE OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS IN THE TREATMENT OF PAIN IN CANCER

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1 Prostaglandins may precipitate or exacerbate pain and they may be produced by several tumours.

2 Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin synthesis and may also inhibit bone metastases and enhance immune responses.

3 NSAIDs alone or in association with narcotics or psychotropics may not only afford the best pain relief in neoplastic disease, but also modify the progress of the tumour.

4 The effect of NSAIDs on the gastrointestinal tract is generally adverse.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are generally classified as mild analgesic drugs. However, they may also control severe pain in many situations. The aim of this paper is to consider the particular role of NSAIDs in the treatment of cancer pain. Their mechanism of action in cancer, their adverse effects and their use in different clinical situations will be discussed.

Prostaglandins, tumours and pain

Growing tumours may directly, or indirectly, by their inflammatory or mechanical effects on adjacent tissues, lead to the production of prostaglandins, bradykinin or 5-hydroxytryptamine, which in turn can precipitate or exacerbate pain in many tissues (Beck, Handwerker & Zimmermann, 1974; Mense, 1977; Hick, Koley & Morrison, 1977; Keele & Armstrong, 1964).

The classical prostaglandins, PGE_2 and $PGF_{2\alpha}$, are weak pain producers in some models, but bradykinin and 5-hydroxytryptamine are relatively potent. Prostaglandins may, however, enhance the intensity and duration of the pain-producing effect of bradykinin. Endoperoxides, intermediate metabolites in the production of prostaglandins, may also produce pain.

Prostaglandin synthesis has been observed in bony metastases in rat and rabbit (Powles, Alexander & Millar, 1978) and in human breast tumours associated with metastases.

The growth of an osseous metastasis may be linked with bone resorption. Although initially this is due to osteoclastic activity, tumours later produce an osteolytic agent which may be PGE_2 (*Lancet*, 1976). Perhaps it is not unexpected, therefore, that bone pain is the single most important contributor to total pain in advanced cancer.

PGE may be implicated in the production of hypercalcaemia, which is reported to occur in 10–20% of cases of advanced malignant disease, particularly of breast and bronchial origin. Hypercalcaemia may itself lower pain threshold (Twycross, 1978) and ionized calcium may also give rise to other symptoms. As patients with carcinomatosis may have hypoalbuminaemia, serum calcium levels should be corrected for this factor, or reported levels may be misinterpreted.

Prostaglandins originating in tumours may impair immune mechanisms, particularly the lymphocyte macrophage system (Eccles & Alexander, 1975) and therefore anti-tumour defence. In this context we should also recognize that cytotoxic chemotherapy and radiation may themselves stimulate prostaglandin synthesis.

Anti-inflammatory drugs

NSAIDs inhibit the biosynthesis of prostaglandins in a wide variety of tissues. Indomethacin, and phenylbutazone to a lesser extent, are more potent inhibitors of prostaglandin synthesis than aspirin (Hick, Koley & Morrison, 1977) and may exert a greater analgesic and anti-inflammatory effect (Ventafridda, 1975). One effect of NSAIDs is believed to be on the prostaglandin-synthesizing enzyme, cycloxygenase, which acts on the precursor arachidonic acid, converting it to the endoperoxide, PGG_2. Most of the natural prostaglandins are subsequently derived from this intermediate.

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The effect of NSAIDs on prostaglandins may be exerted directly or through their metabolites (Ventafridda & Martino, 1976) and their activity may not therefore correlate directly with the plasma concentrations and half-life of the parent compound (Martino *et al.*, 1978).

It is clear that the NSAIDs may have activity which extends beyond their accepted role as analgesics and anti-inflammatory drugs. Aspirin, which inhibits bone metastases but not soft tissue metastases in animals (Bennett *et al.*, 1977), may also have a beneficial effect on immune status (Strausser & Humles, 1975). Like indomethacin, it may also lower serum calcium (Seyberth *et al.*, 1975). We believe the most important NSAIDs for use in cancer pain are derivatives of salicylic, indoleacetic and phenylpropionic acids and paracetamol. We do not use pyrazolones because of their haematotoxic effects.

Adverse effects

In our view NSAIDs, with or without narcotics or psychotropics, afford not only the best pain relief in primary or secondary bone tumours, but may have important implications for the progress of the neoplasm. Unfortunately, most of these compounds are assessed in short-term and single-dose studies. The relevance of these in long-term therapy is questionable, particularly regarding adverse effects.

Gastrointestinal disturbances, including abdominal discomfort, burning sensations, vomiting and bleeding, may occur. Gastrointestinal damage results from several mechanisms which lead to disturbance of the integrity of the mucosal barrier, including inhibition of prostaglandins and stimulation of acid secretion through histamine release (Welch, Bentch & Harris, 1978).

Animal studies have shown gastric erosions after administration of phenylbutazone, aspirin, indomethacin and phenylpropionic acid derivatives (Mann, 1977). The new salicylic acid derivative, diflunisal, may induce less gastrointestinal toxicity (Caruso *et al.*, 1977).

Gastric side-effects may be induced or aggravated by any concomitant chemotherapy presumably because the effect of these drugs is greatest on issues which proliferate rapidly such as bone marrow or gastrointestinal mucosa.

A recent report on the use of cimetidine, an H_2-receptor blocker, in the treatment of drug-induced gastrointestinal bleeding, is optimistic (Welch, Bentch & Harris, 1978).

Clinical practice

This section is based on our own clinical experience. Our fundamental objective is to relieve pain. It may be necessary for this purpose to use drugs in high doses and at frequent intervals. This may lead in turn to adverse effects which occasionally necessitate the interruption of therapy. The types of pain particularly suitable for therapy with NSAIDs are: (1) pain due to mechanical compression of tendon or muscle, periosteum, pleura or peritoneum, without involvement of nerve; (2) pain in muscle or joint due to surgical or X-ray trauma; (3) visceral pain unassociated with obstruction, such as in pancreas or colon (Moertel, Ahmann, Taylor & Schwartan, 1971). The time when these drugs can most suitably be used is during the first and middle stages of the disease, or while awaiting pain relief from other therapeutic measures (hormone, chemotherapy, X-ray, surgery).

Drugs with minimal gastrointestinal side-effects such as diflunisal, phenylpropionic acid derivatives and paracetamol are used first, and alone; the alternative NSAIDs later. When gastrointestinal tolerance is a problem, even with concomitant cimetidine, the rectal route can be used. Alternatively, the parenteral route can also be used with such formulations as lysine acetylsalicylate and indomethacin megluminate.

In the last stage, NSAIDs may be used in association with psychotropics, narcotics or local anaesthetics. intravenously administered.

Table 1 shows examples of pain syndromes and their respective treatments which we have found.

A review of clinical results

Thirteen hundred and sixteen patients treated in the Servizio Terapia del Dolore of the Cancer Institute of Milan in a 5-yr period were reviewed retrospectively. Of these, 763 (58%), who had enjoyed at least 1 week of pain control (defined as pain relief equal to or exceeding 50%), were selected for further study over a

Table 1 Pain syndromes and their respective treatments

Pain syndrome	*Typical treatment*
Tumours of head and neck Cervical and facial pain	Indomethacin-megluminate 150 mg daily intramuscularly + amitriptyline 50 mg
Bone pain with nerve fibre involvement	Indomethacin-megluminate 150 mg daily intramuscularly or indoprofen
Visceral pancreatic or colonic pain No obstruction	Lysine acetylsalicylate 4.5 g + 10 ml bupivicaine 0.5% in 250 ml dextrose 5% solution twice daily intravenously

Table 2 Percentage of 763 patients relieved by different types of analgesic compounds

	%	%
NSAID	24	55
NSAID + psychotropic drug	27	
NSAID + narcotic drug	4	
SAID	8	
Psychotropic drug	17	
Narcotic drug	16	
Psychotropic + narcotic	3	
SAID + Psychotropic drug	1	

SAID, steroidal anti-inflammatory drug.

Table 3 Type of pain relieved by different analgesic compounds expressed as a percentage of patients treated

	Pain due to nervous tissue lesion %	*Pain due to other tissue lesion* %
NSAID	6	94
NSAID + psychotropic drug	10	90
NSAID + narcotic drug		100
SAID		100
Psychotropic drug	59	41
Narcotic drug		100
Psychotropic + narcotic		100
SAID + Psychotropic drug	100	

5-week period. They were then analyzed according to the origin of their pain, their treatment, and their pain relief as assessed on an analogue scale. The drug treatment of these 763 patients is shown in Table 2. Fifty-five per cent received NSAIDs alone or with psychotropic or narcotic agents.

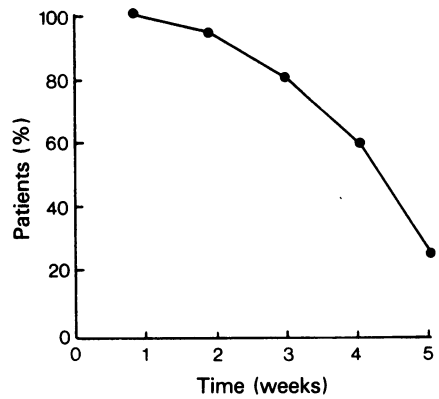

Figure 1 Percentage of patients treated with NSAIDs who achieved pain relief during a 5-week period.

Pain relief analyzed in the context of drug use and tissue origin of pain is shown in Table 3. This illustrates the relative lack of effect of NSAIDs where pain arises from nervous tissue.

Finally, we have studied pain relief at weekly intervals during a 5-week period (Figure 1). By week 5 no more than 25% of patients were enjoying worthwhile (50%) pain relief. However, 60% of the group were in severe pain initially. That they were relieved at all demonstrates that NSAIDs can be more than mild analgesics.

In our view, NSAIDs have an important role in the treatment of pain of all degrees of severity associated with neoplastic disease. The effect of these drugs on the progress of the tumours needs further clarification. New compounds with fewer adverse effects and greater analgesic efficacy already in development will offer welcome additional treatment options.

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Discussion

DR SWERDLOW pointed out that in cancer many circumstances affected the choice of treatment, pain being only one. He also pointed out that there was a place for nerve blocks, spinal injections and chordotomy in addition to the use of analgesic drugs in relieving cancer pain.

PROFESSOR VENTAFRIDDA explained that the patients discussed were specifically selected because they had only been treated with analgesics.

DR SWERDLOW noted a practical observer difficulty in assessing intramuscularly administered drugs, namely that pain relief could be present 10 or more hours later. Intravenous studies produced real shortening of the period of assessment. The disadvantage was that they did not represent normal clinical usage. Intravenous narcotics often put a recently awakened patient back to sleep and patients could be unable to cope with questions after 10 or 15 min when their pain was often much relieved.

DR BLENDINGER replied that it was her normal practice to use intravenous analgesics during the first postoperative day, and that she had not encountered difficulty in obtaining answers to questions during the post-drug assessments.

PROFESSOR KRONEBERG noted that when aspirin was administered intravenously, high blood levels of unmetabolized material were obtained, whereas after oral aspirin there was rapid deacetylation. The suggestion had been made that the inhibition of prostaglandin synthesis was dependent on the acetyl group in acetylated salicylic acid. This could explain the relatively high efficacy of intravenously administered aspirin and account for the relative differences between orally and intravenously administered aspirin and dipyrone.

In response to Professor Novello, Dr Blendinger confirmed that the anaesthetic technique was standardized throughout the study.