Drug Treatment of Disease

ANALGESICS IN RHEUMATIC DISORDERS*

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Of all the disabilities to which man is prone, none equal the rheumatic disorders in the amount of daily recurring or constant pain and discomfort which they cause over long periods of many months or years. Were it possible to measure a unit of pain, one dolor perhaps, rheumatoid-, osteo-, and other types of arthritis would probably head the list in the final reckoning. Adequate analgesic therapy, with controlled rest and exercise, is the bedrock of treatment of these and allied conditions, for which there is no simple or ready cure. No treatment "cures" them, and the patient must come to terms with his unpleasant disability and live in rough harmony with it, taking every day as many analgesic tablets as the average man and woman does in several weeks or months.

Unfortunately the most effective analgesics are habit-forming, and no drugs on the Dangerous Drugs list capable of causing addiction can be given routinely in these disorders. A second drawback is that most of the effective analgesics can cause gastro-intestinal irritation and symptoms of dyspepsia. The general rule, whatever drug is given, is to treat each patient as an individual problem, to select what appears to be the most suitable preparation in that particular case, and to instruct the patient in its regular administration at certain times, usually after or with meals, every 2-6 hours through the day, depending on intensity of symptoms and response to the drug.

This "tailoring" of the drug to the individual patient is most important. The worst time for many rheumatoids is the early morning, when painful stiffness calls for a quick-acting effective analgesic. The night hours also need to be covered in many cases, and, though heavy sedation may keep the rheumatoid patient deeply asleep until morning, the pain and stiffness are then much worse as a result. This nocturnal "gelling," or stiffening, is an important symptom of sufferers with rheumatoid arthritis, and getting out of bed and to work is the hardest part of the day for most of them. Many experience more pain as fatigue sets in towards the end of the day: night for many is a kind of Satanic sandwich of interrupted sleep with pain on each side.

ANALGESIC DRUGS

Acetylsalicylic Acid (Aspirin)

This may be given as tablets, crushed or taken whole, as soluble aspirin dissolved in water (tab. acid. acetylsalicyl. solub. (B.P.) ("disprin" or "solprin") or dissolved on the tongue ("paynocil"), or as compound tablets. The dose usually needed is 10-15 gr. (0.65-1 g.) at a time, preferably taken with food or with a little milk or milky drink and crushed or dissolved rather than taken whole.

Acetylsalicylic acid is analgesic and antipyretic. It is absorbed rapidly from the stomach and its effects are

therefore felt within 10-15 minutes, lasting some 2-4 hours, though the breaking of the pain cycle may give more lasting relief of symptoms. Its excretion through the kidneys begins soon after its administration.

The drug may act as a gastric irritant, and some patients cannot tolerate it. Several workers have shown that the daily loss of a few millilitres of blood from the intestinal tract is by no means uncommon in patients taking regular doses of aspirin, but the amount lost is usually small and the patient suffers no ill effects in the vast majority of cases. Nevertheless, melaena and haematemesis do sometimes occur, and for this reason it is wise, as mentioned above, to instruct the patient to take the drug with food.

The most helpful dose in rheumatoid arthritis is usually the one taken first thing in the morning; sometimes the dose taken last thing at night also gives much relief. It is wise to have an additional dose in reserve at the bedside at night with a biscuit and a small glass of milk. Aspirin is still the main stand-by of most patients with chronic articular disease, and the average rheumatoid sufferer takes usually 8-12 tablets a day (40-60 gr.; 3-4 g.) and sometimes many more.

Allergic skin reactions and asthma are uncommon. A slight prolongation of the prothrombin time of the blood may in itself be unimportant unless there is consistent liver disease or anticoagulant therapy in progress: in such cases haemorrhage may more readily occur. Patients are therefore well advised to take some other analgesic while they are on oral anticoagulant therapy.

Aspirin tablets should be kept in a dry place and should be used within three months of receiving them, for they gradually hydrolyse in the presence of water into acetic and salicylic acids. Mixtures containing acetylsalicylic acid deteriorate more rapidly and should not be kept for more than two to three weeks.

Compound acetylsalicylic tablets and mixtures are legion. It is best to keep to tablet form rather than fluid mixtures for the reasons mentioned above. The *British Pharmaceutical Codex* (1959) contains compound tablets of acetylsalicylic acid and opium, each tablet containing 3 gr. (195 mg.) of aspirin, 1½ gr. (80 mg.) of phenacetin, and 1 gr. (65 mg.) of ipecacuanha and opium powder. Though suitable for treating short febrile illnesses they are not suitable for regular daily long-term administration, but an aspirin-and-opium mixture containing 15-20 gr. (1-1.3 g.) of acetylsalicylic acid with 10 minims (0.6 ml.) of tinct. opii is of great assistance taken occasionally when pain is extremely severe. Such a mixture must, as noted above, be used within a period of two weeks of its being dispensed.

The most popular compound aspirin tablets are those mixed with phenacetin. Acetylsalicylic acid and phenacetin tablets B.P.C. contain 3½ gr. (230 mg.) of aspirin and 2½ gr. (160 mg.) of phenacetin per tablet. Phenacetin is seldom productive of gastro-intestinal irritation, but may cause not only the well-known

*In previous articles in this series Dr. Dudley Hart has discussed corticosteroids in the rheumatic disorders (February 13, 1960, p. 493) and Dr. R. M. Mason the treatment of gout (June 13, 1959, p. 1522).

methaemoglobinaemia, with its characteristic cyanotic hue, but severe renal damage (see *Brit. med. J.*, 1960, **1**, 714, for a recent discussion of this). A very large number of other compound tablets containing aspirin or phenacetin or both have been marketed, for, despite the later introduction of many other mild analgesics, aspirin remains the most generally useful.

Because of its tendency to cause gastric irritation aspirin is sometimes put up in buffered form. Such tablets, though popular, are not always effective in doses which leave the patient free from dyspepsia.

Amidopyrine

This has now been deleted from the *British Pharmaceutical Codex*. Although a useful analgesic, it has an ugly reputation for causing agranulocytosis, and for this reason it has been almost entirely dropped in the United Kingdom. Compound tablets are available which contain it ("cibalgin," "optalidon," "irgapyrin," "corosedine"). Sodium noramidopyrine methane sulphate ("novalgin") carries the same risk.

Codeine

This drug is usually prescribed in small amounts in compound aspirin tablets, for as plain codeine phosphate it is too constipating for most patients. Tab. codein. co. B.P. contains 4 gr. (0.26 g.) each of aspirin and phenacetin and 1/8 gr. (8 mg.) of codeine phosphate. "Veganin" tablets have the same constituents, but with codeine phosphate 1/6 gr. (11 mg.). Patients usually find them superior as analgesics to simple aspirin, the main reason being the larger amount of analgesic substances present per tablet (8:5) rather than the small, but still slightly constipating, dose of codeine present. A soluble form is marketed under the trade name of "codis."

Sodium Salicylate

Though this drug is still given for acute rheumatic fever, it is seldom given for other forms of rheumatism, for large amounts in fluid form are necessary and it is less effective than acetylsalicylic acid as an analgesic, even in maximal doses. In rheumatic fever its use is partly as an analgesic, partly as an antipyretic. The doses given may amount to as much as 20 gr. (1.3 g.) every 2-3 hours. The addition of sodium bicarbonate to the mixture reduces gastric irritation but also increases the excretion of salicylate and lowers the blood concentration to less effective levels.

Paracetamol

This is relatively weak as an analgesic. It is deservedly popular because it causes little or no gastro-intestinal irritation and can be given with relative immunity to patients—with or without peptic ulceration—who experience dyspepsia on acetylsalicylic acid. To be effective, dosage needs to be rather higher than with aspirin, and most patients tolerate 3 or 4 tablets (1.5-2 g.) at a time.

Phenylbutazone

This drug is a long-acting analgesic which is slowly broken down and slowly excreted. Introduced (under the proprietary name "butazolidin") as an antirheumatic rather than analgesic substance, it relieves pain in a host of painful conditions of bones, joints, and soft tissues

other than the rheumatic disorders—for example, metastatic carcinomatosis and Paget's disease of bone. It is particularly effective in acute gout, and, by virtue of its even and prolonged action, in ankylosing spondylitis and osteoarthritis. In painful osteoarthritis of the hip it is frequently very helpful when other analgesics fail to give adequate relief.

It is unwise in prolonged therapy to exceed 400 mg. a day by mouth, for toxic effects—dyspepsia and, less often, rashes, oedema, and buccal ulcers—increase if a higher dose is maintained for long periods. In painful conditions of short duration, such as acute gout, larger doses up to 600 mg. or more may be given on the first day to ease the agonizing symptoms, dosage being then gradually reduced. In osteo- and rheumatoid arthritis and in ankylosing spondylitis it should not be taken lightly to suppress immediate pain but as part of a regular daily programme, for it is not effective as a quick-acting analgesic. It is absorbed more rapidly by mouth than by intramuscular injection, and, whatever its mode of action, does ease painful symptoms in a large variety of conditions. It may be given as suppositories of 250 mg. when it cannot be given by mouth—for instance, when it causes dyspepsia. The dose should be kept at the lowest effective level, and, because of the prevalence of induced dyspepsia, is best given with meals. In many cases a "backcloth" of a small regular daily dose of phenylbutazone diminishes the painful symptoms of arthritis while aspirin or some other short but rapidly acting analgesic is used for quick suppression of painful symptoms which break through the phenylbutazone.

Agranulocytosis has been reported but is extremely rare; gastric intolerance remains the most frequent side-effect. Phenylbutazone should not be given with gold therapy, as toxic effects are very common with this combination of drugs.

REST

It cannot be overemphasized that analgesics should be used in the rheumatic disorders only in conjunction with a proper programme of planned rest and exercise. Different disorders call for different programmes. General bodily rest and local rest by splintage is as helpful in rheumatoid arthritis as it is disastrous in ankylosing spondylitis, where joint stiffness and ankylosis all too readily take place; in this disorder exercise and activity are to be encouraged. Much of the so-called "freezing" or stiffness of a joint is directly due to pain, and full and effective analgesia may prevent true or secondary freezing by enabling simple exercises to be undertaken.

Conclusion

Pain is what brings the patient to the doctor in most disorders, and the rheumatic disorders are no exception. Few patients suffer more continuous day-to-day pain for months or years than the sufferer with arthritis. It is therefore surprising to see when we survey the therapeutic field how relatively few effective pain-relieving substances there are which are non-addictive and are relatively safe to use over prolonged periods. Though many new compounds appear from time to time few are issued without the addition of one or more of the older well-tried analgesics, such as phenacetin or aspirin, to ensure effective analgesia. Acetylsalicylic acid, with its imperfections, remains the most popular and most widely used to-day in the rheumatic disorders.