Azapropazone – its place in the management of rheumatoid conditions

P. M. Brooks, M.B., F.R.A.C.P.
and
W. W. Buchanan, M.D.,
F.R.C.P.(Ed. and Glas.)

The Centre for Rheumatic Diseases
and University Department of
Medicine, Royal Infirmary,
Glasgow, Scotland

Received: 26th September 1975

Summary

The authors review the trials carried out on azapropazone in rheumatoid arthritis and other rheumatoid conditions. They comment that in terms of efficacy azapropazone would appear to be a useful non-steroidal anti-inflammatory analgesic which compares favourably with other established antirheumatic agents against which it has been tested. Its main advantages are its low incidence of side-effects and the fact that in the majority of the trials reported azapropazone treatment was preferred by patients to that with other agents.

Key words: Arthritis – anti-inflammatory agents – azapropazone

Introduction

Despite the vast amount of research into its causation and treatment rheumatoid arthritis is still, in many countries, a common cause of crippling due to joint disease and it continues to present the physician with a tremendous therapeutic challenge. When diagnosis of the condition has been made, total management of the patient based on an individually optimised and frequently reviewed regime is of utmost importance to ensure that patients do not become immobile, unemployed and depressed about their future. Physiotherapists, occupational therapists and social workers may all be called upon at some stage and it must be recognised, therefore, that drug therapy with any of the currently available antirheumatic agents should be regarded as only part of this management programme.

Ten years ago it would have been easy to recommend aspirin as the drug of first choice in the management of rheumatoid arthritis. With the advent of the newer, non-steroidal anti-inflammatory drugs, however, it is not possible to be so dogmatic. Recent studies on the prescribing habits of both general practitioners and hospital doctors show that, in the Glasgow area, for example, only 40% of both in-patients and out-patients with rheumatoid arthritis receive aspirin, and many of these in less than what is generally considered as an adequate dosage (3 g. per day).4 Certainly, about one-third of patients will develop dyspepsia on long-term aspirin treatment at full dosage, and there is no doubt that patients have a psychological barrier to a drug they can buy for themselves without prescription. Whether the decline in popularity of aspirin is due to its non-acceptance by patients for one reason or another, or because of the availability of the increasing number of newer non-steroidal anti-inflammatory agents is difficult to decide. From the results of a
bewildering array of clinical trials, most of these newer agents are claimed to be more effective or better tolerated, or both. Each has its own supporters, both in prescribers and takers, but none has been shown to alter significantly the course of the disease and basically they provide symptomatic relief by their analgesic and/or anti-inflammatory activity.

The mechanism of action of antirheumatic drugs presents an equally confused picture of conflicting claims and counter-claims from which the reader emerges without any clear idea of a central unifying theme. The exact role of the various mediators of inflammation in the generation of inflammatory response has not yet been determined. There is no doubt that prostaglandins, kinins and the complement system all have a part to play. Vane has shown recently that indomethacin and aspirin can inhibit synthesis of prostaglandins, and similar effects have also been demonstrated for phenylbutazone, mafenamic acid and fenoprofen. A rapid lowering of raised plasma kininogen has recently been described when patients with rheumatoid arthritis are administered indomethacin or aspirin. Whaley et al. have studied the effect of various anti-inflammatory drugs on complement-mediated haemolysis and found that those non-steroidal anti-inflammatory agents which are highly protein bound, such as phenylbutazone, did inhibit immune lysis, but only in concentrations higher than those found therapeutically.

Although there is uncertainty over the mode of action or the relative superiority of the newer drugs over aspirin or one another, there is no doubt that many are clinically effective for some rheumatoid arthritis patients if not for others, and they provide the physician with a range of products from which to choose, if only by trial and error, the most appropriate drug as part of the individual patient's management programme.

One of the more recent agents to enter the list is azapropazone. Although azapropazone is distantly related to phenylbutazone there is no evidence of this relationship causing similar side-effects nor, indeed, is there any evidence of marked similarity in pharmacokinetic and pharmacological properties. Extensive pharmacological and pharmacokinetic studies show that it has definite anti-inflammatory activity, approximately half that of phenylbutazone. Unlike phenylbutazone, however, it does not appear to be extensively metabolised before excretion. Elimination of azapropazone is primarily via the kidneys, over 60% of the administered dose being excreted as unchanged drug. The relatively long biological half-life (approx. 20 hours) suggests that stable plasma levels can be maintained easily with a 3-times daily dosage. Toxicological investigations in 12 different animal species support the conclusion that azapropazone appears to be a very safe anti-inflammatory agent, especially when compared with other anti-rheumatic compounds in common use.

Clinical studies on azapropazone

Open studies
Clinical impressions from the early open studies of azapropazone carried out in Europe and Japan by a number of investigators suggested that azapropazone was not
Azapropazone – its place in the management of rheumatoid conditions

only effective in the treatment of a wide range of articular,\textsuperscript{3,13,19,26,34,38} soft-tissue rheumatological\textsuperscript{1,6,20,23,25,32,37,38,51,52,54} and traumatological\textsuperscript{9,17,38,41,44,47,50} conditions, but also appeared to be well tolerated with a low frequency of side-effects. Most of the investigators used doses of 600 mg. per day, but in about one-third of patients 1200 mg. azapropazone per day was given. The majority of the studies were carried out over short-term periods (up to 4 weeks); a number of patients, however, were observed for longer, some for 2 years or more.\textsuperscript{26,31}

No serious adverse reactions were recorded during any of these studies. There was no incidence of blood dyscrasia or gastro-intestinal ulceration, although about 6% of the patients reported minor gastric upsets.

\textit{Azapropazone versus placebo}

A number of controlled studies have now been carried out comparing azapropazone with placebo in patients with rheumatoid arthritis\textsuperscript{10,11,42} and with ankylosing spondylitis.\textsuperscript{8,14}

In a multi-centre crossover trial\textsuperscript{42} conducted under the auspices of the Committee of Clinical Drug Trials of the Japan Rheumatism Association, 900 mg. azapropazone daily was compared with placebo in 97 patients with rheumatoid arthritis. Azapropazone showed a significant therapeutic effect compared with placebo, improving morning stiffness, joint tenderness, and grip strength. Few side-effects were reported. Grennan \textit{et al.}\textsuperscript{11} in a single-blind crossover study against placebo in 12 patients with rheumatoid arthritis also showed that azapropazone at two dose levels (900 mg.\textsuperscript{/day} and 1800 mg.\textsuperscript{/day}) had a significant anti-rheumatic effect in terms of pain relief and morning stiffness. Although there was no statistically significant difference between the effect of the different dose levels, the trend in all of their results, except the isotope studies, was towards greater effectiveness of the higher dose. Because of the incidence of side-effects at the 1800 mg.\textsuperscript{/day} level, they suggested that the correct dose of azapropazone lay somewhere between the two, as was found in the dose range studies such as those by Mathies and Kilani,\textsuperscript{20} Mennet,\textsuperscript{22} and others. In a follow-on trial, Grennan \textit{et al.}\textsuperscript{10} confirmed the effectiveness of 1200 mg. azapropazone, showing that it was significantly superior to placebo in terms of pain relief, diminution in joint tenderness and morning stiffness.

Comparative studies of the effectiveness of azapropazone and other treatments in a variety of different conditions have been conducted by a number of investigators.\textsuperscript{5,12,14,15,22,26,34,38,44,49}

\textit{Azapropazone in rheumatoid arthritis}

Vilogron\textsuperscript{46} and Nagai \textit{et al.}\textsuperscript{36} in their open crossover studies, each in 15 patients, found that 1200 mg. azapropazone daily had an antirheumatic effect equal respectively to 3 g. or more than 2.5 g. aspirin daily. Mintz and Fraga\textsuperscript{34} also showed in their double-blind trial in 16 patients that 900 mg. azapropazone daily was at least as effective as 3 g. aspirin daily. Recently, Brooks \textit{et al.}\textsuperscript{9} have shown by the novel method of Lee \textit{et al.}\textsuperscript{28} that 1200 mg. azapropazone daily is better than aspirin (3.9 g. per day), but the difference between the treatments in the 85 patients they assessed was not statistically significant.
Thune\textsuperscript{45} compared azapropazone with indomethacin in a double-blind study of 50 patients. The results of this study indicated that 800 mg. azapropazone per day was at least as effective as 100 mg. indomethacin per day, and these findings are supported by those of Hamilton \textit{et al.}\textsuperscript{12} in their multi-centre study in which azapropazone was shown to be preferable to indomethacin by both subjective and objective assessments.

In a double-blind study in 93 patients, Josenhans \textit{et al.}\textsuperscript{22} found that a greater number of patients in the azapropazone-treated group (600 mg/d) experienced good analgesic effect compared with those receiving 600 mg. phenylbutazone daily.

\textit{Azapropazone in osteoarthritis and other conditions}

In osteoarthritis of the knee, Nagai \textit{et al.}\textsuperscript{26} showed that 1200 mg. azapropazone compared favourably with 2.25 g. aspirin in providing pain relief, and the results of Hingorani\textsuperscript{14} in his double-blind trial in 41 patients indicate that, although there was no measurably significant difference between ibuprofen (1600 mg.) and azapropazone (1200 mg.) in improving knee joint mobility and pain relief, there was a highly significant patient preference for azapropazone.

Whilst azapropazone has been shown to be effective in patients with active early arthritic conditions, some workers suggest that the drug may be more effective in chronic cases. For example, Lassus\textsuperscript{28} showed that patients with the more chronic arthritis associated with psoriasis responded better to azapropazone than to indomethacin, but it was not as good as indomethacin in the more acute cases of arthritis associated with Reiter's disease. Azapropazone would certainly appear to be a useful drug in the long-term treatment of patients with chronic rheumatoid conditions as has been shown by Thune\textsuperscript{46} and Eberl\textsuperscript{,7} and such long-term studies highlight the low incidence of side-effects with azapropazone.

\textit{Adverse reactions to azapropazone}

Biological tolerance of azapropazone has been demonstrated by the routine laboratory investigations which formed part of many of the trials reported, and no abnormalities have been revealed in the blood picture, liver or renal function or coagulation factors. Side-effects have been noticeable by their absence in the majority of the trials, and most investigators comment on this finding. Of those adverse reactions reported in the occasional patient, the principal ones are gastric intolerance and skin rashes. Gastric intolerance is a problem with all anti-rheumatic drugs, but the clinical studies on azapropazone used at the normal dosage level would appear to support the findings from the animal work\textsuperscript{2} that this drug is better tolerated than most. In the studies so far reported, the drop-out rate because of gastric intolerance is less with azapropazone than with aspirin or with indomethacin; only about 3\% of patients have reported minor gastro-intestinal upsets with azapropazone. Mintz and Fraga\textsuperscript{23} have shown that compared with aspirin\textsuperscript{35} the amount of gastric microbleeding during azapropazone treatment is within normal levels, is not dose related, and that there was no correlation between blood loss and the occasional, mild gastric upsets reported in the patients they investigated. Skin rashes also seem to occur rarely (less than 3\% of patients in the
trials reported). When they do arise, it is usually early in treatment and resolve spontaneously when the drug is stopped.

Conclusions
Sensible drug prescribing is of paramount importance in a disease area where iatrogenic morbidity is high, and care should still be taken with the initial treatment of patients with rheumatoid disease. As with all new drugs, particularly in the anti-rheumatic field, there is a temptation for the physician to be carried away by initial enthusiasm for a recently introduced non-steroidal anti-inflammatory agent; enthusiasm born more out of hope than generated by the unbiased scientific confirmation of the new drug’s superiority over already established products. Unhurried controlled trials with close observation of the patient – clinically, biochemically and haematologically – are part of the answer before a product is marketed for general use, but only long-term experience by a large number of investigators will establish the true value or side-effect liability of the drug under the normal conditions of rheumatological practice.

From the many short-term but only few long-term studies so far reported, azapropazone would appear to be a useful non-steroidal anti-inflammatory analgesic. Judged by the Lee et al.26 method of assessment, which has the advantage of being able to compare, using a relative efficacy score, any new anti-rheumatic drug with those already tested, azapropazone seems to fit in the middle of the table of the 14 drugs tested to date.9 In terms of comparative efficacy, therefore, as shown by the clinical trials in man it is probably better than many of the currently available drugs and will no doubt prove that it can play an effective part in the management of a variety of rheumatoid conditions.

Many of the patients included in the trials had suffered from their disability for a considerable period of time, had been treated previously with a wide range of different agents, and may be classed, therefore, as good judges of the subjective pain relief achieved with a new drug and of the acceptability of treatment. A number of workers14,18,28 have now shown that the patient’s own subjective preference for one of a variety of alternative therapies is probably the most useful single measure of the efficacy of an anti-rheumatic drug. Only the long-term use of the drug, however, will bear out these early conclusions: in the meantime, there seems no reason why azapropazone should not prove a useful addition to the range of anti-rheumatic drugs currently available for general use. The real advantages of azapropazone at present would seem to be its low incidence of side-effects and the fact that, in the majority of the trials, patients preferred azapropazone treatment to that with other agents with which it was compared, even though objective measurements may not always have revealed any statistically significant difference.

References