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Original Research Article

Treatment of ankylosing spondylitis with indomethacin and phenylbutazone

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Abstract:
In a parallel, double-blind and randomized trial of 6-weeks' duration, phenylbutazone (150 mg to 300 mg daily) was compared with indomethacin (75 mg to 100 mg daily) in the management of 26 patients with active ankylosing spondylitis. None of the patients in either group withdrew from the study because of lack of eficacy of the drugs. Both drugs were equally effective in the relief of pain and tenderness of the afected joints. Overall subjective improvement, assessed by the patient and the investigator at the end of the trial, was present in 90% of the patients in the phenylbutazone group and in 75% of those in the indomethacin group. The mean values of all the spinal motion tests improved in the phenylbutazone group but not in the indomethacin group. Statistically signijkuant improvement in the Schober test was achieved in the phenylbutazone group and in chest expansion in the indomethacin group. Characteristic untoward effects related to the central nervous system and gastro-intestinal tract were present in a few patient in both groups.(5)

Key words: phenylbutazone - indomethacin - anti-infammatory agents - spondylitis, ankylosing

1. Introduction :-

Phenylbutazone a non-steroidal anti-inflammatory drug, has been shown to be effective in the control of symptoms of rheumatoid arthritis' and osteoarthritis(10)The purpose of this study was to compare the effects of phenylbutazone with indomethacin in the symptomatic management of an exacerbation of ankylosing spondylitis.
Patients and methods:-
Twenty-six patients were randomly assigned to a phenylbutazone or an indomethacin treatment group (13 patients to each). All the patients had abnormal or ankylosed sacro-iliac joints by radiographic criteria, except for 1 patient in the indomethacin group. In this case, the radiographic changes of the sacro-iliac joints were read as suspicious, but the patient fulfilled all the Rome clinical criteria of ankylosing spondylitis.9 All the patients enrolled in the study had at least 2 Rome clinical criteria of the disease. HLA-B27 antigen was tested in 8 patients and only 1 was negative. All the patients were of the white race, and there were 2 females in each group. The mean age and duration of the disease was similar in both treatment groups. A written consent to participate was obtained from the patients after they had been informed of the purpose and possible risks of the study.
At the time of entering the study, the patients were suffering an exacerbation of their disease. An exacerbation was defined as a clear increase in spinal or sacro-iliac pain and one or more of the following: (i) muscle spasm in the back; (ii) decreased range of motion of some part of the spine; and (iii) elevation of the erythrocyte sedimentation rate. Patients with any of the following characteristics were excluded : age below 19 years, involvement of more than two peripheral joints not including the shoulders or hips, probability of pregnancy during the trial, hypersensitivity to the experimental drugs, other rheumatoid variants, positive rheumatoid factor or serious concomitant diseases.The drugs were available as identical-looking capsules of 50 mg indomethacin or 100 mg phenylbutazone. The contents of the capsules were not known to the patient. The patients were instructed to take 3 or 4 capsules daily for 6 weeks. The use of any other analgesic or anti-inflammatory drug was discouraged.
Patients were evaluated at the beginning of the study and every 2 weeks thereafter. The following assessments were made at each visit: (i) subjective evaluation by the patient of pain during the day and night, graded on the Keele scale* from 0 to 4 (no pain, slight, moderate to severe, and severe); (ii) spinal tenderness and motion - evaluated by the investigator by palpation, percussion and motion of the cervical, thoracic, and lumbar spine andgraded from 0 to 4 on a similar pain scale; (iii) occiputto-wall test - the distance between the occiput and the wall while standing with the back and the heels against the wall and the chin raised not above its usual carrying level; (iv) chest expansion - measured as the difference between full expiration and full inspiration at the nipple line; (v) Schober test - measured above the level of L5 and recorded as 10 cm plus the extension of the lumbar spine during maximum flexion; (vi) finger-to-floor test - the distance between the finger and the floor during a maximum effort to touch the floor with the knees straight; (vii) intercondylar distance - the distance between the medial femoral condyles at maximum external rotation of the hips with the knees flexed at 90"; (viii) average

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duration of morning stiffness, based on a written daily card kept by the patient; (ix) patient and investigator assessment of improvement compared with the condition immediately prior to the trial, and rated as much better, better, same, worse, or much worse; and (x) erythrocyte-sedimentation rate (Westergren method).
To evaluate the safety of the medications the following laboratory tests were done at each evaluation interval : complete blood count, platelet count, urinalysis, serum creatinine, alkaline phosphatase, SGPT, total bilirubin, and stool occult blood (by 'Hemoccult'@ slides). Prothrombin time, serum glucose and a 14-hour urine concentration test were done at the beginning and end of the trial. Spontaneous report of patients' complaints and those obtained by non-directive questioning were recorded at each visit.

2. Results :-

Efficacy
None of the patients in either group discontinued the study because of lack of efficacy of the treatment. The same number of patients in both groups took 3 or 4 capsules daily during the entire length of the trial or increased the dosage to 4 capsules daily.
Table I summarizes the efficacy end-point results. In the phenylbutazone group the mean values of all the parameters, except the erythrocyte sedimentation rate, improved by the end of the trial. In the indomethacin group, all the mean values also improved, except for the occiput-to-wall and finger-to-floor tests. The magnitude of mean improvement of the parameters was very similar for both treatment groups, except the intercondylar distance and the duration of morning stiffness which were greater for the phenylbutazone group.
Table--Mean results before treatment with indomethacin or phenylbutazone and mean changes after 6 weeks in patients completing trial Assessment.

assessment	indomethacin			phenylbutazone			
	week-0 ,n13	week-6, n12	p	week-0,n 13	week6 n 9	p	
pain severity							
day	2.6	-0.9	0.02	2.5	-0.7	NS	
night	1.9	-0.8	0.05	1.8	-0.8	0.01	
spinal tenderness	1.8	-0.7	NS	1.9	-0.9	0.01	
occiput to wall test	5.9	0.3	NS	5.9	-0.9	NS	
chest expansion	2.9	0.8	0.05	3.9	0.7	NS	
finger to floor test	31.8	0.9	NS	9.3	-5.0	NS	
schober test	11.8	0.5	NS	12.2	0.8	0.05	
intercondylar distance (cm)	50.4	2.1	NS	58.4	7.1	NS	
duration of morning stiffness (hr)	4.2	-2.2	NS	5.0	-4.2	NS	
ESR rate	42	-1.5	NS	32	0.6	NS	

NS- not significant		

Statistical analysis (t-test) revealed no significant difference between the two treatment periods. Assuming that this analysis is valid, the results in bothgroups can be pooled together to determine the significance of time improvement in each test. This analysis showed a mean improvement within the 95 % coddence levels in all the efficacy parameters except occiput-to-wall and finger-to-floor tests and erythrocyte sedimentation rate. Fewer parameters showed statistical significant improvement if the p value for improvement between Weeks 0 and 6 is calculated independently for each drug (Table I). The statistically signiiicant improvement of the intercondylar distance and morning stiffness is lost by both groups, the spinal tenderness and the Schober test by the indomethacin group, and the pain during the day and chest expansion by the phenylbutazone group. The percentage of patients who felt better during the treatment with phenylbutazone was higher than for those treated with indomethacin.

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Tolerance --
One patient in each group withdrew from the study because of drug-related headaches. Another patient in the phenylbutazone group was withdrawn because of a transitory fall in the white blood count from 7.0 to 4.7 x 109/l. One patient complained of gas pains and nausea during the 4 weeks she was on phenylbutazone and another patient had a drop of the haematocrit from458 % to40.0 % while on indomethacin. Positive stools for occult blood were found once in 1 patient in the phenylbutazone group who had been positive prior to the onset of the trial. Mean pulse, systolic and diastolic blood pressure were normal at each evaluation interval, as well as the mean values of the haematological, renal and hepatic function tests. There were no statistically significant changes within time or between the treatment groups in the vital signs or laboratory tests.

3. Discussion

The only accepted standard treatment of ankylosing spondylitis is the symptomatic use of non-steroidal anti-inflammatory drugs. These drugs will probably decrease the progression of the disease(5) and relieve the symptoms, allowing the patient to resume a near-normal life. Phenylbutazone has been the drug of choice for the treatment of ankylosing spondylitis for many years.(6)
Indomethacin has also been found effective and relatively safe by Calabro and Amontez and others. This drug also causes frequent side-effects related to the gastro-intestinal tract and central nervous system. Sturroch and Dudley Hart,' in a 6-week, crossover trial, compared indomethacin (75 mg daily), flurbiprofen (1 50 mg daily) and placebo in 24 spondylitic patients. Flurbiprofen was found to be as efficacious as indomethacin in improving range of back movement and superior in decreasing pain. The erythrocyte sedimentation rate was significantly reduced by flurbiprofen and it had fewer side-effects.
The parallel study reported here was carried out in 26 patients with active ankylosing spondylitis, and it compared phenylbutazone 100 mg to 300 mg daily with 75 mg to 100 mg indomethacin daily. The efficacy of both drugs was very similar. Both drugs produced a significant and consistent improvement in the relief of pain (night or day) and in tenderness of the spine. The magnitude of the improvement was also similar in the two treatment groups. Subjective overall improvement, assessed by the patient and the investigator, occurred in most patients in both treatment groups. The improvement in the spinal range of motion achieved significant levels in a few end-point parameters in both groups. The mean change in all the spinal motion tests improved in the phenylbutazone group, but this consistency was not achieved by the indomethacin group. Mean changes in minor parameters, e.g. duration of morning stiffness and hip motion, were also improved by both drugs. The incidence of side-effects were the same in both groups, and these reactions were related to the central nervous system and to gastro-intestinal tract irritation. Headaches were caused by both drugs. The duration and size of the trial, however, was too small to obtain definitive conclusions about tolerance. The vital signs were not modified by either drug. There were no changes in the haematological, renal and hepatic tests.

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