this possibility in mind by comparing the radiological changes in the vertebral column with the observed clinical responses.

As might be anticipated, it was virtually impossible to re-evaluate these data without introducing bias. The only definitive data which could be salvaged in this regard related to the cervical spine; employing the previously defined criteria for improvement, it was found that of 21 patients with no functionally significant radiological changes of ligamentous ossification and/or apophyseal joint fusion only one patient improved with indomethacin and none with placebo. On the other hand, of the remaining nine patients who were judged to have functionally significant radiological changes, three improved on idomethacin and one while on placebo. These observations would, therefore, suggest that the failure of these patients to demonstrate objective improvement was not due to mechanical restriction of the cervical spine but rather to failure of indomethacin to decrease or abolish active inflammation. It should also be noted that the latter conclusion is supported by the data which demonstrated the inability of indomethacin to prevent acute exacerbations and to relieve morning stiffness.

The laboratory tests (ESR and alpha-2 globulins) employed to assess the anti-inflammatory effect of indomethacin showed no significant change during this study. Once again these data correlate well with the other parameters used to assess indomethacin in this group of patients.

Although indomethacin has been reported to have both anti-inflammatory and analgesic properties,[16,17] the results of this study would indicate that on ankylosing spondylitis the main effect in indomethacin is as an analegisic, since the only significant responses observed were relief of chronic spinal pain and of peripheral arthralgia. The failure of indomethacin to decrease morning stiffness and the frequency and severity of acute exacerbations, to improve the restricted movements in the spinal and peripheral joints, or to suppress the elevated ESR and alpha-2 globulin levels would also indicate that the anti-inflammatory properties of indomethacin in chronic but active ankylosing spondylitis are minimal.

CONCLUSIONS

The majority of patients in this study were unable to tolerate the recommended daily therapeutic dose of up to 200 mg. per day of indomethacin. When 15 patients (50%) received a dose in excess of 150 mg. per day and five others (16%) a dose in excess of 100 mg. per day there was a high incidence of side effects. Accordingly, we would suggest that the maximum daily therapeutic dose of indomethacin be reduced below 150 mg. per day. It would also appear that if a beneficial therapeutic response does not occur with a dose between 100 mg. and 150 mg. per day, the probability that such a response will occur with higher doses is slight.

When the frequency and severity of indomethacin-related side effects, particularly those involving the central nervous system, are considered in conjunction with the apparent lack of an anti-inflammatory effect of indomethacin, the role of this agent in the routine management of ankylosing spondylitis should be questioned. Since in our experience[8] a satisfactory therapeutic program for ankylosing spondylitis can be achieved with physical measures, maintenance doses of acetylsalicylic acid and intermittent administration of phenylbutazone, we can discern no preferential role for indomethacin in such a program.

In order to further evaluate the role of indomethacin in the management of patients with ankylosing spondylitis, we would suggest that a cross-over study comparing phenylbutazone and indomethacin might provide more definitive data than were obtained in the present study. It would also seem appropriate to conduct such a study in a group of patients with spondylitis having a shorter duration of illness, so that objective assessment of the anti-inflammatory effects of the drugs would not be obscured by anatomically restrictive changes in the spine.

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