Gastric ulcer and the anti-arthritic drugs

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Summary

Sixteen cases are described of gastric ulcer in patients receiving anti-arthritic drugs. Half of the ulcers were in the antrum or on the greater curve. Ten patients were under treatment with indomethacin and/or prednisone, seven of them receiving both drugs.

The ulcers healed readily when the drugs were withdrawn, and in the case of prednisone a continued daily dose of 10 mg or less did not prevent healing.

All the patients with haemorrhage were taking aspirin, with or without other drugs.

The literature is reviewed, and it is suggested that the increased incidence of peptic ulcer in patients receiving anti-arthritic drugs is confined to gastric ulcer. There is suggestive evidence of an increased susceptibility to antral ulcer in severe rheumatoid disease, which may largely account for the 'steroid ulcer'.

Indomethacin is potentially ulcerogenic, and its combined use with steroids may be inadvisable. Apart from its tendency to produce haemorrhagic erosions, the role of aspirin in the aetiology of chronic ulcer remains doubtful. No serious ill-effects have been reported in the use of ibuprofen or Distalgesic in ulcer subjects.

INDOMETHACIN is well known to produce gastrointestinal side-effects, and recent reports have suggested that it may induce chronic gastric ulceration, often with a tendency to haemorrhage (Lovgren & Allander, 1964; Taylor *et al.*, 1968). It has been believed for many years that steroid therapy may induce peptic ulceration, at least in rheumatoid patients, and phenylbutazone and oxyphenbutazone are also said to be a cause of gastric ulcer and haemorrhage. With all these drugs the ulcers tend to occur at unusual sites, especially in the antrum. Finally, aspirin which is known to induce gastric bleeding has recently been incriminated in the aetiology of chronic gastric ulcer in women (Chapman & Duggan, 1969).

Many arthritic patients require multiple drugs to

control their symptoms, and when a gastric ulcer supervenes the problem of therapy can be a serious one, particularly as the relative risks of the various drugs are still not understood.

Clinical features

We report our experience with sixteen arthritic patients suffering from gastric ulcer. Five were male and eleven female. Their age ranged from 43 to 80 years with an average of 64 years. Ten suffered from rheumatoid disease (one with psoriasis) and six had degenerative arthritis. Other data are given in Table 1.

Three patients, all with ulcers on the lesser curve, had a past history suggesting that an ulcer may have been present before the administration of anti-arthritic drugs. The site of ulceration in the remaining thirteen cases is shown in Table 2 and compared with the distribution in a control series of 122 non-arthritic cases of gastric ulcer diagnosed during the same period. There is a strong predilection for the posterior wall and greater curve of the antrum, and to a lesser extent of the fundus.

Ten of these thirteen patients were receiving indomethacin and/or steroid drugs. Case 2 had indomethacin alone. Case 4 had taken prednisone (7.5-10 mg daily) for 6 years without ill-effect, and epigastric pains only began 1 month after indomethacin was added. The ulcer healed when indomethacin was stopped but prednisone was continued. In Case 9 epigastric pains began when she was receiving indomethacin alone, although perforation and haemorrhage followed the addition of steroids. Cases 3, 5 and 6 developed acute symptoms while on both drugs but in all three cases the ulcer healed when indomethacin was stopped and steroids were continued.

Cases 10 and 12, both with ulcers on the posterior wall of the antrum, developed symptoms while on regular doses of 10-15 mg of prednisone. This was withdrawn in Case 10 and continued (7.5 mg daily) in Case 12, and both ulcers healed.

All of the nine cases receiving prednisone had rheumatoid arthritis. To view these figures from

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TABLE 1. Features of gastric ulcer in sixteen patients receiving anti-arthritis drugs

Case No.	Sex	Disease	Ulcer site	Haemorrhage	Perforation	Drugs			
						Im	Pred	PB	Sal
1*	M	OA	High lesser curve	—	—	+			
2	F	OA	Mid lesser curve	—	—	+			
3	F	Rh	Mid lesser curve	—	—	+	+		
4	F	Rh	Post. antrum	—	—	+	+		
5	F	Rh	Post. antrum	—	+	+	+		
6	M	Rh	High post. fundus	—	—	+	+		
7*	M	OA	Mid lesser curve	—	—	+		+	
8	F	Rh	Greater curve fundus	++	—	+	+		+
9	F	Rh	Greater curve antrum	++	+	+	+		+
10	F	Rh	Post. antrum	—	—		+		+
11*	M	Rh	Mid lesser curve	—	—		+		+
12	F	Rh	Post. antrum	—	—		+		+
13	M	OA	High lesser curve	+	—			+	+
14	F	OA	Lesser curve antrum	+	—				+
15	F	OA	High post. fundus	—	—				+
16	F	Rh	Mid lesser curve	++	—				+

*Ulcer symptoms preceded therapy

OA, Osteoarthritis; Rh, rheumatoid arthritis; Im, indomethacin; Pred, prednisone; PB, phenylbutazone; Sal, salicylates.

TABLE 2. Site of ulceration in thirteen cases whose symptoms commenced during therapy: comparison with 122 non-arthritis cases

Site	Distribution (%)	
	Arthritic cases	Non-arthritis cases
Antrum:		
Lesser curve	8	8
Posterior wall and greater curve	38	3
Corpus:		
Lesser curve	31	85
Posterior wall and greater curve	23	4

another aspect, of twenty consecutive cases of benign ulceration of the antrum seen in a gastro-intestinal clinic, one-quarter were under treatment for severe rheumatoid disease.

Complications

Cases of haemorrhage and perforation are recorded in Table 1. It is noteworthy that all of the five patients with gastric haemorrhage were taking salicylates at the time. In Case 9 an emergency gastrectomy was performed for continuing haemorrhage and a deep ulcer with local perforation was found on the greater curve of the antrum. Histology showed an unusual degree of surrounding necrosis. The patient had taken indomethacin regularly for 2 years with intermittent aspirin, and had also had Medrone Medules 12 mg daily for 3 weeks. Epigastric pains had been present for 6 months. Case 8 was a woman aged 79 who had a massive and fatal haemorrhage while taking prednisone 15 mg daily, indomethacin 300 mg daily and numerous tablets of

aspirin, phenacetin and codeine. Necropsy revealed a large ulcer on the greater curve of the fundus of the stomach. Histology showed extensive necrosis but confirmed the benign nature of the lesion. In Case 5, following an episode of intense continuous pains, there was radiological evidence of a localized perforation of an ulcer in the posterior wall of the antrum. The patient was on regular doses of both indomethacin and prednisone. The former was discontinued, the latter was reduced from 12.5 to 7.5 mg daily, and the ulcer healed without surgery.

Further management

With the exception of Case 8 who died and Case 9 who was treated surgically, all the remaining cases showed healing of their ulcers within a few months. Medical management included the administration of carbenoxolone sodium in four cases. Indomethacin, salicylates and phenylbutazone were withdrawn in the relevant cases, but as already mentioned prednisone therapy was continued in five of the nine cases who were receiving it, and this did not prevent symptomatic relief and radiological healing. The highest dose which was continued in these cases was 10 mg daily.

Several patients suffered from exacerbation of their arthritic pains on withdrawal of drugs. In these cases paracetamol was the mainstay of treatment, sometimes prescribed as compound tablets with dextropropoxyphene (Distalgesic). Several patients received ibuprofen with moderate success and with no dyspeptic complications. Two cases were treated with mefenamic acid but in one of them this was abandoned because of intractable diarrhoea and a relapse of dyspepsia.

Discussion

Gastric ulcer in rheumatoid disease

The effects of drugs on the stomach in arthritic patients must be considered against the background of the incidence of gastric ulcer, firstly in the general population of comparable age and sex distribution, and secondly in comparable patients suffering from arthritis, particularly rheumatoid disease. With regard to salicylates, it seems impossible to separate the effects of treatment from the effects of rheumatoid disease, since nearly all arthritic sufferers at some time or other take salicylate drugs, whether or not these have been prescribed. In the case of other drugs which have been progressively introduced one can compare the incidence of ulceration with 'controls' before the introduction of the drug. Here however discrepancies may arise because of a changing incidence of ulcer in the population, changing criteria of diagnosis, and the fact that the drugs may alter the manner in which the ulcer presents. Comparability of the 'incidence' in control groups will also depend upon the period of observation during which the occurrence of fresh ulceration was considered. Even if an ideal control group can be studied over a comparable length of time, there is a possibility of bias in the diagnosis of doubtful cases.

Hence it is not surprising that there are wide differences in the reported incidence of peptic ulcer in rheumatoid disease. The evidence has been carefully reviewed by Spiro & Milles (1960) and Crean (1963).

The overall incidence of peptic ulcer in Britain has been estimated at about 8% occurring at some time during life (Doll, Jones & Buckatzsch, 1951), but figures based purely on necropsy findings are higher (Watkinson, 1960). The prevalence of active ulcer at any one time, or the incidence during any single period of a year will obviously be considerably lower, but no accurate figures are available. The incidence of activity of gastric ulcers is higher in the second half of life, when arthritis is common.

With regard to rheumatoid patients, the incidence of peptic ulcer has been variously estimated at between 5 and 8% (Ragan, 1951; Short, Bower & Reynolds, 1957; Baragar & Duthie, 1960; Bowen *et al.*, 1960; Gibberd, 1966). As already mentioned, the estimates include rather variable criteria, and variable periods of observation. The possible role of salicylates cannot be excluded, and none of these series provides adequate data as to changes in the incidence of gastric relative to duodenal ulcer. Overall, the figures do not suggest any significant increase in peptic ulceration due to the rheumatoid process. Conversely they could conceal a minor increase in susceptibility to ulceration at certain sites. This is not impossible in view of the generalized

abnormalities of tissue reactivity which can be demonstrated in rheumatoid disease.

Corticosteroids

The relationship of steroid therapy to peptic ulcer is a complex problem. Whereas Sinclair (1965) stated that the evidence was overwhelming that cortisol and its analogues produced peptic ulceration, according to Croft (1969) 'there is no evidence that corticosteroids in the usual doses cause gastric bleeding or are otherwise harmful to the human stomach'. This problem has also been considered by Spiro & Milles (1960), Crean (1963) and Cooke (1967).

Discrepancies in the literature stem from the fact that a high incidence of peptic ulceration has chiefly been reported in cases of rheumatoid disease, and chiefly in those receiving a higher dose-range of steroids. Bearing in mind all the variables mentioned earlier, one must still consider the massive evidence of correlation between peptic ulcer and steroid therapy (Kern, Clark & Lubens, 1957; Black, Yielding & Bunlin, 1958; Howell & Ragan, 1956; Edgecomb, 1958; Kammerer, Frieberger & Rivelis, 1958; Evans, 1958; Gedda & Moritz, 1959). The incidence of peptic ulcer in these series ranged from 12.5 to 31%. Consistent features of the ulcers were that they occurred with approximately equal frequency in men and women, the presentation was sometimes silent with serious complications, and there was a marked predominance of gastric rather than duodenal ulceration, particularly in the gastric antrum. This unusual distribution of the site of ulceration is the most convincing evidence of a direct association between steroid therapy and the ulcer. It is well illustrated by the prospective studies of Kammerer *et al.* (1958) and Gedda & Moritz (1959). In their combined series, forty-one out of forty-nine ulcers were gastric, and this accentuates the difference as compared with the incidence in their controls examined by radiology or at autopsy. Whereas Bowen *et al.* (1960) found no obvious effect of steroids on the overall figures for peptic ulcer in rheumatoid patients at the Mayo Clinic, they nevertheless were able to demonstrate a marked increase in the incidence of gastric ulcer.

The risk of ulceration seems to be dose-related, and the borderline level of prednisone therapy is of the order of 15 mg daily. In reported series of rheumatoid patients with negative or equivocal findings of peptic ulceration the daily dose has been less than 20 mg daily (Meltzer *et al.*, 1958; Mongan *et al.*, 1964). On the other hand in the series of Gedda & Moritz (1959) twelve out of thirteen patients had received less than 15 mg daily.

In considering the evidence, there are two caveats. Firstly there is the possibility of bias in radiological

diagnosis. A bias in favour of diagnosing gastric ulcer might tend to affect both sexes equally, and it might tend to increase the incidence of antral ulceration, since difficulties of interpretation arise in the antrum rather than on the lesser curve. (In our series the association with arthritis was sought retrospectively, and there should be no bias in the original diagnosis.)

Secondly as Crean (1963) pointed out, steroid therapy tends to be given to the more severe cases of rheumatoid disease; and none of the published evidence excludes the possibility that an increase in peptic ulcer, particularly of the gastric antrum, is a feature of severe rheumatoid disease rather than of steroid therapy.

These views are not incompatible. In rheumatoid disease there may be a diminished resistance to a whole variety of agents which tend to induce gastric erosions. The healing of such erosions may be hindered by additional steroid therapy. There is good evidence that the healing of experimental ulceration is delayed (but not prevented) by steroid treatment, with inhibition of fibroplasia (Janowitz *et al.*, 1958; Kahn, Phillips & Skoryna, 1961). Although prolonged steroid therapy may give rise in some individuals to an increase in gastric acid secretion (Gray *et al.*, 1953; Crean, 1960), most of the literature on 'steroid ulcer' stresses that a reduction of mucosal resistance is the main factor. Hirschowitz *et al.* (1955) and Kammerer *et al.* (1958) recorded a decrease in the viscosity of gastric juice and the former reported a reduction in stainable mucus on the gastric surface.

For these reasons one would expect a combination of steroids and other ulcerogenic drugs to be particularly dangerous. Gastric erosions due to salicylates commonly occur in the antrum and lesser curve (Muir & Cossar, 1955; Croft & Wood, 1967); and it was suggested by Spiro & Milles (1960) that steroids might prevent the repair of such erosions. This is a possibility, although one might expect in these circumstances that multiple ulcers would be common. Moreover the well-recognized tendency to bleeding brought about by salicylates is not a feature of 'steroid ulcers' (Scott *et al.*, 1961).

In view of all the possible discrepancies in estimating ulcer incidence, it is perhaps surprising that (apart from a few reports in the early days of steroid therapy) it is now generally agreed that steroids do not increase the tendency to ulcer in conditions other than rheumatoid disease. An ulcer incidence of the order of 2% over variable periods has been found in cases of asthma (Rees & Williams, 1962), ulcerative colitis (Truelove & Witts, 1955; Palmer & Kirsner, 1959) and chronic skin disease (Spiro & Milles, 1960).

In summary, it becomes clear that in patients with

severe rheumatoid disease treated with steroids there is an increased incidence of gastric ulcer. This increase applies particularly, and perhaps exclusively, to the gastric antrum. Uncertainty remains as to whether this is due to severe rheumatoid disease itself, to steroid therapy, to concomitant aspirin therapy, or to a combination of all these factors.

Indomethacin

Although much less has been written about the gastrointestinal effects of indomethacin, the subject is less controversial. In addition to a high incidence of dyspepsia there is no doubt that in a much smaller number of cases fresh peptic ulceration can occur, with a strong tendency to healing when the drug is withdrawn. Taylor *et al.* (1968) described a series of cases in which no other anti-arthritic drugs had been given. Ulcers attributed to indomethacin tend to occur in similar sites to those occurring in patients receiving steroid therapy. In the case of indomethacin, no evidence has been offered that the incidence of side-effects is dose-related. Nor is there any detailed evidence of the mode of action on gastrointestinal mucosa. Intestinal ulceration has been demonstrated in experimental animals, with a marked species specificity, and can be induced when the drug is injected. Taylor *et al.* (1968) described three cases of gastric ulcer in patients who were receiving indomethacin by suppository only. The tendency to occult bleeding seems to be less than that associated with aspirin (Wanka *et al.*, 1964).

We have described nine cases of gastric ulcer in patients receiving indomethacin, and the histories strongly suggest a causal relationship in at least seven of them. Six of these were also receiving prednisone and it is likely that the two drugs acted synergistically. It is significant that healing was observed while a number of patients continued prednisone in reduced dose.

Phenylbutazone and oxyphenbutazone

The incidence of dyspepsia in patients receiving these drugs was put as high as 20% in earlier reports (Nassim & Pilkington, 1953; Mason & Hayter, 1958), but long-term therapy in a lower dose range gave rise to mild dyspepsia in only 4% of 562 patients (Sperling, 1969). A tendency to erosive gastritis and haemorrhage is well established (Hart & Johnson, 1952; Scott *et al.*, 1961; Roth, 1964). The actual incidence of chronic peptic ulceration arising during therapy is not clear but probably very low (Sperling, 1969; Croft, 1969). Among the small numbers reported, however, there has been a preponderance of cases in the stomach rather than the duodenum, and the sex-incidence is approximately equal. Multiple gastric ulcers have been described (*British Medical Journal*, 1952; Raffensperger,

1953). The action of these drugs is at least partly systemic, as shown by animal experiments and by a high incidence of dyspepsia when the drugs are given by injection (Davis, 1952).

Salicylates

In the enormous literature on the effects of salicylates on the gastrointestinal tract, no positive evidence has emerged that the incidence of chronic peptic ulcer is increased by these drugs. As in the case of phenylbutazone and oxyphenbutazone, a tendency to erosive gastritis and gastro-duodenal haemorrhage is demonstrable, and salicylates also enhance the bleeding tendency of established chronic ulcers (Muir & Cossar, 1959; Scott *et al.*, 1961; Roth, 1964; Croft & Wood, 1967; Valman, Parry & Coghill, 1968). The mucosal damage is greatest with direct contact, but is still apparent after parenteral administration. Menguy & Masters (1965) observed a reduction and altered composition of gastric mucus in animals given aspirin parenterally, the effect being similar to that of cortisone. There may be less occult blood loss with the use of aloxiprin than other forms, but soluble and buffered aspirin have no demonstrable advantage in this respect (Wood, Harvey-Smith & Dixon, 1962), and all aspirin derivatives are liable to exacerbate dyspepsia in ulcer subjects.

This question has been reactivated by the statistical evidence offered from New South Wales on the relation of gastric ulcers in women to the ingestion of aspirin-containing preparations (Douglas & Johnston, 1961; Chapman & Duggan, 1969; Gillies & Skyring, 1969). At present these studies can only be viewed against the background of failure to demonstrate an increase in the incidence of chronic ulcers in patients receiving long-term salicylate therapy for rheumatoid disease (Baragar & Duthie, 1960; Gibberd, 1966). Although the possibilities of such a special relationship have already been discussed, they remain hypothetical.

Other analgesics

Mefenamic acid, which has useful analgesic and anti-inflammatory action in musculo-skeletal disorders, has been shown to induce gastro-intestinal erosions in animals. Occasional dyspeptic symptoms and a rather high incidence of diarrhoea accompany its use in man (Bissell, 1965; Myles, Bacon & Williams, 1967). Although in most patients these side-effects are not incapacitating, the drug is obviously a poor alternative to salicylates and indomethacin in patients with peptic ulcer. Ibuprofen is more promising in this respect. Our experience confirms that of Cardoe (1969) that gastric tolerance is good, even in ulcer subjects. Although the drug is a weak analgesic and is not superior to aspirin, it

has been used successfully in patients who exhibited dyspepsia with aspirin (Chalmers, 1969). It may prove to be the best alternative drug in ulcer patients with arthritis.

Finally, compound tablets of dextropropoxyphene and paracetamol (Distalgesic) provide a combination of two mild analgesics; no specific anti-inflammatory action can be claimed for them, but they have the advantage that the dosage can be built up to relatively high levels with very little risk of gastrointestinal side-effects (Gruber, 1957; *British Medical Journal*, 1963).

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