THE EFFECT OF THALIDOMIDE IN EXPERIMENTAL GASTRIC ULCERS

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A study has been made of the effects of thalidomide, a new sedative hypnotic drug, in stress and phenylbutazone-induced ulcers in the rat. The results have shown that thalidomide inhibits stress induced ulcers but does not affect the local mechanisms involved in the pathogenesis of phenylbutazone-induced ulcers. It does eliminate stress-induced components in phenylbutazone ulcers, which indicates that the mode of action is a central one.

Neurological stimuli play an important part in the aetiology of peptic ulcers, and sedative drugs like phenobarbitone are routinely used in their treatment. It was of interest therefore to examine the value of thalidomide (Distaval)[1], a new sedative hypnotic drug, in experimental gastric ulcers before clinical trial.

Experimental

Ulcers were induced in rats by stress and by injection of phenylbutazone.

Stress Ulcers

These were produced by a modification of the method of Rossi, Bonfils, Lieffoogh and Lambling[2]. Male albino rats (Agricultural Research Council, Compton) weighing approximately 150–200 g. were housed in cages with wire floors to prevent access to sawdust and faeces. They were deprived of food for 24 hours but water was always supplied. Their thoraces and abdomens were then enclosed in Plaster of Paris bandage B.P.C. for 24 hours, food still being withheld, after which the rats were killed for pathological examination. At post-mortem the stomachs were removed between ligatures, washed and filled with formal saline through the oesophageal junction and examined by transmitted light. The stomachs were then opened for closer examination and specimens taken for histological examination. The degree of ulceration was scored according to the following arbitrary scale.

Score 0 .. Normal stomach
Score 0·5 .. Grey discolouration and thinning of the mucosa
Score 1·0 .. Petechial haemorrhages or minute pin point ulcers
Score 2·0 .. One or two small ulcers
Score 3·0 .. Many ulcers
Score 4·0 .. Perforated ulcers

For *prophylaxis*, thalidomide was administered orally as a suspension in water and gum tragacanth before the application of the plaster and again after 12 hours. For *curative effects*, it was first administered 24 hours after the application of the plaster when ulcers had developed in the

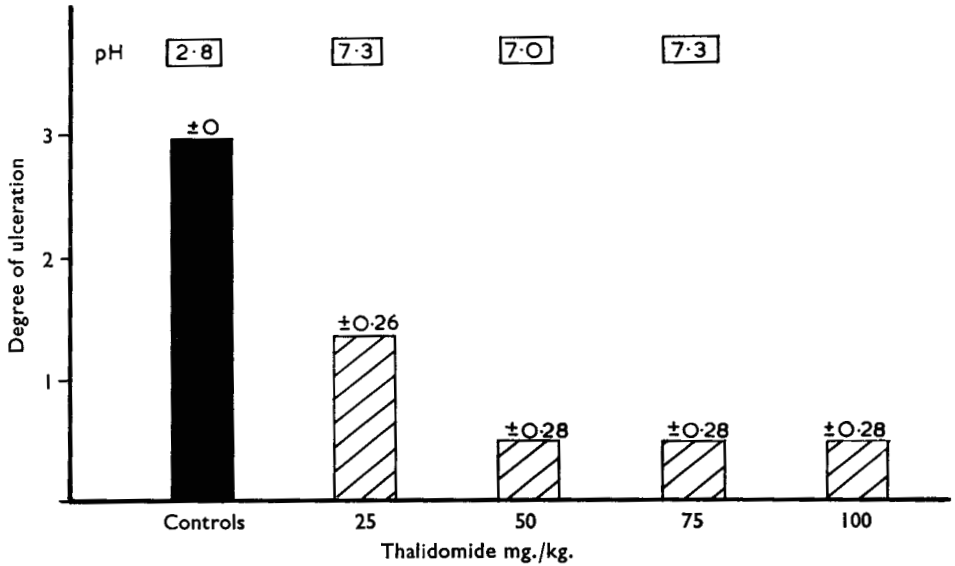

FIG. 1. Anti-ulcerative activity and effect on gastric acidity of thalidomide in partially restrained rats. Each column is the mean with standard error from 4 rats.

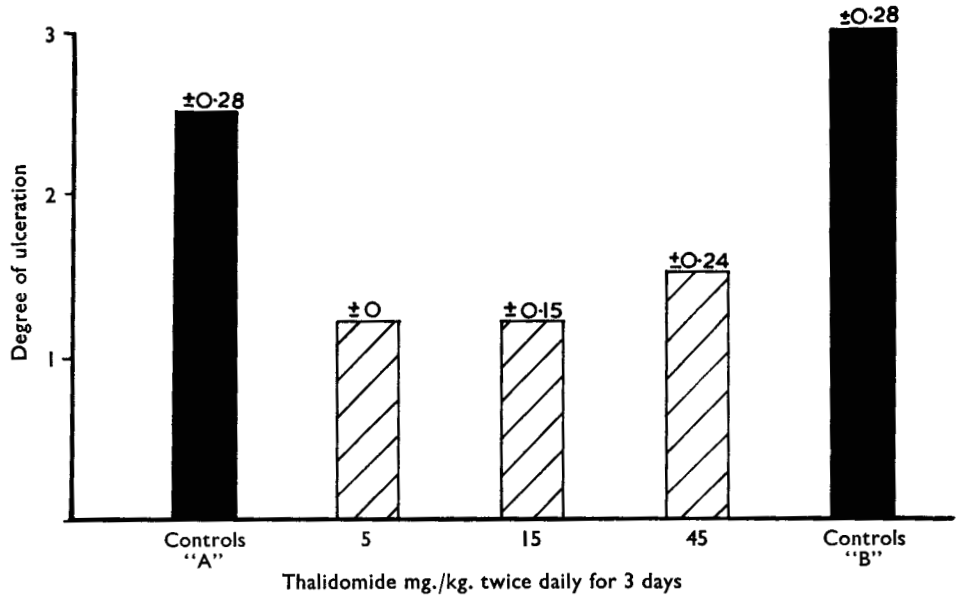

FIG. 2. Curative effect of thalidomide in rats ulcerated by restraint. Each column is the mean with the standard error from 4 rats.

control groups. It was repeated twelve hourly over three consecutive days after which the rats were killed for examination as before. These rats were maintained on sucrose.

Phenylbutazone Ulcers

These were produced by the intramuscular injection of a range of doses of phenylbutazone. Control groups were used in all experiments in a 1 : 1 ratio as recommended by Bonfils and others[3], and the experimental conditions were carefully standardised to avoid external stress. Different sized groups of male rats weighing between 150 and 200 g. were placed in uniform cages for 24 hours before the experiment commenced. They were fed on a pellet diet 41B (J. Rank & Co. Ltd.) and given water throughout the experimental period. The temperature of the animal room was maintained at 27° ± 1° and environmental disturbances were reduced to a minimum. Phenylbutazone ("Butazolidin", Geigy) without added lignocaine was injected intramuscularly into the different groups in a dose range of 12·5–200 mg./kg. 48 and 24 hours before killing the rats. Thalidomide, 100 mg./kg., was administered orally one hour before the first injection of phenylbutazone and repeated 12 hourly during the experimental period. The rats were then killed for pathological examination.

Results

Stress Ulcers

In the control rats ulcers developed in the glandular part of the stomach, beginning as small petechial haemorrhages followed by erosion to the submucosal regions to form typical ulcers. The degree of ulceration was greater when the rats were isolated in individual cages than when they were grouped together. Treatment with thalidomide prevented the ulceration and this was associated with an absence of the hyperacidity which occurred in the control groups (Fig. 1). Treatment with thalidomide after establishment of ulcers had a curative action, the degree of ulceration being much less after four days than in the control groups (Fig. 2).

Phenylbutazone Ulcers

Gastric damage was significantly more severe in rats which were kept singly in individual cages than when they were grouped 2 or 4 in a cage (Fig. 3) and the degree of damage increased in all groups with increasing doses of phenylbutazone. In thalidomide treated rats this difference did not occur, the gastric damage in isolated rats being reduced to the same level as in aggregated rats (Fig. 4). The results from all the thalidomide treated rats may therefore be combined and in Figure 5 these are compared with those from rats treated with phenylbutazone alone at the same time. These combined results show that thalidomide did not diminish the damage caused by small doses of phenylbutazone and at higher doses of phenylbutazone thalidomide had only a slight protective effect.

Discussion

The importance of nervous factors in the pathogenesis of gastric ulcers is shown by the fact that ulcers can be induced by stress alone, using

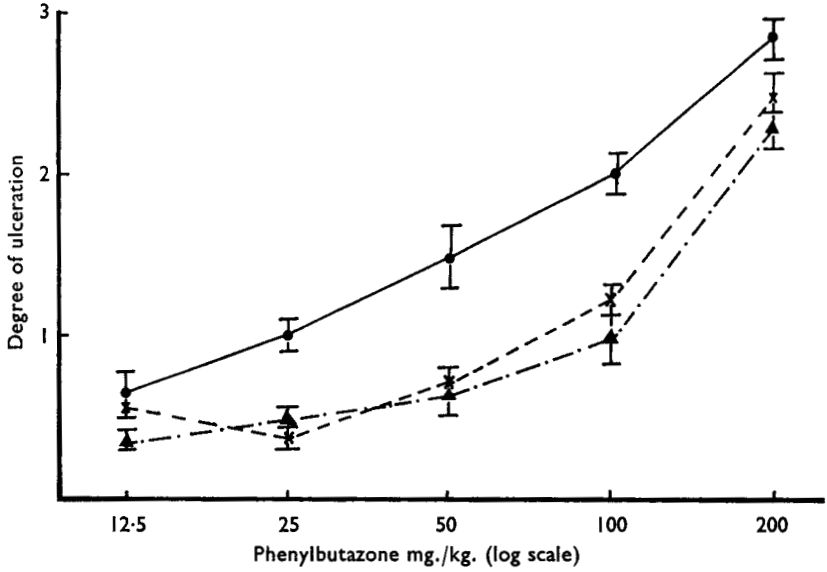

FIG. 3. Ulcerative action of phenylbutazone in grouped and single rats. Each point is the mean with standard error from four rats ●—● 1 per cage, X---X 2 per cage, ▲-·-▲ 4 per cage.

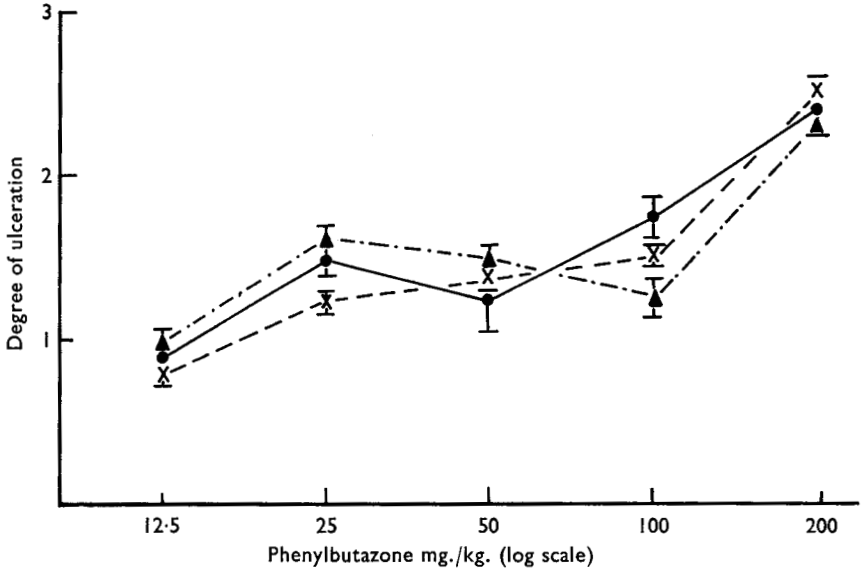

FIG. 4. Ulcerative action of phenylbutazone in grouped and single rats treated with thalidomide, 100 mg./kg. orally. Each point is the mean with standard error from four rats ●—● 1 per cage, X---X 2 per cage, ▲—▲ 4 per cage.

restriction in a Plaster of Paris bandage. However it is possible for stress factors to potentiate ulceration by other means, such as phenylbutazone. Experiments of this kind must be adequately controlled as has been emphasised by Bonfils and others[3]; also it is important carefully to standardise laboratory conditions and to avoid variations in the environment. Without these precautions fallacious results may be obtained[4].

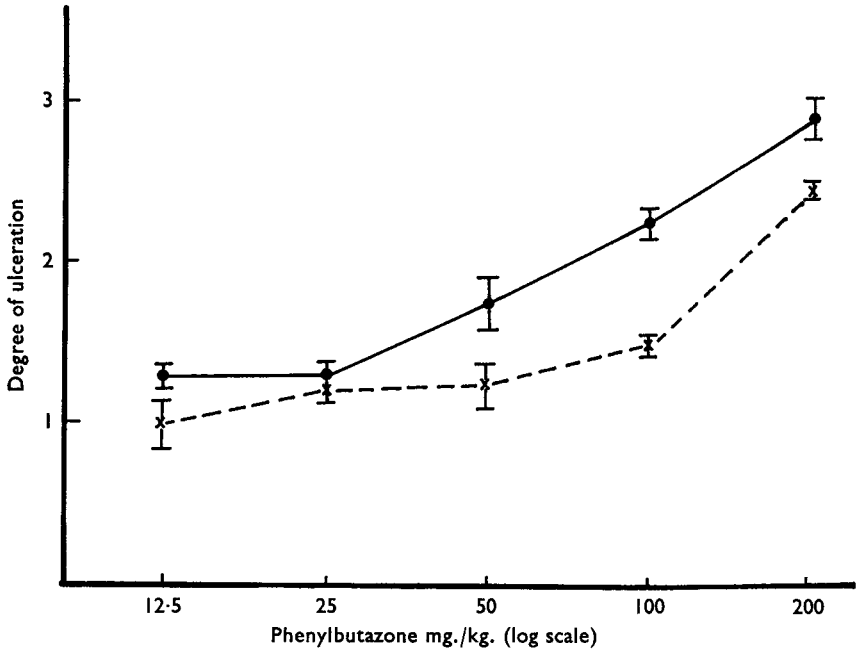

FIG. 5. Ulcerative action of phenylbutazone in normal and thalidomide treated rats. ●—● Phenylbutazone, X--X thalidomide and phenylbutazone.

Stress has been shown by Selye[5,6] to cause gastric ulcers through a central nervous mechanism. Thalidomide presumably prevented ulceration in stressed rats by inhibiting this central nervous mechanism which is responsible for the pathological changes occurring in the gastric mucosa. Preliminary observations which we have made in the guinea pig show that thalidomide in this species has an action against stress ulcers which is not explainable by a change in gastric acid secretion.

The ineffectiveness of thalidomide against phenylbutazone induced ulceration may be explained by the fact that the initial lesion in this type of ulcer is due to a specific local effect, chemical or endocrine, subsequently potentiated by gastric autodigestion[7]. However the different results in grouped and single rats suggest that a concomitant stress reaction may also be involved which is largely dependent on the environmental conditions. This may be inhibited by treatment with thalidomide. This nervous element may pass unrecognised, but by designing experiments such as we have described it is possible to separate the central nervous

mechanisms from other caustive factors involved in gastric ulceration.

The removal of this nervous factor by thalidomide in our experiments suggest that its anti-ulcerative action is mediated through the central nervous system.

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After Dr. Somers presented the paper there was a DISCUSSION.