Further Observations on the Treatment of Superficial Thrombophlebitis with Phenylbutazone (Butazolidin)

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Phenylbutazone is a potent anti-inflammatory agent. It was effective in modifying or causing the resolution of superficial thrombophlebitis in the extremities of 132 patients in whom this condition had proven refractory or difficult to manage. The short course of treatment which proved necessary to accomplish this end, makes this drug a practical and relatively safe addition to the management of superficial vein inflammation.

The rapid subsidence of the inflammation in superficial veins of the limbs was described recently in 50 patients treated with phenylbutazone.* This drug was employed because the superficial phlebitis had been refractory to other measures of treatment, or because it was so vexing a complication that the use of any rapid and effective method was felt to be warranted.

Since publishing this earlier report, 82 new patients have been added, making a total of 132 cases in which phenylbutazone was given in treatment. Our further experiences with phenylbutazone in the management of superficial thrombophlebitis are the subject of this study.

Method

Patients were selected for one of the above reasons. The accessibility of the inflamed veins made the diagnosis of a phlebitis an accurate one and simplified observing the effects of treatment. Color photographs at various stages in the course of the illness made convincing and permanent records.

The 132 patients were screened from a larger group, whose size was difficult to pinpoint because of the diverse sources from which they were obtained. A reasonable estimation would be that they were derived from 600 to 700 individuals who had presented themselves to their private physician, to the hospital ward or clinic with the typical findings of an acute superficial thrombophlebitis. Many, particularly in the early phase of our work, were the problem or refractory cases and had been treated to little avail by periods of bed rest with elevation of the extremity, by local applications of heat or cold, anticoagulants and/or antibiotics. Later on when it became apparent how relatively simple and safe it was to treat this condition in the manner described, more and more patients were treated with phenylbutazone from the start.

We employed a dosage recommended for the treatment of rheumatic conditions. Thus, each individual was instructed to take 200 mg. three times a day for three days and then 100 mg. three times a day for four more days or a total dose of 3 Gm. for the week. In order to prevent gastric irritation the medication was taken after meals. Patients were advised to take a proprietary antacid or a glass of milk if sourness or "acid stomach" did occur.

No patient was kept in bed unless the pain was severe enough to incapacitate him or the systemic reaction to the phlebitis made bedrest advisable. As a rule within 24 hours, most patients were able to get up and walk about; all were able to do so by the end of the second day. No attempt was made to limit fluids or salt intake for the sake of the phlebitis alone during the week of treatment although each patient was requested to drink or eat the equivalent of two oranges a day as a source of potassium ion. None of the patients studied had gout or polycythemia vera.

The many possible grave complications reported from use of the drug alerted us for early toxic reactions. The patient was either examined daily when hospitalized or every other day if treated outside an institution. Blood counts in ambulant patients were done 48 hours after start of therapy and again on termination. In most hospitalized patients blood counts were done every day. It was felt that the short course of treatment, limited usually to one week, was an additional and satisfying safeguard. In a few instances, notably in individuals with migratory thrombophlebitis or visceral neoplasm, this form of symptomatic treatment was continued for longer periods of time to suppress or abort the development of new areas of superficial thrombophlebitis.

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* Adequate supplies of phenylbutazone (Butazolidin) were donated by the Geigy Pharmaceutical Co.
RESULTS

The earliest positive response to treatment is a decrease in pain which becomes apparent to the patient in 8 to 12 hours. By the end of 24 hours, the local redness and swelling overlying the inflamed vein has definitely regressed and the systemic fever, if present, is on the downgrade, usually precipitously. Further subsidence takes place in the next 24 hours and the bright redness of the phlebitic area begins to darken and lose its angry color. All patients are able to walk with little discomfort at this time. In the next few days there is gradual further resolution towards the normal appearance of the limb. The last physical sign to disappear is the indurated and thrombosed vein which may take one to two weeks to shrink down to a fibrous cord.

The early and marked regression seen 8 to 12 hours after use of phenylbutazone in the human subject corresponds quite closely to the changes seen in experimentally induced venous thrombosis.9

We have divided the patients studied into five groups in an attempt to indicate the

| Table 1.—Results of Treatment with Phenylbutazone in One Hundred and Thirty-Two Patients |
|-----------------------------------------------|-----|-----|
| Type of Superficial Phlebitis         | No. of Cases | Resolution |
|-----------------------------------------------|-----|-----|-----|
| In varicose veins                        | 104 | 102 | 2   |
| Associated with malignant disease        | 7   | 5   | 2   |
| Associated with thromboangiitis obliterans| 7   | 7   | 0   |
| Due to medications, diagnostic dyestuffs or chemical irritants, locally introduced | 8   | 8   | 0   |
| In presumably normal veins*              | 6   | 4   | 2   |
| Total                                     | 132 | 126 | 6   |

* This term is used for want of a better one, since it is obvious that the vein or its contents must be altered for thrombosis to occur. We have employed it arbitrarily to describe the spontaneous development of phlebitis in the superficial veins, where no local or systemic factor could be found

association of the phlebitis with an etiologic factor:

Superficial phlebitis: (1) In varicose veins, (2) in malignant disease, (3) in thromboangiitis obliterans, (4) following intravenous injection of solutions for therapeutic or diagnostic intent and (5) in clinically normal veins of spontaneous origin as in idiopathic migratory thrombophlebitis.

COMMENT

Phlebitis of the superficial veins in the arms and legs is not always a simple and easy condition to treat. On occasion, inflammatory changes may persist despite the usually effective management with bed rest, soaks and anticoagulant drugs. In coexisting conditions, such as pregnancy, congestive heart failure or pre- and postoperative states, one wishes there were some rapid and effective means of coping with this troublesome complication. We believe that phenylbutazone does this. Its use in superficial phlebitis was empiric, based upon its potent anti-inflammatory behavior, which was evident in a variety of disorders.10-13

Our previous experience with phenylbutazone in the management of acute superficial thrombophlebitis1 is confirmed. The anti-inflammatory and analgesic properties of this drug have a marked influence on the course of this disorder, causing resolution of considerable degree within 24 to 48 hours of its use. This is all the more impressive because the treated patients represented a difficult and refractory group.

The superficial phlebitis was found most frequently in the patient with varicose veins. Of this group, 102 of 104 patients were treated expeditiously and effectively by a single course of treatment lasting one week or less. As the phlebitis is only an incident in the course of this disorder, more specific measures, i.e., saphenous vein ligation and stripping, were recommended after a period of convalescence. Of the two patients who responded incompletely, one later turned out to have a lymphosarcoma of the small bowel and the other a carcinoma of the uterus. These partial and incomplete responses have been found to be a
characteristic in the presence of some grave underlying disease, usually an occult malignancy which is not manifest at the start of treatment.

The second group numbered seven patients. All had malignant disease of visceral organs which was confirmed at operation or by autopsy. Two patients had carcinoma of the pancreas, three had pulmonary neoplasms, one had an adrenal gland carcinoma and one a carcinoma of the uterus. The superficial phlebitis was controlled completely in five patients by the use of phenylbutazone. In the remaining two, the phlebitic activity and systemic reaction were greatly lessened but would always flare up with the discontinuing of the drug. Administration in these instances continued as long as the patients were alive.

A third and extremely interesting group was that in which the superficial thrombophlebitis was part of active thromboangiitis obliterans. In the seven patients with this panvascular disease, the highly active anti-inflammatory properties of the drug was demonstrated. The painful and disabling phlebitis responded readily to treatment. Second attacks, which occurred months later, in four instances, were treated just as readily and with dispatch. As we have pointed out, this is the first time to our knowledge that vein activity in Buerger's disease has been inhibited by medication. Incidentally, none of these seven patients had smoked for months to years prior to the onset of the superficial phlebitis. Since it would be of considerable importance to determine whether the arteritis which is of paramount interest in this enigmatic disease is similarly inhibited, our future plans include the microscopic study of block sections taken from involved areas of superficial phlebitis before and after use of phenylbutazone.

The fourth group consisted of five patients in whom the superficial phlebitis was the result of the introduction of irritants into the regional veins for therapeutic purposes. Three were patients undergoing injection of varicose veins with sclerosing solution. The inflammatory reaction had proved so violent in these instances, that modification was attempted with phenylbutazone. In each of these three instances of iatrogenic disease, the troublesome local and systemic manifestations were dramatically aborted. In the remaining two cases, the superficial phlebitis was the result of intravenous infusions in postoperative cases. Noradrenalin was the offending agent in one, and glucose in saline in the other. The involved veins were rapidly and successfully resolved with the aid of phenylbutazone.

In the six patients comprising the fifth and last group, i.e., patients with superficial phlebitis in presumably normal veins, some interesting facts came to light. Three patients had typically recurrent (migratory) superficial thrombophlebitis without clinical involvement of the peripheral arteries. In one the condition had been present for 15 years, in another for five years and in a third for two years. Each one was completely symptom-free provided a maintenance dose of phenylbutazone (100 to 200 mg.) daily was taken. The drug has been taken, therefore, for eight months, two years and two and one half years, respectively, and without incident. In connection with this long term use, it was interesting to read of similar freedom from toxicity in the management of arthritics who were maintained on minimal dosage but exposed to prolonged administration of phenylbutazone. Another patient in this group developed a spontaneous phlebitis of one of the antecubital veins while receiving hydrocortone for rheumatoid polyarthritis. This and more serious vascular complications are seen not too infrequently in the course of long continued use of the corticosteroids. The phlebitis responded quite promptly to phenylbutazone. The fifth and sixth patients were both women who developed spontaneous phlebitis of the antecubital vein of the homolateral arm following radical mastectomy. In the one instance, the time relationship to the operation was one and one half years, in the other five days. In neither was there clinical evidence of metastatic disease and in both the phlebitis regressed completely with phenylbutazone.

As previously stated, the major premises for limiting this study to patients with superficial phlebitis were for the sake of accuracy in diagnosis and for simplicity and convenience
in following the effects of treatment. This choice was fortunate. Had we chosen to study deep vein phlebitis, it is possible that the study might have been prematurely terminated. On the occasions when we used phenylbutazone in the treatment of the deep vein variety, the pain is definitely lessened as are the systemic reactions. However, the most prominent feature of a deep vein thrombosis, the swelling of the limb distal to the obstructed segment, remains unchanged. This is understandable because such swelling represents the engorgement secondary to mechanical plugging in the main channels of venous return rather than the localized inflammatory edema of a superficial phlebitis. We have, therefore, continued to advocate its use in the latter condition rather than in deep vein phlebitis.

**Summary and Conclusions**

One hundred and thirty-two patients with superficial thrombophlebitis in the extremities were treated with phenylbutazone (Butazolidin).

Although the causes of the phlebitis were varied, being associated with varicose veins in most cases, but also as part of Buerger's disease, following the intravenous administration of fluids or drugs in others or as complication or manifestation of malignant disease, the response to the drug was a remarkably uniform and rapid regression of the vein inflammation.

Treatment with phenylbutazone (Butazolidin) was limited to one week during which a total of 3.0 to 3.5 Gm. were administered. With this small and limited dosage, major toxic reactions were not seen. In a few patients, short-lived skin eruptions were seen.

With phenylbutazone (Butazolidin) treatment is simplified in that the patient remains ambulant and local management is eliminated. There were no attempts at dietary or salt and fluid restrictions. There is definite advantage in the reduction of time spent at bed rest, in disability and in economic loss. Phenylbutazone in our estimation is a valuable drug for the treatment of superficial thrombophlebitis.

**SUMMARY IN INTERLINGUA**

Un gruppo de 132 patientes con thrombophlebitis superficial in le extremitates esseva tractate con phenylbutazone (Butazolidina). Le responsa esseva un remarcabilemente uniforme e rapide regression del inflammation venose ben que le causas del phlebitis esseva diversissime. In le majoritate del casos le syndrome esseva associate con varices, sed illo etiam appareva como parte de morbo de Buerger, como sequela de intravenose administrationes de fluidos o drogas, o como complicasion o manifestation de un morbo maligne.

Le tractamento con phenylbutazone (Butazolidina) esseva limitate a un septimana. Durante iste periodo quantitates total de inter 3,0 e 3,5 g esseva administrate. Iste basses e breve dosage non resultava in reactiones toxic. In alicun patientes eruptiones dermatice a brevissime durantia esseva notate.

Le uso de phenylbutazone (Butazolidina) resulta in un simplification del tractamento proque le patiente remane ambulante. Nulle restrictiones del dieta, del ingestion de sal o de fluido esseva recommendate. Le methodo offere clar avantages in tanto que illo reduce le requimentos de allectament, le invaliditate, e le perdita economic. In nostre opinion, phenylbutazone es un droga de alte valor in le tractamento de thrombophlebitis superficial.

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Circulation. 1955;12:833-837
doi: 10.1161/01.CIR.12.5.833

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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