

THE USE OF PH 203 (PANTHESINE HYDERGINE) IN THROMBO-EMBOLIC DISEASES IN OBSTETRICS AND GYNAECOLOGY*

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Thrombophlebitis, phlebothrombosis and pulmonary infarction are amongst the most serious complications following operations and deliveries. Progress in medicine has not succeeded in limiting them.¹⁻³ Out of the great number of prophylactic and therapeutic methods tried, viz. exercises, early ambulation, elastic bandaging, zinc-lime casts, vein ligation and others, anticoagulants—dicoumarol and heparin—are the most successful. However, the possibility of serious bleeding should always be considered when anticoagulants are used.⁴

The action of dicoumarol has a latent period of 24-96 hours. The fact that it is given orally prevents its use in the immediate post-operative period. The drug is dangerous in patients who have a low albumin blood level or liver damage, as well as in patients suffering from ulcers in the intestinal tract. It presents hazards during and immediately after delivery as well as during and after an operation. It crosses the placental barrier and it is excreted in the milk, thus endangering the foetus and the newborn.^{5,6} The action of heparin is of short duration and necessitates frequent determination of clotting time.

These disadvantages do not deter us from using anticoagulant drugs, although they compel constant readiness and necessitate laboratory facilities and rather frequent examination, and the search continues for new and more advantageous drugs in this field.⁷⁻¹²

In 1940 Ochsner and De Bakey,¹³ from New Orleans, following Leriche and Kunlin,¹⁴ published a report which laid stress on the occurrence of reflex constriction of arterioles and veins in a whole region as a result of a lesion of part of it. This leads to extensive damage to the circulation of the region, resulting in hypoxia and damage to the capillary endothelium. Increased exudation occurs as well as a rise in tissue pressure, resulting in oedema and pain. Leriche¹⁵ believes that novocaine used as a local anaesthetic blocks the painful reflex induced by trauma or vascular diseases and restores the neurovegetative equilibrium. Others¹⁶⁻¹⁹ used novocaine or alcohol with good results, injecting them directly into the sympathetic ganglia or the connective tissue surrounding them to relieve pain in a determined region.

In 1951 Rappert,⁹ of Vienna, in acute cases of thrombophlebitis, tried the action of procaine by intravenous drip, combined with hydergine in tablet form or by injection. In the course of experiments procaine was replaced by its derivative, panthesine, which was found as efficient yet less prone to produce unpleasant side-effects such as dizziness, nausea and a fall in blood pressure.

In contrast to anticoagulants, clinical trials with a combination of panthesine and hydergine have shown that they do not affect the coagulation of the blood. Panthesine is a local anaesthetic (p-aminobenzoyl-N-diethyl-leucinol methane sulphionate). It also produces anticholinergic,

antihistaminic, spasmolytic and sedative effects. It is less toxic than procaine. Hydergine is a mixture of the methane sulphonates of dihydro-ergocornine, dehydro-ergocristine and dihydro-ergokryptine in equal proportions. Contrary to their natural forms, which constrict blood vessels, the hydrogenated alkaloids relax the arteriolar tonus.²⁰

Recently, Hausammann²¹ reported good results after prophylactic treatment with PH 203 (panthesine 200 mg. + hydergine 0.3 mg.) of 309 surgical patients, as compared to an untreated control group of 253 cases. Königs²² published a postpartum case of multiple thrombosis and embolism, in which anticoagulant therapy was unsuccessful but treatment with PH 203 led to rapid improvement and cure. Morger²³ also employed PH 203 as a prophylactic before operation, and reported good results as compared with untreated cases in previous years.

In view of these good reports we have used PH 203 in patients with thrombophlebitis in obstetric and gynaecological practice.

MATERIAL AND METHOD

The number of patients with thrombo-embolic complications treated with PH 203 during the period from 1 November 1956 to 1 March 1958 can be seen from Table I. Besides PH 203, and hydergine in tablet form at the conclusion

TABLE I

	Therapeutic	Prophylactic	Total
Obstetrics	58	4	62
Gynaecology	18	8	26
	76	12	88

of the treatment, these patients were not given any other therapy than antibiotics where this was considered necessary. In most cases the patients received the usual physical treatment, viz. elevation of the affected limb, wet dressing or elastic bandage. In our department the usual routine is ambulation 24 hours after delivery or operation.

Therapy

We have divided our therapeutic cases into 3 groups, viz.:

1. Light: Superficial thrombophlebitis of the leg, 26 cases.
2. Medium: Deep thrombophlebitis of the leg, 36 cases.
3. Severe: Pulmonary infarction, phlegmasia alba dolens, or deep pelvic thrombophlebitis, 14 cases.

We did not take into consideration temperature and pulse, since these signs may be produced by the primary condition (after delivery or operation). Moreover, most patients received antibiotic therapy, which influenced these signs.

Group 1. Patients belonging to this group received 2 intramuscular injections daily of PH 203 for a period of 3-8 days, followed by one injection of PH 203 plus one injection of 0.3 hydergine for 1-3 days. At the conclusion of the treatment by injections, the patient received 2-3 hydergine sublingual tablets daily at home for 7-10 days.

Group 2. Patients showing symptoms of moderate severity received one intravenous infusion of PH 203 plus one intra-

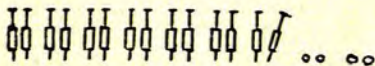
* We are indebted to the Pharmaceutical Laboratories Sandoz, Basle, Switzerland, for placing at our disposal the necessary quantity of PH 203.

muscular injection daily, for 3-5 days. After this, 2 intramuscular injections were given per day till disappearance of signs. Finally, hydergine injections and tablets were administered, as with group 1.

Group 3. Patients with severe thrombosis and embolism received one ampoule of PH 203 as an intravenous infusion twice daily for 3-5 days; then intramuscular injections twice daily till disappearance of all signs. Hydergine injections and tablets were given as with groups 1 and 2.

The following diagram indicates the methods of treatment.

GROUP 1



GROUP 2



GROUP 3



INFUSION OF 200 cc GLUCOSE PLUS ONE AMPULE OF PH 203



I.M. INJECTION OF PH 203



I.M. INJECTION OF 0.3 HYDERGINE

OO HYDERGINE TBL. SUBLINGUAL 0.3 mg.

For intravenous infusion PH 203 was diluted in 200 ml. of 5% glucose. The duration of the intravenous drip was 90-120 minutes.

Only 6 patients, all from the first group, did not require complete bed rest; all the other patients were confined to bed for various periods. All were permitted to ambulate before conclusion of the treatment and disappearance of the symptoms.

Table II shows in summary for each group how long it was before the marked improvement took place in the patients' condition, the length of confinement to bed, and the average length of treatment.

Group	Marked Improvement after (days)	Length of Bed Confinement (days)	Average Length of Treatment (days)
Light	1-3	1-5	5
Medium	1-3	1-9	8
Severe	2-4	3-13	11.7

In 9 patients (7 of these receiving intravenous drips and 2 receiving intramuscular injections) secondary side-effects appeared. These were: dizziness, feeling of fainting, tinnitus, and feeling of 'pressure' in the head. Drop in blood pressure was not noted. The side-effects lasted for a short period and disappeared on continuation of the treatment. In

patients who were receiving intravenous infusion the rate of administration was slowed down when side-effects appeared.

Two patients received intramuscular injections of PH 203 because of thrombosis in one leg; both developed thrombosis in the other leg on the 8th day of treatment. This condition cleared up on continuation of treatment.

Prophylaxis.

The drug was administered prophylactically to 12 women, 8 before gynaecological surgery, and 4 before delivery. All had a history of severe and repeated thrombophlebitis; some of them had had pulmonary infarction as well. These patients received intramuscular injection of PH 203 only—one ampoule twice daily for 3-4 days before the operation or delivery, on the day of operation or delivery and after it for 6-10 days. In none of this small series of 12 cases was the post-operative or postpartum course complicated by thrombo-embolic disease. Side-effects were light and disappeared on continuation of the treatment.

DISCUSSION

An improvement in the local status, as well as in the general condition of the patient, was noted soon after therapy with PH 203 was started. An outstanding feature was disappearance of pain from the affected area. Oedema, tenderness and Homans' sign,* if present, disappeared rapidly. It seems that the drug acts on those arterioles and veins that are not affected by the thrombosis but react by reflex action from affected blood vessels.^{24,25} Apparently even the affected section benefits from the circulation in the surrounding tissue and tends towards better and more rapid organization, and even recanalization.²⁶ Probably the drug has an identical effect on the pulmonary blood vessels.

It is interesting to note that few of our patients needed sedation. As is well known, panthesine has a general analgesic effect like that of procaine. We were rather impressed by the rapidity of pain relief; the pain disappeared in the affected region very soon after the treatment was started.

As regards administration and dosage, we believe that in severe cases one should start with 2 intravenous infusions daily, at least for the first few days. Our experience in prophylactic treatment is limited, but we were much impressed by the 12 patients with a past history of thrombo-embolic disease whose course after prophylactic administration of PH 203 was not complicated by the disease after operation or delivery.

Side-effects were light and disappeared in spite of continuation of the treatment. The therapy, both in thrombophlebitis and pulmonary infarction, and also prophylaxis, appear to be efficacious.

The treatment is easy and convenient. There is no need for laboratory examinations during therapy, and the drug may therefore be used in certain cases on an ambulatory basis.

SUMMARY

1. A survey of therapy with PH 203 in thrombo-embolic diseases following operation or delivery is presented.
2. 76 women, whose primary condition was complicated

* Discomfort behind knee on forced dorsiflexion of foot—a sign of thrombosis in the leg.

by thrombo-embolic disease, were treated, and 12 cases were treated prophylactically.

3. The results obtained were satisfactory.

4. In the course of the therapy no laboratory facilities are required, no danger of bleeding exists, as far as the drug is concerned, and side-effects are rare and mild.

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