**FATAL AGRANULOCYTOSIS DUE TO PHENYLINDANEDIONE: REPORT OF A CASE**

By PERRY C. SMITH, Captain MC, USA, Fort Sam Houston, Texas

Phenylindanedione is one of several oral anticoagulants in wide use at the present time. It is generally considered to be non-toxic, but adverse reactions to the drug have been reported. We have been able to find six instances of agranulocytosis, two of jaundice, and six of rash without fever in the world literature. One of the instances of agranulocytosis was fatal. The purpose of this communication is to report the second known case of fatal agranulocytosis due to phenylindanedione.

**Case Report**

A 64 year old white male was admitted to Brooke Army Hospital July 30, 1957, because of a stroke. Symptoms dated back approximately one and one-half years, when he had first begun to notice transient bouts of numbness of the left upper ex-
tremor. For the several months prior to admission he had experienced occasional episodes of slurred speech and hypesthesia of the left side of his face. Two weeks prior to admission his condition deteriorated abruptly. He was seen by his local physician, who obtained a cerebral angiogram. Over the next week he gradually became worse and was hospitalized. Past history and system review added no additional information.

On physical examination the patient was noted to be aphasic, with an obvious left hemiparesis. Blood pressure, 112/64 mm. Hg; pulse, 82 and regular; temperature, 98.6° F. The pupils were unequal, the left being larger than the right. There was a lack of conjugate deviation to the left, with a suggestion of nystagmus on right lateral gaze. Fundi showed grade I arteriosclerotic changes only. The neck was supple. There was a definite lag of the left hemithorax. The lungs were clear to percussion and auscultation. The heart was not enlarged, rhythm was regular, and no murmurs were heard. The prostate was firm but not enlarged. There was a flaccid paralysis of the entire left side. Slight atrophy of the left lower extremity was present. Sensory changes could not be evaluated. Deep tendon reflexes were hyperactive on the left. No pathologic reflexes were elicited.

White blood count on admission was 13,400, with 92% neutrophils, 7% lymphocytes and 1% monocytes. Hemoglobin was 13.8 gm.%; hematocrit, 42. Blood urea nitrogen, 26 mg.%. Urinalysis showed a specific gravity of 1.013, with 3 plus albumin and many red and white blood cells in the sediment. Spinal fluid examination revealed an opening pressure of 48 mm. of spinal fluid. The fluid was clear and contained a few crenated red blood cells; protein, 49 mg.%. (normal, 20 to 25 mg.%). A chest x-ray and an electrocardiogram were within normal limits. Multiple urine cultures grew out a varied flora of *Escherichia coli*, aerobacter, pseudomonas and *Staphylococcus albus*. The white blood cell count on August 29, 1957, was 8,600.

Shortly after admission the results of the angiogram were obtained from the patient's private physician. This study was said to show intracranial occlusion of the right internal carotid artery. On August 5, 1957, phenylindanedione therapy was begun with an initial dose of 150 mg., followed in 12 hours by 100 mg. Subsequent doses were given on a 12-hour schedule in amounts sufficient to maintain the prothrombin time within the therapeutic range. The average maintenance dose was found to be 75 mg., with variation from 25 mg. to 75 mg. over the first 10 days of therapy. The drug was discontinued on September 6, 1957, a total of 5,025 mg. having been administered over the 33-day period. Hemorrhagic complications did not occur. Continued urinary incontinence compelled the use of an indwelling catheter. The resulting urinary tract infection was treated with several courses of antibiotics as indicated by appropriate culture and sensitivity studies. Tetracycline, Furadantin, penicillin and streptomycin were used. The last of these (penicillin and streptomycin) were stopped August 17, 1957. From this date to September 6, 1957, phenylindanedione was the only drug administered.

By September 1, 1957, the patient was out of bed in a chair most of the day, actively participating in physical therapy and eager to undertake any and all measures which might promote a speedier recovery. On the morning of September 6, 1957, he spiked a temperature to 104° F. and was noted to be drowsy and to react poorly. Physical examination at that time revealed rapid shallow respirations, with diminished breath sounds over both lower lobes. No râles or rhonchi were heard. Blood pressure was 110/70 mm. of Hg; pulse, 96/minute and regular. No murmurs were heard. The abdomen was soft; liver, spleen and kidneys were not palpable. The legs were not swollen and the calves were not tender. No skin rash was noted. A white count was reported as 1,700, with 70% lymphocytes.

Phenylindanedione was stopped and the patient was immediately started on
20,000,000 units of penicillin intravenously, 1 gm. of streptomycin intramuscularly, and cortisone, 200 mg. intramuscularly per day. A bone marrow aspiration showed large numbers of erythroid cells and lymphocytes, with relatively few cells of the myeloid series. The myeloid-erythroid ratio was 1.6/6. Small numbers of myelocytes (6%) were the most mature cells of the granulocytic series present. Over the next three days the patient went progressively downhill despite steroids, massive antibiotic therapy and pressor agents. White blood count on the day of death was 400 (100% lymphocytes).

At autopsy the entire right carotid artery from its origin into the cranial vault was found to be thrombosed. Multiple areas of cystic encephalomalacia were encountered in the right hemisphere. Acute and chronic cystitis was the only infectious process detected. On microscopic examination the hematopoietic tissues were noted to be hyperactive, as revealed by enlarged, hyperplastic splenic corpuscles and by reticulum cell and myeloid proliferation in the bone marrow, with a relative paucity of mature myeloid elements.

**DISCUSSION**

To the best of our knowledge, this is the seventh reported case of agranulocytosis due to phenylindanedione, and the second where death was directly attributable to the drug. In each of these cases agranulocytosis developed between the fourth and fifth week of therapy. Fever, rash or other minor toxic manifestations have not been reliable signs of impending serious reactions—in fact, leukopenia was the presenting sign in four of the seven cases. Four cases have been treated with ACTH or cortisone; two recovered, two died.

The possibility of fatal toxic reactions, even though of infrequent occurrence, must be taken into consideration when selecting a drug for long-term use. Phenylindanedione is preferred by some observers because of its rapid action and greater maintenance stability. Since it is only the latter advantage which must be weighed against its toxic potential, it occurred to us that it might be feasible to use phenylindanedione to initiate anticoagulant therapy, and to switch to another, less toxic agent for maintenance. Such a plan was instituted and proved to be quite practical. We now initiate anticoagulant therapy with full doses of phenylindanedione and Dicumarol simultaneously. Subsequent doses of both drugs are administered as if each drug were being used alone, except that phenylindanedione is tapered off and discontinued by the third day. With this technic, the onset of anticoagulant action is rapid, smooth and predictable. We feel that this technic takes full advantage of the merits of phenylindanedione while at the same time obviating the danger of a possibly fatal agranulocytosis. In view of the fact that other anticoagulants without demonstrated toxic potential are equally efficacious for maintenance therapy, we feel that there is little indication for the use of phenylindanedione beyond the first week of therapy.

**SUMMARY**

A case of fatal agranulocytosis due to phenylindanedione is reported. This is the seventh reported instance of agranulocytosis due to phenylindanedione, the second where death was attributable to the drug. A method of initiating anticoagulant therapy designed to take advantage of the rapid action of phenylindanedione is described. It is suggested that the use of phenylindanedione beyond the first week of therapy be discontinued.
SUMMARIO IN INTERLINGUA

Es reportate un caso de mortal agranulocytosis causate per le anticoagulante phenylindanediona.

In iste caso, therapia anticoagulante a longe vista esseva initiate post le demonstration de un thrombose del arteria carotidic dextero-interne. Agranulocytosis appareva subitemente inter le quarte e le quinte septimana del therapia e resultava in le morte del patiente intra tres dies.

Durante que iste droga es considerate generalmente como nontoxic, sex casos de agranulocytosis causate per illo se trova reportate in le litteratura, inclusive un le qual esseva mortal. In omne le casos, le agranulocytosis se disveloppava sin premonition inter le quarte e le quinte septimana del therapia.

Le droga es preferite per multes a causa del rapiditate de su efficacia. Es describite un methodo pro le initiation de un therapia anticoagulante que prende avantage del mentionate qualitate de phenylindanediona sed que evita simultaneemente le risco de un possibile reaction mortal.

Es presentate le opinion que le uso de phenylindanediona es rarmente indicate post le prime septimana del therapia.

BIBLIOGRAPHY

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621