Haemoglobinaemia and Haemoglobinuria Following the Administration of Neodymium 3-Sulpho-Isonicotinate (Thrombodym)

From the Department of Pharmacology and Therapeutics, St. Andrews University, Queen's College, Dundee

C. R. Rizza, D. M. Shepherd, W. Walker

Neodymium 3-sulpho-isonicotinate (Thrombodym), given once or twice daily by intravenous injection, has been widely used in Germany in the last few years in the successful prophylaxis and treatment of thrombotic conditions, particularly in surgical and obstetric practice (Thiess and Boecker, 1953; Wilbrand, 1953; Hartenbach, 1955). Its anticoagulant action depends on the size of the dose: 50 mg/kg in rabbits gives a very long whole blood clotting time associated with inactivation of antihaemophilic globulin and several other coagulation factors, while the therapeutic dose of about 5 mg/kg leads only to moderate prolongation of the one-stage "prothrombin" time due to inactivation of factor VII, and to impaired blood thromboplastin generation due to inhibition of factor IX (Christmas factor) and another serum thromboplastin factor, probably factor X (Hunter and Walker, 1956). Virtually no toxic effects had been observed by German workers with very extensive experience of this drug, although Hartenbach (1955), noting that most of the administered neodymium was retained in the reticulo-endothelial system, advised that courses of treatment should be limited to ten days at longest.

This paper reports the finding of *haemoglobinaemia in nine of thirteen patients receiving* this drug for periods of more than three consecutive days. It was at the time an entirely unexpected finding, although Beaser et al. in 1942 reported haemoglobinaemia and haemoglobinuria in man and animals following the administration of neodymium acetate and lactate. In the present series, the dose used in a clinical trial of Thrombodym was 375 mg daily, this being the smallest dose which consistently produced impairment of blood thromboplastin generation. One of the first patients so treated showed haemoglobinuria on the eighth day. No further doses were given but the haemoglobinuria persisted for three days, accompanied by haemoglobinaemia and methaemalbuminaemia which were detected spectroscopically. The plasma showed a positive Schumm's test for albumen haemochromogen. There was no significant fall in blood haemoglobin or red cells, nor rise in serum bilirubin or reticulocytes, and no other cause of haemolysis was found. There were no untoward symptoms,

and the biochemical abnormalities disappeared in a few days and did not recur.

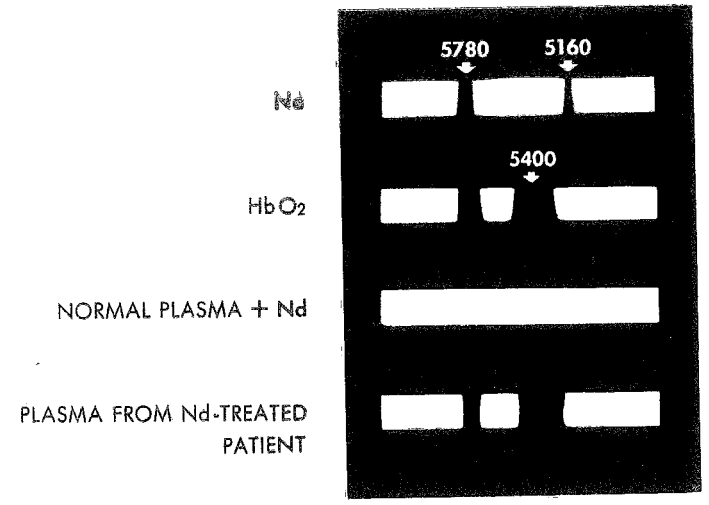
Thereafter the plasma and urine of every patient given Thrombodym was examined daily for haemoglobin or other abnormal pigments. Blood was taken into heparin with a standardised technique, and special care to avoid in vitro haemolysis. In no patient was any abnormality found during the first three days of treatment, but haemoglobinaemia was found with increasing frequency from the fourth day onward (Fig. [4]). Of twelve patients treated for more than three days, in addition to the one already described, eight showed haemoglobinaemia. Of the four who did not show this abnormality, none received more than four daily injections, and no patient was given more than eight doses in all. No further examples of methaemalbuminaemia or haemoglobinuria were found, and none of these patients had symptoms attributable to the neodymium injections. Only one, after eight injections, showed a slight but significant fall in red cell count, and in none was the serum bilirubin raised. Tests of red cell osmotic fragility were made in two patients with haemoglobinaemia, and found to be normal. Unlike the rabbits described below, no patient showed a rise in plasma cholesterol. The haemoglobinaemia disappeared within 3—5 days of the last injection.

Since it has been suggested that the principal absorption bands of neodymium might be mistaken for oxyhaemoglobin (Vincke, 1957), Thrombodym itself (2.25% solution of neodymium 3-sulpho-isonicotinate) and neodymium chloride (3.6% solution) were examined spectroscopically; the absorption bands were readily distinguishable from those of oxyhaemoglobin (Fig. [1] and [2]). Furthermore, the pigment present in the plasma of treated patients was converted by means of ammonium sulphide to reduced haemoglobin, with its characteristic absorption band. Finally, normal plasma containing Thrombodym in a concentration corresponding to the maximum which could be expected in the circulation after a therapeutic dose showed very faint absorption bands which were just visible on direct inspection but which would not photograph (Fig. [3]).

Five rabbits were given from seven to twelve daily injections of neodymium 3-sulpho-isonicotinate, 15 mg/kg, and heparinized plasma, taken by cardiac puncture, was examined on the day after the last injection. In four of these animals the plasma was reddish, but spectroscopy was made very difficult by an intense and persistent cloudiness, presumably due to a high lipoidal content; plasma cholesterol levels ranged between 350 and 500 mg per 100 ml.

Haemoglobin was positively identified in only two of these plasmas. In the fifth rabbit the plasma after nine injections was clear, with a cholesterol content of 90 mg per 100 ml, and showed haemoglobin but no methaemalbumin on spectroscopic examination.

No haemolysis was produced in vitro when 0.5 ml Thrombodym was added to 4.5 ml human blood and allowed to stand at 37° C for four hours.



The spectra reading from top to bottom are as follows: (1) neodymium showing principal bands at 5780 Å and 5160 Å; (2) oxyhaemoglobin with one band at 5780 Å and a distinctive wide band with its centre at 5400 Å; (3) neodymium at therapeutic concentration added to normal plasma; (4) plasma from neodymium-treated patient showing typical oxyhaemoglobin bands.

The most probable *cause of the haemoglobinaemia* is intravascular haemolysis, and this is the conclusion of Beaser et al. (1942). It is tempting, however, to speculate on another possible pathogenesis, namely a block in the clearance of haemoglobin from the plasma by the reticulo-endothelial system brought about by the neodymium deposited there. This mechanism would explain the delay of several days before the appearance of haemoglobinaemia, the failure of the red cells to decrease or the bilirubin to rise appreciably, and also the hypercholesterolaemia that developed in the rabbits — presumably due to a similar block in the clearance of cholesterol. There is as yet no real evidence for this, however, and the cause must be presumed to be intravascular haemolysis, possibly due to increased mechanical fragility of the red cells.

Summary

Nine of thirteen patients receiving daily intravenous injections of 375 mg. 3-sulpho-isonicotinate for four to eight days developed haemoglobinaemia, accompanied in one case by haemoglobinuria and methaemalbuminaemia. In addition to haemoglobinaemia, a rise in blood cholesterol was observed in rabbits given larger doses.

Résumé

On a injecté à 13 patients journellement 375 mgr de 3 sulfo-isonicotinate ceci pendant 3 à 8 jours. 9 d'entre eux développèrent une hémoglobinémie qui, dans un cas, fut accompagnée d'hémoglobinurie et de méthémalbuminémie.

Chez des lapins, qui reçurent des doses encore plus élevées, on observa une augmentation de la cholestérolinémie, en plus de l'hémoglobinémie.

Zusammenfassung

Neun von 13 Patienten, welche tägliche Injektionen von 375 mg 3-sulpho-isonicotinat während 3 bis 8 Tagen erhielten, entwickelten eine Hämoglobinämie, welche in einem Falle von Hämoglobinurie und Methämalbinämie begleitet war.

Bei Kaninchen, welche höhere Dosen erhielten, wurde außer der Hämoglobinämie ein Anstieg des Blut-Cholesterins beobachtet.

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