The Course of Experimentally Induced Hemolytic Anemia in a Primaquine-Sensitive Caucasian
A Case Study

By Ivo Pannacciulli, Alberto Tizianello, Franco Ajmar and Emanuele Salvio

The self-limited nature of drug-induced hemolytic crises has been effectively demonstrated by Dern and associates in American Negroes, and is believed to be a peculiar feature of primaquine sensitivity. It is well known that glucose-6-phosphate dehydrogenase (G-6-PD) deficient states affect also the Caucasian racial group and particularly the Sardinians among whom 15 per cent are affected. Drug sensitive Caucasian males show a considerably lower erythrocyte G-6-PD activity as compared with the enzymatic activity of the red blood cells of sensitive Negro males. In fact in mutant Sardinian males red blood cell G-6-PD activity is 5.2 per cent of the activity of normal erythrocytes whereas the red blood cells of mutant Negro males have 16.7 per cent of the normal G-6-PD activity. Furthermore Bonsignore and co-workers, after hemolytic crises in favism, and ourselves, could find no increase in G-6-PD activity in the red blood cells during the reticulocytosis of the recovery phase. This is in contrast with the observations of Marks and Gross in primaquine sensitive Negroes.

In mutant Negroes the self-limited course of the drug-induced hemolytic crisis is linked to a relative insensitivity to the drug of the younger red cells which have higher levels of G-6-PD activity. It seems therefore predictable that in mutant Caucasian males, whose younger red cells are almost completely devoid of G-6-PD activity, the course of the hemolytic crisis may have a somewhat different pattern.

To elucidate this problem we have studied the effects of repeated administrations of primaquine in a mutant Sardinian male. The drug sensitivity of the patient's erythrocytes, collected both before and after hemolytic crises, was also tested by transfusing the labeled red blood cells into normal recipients.

Methods and Materials

The usual hematologic technics were employed in this study. G-6-PD activity was measured according to Kornberg and Horecker. Red blood cells were tagged with radioactive sodium chromate according to Mollison and Veall. Fe59 Cl2, given intravenously...
after binding with the subject's plasma, was used to label red blood cells of a narrow age range.

Priminaquine was administered orally at a daily dose of 30 mg.

A mutant Sardinian male, aged 48 years, volunteered for this experiment. He had been under our observation for the past 2 years. His ancestry was unequivocally Sardinian. He was in good hematologic condition: Hct 43 per cent, Hb 14.9 Gm., red cell mass 1547 ml. (body weight 49 Kg.).

RESULTS

1. The G-6-PD activity of the erythrocytes of the subject was 0.1 U/Gm. HbP, before and after the administration of primaquine, i.e., during the reticulocytosis of the recovery phase. His leukocyte and platelet G-6-PD activities, calculated according to Marks and Gross, were 6.5 U/10⁹ cells/⁹, and 0.1 U/10⁹ cells/⁹ respectively, about 25 per cent of our values for normal leukocytes and platelets.

2. In previous experiments Cr⁵¹-tagged red blood cells of the subject had been transfused into a normal recipient who then received primaquine. The cells had been rapidly destroyed: T/2 of the Cr⁵¹ was 19 days before and 1 day after the administration of primaquine. The subject himself received primaquine for the first time on April 7, 1963, and his hematocrit fell rapidly from normal levels to 26 per cent. Twelve days after he had been started on primaquine, and while the hematocrit was still 26 per cent, his red cells were collected, tagged with Cr⁵¹ and transfused into a normal recipient. The cells were again rapidly destroyed by the drug; T/2 of the Cr⁵¹ was 25 days before and 2.5 days after the administration of the drug.

3. After a few months the patient was again hospitalized, and on October 19, 1963, he was started on primaquine (fig. 1). The hematocrit dropped from 43 per cent to 21 per cent and the Cr⁵¹-tagged red cells showed a half life of 4 days. Priminaquine was withdrawn on October 26. Red blood cells collected on October 25 were labeled with Cr⁵¹ and transfused into a normal subject, who received primaquine. They were rapidly destroyed: T/2 of the Cr⁵¹ was 25 days before and 7 days after the drug.

The Sardinian subject received Fe⁵⁹Cl₃ on November 2; maximal red cell utilization of the isotope was observed on November 8. On November 10, when the hematocrit was 34 per cent, primaquine was again administered. In eleven days the hematocrit fell to 19 per cent, and 75 per cent of the Fe⁵⁹-tagged red cells were destroyed. This implies that red cells of 10 to 16 days of age were destroyed as the consequence of the administration of the drug. Priminaquine was stopped on November 19th, and the hematocrit rapidly returned to 36 per cent on December 2nd, and on December 9th was again 42 per cent.

DISCUSSION

In a primaquine-sensitive Sardinian male we were able to induce two severe hemolytic crises in a month's period, as a consequence of two courses of primaquine (fig. 1). An Fe⁵⁹-labeled red cell population ranging in age from 10 to 16 days, was rapidly destroyed after the second administration of the drug.
In a month's period, two severe hemolytic crises were caused in a mutant Sardinian male by two courses of primaquine (30 mg. daily). In the second hemolytic episode a young population (10-16 days) of Fe$^{59}$-tagged red blood cells was rapidly destroyed.

In our patient, during the first seven days of the second course of primaquine administration, the hematocrit did not follow its upward trend, but maintained a steady state. The increased production of red cells was offset by the hemolytic drug. Continuing administration of the primaquine caused a sudden drop of the hematocrit as the younger red cells became increasingly drug sensitive. Transfusion experiments with Cr$^{51}$-tagged erythrocytes, collected immediately after the hemolytic crises, confirm the susceptibility of the younger red cells to drug-induced hemolysis during the recovery phase.

It is questionable whether the drug-induced hemolytic crises in this Sardinian subject may be considered self-limited, and the same question must extend to the reaction of those mutant Caucasian males whose red cell G-6-PD activity, before and after primaquine administration, is practically absent. If our subject is typical, one may conclude that the pattern of the hemolytic crisis in Caucasians differs from the crisis in Negroes as demonstrated by Beutler and associates.8

From our experiments it is evident that mutant Sardinian males may develop extremely severe hemolytic crises. We received the impression that a continuous administration of primaquine to our patient would have induced a severe anemia, leading to a poor prognosis. This strongly recalls the dramatic course of favism in which the hemolytic episodes may be fatal.

SUMMARY

Two severe hemolytic crises, in a month's period, were induced by primaquine in a glucose-6-phosphate dehydrogenase deficient Sardinian male.
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Young red blood cells tagged with Fe$^{59}$ 10 to 16 days earlier were destroyed in the second hemolytic episode.

The implications of these experiments on the nature of drug-induced hemolysis in Caucasians are briefly discussed.

SUMMARIO IN INTERLINGUA

Duo sever crises hemolytic esseva inducite intra un mense in un sardiniano mascule a carentia de dehydrogenase de glucosa-6-phosphato per le administration de primaquina. Juvene erythrocytos marcate con Fe$^{59}$ inter 10 e 16 dies previamente esseva destruite in le secunde episodio hemolytic.

Es discutite brevemente le signification de iste experimentos pro le clarification del natura de hemolyse pharmacogene in caucasianos.

REFERENCES


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