VINCRISTINE SULPHATE INDUCED ECTODERMAL DYSPLASIAS IN CHICK EMBRYOS

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Two hundred and forty nine eggs of the white leghorn were injected on day 3, 4 and 5 of their incubation, with 0.03 mg/kg egg weight, of vincristine sulphate. Most embryos were removed 24, 48 and 72 hours after administration and examined histologically. A few eggs were opened on day 18 of incubation. The results of this study indicate that the drug is embryo-lethal in a majority of chicks, and those that survive the toxic effects of vincristine show pronounced neuro/ectodermal dysplasias. Malformations of the neural tube and neural crest with depigmentation of the feathers and their loose anchoring were observed. The possible mechanism of these dysplasias is discussed.

Key Words : Vincristine, Chick embryos, Neurotoxicity, Ectodermal dysplasias.

Hypopigmentation and depigmentation of the skin is caused by a wide variety of drugs.[1] Chemical agents have also been known to cause alopecia.[2] In this study, we chose an ectodermal toxic drug, vincristine sulphate, an anti-mitotic agent used in leukemias.[2] The effect of the drug on the developing ectodermal system was observed in the chick embryos, as the derivatives of the avian ectoderm are highly differentiated.[3] The neurotoxic effect of the drug was also concurrently followed, since the surface ectoderm and neuro-ectoderm closely interact developmentally in the early embryogenesis of vertebrates.[4]

Materials and Methods

Fertilized eggs of the white leghorn, obtained from the Government poultry farm were incubated from '0' hours at 37-38° C. in a 75% relative humidity. All eggs were turned over thrice daily.

Three hundred and thirty six eggs were used in different groups. Two hundred and forty nine eggs were drilled using a fine dissection needle; vincristine sulphate in a dose of 0.03 mg/kg was injected through the shell using a tuberculin syringe. One milligram of the drug was dissolved in 10 ml distilled water for the injections. The maximum volume of injected fluid was kept below 0.04 ml. The eggs were paraffin sealed and allowed to incubate. Uninjected and water injected controls were run in all series. Eighty two eggs were injected on day 3 of incubation, seventy nine on day 4, and eighty eight on day 5. Eighty seven eggs were kept as controls.

The eggs were opened at 24, 48 and 72 hours after injection. All the embryos were observed grossly and compared with controls. A few treated specimens were fixed in Bouin's fixative and processed histologically. Eggs which showed viability after day 3 of injection were incubated till day 18, when they were broken under-water. Skin sections were made in the 18-day-old embryos and whole mounts of floplumes were also prepared.

Results

Ninety five per cent of all embryos were found dead showing the high embryo-lethality of vincristine sulphate. Transverse sections of these early embryos showed neural tube malformations, and ventral neuroaxial defects. The viable 18-day chick embryos were grossly underweight and hypomorphic for age. Their plumage was a remarkable dull white or grey.

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The feathers were shed even on light touch or underwater immersion. Depigmentation and loose anchorage of the plumage were seen in all injected specimens. Besides these ectodermal anomalies, the embryos had rotational deformities of the limbs. The dysmelias included ectrodactyly. Skin sections histologically showed erosion of the keratin layer and hypoplasia of the floplume end bulb papilla. Excepting size, no morphological changes were seen in whole mounts of the floplumes.

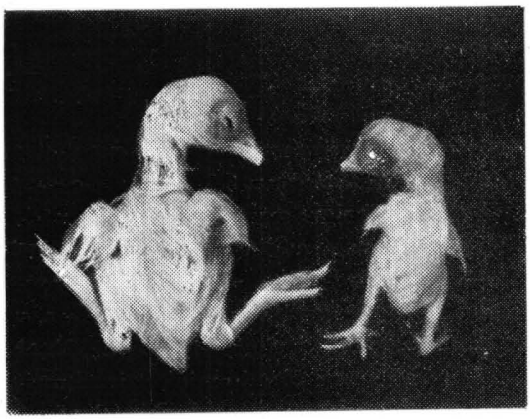

Fig. 1. Vincristine sulphate treated specimen on the right showing sparse plumage, dull colour, limb rotational deformity with ectrodactyly and low weight with hypomorphism. (Control on the left).

Comments

Vincristine sulphate is known to produce alopecia in man.[2] Neurotoxic effects of the drug have also been recorded.[5,7] The drug interferes with the cytoskeletal elements,[8] microtubules, and prevents cell shape and size alterations. It also impedes axoplasmic flow.[7] Mitotic inhibition in the rapidly proliferating neural cells causes the neural tube defects. Melanoblasts which are of neural origin, invade the dermis at an early but undetermined embryonic stage and undergo a complex process of differentiation[10] to form the pigmentary melanocytes. The long processes[11] of these melanocytes reach the feather roots and colour them. Vincristine disturbs these mechanisms at two levels, (1) at the neural level impeding the axoplasmic flow in the melanocytic processes, and (2) by causing erosion of the keratin layer. These effects manifest as the dull colour of feathers and also in their loose anchoring. The control specimens showed golden yellow feathers which were firmly rooted.

Modifications of the stratum corneum layers produces ectodermal derivatives like feathers.[9,11] Vincristine by thinning out the beta keratin layer probably effects the plumage colour and hold. The complex interaction between mesoderm and surface ectoderm in normal limb development, especially at the apical ectodermal ridge, is possibly disturbed by vincristine sulphate, leading to dysmelias like malrotation and ectrodactyly.

The wide range of the toxic effects of the drug on the chick embryo closely simulate those seen in the vincristine treated patients. Given in early embryonic life of the chick, the drug induces gross hypomorphism, low weight and neural tube malformations besides ectodermal dysplasias.

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