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The Toxicity Effect of Vincristine at During Pregnancy in Newborn Mice

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Abstract: Vincristine is an alkaloid derived from *Vinca rosea* that its mechanism is to stop the mitosis cell cycle. Therefore, this drug is used in chemical treatment with high multiplication as ovarian cancer, cervical cancer and mammary cancer. This drug can have teratologic effects on fetus. But there is not enough information about pregnant women. Therefore, researchers have been tried in this study to evaluate the toxic effects of this drug in pregnant women on the newborn infants. In this study, researchers choose 40 pregnant mice and sampling units consists of the newborn infants. Firstly, the female mice have been placed near male mice and after observing the vaginal plaque, pregnant mice's were divided randomly into 2 groups as control and experimental. Mice's of the experimental group were injected by vincristine (3 mg kg^{-1}-IP) on day 10th and 16th of gestation. The control group received distilled water. After parturition, the newborn infants were evaluated by the parameters of external morphology anomaly and the data was evaluated by t-test test and SPSS Software. The analysis of the statistics showed that the use of vincristine at during pregnancy on the newborn infants was teratologic effects. In comparing the average of the parameters in the experimental group with control group, there was significant difference ($p<0.001$).

Key words: Pregnancy, teratology, vincristine, experimental group, significant

INTRODUCTION

Vincristine is a vinca alkaloid from the *Catharanthus roseus* (*Madagascar periwinkle*), formerly *Vinca rosea* and hence its name. It is a mitotic inhibitor and is used in cancer chemotherapy. Vincristine is created by the coupling of indole alkaloids vindoline and catharanthine in the vinca plant (Graf *et al*., 1996). Tubulin is a structural protein that polymerizes to microtubules. The cell cytoskeleton and mitotic spindle, among other things are made of microtubules. Vincristine binds to tubulin dimers, inhibiting assembly of microtubule structures. Disruption of the microtubules arrests mitosis in metaphase. Therefore, the vinca alkaloids affect all rapidly dividing cell types including cancer cells but also those of intestinal epithelium and bone marrow. Vincristine is delivered via intravenous infusion for use in various types of chemotherapy regimens. Its main uses are in non-Hodgkin's lymphoma as part of the chemotherapy regimen CHOP, Hodgkin's lymphoma as part of MOPP, COPP, BEACOPP or the less popular Stanford V chemotherapy regimen in acute lymphoblastic leukemia and in treatment for nephroblastoma (Wilms tumor, a kidney tumor most common in young children). It is also used to induce remission in all with Dexamethasone and L-Asparaginase. Vincristine is occasionally used as an immunosuppressant for example in treating Thrombotic Thrombocytopenic Purpura (TTP) or chronic Idiopathic Thrombocytopenic Purpura (ITP). It is used in combination with prednisone to treat childhood leukemia.

The main side-effects of vincristine are peripheral neuropathy, hyponatremia, constipation and hair loss. Peripheral neuropathy can be severe and hence a reason to avoid, reduces or stops the use of vincristine. One of the first symptoms of peripheral neuropathy is foot drop: A person with a family history of foot drop and/or Charcot-Marie-Tooth disease (CMT) may benefit from genetic testing for CMT before taking vincristine (Qweider *et al*., 2007).

Accidental injection of vinca alkaloids into the spinal canal (intrathecal administration) is highly dangerous with a mortality rate approaching 100%. The medical literature documents cases of ascending paralysis due to massive encephalopathy and spinal nerve demyelination, accompanied by intractable pain, almost uniformly leading to death; a handful of survivors were left with devastating neurological damage with no hope of recovery. Rescue treatments consist of washout of the cerebrospinal fluid and administration of protective medications (Johnson *et al*., 1963). A significant series of inadvertent intrathecal vincristine administration occurred in China in 2007 when batches of cytarabine and methotrexate (both often used intrathecally) manufactured by the company Shanghai Hualian were found to be contaminated with vincristine (Qweider *et al*., 2007; Graf *et al*., 1996). Therefore, in this study, researchers have tried to evaluate the teratologic effects of the drug on newborn infants with an overdose prescription of the drug during pregnancy.

Fig. 1: The injection of the drug to pregnant mice

MATERIALS AND METHODS

The data consisted of 20 pregnant female mice with a sample group of 48 infants. First of all the female mice were placed near the male ones. Also, the plaques were observed in vagina (Noakes *et al*., 2001). The female pregnant mice were divided into two experimental and control groups at random. Due to high sensitivity to teratology in organogenesis period (Hodgson, 2004), the experimental group took 3 mg kg^{-1}, I.P (Adamson *et al*., 1965; ASHP, 1990; Hellmann *et al*., 1987) of vincristine on the tenth and fifteenth of their pregnancy. The new-born infants were evaluated according to extend morphologic examination parameters (ASHP, 1990; Barana *et al*., 2006; Ebert *et al*., 1997; Zhang *et al*., 2007) (Fig. 1) and were statistically evaluated (Zhang *et al*., 2007; Barana *et al*., 2006) in terms of t-test as well as SPSS Software.

RESULTS AND DISCUSSION

The drug-injection process of vincristine was performed in both experimental as well as control on the 19th and 20th of pregnancy. No significant changes were observed in the duration of pregnancy as well as the behavior of female mice. In the observed samples, there were new-born live infants in the control group as well as live and dead infants in the experimental group (Fig. 2).

The teratologic effect of the drug was significantly observed in the experimental group and the external morphologic effects was detected in terms of quality parameters number of litters, anencephaly, survived newborns, dead newborns, dead number of pregnant mice, examined, tail defect, cleft palate, pregnant mice, degenerative change, eye defect and abortion (Table 1). External morphologic observations in control group infants (Fig. 1).

To evaluate the groups statistically, researchers gathered some statistical variables (such as the length of body, the length of head, the length of tail, the length of foot, the width of head and weight) were gathered in both groups (Fig. 2-7) which showed a significant relation between means of two groups ($p<0.001$) (Table 2).

Table 1: External morphologic examination of newborn of experimental group

Alternations	Vincristine (3 mg kg^{-1}, I.P)
Number of litterers examined (N/N)	48
Number of pregnant mice (N/N)	10
Dead pregnant mice (N/N)	1/10
Dead newborns (N/N)	25/48
Survived newborns (N/N)	13/48
Anencephaly (N/N)	3/48
Cleft palate (N/N)	0/48
Degenerative change (N/N)	1/48
Tail defect (rudimentary) (N/N)	30/48
Tail defect (kinky) (N/N)	1/48
Eye defect (anophthalmia) (N/N)	4/48
Abortion (N/N)	1/10

Vincristine is an alkaloid derived from *Vinca rosea*. The functioning mechanism of this drug includes the following: depolymer of microtubules that are a vital part of the cellular skeleton as well as spindle division of cell mitoses this drug stops mitosis cycle (ASHP, 1990; Ungthavorn and Joneja, 1969). The drug is used for cancerous cells with high multiplication rate. The medication uses of this drug are as follows: brain tumors, breast cancer, cervical cancer, ovarian cancer and so on (Johnson, 1968). Vincristine has the capacity of penetration from the blood-fetus blocks so that it has a high negative effect on the maturation of the fetus (Joneja and Ungthavorn, 1969). This drug may also have teratogenic effect on the fetus however an over all information about pregnant women is not available yet (ASHP, 1990).

The result of the study reveals that vincristine usage has taratologic effects on the fetus as well as clinical effects. The study also accords with studies based on the penetration of the drug through blood-fetus and the cause of birth defects (Joneja and Ungthavorn, 1969; Jacqz-Aigrain and Koren, 2005; Hodgson, 2004; Sadler, 2000). Beside, in statistical analysis there was detected a meaningful relation between the variants of control and experimental groups. The toxic effects of this drug were also show to be irreversible like other teratology drugs (Ebert *et al*., 1997). Dorr *et al*. (1988) showed both time and dose-dependent decrements in ATP/protein ratios 72 h following exposure to DOX at concentrations >0.1 μg mL^{-1}. Leakage of lactate dehydrogenase activity, trypan blue uptake and myocyte beating rates were variable and not as sensitive as ATP levels for evaluation of myocyte viability. Other cytotoxi agents which are not known to be cardiotoxic (dactinomycin, 1-beta-D-arabinofuranosylcytosine, fluorouracil, melphalan and vincristine), required extremely

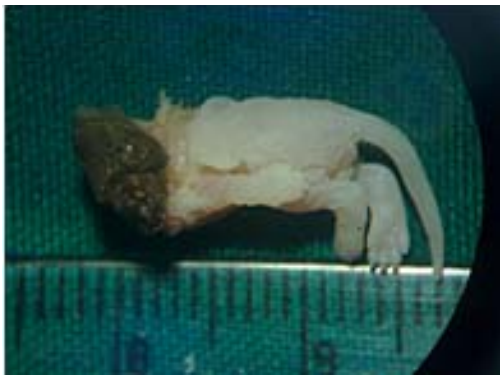

Fig. 2: Live and malformed infants in experimental group

Fig. 3: Aborted infants forms a female mouse in experimental group

Fig. 4: A malformed infant from experimental group

high concentrations to produce myocyte damage *in vitro*. Tests with anthracycline analogues also demonstrated the ability of the assay to rank-order cardiotoxic agents on a weight basis: idarubicin greater than DOX greater than daunomycin greater than aclarubicin. When the *in vitro* drug concentrations required to lower ATP/protein ratios to 50% of controls were related to clinically achievable

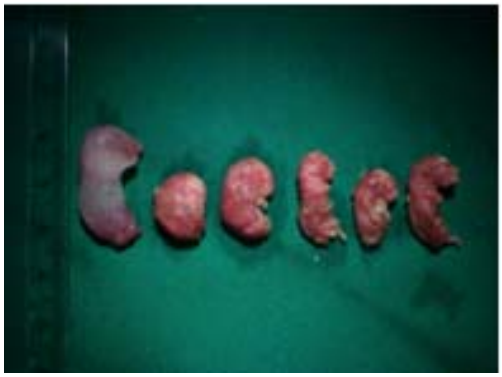

Fig. 5: Tale-malformed infants from experimental group

Fig. 6: A head-mal formed infant from experimental group

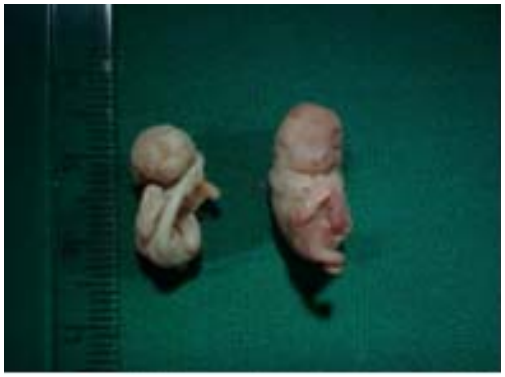

Fig. 7: A live infant from control group

Table 2: The toxicity effect of vincristine at during pregnancy on the incidence of external malformation of newborn mice

Parameters (mean±SEM)	Control	Experimental	p-vlue
Litter weight (g)	1.63±0.04	0.97±0.04	0.001
Litter length (mm)	24.76±0.51	19.97±0.65	0.001
Foot length (mm)	6.8±0.110	5.49±0.10	0.001
Tail length (mm)	12.54±0.13	10.54±0.25	0.001
Head length (mm)	10.56±0.26	9.13±0.18	0.001
Head wide (mm)	7.77±0.13	6.79±0.11	0.001

The mice received (3 mg kg^{-1}-IP) days 10th and 16th of pregnancy. *Significant values in relation to control group ($p<0.001$)

concentration x time products, DOX and daunomycin proved to be the most cardiotoxic in this series. Their results suggest that comparative cardiotoxic screening studies may be performed in vitro using ATP levels in beating neonatal myocytes.

King and Boder (1979) demonstrated that vincristine at a dose as low as 0.004 μg mL^{-1} affects the cells with processes in cultures of dissociated newborn rat midbrain.

In 3 days old cultures after 24 h of drug treatment there is a loss of processes and swelling of the cell body. They have used this observation as the basis for a quantitative assay of the toxicity of a series of vinca compounds and have found that for a dose range of 0.1-0.004 μg mL^{-1} the relative toxicity of vincristine, vinblastine and vindesine in this system correlates with their relative clinical neurotoxicity. They concluded that validation of the predictive elements of this system awaits clinical experience with novel vinca compounds. It is strongly advised that patients suffering cancer never use the drug event in low dose during pregnancy as well as feeding period.

CONCLUSION

The results show that treat vincristine is teratologic effect on fetus and is accompanied by clinical manifestations. Effects of this drug are considered as an un-returnable effect on fetus. However, taking this drug for cancerous patients during pregnancy and lactation for women is not recommended.

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