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Spinal cord damage in Zalcitabine maternally treated mice fetuses

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ABSTRACT

The present article explores the impacts of the anti-Aids drug (Zalcitabine) on the histological structure and morphometric analysis of the spinal cord of 14-day old mice fetuses. Pregnant mice received two oral concentrations of Zalcitabine (600 and 1000 mg/kg) for five consecutive days (from day 9 to day 13 of gestation). The histological structure of spinal cord in 14 day old control fetuses revealed an outer marginal layer (white matter), an inner mantle layer (grey matter), and a central neural canal. The spinal cord of fetuses of mothers fed the low dose of the drug was either slightly affected or did not show any change relative to the controls. On the other hand, the high dose treatment was found to produce a significant decrease of spinal cord diameter, great morphometric variations as well as several histopathological changes. Cellular disorientation of the neuroepithelium and distortion of the neural canal were the most frequent anomalies encountered.

KEYWORDS: anti-aids drug, mice fetuses, neural canal, neuroepithelium.

INTRODUCTION

The nucleoside analogue, Zalcitabine (2'-3'-dideoxycytidine) is a potent antiretroviral agent that was approved for treatment of acquired immune deficiency syndrome (AIDS) caused by infection with human immunodeficiency virus (HIV). It is phosphorylated to its active metabolite -2',3'-dideoxycytidine 5'-triphosphate (ddCTP)- within both uninfected and HIV-infected cells (Jeffries 1989). At therapeutic concentrations, ddCTP inhibited HIV replication by inhibiting the enzyme reverse transcriptase and terminating the elongation of the proviral DNA chain (Adkins *et al.* 1997). Because of its effective role in Aids treatment, the biology of Zalcitabine was extensively characterized from a toxicological viewpoint. In this concern, several observations suggested a relatively low cytotoxicity of Zalcitabine *in vitro* (Chen & Cheng 1989; Toltzis *et al.* 1994; Monte *et al.* 1997). However, other studies indicated that Zalcitabine treatment induced neurotoxicity in rabbits (Anderson *et al.* 1992; Feldman & Anderson 1994), carcinogenicity in mice (Rao *et al.* 1996) and a dose limiting peripheral neuropathy in humans (Dalakas 2001).

In spite of dideoxynucleosides such as 2',3'-dideoxycytidine (ddC), 3'-deoxy-3'-azidothymidine (AZT), 2',3'-dideoxyinosine (ddI), and 2',3'-didehydro-3'-deoxythymidine were approved for use in the general population. The administration, the efficacy, and the toxicity of these compounds during pregnancy and development are now being investigated (Newshan & Hoyt 1998 and Kass *et al.* 2000). Initial human studies showed that maternal use of ddC, AZT, and ddI resulted in fetal exposure to these drugs since they rapidly cross the placenta by simple diffusion (Sandberg & Slikker 1995).

In the literature the data on Zalcitabine included, among other studies, a developmental toxicity study in C57B1/6N mice (Lindström *et al.* 1990), embryological and cytogenetical studies in NMRI mice (Mobarak 1995; Banhawy *et al.* 1996a,b), a biochemical study on the short-term cardiac side effects on rat embryos (Skuta *et al.* 1999), as well as an *in vivo* study of its effect on the developing heart of mice fetuses (Mobarak 2001). Therefore, the study in this paper was conducted to collect supplementary information about the possible damaging effect of this anti-Aids drug on the spinal cord of mouse fetuses.

MATERIALS AND METHODS

Fertile Swiss albino (NMRI) female mice aged 6-8 weeks and weighing 24-28 grams were kept (each two females with one fertile male/cage) in a controlled environment, at temperature of 22°C and 50-60% humidity with a dark/light cycle of 12 hours, and were allowed free access to food and water. The plug day was denoted as "day 0" of gestation.
The experimental drug (Zalcitabine) was purchased from Fluka Feinchemikalien GmbH, New-Ulm, Germany with a purity exceeding 98%.
The pregnant mice were given either vehicle or two doses of Zalcitabine (600 mg or 1000 mg/kg b.wt.) suspended in 0.5% aqueous methyl cellulose by oral gavage, from day 9 to day 13 of gestation. The election of these doses was based on the observation of Luster *et al.*. (1989) who found that 600 mg Zalcitabine/kg as a single dose, for one month, did not alter the survival rate or body weight of mice. Both control and Zalcitabine treated animals were sacrificed by cervical dislocation on the morning of day 14 of fetal life.
Sixty two fetuses of control and treated animals (externally normal and malformed fetuses) were randomly selected and fixed in Bouin's solution for 48 hours, washed in 70% ethanol, dehydrated, cleared in xylene and infiltrated with the embedding medium (a mixture of equal volumes of parablast and paraffin wax). Transverse serial sections of the whole fetuses (from the neck region to the beginning of the tail) were prepared, stained in haematoxylin and eosin, cleared with xylene and mounted in neutral canada balsam. Then the spinal cords of these fetuses were carefully examined with the light microscope, described, and illustrated by microphotographs.
Morphometry: The morphometric analysis of the spinal cord were based on measurements of diameter in serial sections, in control as well as in maternally treated fetuses. Measurements were made with an eye piece micrometer connected to the light microscope. They were taken every eighth section of the prepared specimens (along body length, from the neck region to the beginning of the tail). Three measurements were recorded for each section, two horizontals and one mid-vertical. The exact diameter of the spinal cord was estimated as the mean of horizontal and mid-vertical diameters. The significance of these measurements was evaluated by using the Student t-test.

RESULTS

Spinal cord of control fetuses: Figure (1a) illustrates the histological appearance of the spinal cord on day 14 of mouse prenatal development. It is composed of an outer marginal layer (white matter), an inner mantle layer (grey matter) and a central neural canal. The marginal layer exhibited a faintly stained appearance than that of the mantle layer. The later layer showed a characteristic butterfly shaped configuration of two wide dorsal horns and two relatively narrower ventral ones. The mid-dorsal and mid-ventral parts of the spinal cord showed two slight depressions. In the control fetuses, the lumens of the spinal cords (the central neural canals) had approximately similar morphological appearance, an inverted pear-shaped throughout its length from the neck region to the beginning of the tail. The spinal cord of these fetuses was surrounded externally by outer loose connective tissue zone (dura matter) rich in blood supply and mesenchyme cells. This zone was bounded by an external limiting membrane (the basement membrane) to which a thin layer of pia cells was attached. Pia cells were squamous in shape, contained long flattened nuclei and blood corpuscles were frequently seen among them as designated in Figures (1b,c & 2a).
The lumen of the spinal cord (the neural canal) was lined by a thin internal limiting membrane upon which a layer of neuroepithelial cells, called the ependymal layer or neuroepithelium, was resting. The boundaries of individual neuroepithelial cell were indistinguishable. These

cells gave a roof plate and a floor plate at the top and at the bottom of the central canal, respectively. The nuclei of the ependymal cells were of the granular type, arranged at different distances from the lumen and took elongated or oval shapes. The psuedostratified arrangement of the nuclei gave the neuroepithelium a condensed appearance. Different mitotic figures were mainly observed adjacent to the central canal and occasionally in the innermost cells of the grey matter as represented in Figures (1a,b & 2b).

The mantle layer was formed of cells migrating out the neuroepithelium to form a loose layer of three types of nerve cells, namely the neuroglia cells (astrocytes), the neuroblasts and a few neurons. The astrocytes had elongated granular nuclei, similar to those of the neuroepithelium, and 1-3 peripheral nucleoli while the neuroblasts contained rounded to oval shaped nuclei larger in size and less granular than those of the neuroepithelium. The few neurons observed were found mainly in the ventral horns (Figures 1b & 2a,b).

The outer marginal layer of the spinal cord consisted of numerous cytoplasmic processes that grown out from the neuroepithelium. In addition, a few nueroglia cells, neuroblasts and neurons were seen among the cytoplasmic processes of the marginal layer as marked in Figures (1c & 2a).

No signs of morphological changes were detected in the spinal cord of control fetuses. Also, the differences in the mean diameter of the control spinal cord, in different body regions, were not statistically significant. Therefore, the mean diameters measured from the neck to the beginning of the tail were taken as the exact diameter. This mean diameter was 2.5 ± 0.2 mm as shown in Table (1).

Spinal cord of maternally treated (600 mg Zalcitabine/kg b.wt.) fetuses: A slight histological change was observed in the spinal cord of 5% of fetuses their mothers received the low dose of Zalcitabine.This change is represented by a delay of spinal cord development in which the neural canal took a slit shape (Figure. 3a). On the other hand, the mean diameter, 2.4± 0.04 mm, of the spinal cord was slightly -but insignificantly- decreased than control (P>0.05) as illustrated in Table (1).

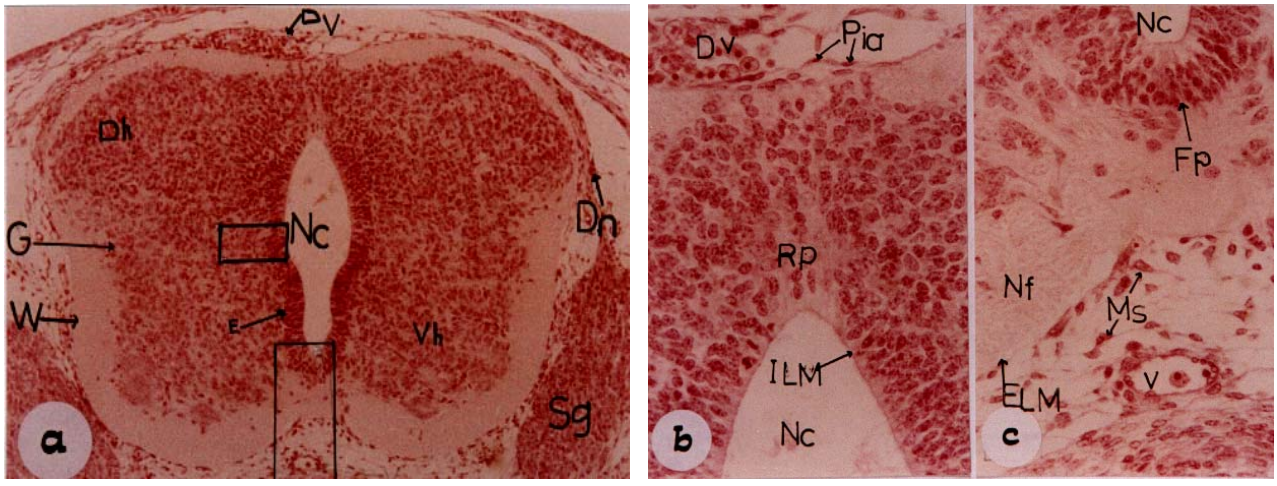


Figure 1 (a - c). Transverse sections of the spinal cord of a 14-day old control mouse fetus.

a: The general structure of the normal spinal cord (X 100).

b: Higher magnification of the mid-dorsal part shown in Figure 1a displays the psuedostratified character of the ependymal cells, a part of the neural canal, internal limiting membrane, the roof plate and pia matter. (X 400)

c: A magnified part (in the large rectangle) of Figure 1a showing the floor plate, external limiting membrane, nerve fibers and mesenchymal cells. (X 400)

Abbreviations : Dorsal vein (Dv), dorsal horn (Dh), grey matter (G), white matter (W), ependymal cells (E), neural canal (Nc), ventral horn (Vh), dorsal neuron (Dn), spinal ganglion (Sg), pia matter (Pia), roof plate (Rp), internal limiting membrane (ILM), floor plate (Fp), nerve fibers (Nf), ventral vein (V), external limiting membrane (ELM) and mesenchyme (Ms).

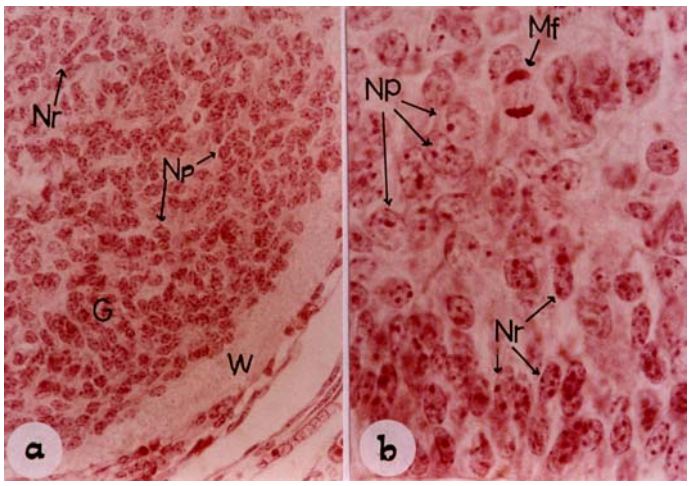


Figure 2 (a, b).
a: A magnified part of the left dorsal horn of Figure 1a shows the cellular components of the grey and white matters. (X 400)
b: A high magnification of a part (in the small rectangle) of Figure 1a displays the nuclear components of the neuroglia cells and neuroplasts. (X 1000)
Key: Neuroglia cells (Nr), neuroplasts (Np) and mitotic figure (Mf). Rest of key as in Figure (1).

Spinal cord of maternally treated (1000 mg Zalcitabine/kg b.wt.) fetuses: This mode of treatment evoked the value of 59.1% of fetuses with spinal cord abnormalities. Table (1) shows that the mean diameter of the spinal cord for this group was significantly ($P<0.05$, versus control) decreased to 2.1±0.1 mm.

In most fetuses, the spinal cord lost its normal morphology and exhibited a more or less square (Figures 3b & 4a) or rectangular shapes (Figures 5a & 6a). Also, the horn like structure was absent in the majority of spinal cords due to cellular disorganization in the mantle layer. The shape of the marginal layer was highly dependent on the changes of the mantle layer cells as well as the distortion degree of the neuroepithelium. On the other hand, the inverted pear-shaped structure of the normal neural canal was severely damaged and showed great morphological variations in all affected fetuses. Such spinal cord malformations were seen most frequently in the lumbo-sacral and then cervical regions.

In some cases, the neural canal was more or less closed where the lateral parts of the inner limiting membrane of the neuroepithelium were closely applied or completely fused, as marked in Figures (3b-d). Enlargement of the neural canal associated with downgrowths of the neuroepithelial cells was frequently observed. In such cases the neuroepithelium was thin and there was a large degree of cellular disorientation, with irregular tissue projecting into the lumen of the spinal cord, as designated in Figures (4a,b; 5a & 6a). The neuroepithelial cells of these spinal cords were less densely packed than in control and their nuclei were often in close apposition to the internal limiting membrane. Moreover, the majority of these cells were darkly stained with condensed chromatin material in their nuclei, while others were fragmented, and many dark particles became distributed throughout the neuroepithelial layer and roof plate area, as marked in Figures (4c,d & 6b,c). The mitotic figures were not visible at the lumen margin of the neuroepithelium and they were scarcely observed in the mantle layer. Cell death and necrosis were frequently seen in the dorsal and ventral horns and roof plate cells. On the other hand, the other mantle layer cells were loosely packed and in some cases their nuclei became much smaller and darker than in controls, as represented in Figures (4d, 5b & 6c). In some fetuses, these lesions were accompanied by extensive cystic and haemorrhagic changes (Figure 6a-c). These results thus indicate that Zalcitabine may exert its teratogenic effects by inducing fetal hypoxia, leading to vascular disruption and necrosis of existing and developing structures.

Table 1: Effect of Zalcitabine on the spinal cord of 14-days old mice fetuses. Animals were treated with 600 or 1000 mg Zalcitabine/kg from 9-13 days of gestation. °P> 0.05 and *P< 0.05 versus control (Student t-test).

Animal Group	Number of fetuses examined	% of fetuses with abnormal spinal cord	Mean diameter of spinal cord ± S.D (mm)
Control	20	0	2.5 ± 0.2
Treated (600mg/kg)	20	5	2.4 ± 0.04°
Treated (1000mg/kg)	22	59.1	2.1 ± 0.1*

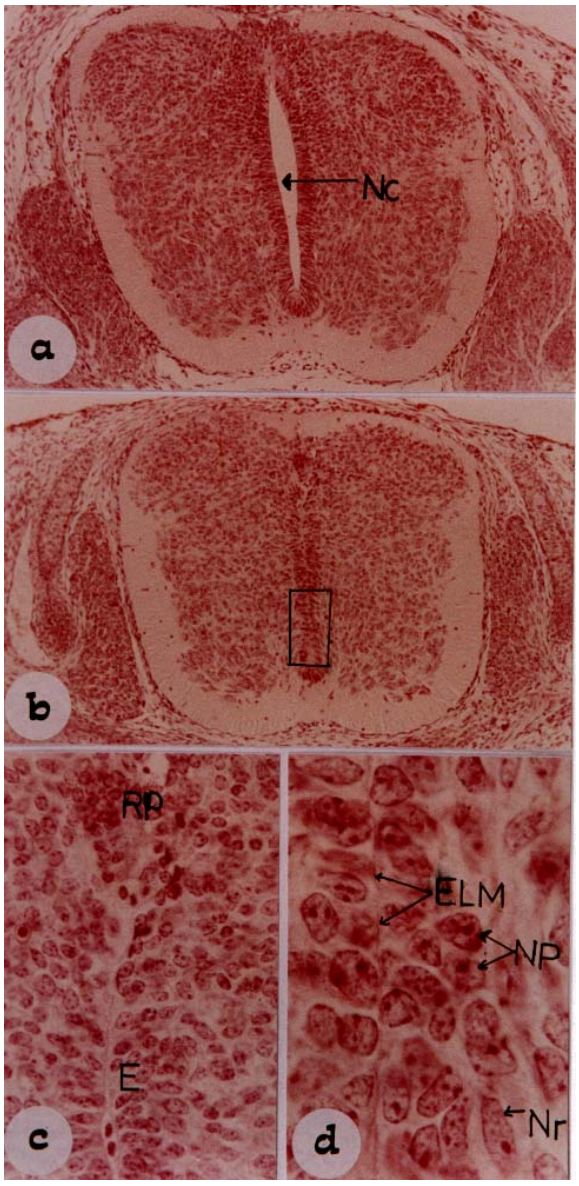


Figure 3 (a – d).
a: A transverse section of a spinal cord from a maternally treated (600 mg Zalcitabine /kg) fetus showing elongation of the neural canal **(X 100).**
b: The spinal cord of a maternally treated (1000 mg Zalcitabine/kg) fetus shows absence of the neural canal **(X 100).**
c: Higher magnification of the mid-dorsal part shown in Figure **3b** displays the roof plate cells disorganized, some necrotic cell (arrows) and fused internal limiting membrane **(X 400)**.
d: A magnified part (in box) of Figure **3b** shows irregularity of ependymal cells, fusion and sometimes absence of the internal limiting membrane and cytoplasmic clearance (arrows) **(X 1000)**. Key as in Figures 1&2.

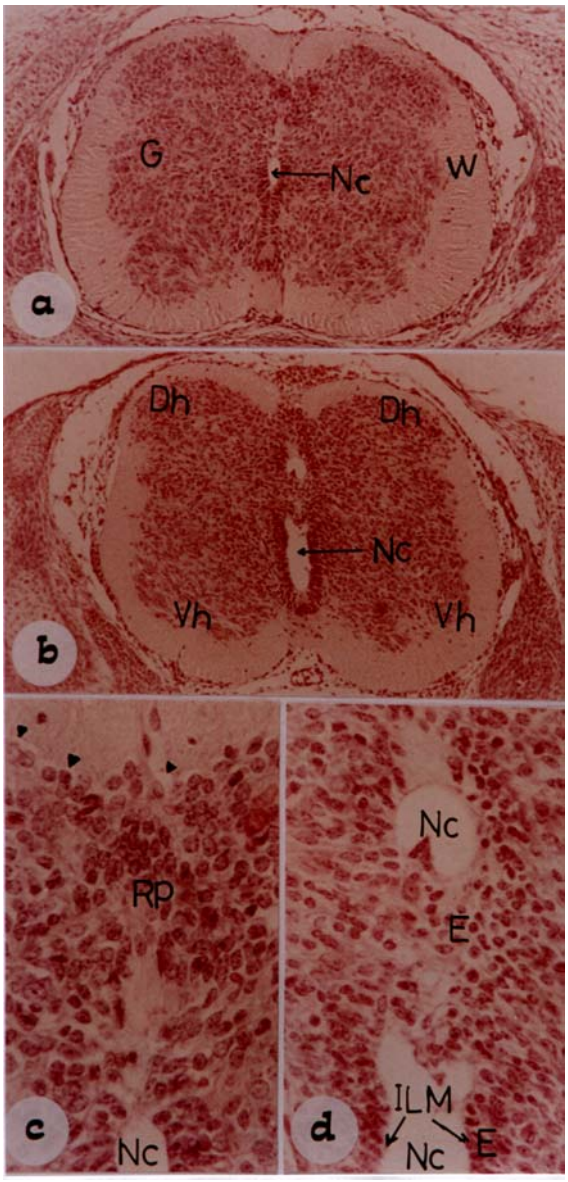
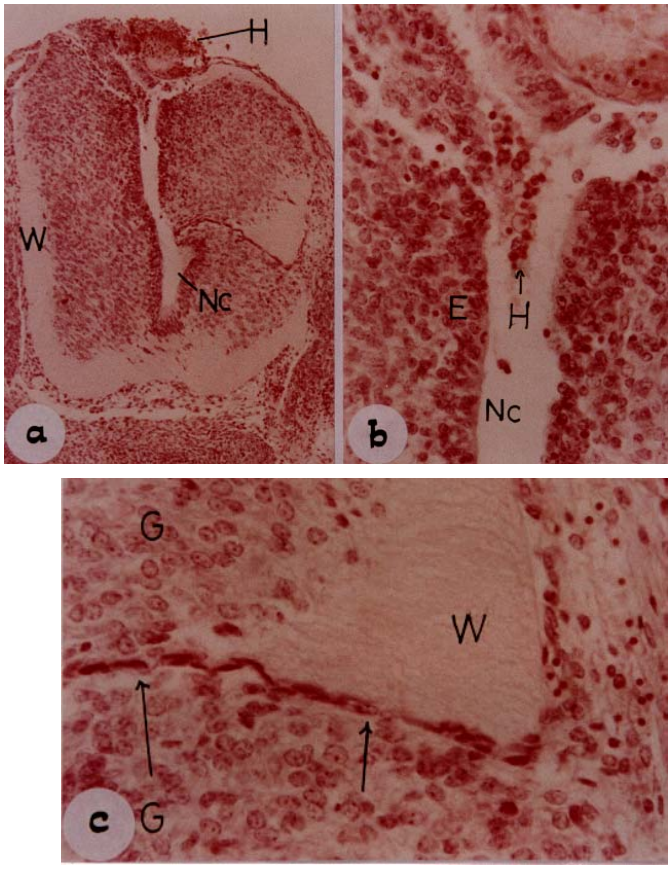
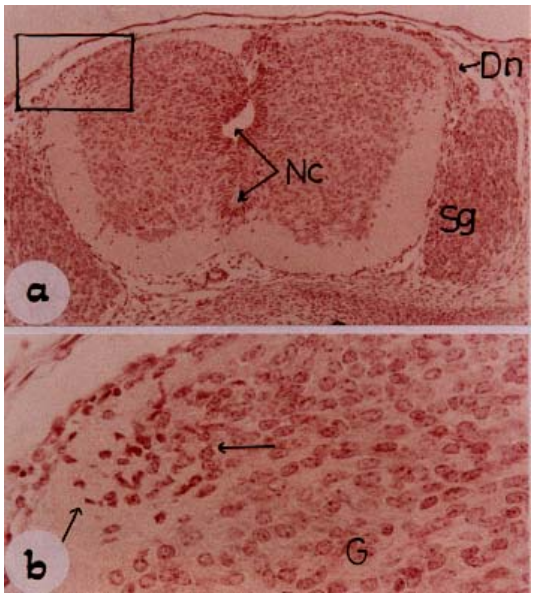


Figure 4 (a - d).
a: A more or less rectangular shaped spinal cord, from a maternally treated (1000 mg Zalcitabine/kg) mice fetus, has a very small neural canal. **(X 100)**
b: Spinal cord of another maternally treated (1000 mg Zalcitabine/kg) fetus exhibited a square shape and the central canal is distorted by downgrowths of the neuroepithelial cells **(X 100).**
c: Higher magnification of the mid-dorsal part shown in Figure **4a,** exhibits disorganization of roof plate cells and a discontinuity between the white matter nerve fibers and the cells of the grey matter (arrow heads).
(X 400)
d: A magnified part of the neural canal shown in Figure **4b,** displays partial closure of the canal by downgrowths of ependymal cells. These cells are highly disorganized, vacuolated and the nuclei are pyknotic. **(X 400)**

Figure 5 (a, b). →
a: A transverse section of a maternally treated (1000 mg Zalcitabine/kg) fetus showing a rectangular shaped spinal cord with deformed central neural canal. (X 100)
b: A magnified part of (in box) Figure 5a shows that many cells of the grey matter are disorganized while others exhibiting necrosis (arrows). (X400)





← Figure 6 (a-c).
a: A highly damaged spinal cord, of a maternally treated (1000 mg Zalcitabine/kg) fetus, exhibiting extensive hemorrhage (H) and damaged neural canal. (X 100)
b: Higher magnification of the mid-dorsal part shown in Figure 6a, displays excessive hemorrhage, cell death and necrosis, damaged internal limiting membrane and elongated neural canal. (X 400)
c: Higher magnification of the middle part of the left side of Figure 6a shows the replacement of a grey matter part with another of the white matter and a thin layer of dead cells separating them (arrows). (X 400)

DISCUSSION

The described histological structure of the spinal cord, of 14-days old control mice fetuses, was quite similar to the observations suggested previously by Rugh (1990) on the laboratory mouse. Previous studies on mouse fetuses showed that Zalcitabine was a strong teratogenic compound that produced *in vivo* developmental toxicity including external and endoskeletal malformations, reduced fetal body weight and length, resorptions and *in vitro* chromosomal aberrations (Mobarak 1995). It was also found that Zalcitabine caused histological and ultrastructural changes of prenatal mouse ovaries and damage to the developing heart (Banhawy *et al.* 1996 a,b and Mobarak 2001 respectively). In the present study, the spinal cord of fetuses exposed to the lower dose of Zalcitabine showed either a slight alteration or did not show any change relative to the controls. Moreover, the mean diameter of the spinal cord was insignificantly decreased comparable to controls. These findings confirm previous reports both *in vitro* (Benbrik *et al.* 1997) and *in vivo* (Mobarak 2001) that Zalcitabine treatment produce teratogenic effects and cytotoxicity in a dose-dependent manner.
However, the higher concentration of Zalcitabine caused severe changes in the spinal cord of the same age (14-days) fetuses. Generally, there was a rise in the percentage of fetuses exhibiting spinal cord damage as well as a significant incidence in the decrease of spinal cord diameter. These results could be attributed to the teratogenic effect of Zalcitabine, on the

development of the spinal cord of these fetuses, during the selected period of treatment (from day 9-13 of prenatal life). This assumption is further supported by Nishimura & Tanimura (1976) and Rugh (1990) who suggested that on day 9 of mouse embryonic development, the closure of the anterior neuropore is followed by closure of the posterior neuropore on day 10 of gestation. In addition, they indicated that in 9-day old mice embryos, the neural tube and the heart are susceptible to the actions of teratogens.

In all affected fetuses, the inverted pear-shaped structure of the neural canal was severely distorted. This dysmorphology of the neural canal was similar to changes induced by zinc (Harding *et al.* 1988), zinc and vitamin A excesses (Joschko *et al.* 1989) and salicylic acid (Marion *et al.* 1993) in rat embryos.

The neuroepithelium was thinner than in controls. Neuroepithelial cells were less densely packed and there was a large degree of cellular death, necrosis and disorientation. Also, in the majority of these cells, the mitotic figures were absent or rarely observed. Such disturbances could be due to the property of Zalcitabine in producing cytotoxicity and inhibition of DNA synthesis after administration for five days. Spector *et al.* (1989) stated that the prolonged administration of either 2'-3'-dideoxycytidine or 3'-azido-3'-deoxythymidine *in vitro* was associated with significant toxicity. Also, Zalcitabine was designated by Mitsuya *et al.* (1987) to be an active inhibitor of DNA synthesis that may lead to different patterns of cytotoxicity and cell death. In addition, Cinalt *et al.* (1991) and Mobarak (2001) showed that Zalcitabine caused cytotoxicity, necrosis, and inhibition of cell division *in vitro* and *in vivo,* respectively. Zalcitabine interferes with early neurogenesis of the spinal cord, and therefore may be associated with abnormal neural tube closure, through its inhibition of cell proliferation and the subsequent delay of neural canal appearance. Furthermore, the neurotoxic effects of Zalcitabine has been found in rabbits (Anderson *et al.* 1992; Feldman & Anderson 1994) and in humans (Dalakas 2001).

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الملخص العربي

تشوه الحبل الشوكي في أجنة الفئران المعالجة بعقار ذالسيتابين

يُمن محمد شحات مبارك

قسم علم الحيوان ـ كلية العلوم ـ جامعة قناة السويس ـ الإسماعيلية - مصر

تناول البحث دراسة التركيب النسيجي والقياسات المورفومترية للحبل الشوكي في أجنة الفئران الصغيرة البيضاء، وذلك في اليوم الرابع عشر من التكوين الجنيني. كما استهدف البحث أيضا دراسة تأثير عقار ذالسيتابين المضـاد لفيـروس مرض الإيدز علي تكوين الحبل الشوكي لتلك الأجنة. وقد عولجت إناث الفئران بجرعتين مقـدارهما (600 أو 1000 مجم/كجم من وزن الجسم) لمدة خمسة أيام متتالية بدءاً من اليوم التاسع حتى اليوم الرابع عشر من بداية الحمل.

أوضحت النتائج ،من خلال دراسة مقاطع عرضية متتالية، أن التركيب النسيجى للحبل الشوكي في أجنـة المجموعـة الضابطة يتكون من طبقة خارجية تسمي المادة البيضاء وطبقة داخلية تسمي المادة الرمادية وقناة عصبية مركزية ذات شكل كمثري مقلوب. أما الحبل الشوكي للأجنة المعالجة أمهاتها بالجرعة المنخفضة من العقار لم تظهـر أي تغييـرات واضحة حيث تأثرت بدرجة طفيفة بالمقارنة بالمجموعة الضابطة. ومن ناحية أخري فان الجرعة المرتفعة مـن نفـس العقار قد تسببت فى إحداث نقصاً ذو دلالة إحصائية في متوسط نصف قطر الحبل الشوكي. هذا بالإضافة إلي إحـداث العديد من التغييرات المرفومترية والهستولوجية في تركيب الحبل الشوكي وكان من أهمها موت وتشتت خلايا الطبقـة الطلائية العصبية وتشوه القناة العصبية المركزية.