Toxicology Reports 2 (2015) 654–663

Contents lists available at ScienceDirect

Toxicology Reports

journal homepage: www.elsevier.com/locate/toxrep

# The teratogenic effects of imatinib mesylate on rat fetuses

M.M. El Gendy[a], A.M. Kandil[b], M.A. Helal[a,*], F.M. Zahou[c]

[a] Department of Zoology, Faculty of Women for Arts, Science & Education, Ain Shams University, Cairo, Egypt
[b] National Organization for Drug Control and Research, Giza, Cairo, Egypt
[c] ALJouf University, Sakaka, Saudi Arabia

ARTICLE INFO

*Article history:*
Received 14 January 2015
Received in revised form 4 May 2015
Accepted 4 May 2015
Available online 12 May 2015

*Keywords:*
Imatinib
Pregnant rat
Fetuses
Congenital deformities
Skeleton

ABSTRACT

Imatinib mesylate, a selective tyrosine kinase inhibitor, is the first line treatment against chronic myelogenous leukemia and gastrointestinal stromal tumors. The aim of the present study is to investigate the effects of imatinib mesylate on the pregnant rats and their fetuses. Pregnant rats were divided into three groups; the first group served as a control group. The second and third groups were orally administered imatinib at doses of 36 mg/kg body weight or 54 mg/kg b.wt. on gestation days (SDs) 6 through 13 or SDs 13 through 19, respectively. All animals were sacrificed on the 20th day of gestation. Treatment with imatinib caused a reduction of maternal body weight gain, uterine and placental weights, increased rate of abortion and fetal resorptions. High dose of imatinib caused fetal congenital deformities represented in harelip, contraction of the fore limbs, and paralysis of the hind limbs, exencephaly, encephalocoele and distended abdominal wall, besides occurrence of wavy ribs and absence of other ribs in addition to skeletal growth retardation and lack of ossification of the most skeletal elements. The present work concluded that imatinib is teratogenic when given orally to pregnant rats at 54 mg/kg b.wt. and causes direct maternal or developmental toxicity.



## 1. Introduction

Pregnancy and cancer are complex situations. The treatment of cancer during pregnancy is a difficult problem because of the potential effects of the therapy on the mother and fetus [1]. Cancer, known medically as a malignant neoplasm, is a broad group of various diseases, all involving unregulated cell growth. In cancer, cells divide and grow uncontrollably, forming malignant tumors, and invade nearby parts of the body. Cancer may also spread to more distant parts of the body through the lymphatic system or bloodstream. Not all tumors are cancerous. Benign tumors do not grow uncontrollably, nor invade neighboring tissues, and do not spread throughout the body [2]. There are over 200 different known cancers that afflict humans, 90–95% of cases attributed to environmental factors and 5–10% are due to genetics [3]. Researchers have long searched for a more selective method of targeting cancer cells exclusively. The ideal drug would "zero in" on cancer cells and leave other body cells unharmed. Recently, the drug imatinib, which is referred to as a "guided missile" against cancer has captured the interest of oncologists [4]. It is the first anticancer drug to specifically inhibit a molecular abnormality unique to human cancer cells. Imatinib selectively inhibits BCR-ABL gene which has been identified being the cause of chronic myeloid leukemia and was approved by the United States of America FDA as a first line treatment for chronic myeloid leukemia [5].

* Corresponding author at: Flat 16, 12 Asmaa Fahmey St., Heliopolis, Cairo, Egypt. Tel.: +20 0224147745.
*E-mail address:* monaamhelal@yahoo.com (M.A. Helal).

http://dx.doi.org/10.1016/j.toxrep.2015.05.001

Imatinib is rapidly absorbed when given by mouth, and is highly bioavailable: 98% of an oral dose reaches the bloodstream. Metabolism of imatinib occurs in the liver and is mediated by several isozymes of the cytochrome P450 system, including CYP3A4 and, to a lesser extent, CYP1A2, CYP2D6, CYP2C9, and CYP2C19. The main metabolite, *N*-demethylatedpiperazine derivative, is also active. The major route of elimination is in the bile and feces; only a small portion of the drug is excreted in the urine. Most of imatinib is eliminated as metabolites; only 25% is eliminated unchanged. The half-lives of imatinib and its main metabolite are 18 and 40 h, respectively. It blocks the activity of Abelson cytoplasmic tyrosine kinase (ABL), c-Kit and the platelet-derived growth factor receptor (PDGFR). As an inhibitor of PDGFR, imatinib mesylate appears to have utility in the treatment of a variety of dermatological diseases. Imatinib has been reported to be an effective treatment for FIP1L1-PDGFRalpha+ mast cell disease, hypereosinophilic syndrome, and dermatofibrosarcoma protuberans [6].

Although imatinib is an effective therapy for newly diagnosed CP-CML patients, 40–45% of patients discontinue treatment due to adverse events (20–25%) or imatinib resistance (20%) [7]. Importantly, 7–8% of patients transform to accelerated phase (AP) or blast crisis (BC), with most transformations occurring within the first 3 years of imatinib therapy [7,8]. Treatment with imatinib is generally well tolerated, and the risk for severe adverse effects is low. Adverse effects most commonly include mild-to-moderate edema, nausea and vomiting, diarrhea, muscle cramps, and cutaneous reactions. Hepatic transaminase level elevations and myelosuppression occur less frequently and resolve with interruption of imatinib therapy [9].

The beneficial effects of treatment with imatinib in pregnant patients with chronic myelogenous leukemia should be balanced with the risk of teratogenicity and congenital abnormality in fetus. The risk of teratogenicity has been variable and in most cases it is low and is not well established. A more extensive surveillance is needed for better decision making in treating pregnant women with chronic myelogenous leukemia [10]. So, the aim of the present study is to investigate the possible side effects from the use of imatinib on the pregnant rats and their fetuses.

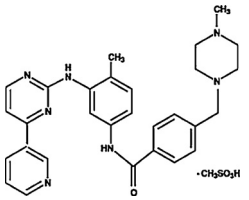
## 2. Material and methods

### 2.1. Animals

Total number of 40 adult female Sprague Dawley rats weighing 150–170 g and 20 male rats weighing 150 g of the same strain were obtained from the Farm of National Organization for Drug Control and Research. Animals had free access to tap water and to standard food diet ad libitum. All rats were allowed to adapt to the laboratory environment for 1 week before being used. The experimental procedures complied with the guidelines of the Committee on Care and Use of National Organization for Drug Control and Research Center, Cairo, Egypt. Each two adult virgin females in proestrus were caged overnight in an animal plastic cage with normal mature male. Vagina was examined daily for suggesting pregnancy by a vaginal smear technique according to the method of Matthews and Kenyon [11]. Females with positive vaginal smears were considered pregnant at zero day of gestation.

### 2.2. Chemical used

Imatinib mesylate film-coated tablets containing imatinib mesylate equivalent to 100 mg of imatinib free base was used (Novartis.Com, Switzerland). Imatinib mesylate is designated chemically as 4-[(4-Methyl-1-piperazinyl) methyl]-*N*-[4-methyl-3-[[4-(3-yridinyl)-2-pyrimidinyl]amino]-phenyl] benzamidemethanesulfonate and its structural chemical formula is




Imatinib mesylate is a white to yellowish tinged crystalline powder. Its molecular formula is $C_{29}H_{31}N_7O\cdot CH_4SO_3$ and it has low molecular weight which is 493.603 g/mol. Imatinib mesylate is freely soluble in water and aqueous buffers ≤pH 5.5.

### 2.3. Experimental design and procedures

All pregnant rats were divided into three main groups. The first main group (about 8 animals) served as control. The second main group was divided into two subgroups (8 rats each) and was orally administered low dose of imatinib mesylate free base pure active compound (36 mg/kg body weight dissolved in 1 ml distilled water) on gestation days (SDs) 6 through 13 and on SDs 13 through 19. The third main group of pregnant rats was divided into two subgroups (8 rats/each) and was orally administered high dose of imatinib (54 mg/kg b.wt.) dissolved in 1 ml distilled water from 6th day to 13th day of gestation and from 13th day to 19th day of gestation, respectively. The drug doses (36 mg/kg and 54 mg/kg) are related to the low and high human therapeutic doses [12–15]. The drug doses (36 mg/kg and 54 mg/kg) were chosen in the present work as the dose 36 mg/kg body weight is considered the lowest-observed-adverse-effect level (LOAEL) of imatinib that can cause the least developmental toxic effects and mortality rate to the pregnant rats and their fetuses. Lower than 36 mg/kg showed no observed adverse effect level (NOAEL) of imatinib. The dose equal to 54 mg/kg b.wt. was considered as the maximum dose that can cause direct maternal and developmental toxicity. Higher than 54 mg/kg b.wt. showed complete mischarge and increased percentage of dams mortality rates. At the 20th day of gestation – one day before the date of expected delivery, because mothers usually cannibalize malformed or incompletely vital neonates [16] – pregnant females are sacrificed. The ovaries and uteri from each female were removed and examined for the number of corpora lutea, status of all the implantation sites (i.e., live and dead fetuses, early and late resorptions