International Journal of Pediatric Otorhinolaryngology (2006) **70**, 779—784

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International Journal of Pediatric Otorhinolaryngology

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Investigation of ototoxic effects of Taxol on a mice model

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Received 20 October 2004; received in revised form 1 November 2005; accepted 16 November 2005

KEYWORDS
Taxol;
Paclitaxel;
Ototoxicity;
Sensorineural hearing loss;
Animal experiment

Summary

Objective: To investigate the effects of taxol on the inner ear in a mice model.
Methods: This study was performed on 112 ears of 56 albino Swiss mice. All animals underwent baseline auditory brainstem response (ABR) testing bilaterally and baseline Peak Equivalent Sound Pressure Levels (PESPLs) were obtained. The mice were randomly assigned to seven groups consisting of one control and six study groups. The control group received no medications while the mice in groups 1—6 received 1×60, 1×20, 2×20, 3×20, 4×20 and 5×20 mg/kg taxol intraperitoneally. Control ABR assessments were performed 3 weeks after the last dose. The animals were then sacrificed while still anaesthetised and the bullae (cochleae included) were dissected from their temporal bones. Haematoxylin—eosin and Masson's trichrome stains were used to demonstrate connective tissue, and periodic acid Schiff (PAS) stain was used to highlight epithelial elements.
Results: Significant decreases in the hearing levels were observed in all the groups which received taxol. No correlation was observed between the dose given and the degree of hearing loss. The sections from the control group showed no histopathologic abnormalities while the sections from the study groups demonstrated vacuolisation in the epithelial cells of the spiral limbus, and the stria vascularis, vacuolisation of the fibroblasts and decreasing the number of the fibroblasts in the spiral limbus.
Conclusion: Taxol causes mild to moderate sensorineural hearing loss in mice. Histopathologically, there were degenerative changes in the cochlea resembling the ones that take place in salisylate and interferon alpha 2a ototoxicity which are thought to be reversible. There was no sensory cell loss. The hearing loss begins

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0165-5876/$ — see front matter
doi:10.1016/j.ijporl.2005.11.011

with doses less than or equal to 20 mg/kg and is not dose dependent after this dose. Hearing monitorisation with audiologic evaluation is strongly recommended before and during the use of the drug in human subjects.

1. Introduction

Taxol (paclitaxel) is a novel antineoplastic agent with antimicrotubule properties. It is a diterpene plant product isolated from the western yew, *Taxus brevifolia*. Unlike other antimicrotubule agents, namely the vinca alkaloids, that induce microtubule disassembly, taxol shifts the equilibrium towards microtubule assembly which are excessively stable thereby inhibiting the dynamic reorganisation of the microtubule network [1]. It is among the most active agents available for ovarian cancer. Currently taxol combined with a platinum agent is considered to be the one of the most promising adjuvant chemotherapy regimens in advanced ovarian cancer [2]. It has also been reported to be effective against various carcinomas including non-small cell carcinoma of the lung [3], breast [4] and head and neck cancer [5] in adult population as well as the pediatric age group. Like the other antineoplastic agents, taxol also has many side effects of which neutropenia and peripheral neuropathy are the major dose-limiting ones [6]. Although the other antimicrotubule agents has been shown to be ototoxic [7,8], the data on the effects of taxol on the inner ear are very limited. There are a few studies addressing the possible ototoxic effect of taxol in both of which taxol was administered in combination with antineoplastic agents whose ototoxic effects were well established. The aim of this experimental study is to investigate the effects of taxol on the inner ear.

2. Materials and method

This study was performed on 112 ears of 56 albino Swiss mice weighing 40 ± 10 g. The mice were anaesthetised by injection of 7 mg/g ketamine HCl (Ketalar®, Eczacibasi, Turkey) and 1 mg/g xylazine HCl (Rompun®, Bayer, Turkey) into the right femoral muscle. All animals underwent baseline auditory brainstem response (ABR) testing bilaterally and baseline Peak Equivalent Sound Pressure Levels (PESPLs) were obtained in terms of decibel (dB). For ABR assessment Amplaid MK 15 (Italy) was used. An insert receiver was placed in each ear and the ABR responses were detected by four subdermal needle electrodes. These electrodes are placed two in the mastoid region and one in vertex as positive and fourth electrode was placed on forehead as the ground electrode [9]. The parameters used in the ABR measurements were given in Table 1. Then the mice were randomly assigned to seven groups consisting of one control and six study groups. Two groups of the study group received a single dose of taxol and the remaining four received repeated doses of the drug. The number of the animals, the administered doses and the time of the ABR tests for each group were given in Table 2. The repeated doses were administered 3 weeks apart and the control ABR assessments were performed 3 weeks after the last dose. After the control ABR tests, the animals were sacrificed while still anaesthetised and the bullae (cochleae included) were dissected from their temporal bones. The bullae were fixed in 10% formalin and remained in a solution of 10% formic acid for 24 h. Routinely processed, paraffin-embedded tissues were sectioned at 4 μm thickness. Haematoxylin—eosin and Masson's trichrome stains were used to demonstrate connective tissue, and periodic acid Schiff (PAS) stain was used to highlight epithelial elements. Then the pathological slides were examined under the light microscope and the spiral limbus, spiral prominence, stria vascularis, Reissner's membrane and the Organ of Corti were evaluated. The pathologist was blinded as to the group identity of the mice. Statistical analysis was carried out using SPSS for Windows version 11.0 computer program. One-way ANOVA test was used to compare the initial threshold levels between groups. *T*-test for two related samples was used to compare the initial and the second hearing threshold levels for each group individually. Correlation

Table 1 The parameters used in ABR measurements

Parameter	Value
Duration of analysis (ms)	15
Frequency of the stimulus (s^{-1})	41
Stimulus type	Click
Number of stimulus	2000
Channel 1 low-frequency filter (Hz)	50
Channel 1 high-frequency filter (Hz)	2500
Channel 2 low-frequency filter (Hz)	50
Channel 2 high-frequency filter (Hz)	2500
Channel 3 low-frequency filter (Hz)	50
Channel 3 high-frequency filter (Hz)	2500