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MORPHINE DECREASES CYTOTOXICITY AND MUTAGENICITY OF DOXORUBICIN IN VITRO: IMPLICATIONS FOR CANCER CHEMOTHERAPY

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INTRODUCTION: Morphine is the most common opioid analgesic administered to treat pain in patients undergoing cancer chemotherapy. While it is effective for pain management, its potential interactions with chemotherapeutic agents, such as doxorubicin (Dox), remain poorly understood. Dox is widely used for treating solid tumors, but its therapeutic efficacy is often limited by its cytotoxic and mutagenic effects. Given that cancer patients frequently receive morphine concomitantly with chemotherapy, it is crucial to investigate whether morphine influences Dox cytotoxicity and mutagenicity. Understanding this interaction is essential to optimize treatment protocols and ensure both the efficacy and safety of chemotherapy regimens. **OBJECTIVE:** This study aimed to evaluate the cytotoxic and mutagenic effects of morphine alone and in combination with Dox. **MATERIALS AND METHODS:** Cytotoxicity was evaluated in neuroblastoma (SH-SY5Y) and fibroblast (V79) cells using 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide (MTT) colorimetric assay while mutagenicity was assessed using the *Salmonella/microsome* assay in the absence and in the presence of S9 mix. **RESULTS:** Morphine showed a cytotoxic effect mainly on SH-SY5Y cells and reduced the cytotoxic effects of Dox when evaluated in a co-treatment procedure. In the *Salmonella/microsome* assay, it was observed that morphine did not induce mutations and, in fact, decreased the mutagenic effects induced by Dox in TA98 and TA102 strains in the absence of metabolic activation. Furthermore, in the presence of metabolic activation, no induction of mutations was observed with morphine. **CONCLUSION:** In conclusion, morphine decreased Dox cytotoxicity in both neuronal and non-neuronal cells and showed antimutagenic effects in the TA102 strain which detects mutagens inducing DNA oxidative damages. However, morphine decreased frameshift mutations induced by Dox in non-cytotoxic concentrations, an effect suggesting interference of Dox intercalation activity that could decrease its chemotherapeutic efficacy. These compelling findings highlight the importance of conducting further studies to explore the potential implications of co-administering morphine and Dox during cancer chemotherapy.

Keywords: Ames test; Cytotoxicity; Doxorubicin; Morphine; Mutagenicity

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