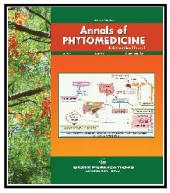
Annals of Phytomedicine 13(1): 863-867, 2024

DOI: http://dx.doi.org/10.54085/ap.2024.13.1.92

Annals of Phytomedicine: An International Journal
http://www.ukaazpublications.com/publications/index.php

Print ISSN : 2278-9839 Online ISSN : 2393-9885



Original Article : Open Access

Navigating the therapeutic paradox: A case report on dexamethasone's role in nerve regeneration and associated toxic risks in Wistar rats

Mohammed H. Karrar Alsharif *◆, Juman M. Almasaad **, Nagi M. Bakhit*, Mahmoud H. El-Bidawy****, *****, Abdulaziz Ali Al Talib******, Moataz K. Y. Jarour******* and Sarah Ali Altaleb******

* *Department of Basic Medical Science, College of Medicine, Prince Sattam Bin Abdulaziz University, Al Kharj, Saudi Arabia*
** *Department of Basic Medical Sciences, College of Medicine, King Saud Bin Abdulaziz University, for Health Sciences Jeddah, Saudi Arabia*
*** *Department of Anatomy, Arabian Gulf University, Manama, Bahrain*
**** *Department of Physiology, Faculty of Medicine, Cairo University, Kasr Al-Aini, Cairo, Egypt*
***** *Department of BMS, Physiology Division, College of Medicine, Prince Sattam bin Abdulaziz University, Al-Kharj 11942, Saudi Arabia*
****** *Hotat Bani Tamim General Hospital, Hotat Bani Tamim, Saudi Arabia*
******* *Dallah Clinic, Riyadh, Saudi Arabia*

Article Info

Article history
Received 13 February 2024
Revised 28 March 2024
Accepted 29 March 2024
Published Online 30 June 2024

Keywords
Dexamethasone
Nerve regeneration
Toxic risks
Therapeutic paradox
Peripheral nerve injury

Abstract

This manuscript presents an exploration into the dual nature of dexamethasone, a potent corticosteroid, in the context of peripheral nerve regeneration and its associated toxic risks in wistar rats. By examining the drug's efficacy in enhancing nerve repair post-injury through anti-inflammatory actions and the promotion of neurotrophic factors, alongside a significant observation of toxicity resulting in high mortality rates, we delve into the therapeutic paradox that dexamethasone represents. Conducted in a controlled experimental setup, this study utilised albino wistar rats to assess the regenerative potential and adverse effects of dexamethasone, administered intraperitoneally at a dosage of 2 mg/kg body weight daily for ten consecutive days. Despite promising indications of its role in nerve regeneration, over 50% of the rats succumbed, underscoring a severe adverse reaction. This manuscript discusses the possible causes of this toxicity, including dosage sensitivity, drug accumulation, species-specific responses, off-target effects, immune system suppression, adrenal suppression, and apoptosis induction, thereby highlighting the complex challenge of optimising dexamethasone's therapeutic use while mitigating its risks. The findings stress the need for meticulous dosage considerations, understanding interspecies differences in drug metabolism, and further investigation into the drug's pharmacokinetics and biological impacts.

1. Introduction

Dexamethasone, a synthetic long-acting corticosteroid, is renowned for its potent analgesic and anti-inflammatory effects, making it a cornerstone in the treatment of a wide range of conditions. Its applications span from managing arthritis, blood and hormonal abnormalities, and allergic reactions to treating skin disorders, ocular complications, and respiratory issues and mitigating postoperative nausea and vomiting. This wide range of applications underscores its significance in the clinical med (Ciobotaru *et al*., 2019; Williams, 2018; Harish *et al.,* 2016). In a lower dose, dexamethasone has also been advised for COVID-19 patients who are under mechanical ventilation (Adnan *et al.,* 2020).

Chemically characterized as 9-fluoro-11β, 17-dihydroxy-16α-methyl-21-(phosphonooxy) pregnant-1, 4-diene-3, 20-dione disodium salt, dexamethasone's structure is pivotal to its long-acting nature and wide-ranging pharmacological actions (Umari *et al*., 2021). Despite its broad usage, the precise mechanisms by which dexamethasone aids in the treatment of peripheral nerve damage are not fully elucidated. The drug's potential to enhance peripheral nerve regeneration, particularly after injury, remains a critical area of research in the field (Venkata *et al*., 2014).

Recent studies have begun to uncover the multifaceted roles of corticosteroids in nerve repair and regeneration. Dexamethasone has been shown to modulate inflammation, reduce scar formation, and potentially enhance the expression of neurotrophic factors, which are vital for nerve healing processes (Elhessy *et al*., 2023). Moreover, its ability to suppress the immune response in the acute phase of injury could prevent further damage to the nerve tissue, thereby facilitating a more conducive environment for regeneration (Tang *et al*., 2022).

This manuscript aims to delve into the efficacy of dexamethasone in promoting peripheral nerve regeneration post-injury, synthesizing insights from animal model studies. Research utilizing rat and rabbit models has provided valuable data on functional and histological outcomes, contributing to our understanding of dexamethasone's role in nerve healing (Feng and Yuan, 2015). By exploring these studies, we seek to bridge the gap in knowledge regarding dexamethasone's action mechanisms in peripheral nerve regeneration, offering a comprehensive overview that could guide future therapeutic approaches in neuropathy treatment.

Corresponding author: Dr. Mohammed H. Karrar Alsharif
Department of Basic Medical Science, College of Medicine, Prince Sattam Bin Abdulaziz University, Al Kharj, KSA.
E-mail: m.alshrif@psau.edu.sa
Tel.: +966-552644088

2. Materials and Methods

2.1 Animals and housing

In this detailed study, we selected 64 healthy adult albino wistar rats, ensuring they each fell within the weight range of 250 ± 30 g and were aged between 12 to 14 weeks to maintain consistency across the experimental cohort. The animals were housed in a controlled environment, where temperature was consistently maintained at 22 ± 2°C and humidity levels were kept between 50-60% to simulate optimal living conditions that minimize external stress factors potentially affecting the study's results. The lighting schedule was regulated to a 12 h light/dark cycle to accommodate natural circadian rhythms, which could influence the physiological and behavioural outcomes of the subjects.

Unrestricted access to standard rodent food and water was provided, emphasizing the welfare and health of the animals throughout the study duration. The housing setup was carefully designed to surpass ethical standards for animal care. Approval for the research protocol was granted by the Institutional Review Board of Ondokuz Mayis University (meeting number 2018/45), reinforcing our commitment to ethical research practices and the humane treatment of the animals involved (Figure 1).

Figure 1: Optimal animal housing conditions. Photo depicting the controlled environment for the study's animals, highlighting temperature control at 22 ± 2°C, humidity between 50-60%, and the 12 h light/dark cycle for circadian rhythm support.

2.2 Drug administration and injury model

The administration of dexamethasone was carefully planned, following established pharmacological recommendations. Dexamethasone phosphate was intraperitoneally administered at a calculated therapeutic dosage of 2 mg/kg body weight. This dosage was selected after an extensive review of existing literature (Earp *et al*., 2008), which highlighted its effectiveness in promoting tissue regeneration and reducing inflammatory responses in comparable experimental frameworks. The chosen dosage was administered daily for ten consecutive days to each rat, following the induction of a standardized peripheral nerve injury model.

The peripheral nerve injury model was applied under anaesthesia to minimize stress and discomfort to the subjects. This model aimed to closely mimic clinical instances of nerve damage, thereby allowing for an investigation into dexamethasone's potential for regeneration and its systemic effects in a live model. The intraperitoneal route for drug administration was chosen for its effectiveness in systemic drug delivery, facilitating an accurate evaluation of dexamethasone's pharmacodynamics and therapeutic impact concerning peripheral nerve regeneration.

This methodical approach to drug administration, aligned with rigorously maintained animal housing conditions and ethical study protocols, highlights our dedication to conducting scientifically robust and ethically sound research. Such meticulous methodology is crucial for assessing the effects of dexamethasone on nerve regeneration and its potential applications in clinical settings.

3. Case presentation

This case report details an investigation into the effects of dexamethasone phosphate (fosfat), administered as a daily dose of 2 mg/kg body weight daily for 10 consecutive days *via* the intraperitoneal route to albino wistar rats. Adherence to the Ethical

Committee's Rules and guidelines was stringent, ensuring the welfare of the animals throughout the study.

3.1 Experimental design and conditions

A cohort of 64 healthy adult wistar albino rats, each weighing approximately 250 ± 30 g and aged between 12 to 14 weeks, was selected. Housed in stainless steel cages under controlled temperature (22 ± 2°C) and humidity (50-60%) conditions with a consistent 12 h dark/light cycle, these conditions minimized external stressors, contributing to the reliability of the study's outcomes. The rats had unrestricted access to standard rodent laboratory food and water.

3.2 Observations and results

Significant and concerning outcomes were observed following the administration of dexamethasone phosphate. Throughout the treatment period, mortality exceeded 50% among the rats, with the first death being recorded on the third day. This pattern of fatalities, continuing sporadically throughout the dosing period, suggested a possible dose-related response.

To mitigate these effects, a pilot study was conducted using a tapering withdrawal strategy on two rats. This strategy entailed a gradual reduction in the dexamethasone dosage over the last three days of treatment. Despite this adjustment, a significant improvement in survival rates was not observed, indicating that the adverse effects may not be easily reversible.

Behavioural changes were noted in the majority of treated rats, characterized by decreased activity levels, reduced food and water intake, and signs of distress such as increased grooming and agitation. These behavioural alterations were seen to escalate in severity as the treatment period progressed (Figure 2).

Figure 2: Behavioural changes in treated rats. Photo showing idleness, reduced food and water consumption, and heightened distress indicators such as increased grooming post-treatment.

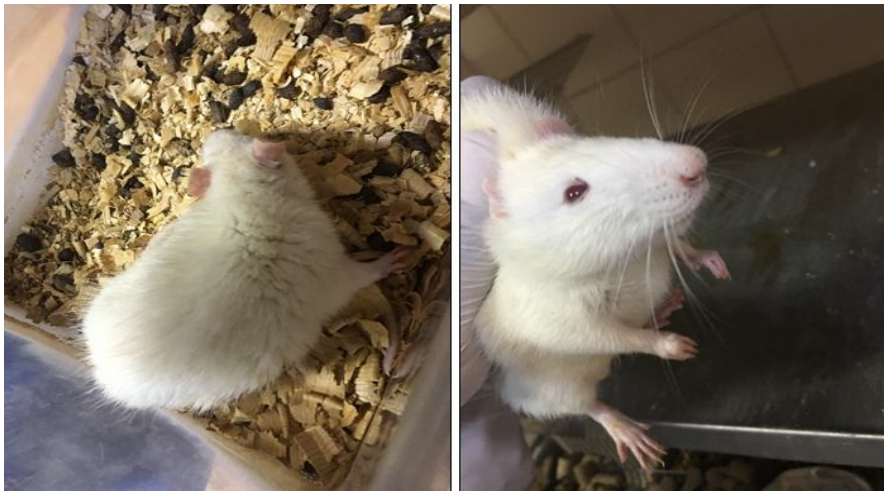


Figure 3: Dermatological and ocular changes in treated rats. The first photo displays extensive skin thinning and the presence of lesions and ulcerations, while the second photo highlights a distinct crescentic black shape around the eyes, suggestive of haemorrhaging or vascular problems.

Upon pathological examination, notable changes were observed, particularly in the skin and around the eyes. Thinning and fragility of the skin were noted, with some areas displaying lesions and ulcerations. A distinct crescentic black shape around the eyes of several rats was indicative of haemorrhaging or other underlying vascular issues. These findings suggest significant adverse systemic and local effects were induced by the administered dexamethasone phosphate at the chosen dosage and route (Figure 3).

4. Discussion

The research manuscript provides a detailed examination of dexamethasone's efficacy in nerve regeneration and its potential toxicity in wistar rats, presenting a scenario often termed the therapeutic paradox. The introduction aptly sets the stage by elucidating the drug's potent analgesic and anti-inflammatory effects, crucial in managing various medical conditions. Furthermore, it delves into the structural composition of dexamethasone, highlighting its importance in dictating pharmacological actions (Elhessy *et al*., 2023; Wang *et al*., 2015).

Recent studies referenced in the manuscript underline dexamethasone's multifaceted potential in modulating crucial factors involved in nerve repair. Beyond its conventional anti-inflammatory properties, these studies suggest a broader role for dexamethasone in reducing scar tissue formation and fostering the production of neurotrophic factors, both pivotal for effective nerve regeneration. This multifunctional aspect of dexamethasone suggests a more profound impact beyond mere symptom alleviation, potentially altering the trajectory of nerve repair processes (Mekaj and Mekaj, 2017).

However, the manuscript also addresses the inherent paradox observed in recent studies, wherein dexamethasone demonstrates promising effects on inflammation modulation and enhanced expression of neurotrophic factors, juxtaposed with instances of observed toxicity. The materials and methods section ensures scientific integrity and ethical rigour, meticulously planning the drug administration protocol to investigate dexamethasone's role in peripheral nerve regeneration within a controlled experimental framework.

The case presentation, however, unveils a significant concern: a mortality rate exceeding 50% among treated rats, indicating severe adverse reactions to the therapeutic regimen. This unexpected toxicity prompts a thorough discussion of potential causes:

- **Dosage sensitivity:** The narrow therapeutic window of dexamethasone suggests that the observed adverse reactions may stem from a dosage that is beneficial in one aspect but harmful in another (Ni *et al*., 2019; Rice and McLysaght, 2017).
- **Drug accumulation:** Failure to consider the drug's half-life in daily administration may lead to accumulation and subsequent systemic toxicity (Li *et al*., 2013).
- **Species-specific responses:** Variations in drug metabolism across species imply that Wistar rats may exhibit unique sensitivity to Dexamethasone (Nguelefack-Mbuyo *et al*., 2022).
- **Off-target effects:** Dexamethasone might be inadvertently affecting cellular pathways that are not directly linked to inflammation or nerve regeneration, thereby contributing to toxicity (Garrud *et al*., 2023).
- **Immune system suppression:** While reducing inflammation, dexamethasone's immunosuppressive effects could render subjects vulnerable to infections, potentially exacerbating mortality rates (Wu *et al*., 2023; O'Neil *et al*., 2023).
- **Adrenal suppression:** Prolonged exogenous steroid use may lead to adrenal suppression, posing a risk of adrenal insufficiency and potential crises upon drug withdrawal (Prete and Bancos, 2021).
- **Apoptosis induction:** Glucocorticoids' ability to induce apoptosis raises concerns about inadvertently affecting regenerating nerve cells, warranting further investigation (Gruver-Yates and Cidlowski, 2013).

These potential causes underscore the complexity of the challenge in optimizing the therapeutic use of dexamethasone. The study emphasizes the importance of meticulous dosage considerations and administration routes to mitigate adverse effects while leveraging dexamethasone's regenerative potential. Furthermore, it highlights the need to understand interspecies differences in drug metabolism and the imperative of delving deeper into the drug's pharmacokinetics and biological impacts to strike a delicate balance between efficacy and safety.

5. Conclusion

This study meticulously examines the paradoxical role of dexamethasone in the context of peripheral nerve regeneration juxtaposed with its significant toxic risks in wistar rats. Our findings illuminate the corticosteroid's potential to enhance nerve repair mechanisms through anti-inflammatory actions and the promotion of neurotrophic factors, which are critical for the healing process post-injury. However, the observed high mortality rate, exceeding 50% among the treated subjects, underscores a critical concern regarding the therapeutic application of dexamethasone. This adverse outcome points to the imperative need for a nuanced understanding of the drug's pharmacological profile, emphasizing the balance between its regenerative benefits and potential toxicities.

6. Recommendations

- **Optimized dosage:** Future research should focus on identifying the optimal dosage that maximizes regenerative benefits while minimizing toxicity.
- **Alternative administration routes:** Exploring different administration routes could offer ways to reduce adverse effects and improve therapeutic outcomes.
- **Species-specific studies:** Further studies are needed to understand how interspecies differences affect drug metabolism and response, aiding in the translation of findings from animal models to humans.
- **Mechanistic understanding:** A deeper investigation into the drug's mechanisms of action will help in developing targeted strategies to enhance its efficacy in nerve repair.

By addressing these areas, we can better navigate the therapeutic paradox of dexamethasone, potentially unlocking its full potential in treating peripheral nerve injuries with minimized risks.

Acknowledgements

This publication was supported by the Deanship of Scientific Research at Prince Sattam bin Abdulaziz University, Alkharj, Saudi Arabia.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

References

Adnan A.K.; Shiba, K.; Unaiza, K. and Kuntal, D. (2020). The COVID-19 pandemic and its implications on research. Ann. Phytomed., **9**(1):18-26.

Ciobotaru, O.R.; Lupu, M.N.; Rebegea, L.; Ciobotaru, O.C.; Duca, O.M.; Tatu, A.L.; Voinescu, C.D.; Stoleriu, G.; Earar, K. and Miulescu, M. (2019). Dexamethasone-chemical structure and mechanisms of action in prophylaxis of postoperative side effects. Rev. Chim (Bucharest), **70**(3):843-847.

Earp, J.C.; Pyszczynski, N.A.; Molano, D.S. and Jusko, W.J. (2008). Pharmacokinetics of dexamethasone in a rat model of rheumatoid arthritis. Biopharm. Drug Dispos., **29**(6):366-372.

Elhessy, H.M.; Habotta, O.A.; Eldesoqui, M.; Elsaed, W.M.; Soliman, M.F.; Sewilam, H.M.; Elhassan, Y. and Lashine, N.H. (2023). Comparative neuroprotective effects of cerebrolysin, dexamethasone, and ascorbic acid on sciatic nerve injury model: behavioral and histopathological study. Front. Neuroanat., **17**:1090738.

Feng, X. and Yuan, W. (2015). Dexamethasone enhanced functional recovery after sciatic nerve crush injury in rats. Biomed. Res. Int., **2015**:627923.

Garrud, T.A.; Teulings, N.E.; Niu, Y.; Skeffington, K.L.; Beck, C.; Itani, N.; Conlon, F.G.; Botting, K.J.; Nicholas, L.M. and Tong, W. (2023). Molecular mechanisms underlying adverse effects of dexamethasone and betamethasone in the developing cardiovascular system. Reviews, **37**:e22887.

Gruver-Yates, A.L. and Cidlowski, J.A. (2013). Tissue-specific actions of glucocorticoids on apoptosis: a double-edged sword. Cells, **2**(2):202-223.

Harish, B.S.; Aasin, M.; Sathish, S.; Kesavan, P.K.; Subasranjan, A. and Shri, N.A. (2016). Immunomodulatory and antimicrobial activity of a polyherbal composition, Panchatulasi drops, derived from essential oils of five species of basil. Ann. Phytomed., **5**(2):130-139.

Li, L.; Li, X.; Xu, L.; Sheng, Y.; Huang, J. and Zheng, Q. (2013). Systematic evaluation of dose accumulation studies in clinical pharmacokinetics. Curr. Drug Metab., **14**(5):605-615.

Mekaj, A. and Mekaj, Y. (2017). The role of pharmacological agents in nerve regeneration after peripheral nerve repair. Peripher. Nerve Regen. Surg. New Ther. Approaches Incl. Biomater. Cell-Based Ther. Dev., pp:10.

Nguelefack-Mbuyo, E.P.; Peyembouo, F.P.; Fofié, C.K. and Nguelefack, T.B. (2022). Dose-dependent and time-dependent metabolic, hemodynamic, and redox disturbances in dexamethasone-treated Wistar rats. J. Basic Clin. Physiol. Pharmacol., **33**(4):457-469.

Ni, Z.; Zhou, X.Y.; Aslam, S. and Niu, D.K. (2019). Dosage-sensitivity of human transcription factor genes. Bio. Rxiv., 528554.

Neil, J.D.; Bolimowska, O.O.; Clayton, S.A.; Tang, T.; Daley, K.K.; Lara-Reyna, S.; Warner, J.; Martin, C.S.; Mahida, R.Y. and Hardy, R.S. (2023). The glucocorticoid dexamethasone impairs the expression of anti-viral mediators in activated macrophages by inhibiting both expression and function of interferon β. Bio. Rxiv., **14**:1190261.

Prete, A. and Bancos, I. (2021). Glucocorticoid-induced adrenal insufficiency. BMJ. **12**;374: n1380.

Rice, A.M. and Mclysaght, A. (2017). Dosage-sensitive genes in evolution and disease. BMC Biology, **15**(1):78.

Tang, X.; Li, Q.; Huang, T.; Ling, J. and Yang, Y. (2022). Regenerative role of T cells in nerve repair and functional recovery. Front. Immunol., **13**:923152.

Umari, M.; Paluzzano, G.; Stella, M.; Carpanese, V.; Gallas, G.; Peratoner, C.; Colussi, G.; Baldo, G.M.; Moro, E. and Lucangelo, U. (2021). Dexamethasone and postoperative analgesia in minimally invasive thoracic surgery: A retrospective cohort study. J. Anesth. Analg. Crit. Care., **1**(1):23.

Venkata S.K.; Thejaswini, J.; Raju, M.P.; Chandan, R.; Gurupadayya, B. and Mruthunjaya, K. (2014). Rp-Hplc method development for the quantitative determination of dexamethasone in herbal formulation. World J. Pharm. Res., **4**(2):1148-1157.

Wang, P.H.; Tsai, C.L.; Wu, K.C.; Shao, C.J.; Kuo, L.C. and Jou, I.M. (2015). Effects of different dosages of dexamethasone on behavioural, electrophysiological, and histomorphological recovery in a chronic sciatic nerve compression model. Pain Med., **16**(4):765-776.

Williams, D.M. (2018). Clinical pharmacology of corticosteroids. Respir. Care, **63**(6):655-670.

Wu, S.; Zhao, S.; Zhong, Y. and Wang, B. (2023). Revisit the Inhibitory Effects of Glucocorticoids on Immunocytes. Bio. Rxiv., 28.525640.

Citation **Mohammed H. Karrar Alsharif, Juman M. Almasaad, Nagi M. Bakhit, Mahmoud H. El-Bidawy, Abdulaziz Ali Al Talib, Moataz K. Y. Jarour and Sarah Ali Altaleb (2024). Navigating the therapeutic paradox: A case report on dexamethasone's role in nerve regeneration and associated toxic risks in wistar rats. Ann. Phytomed., 13(1):863-867. http://dx.doi.org/10.54085/ap.2024.13.1.92.**