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SCIENTIFIC ARTICLE

Evaluation of genotoxicity induced by repetitive administration of local anaesthetics: an experimental study in rats

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Abstract
Background and objective: Previous studies regarding the effects of some local anaesthetics have suggested that these agents can cause genetic damage. However, they have not been tested for genotoxicity related to repetitive administration. The aim of this study was to evaluate the genotoxic potential of local anaesthetics upon repetitive administration.
Methods: 80 male Wistar rats were divided into: group A – 16 rats intraperitoneally injected with lidocaine hydrochloride 2%; group B – 16 rats IP injected with mepivacaine 2%; group C – 16 rats intraperitoneally injected with articaine 4%; group D – 16 rats IP injected with prilocaine 3% (6.0 mg/kg); group E – 8 rats subcutaneously injected with a single dose of cyclophosphamide; and group F – 8 rats intraperitoneally injected with saline. Eight rats from groups A to D received a single dose of anaesthetic on Day 1 of the experiment; the remaining rats were dosed once a day for 5 days.
Results: The median number of micronuclei in the local anaesthetics groups exposed for 1 or 5 days ranged from 0.00 to 1.00, in the cyclophosphamide-exposed group was 10.00, and the negative control group for 1 and 5 days was 1.00 and 0.00, respectively ($p < 0.0001$). A significant difference in the number of micronuclei was observed between the cyclophosphamide group and all local anaesthetic groups ($p = 0.0001$), but not between the negative control group and the local anaesthetic groups ($p > 0.05$).
Conclusion: No genotoxicity effect was observed upon repetitive exposure to any of the local anaesthetics evaluated.

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PALAVRAS-CHAVE
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Testes para micronúcleos;
Prilocaína

Avaliação da genotoxicidade induzida pela administração repetida de anestésicos locais: um estudo experimental em ratos

Resumo
Justificativa e objetivos: Estudos anteriores sobre os efeitos de alguns anestésicos locais sugeriram que esses agentes podem causar alterações genéticas. No entanto, esses agentes não são testados para genotoxicidade relacionada à administração repetida. O objetivo deste estudo foi avaliar o potencial genotóxico de anestésicos locais após repetidas administrações.
Métodos: 80 ratos Wistar machos foram alocados em: grupo A – 16 ratos receberam injeção por via intraperitoneal (IP) de cloridrato de lidocaína a 2%; grupo B – 16 ratos receberam injeção IP com mepivacaína a 2%; grupo C – 16 ratos receberam injeção IP de articaína a 4%; grupo D – 16 ratos receberam injeção IP de prilocaína a 3% (6,0 mg kg^{-1}); grupo E – 8 ratos receberam injeção subcutânea em dose única de ciclofosfamida; grupo F – 8 ratos receberam injeção IP com solução salina. Oito ratos dos grupos de A a D receberam uma dose única de anestésico no Dia 1 da experiência; os ratos restantes foram dosados uma vez por dia durante cinco dias.
Resultados: A mediana do número de micronúcleos nos grupos com anestésicos locais expostos por um ou cinco dias variou de 0,00 a 1,00; no grupo exposto à ciclofosfamida foi de 10,00 e no grupo controle negativo no primeiro e quinto dias foi de 1,00 e 0,00, respectivamente ($p < 0,0001$). Uma diferença significativa foi observada no número de micronúcleos entre o grupo ciclofosfamida e todos os grupos com anestésicos locais ($p = 0,0001$), mas não entre o grupo controle negativo e os grupos com anestésicos locais ($p > 0,05$).
Conclusão: Nenhum efeito de genotoxicidade foi observado após a exposição repetida a qualquer um dos anestésicos locais avaliados.

Introduction

The development of safe and effective local anaesthetic agents has been one of the most important advances in dental science over the last century. The dental agents currently available are extremely safe and meet most of the criteria for an ideal local anaesthetic. These local anaesthetic agents induce minimal tissue irritation and have a low risk of inducing allergic reactions.[1]

A local anaesthetic is most often used in dentistry to control pain and is also widely used in other fields of medicine. Among the various formulations of local anaesthetics, the most commonly used types are anaesthetic salts of lidocaine, mepivacaine and prilocaine.[2]

The combined use of a vasoconstrictor and a local anaesthetic agent was first reported in 1901, when Braun simultaneously administered adrenaline and cocaine.[3] Due to the vasodilation properties of most anaesthetic salts, the duration of anaesthesia is not always suitable, illustrating the necessity of concomitant administration with a vasoconstrictor. Some advantages of the combined administration of vasoconstrictors and anaesthetics are the slow absorption of the anaesthetic salt (which reduces toxicity and increases the duration of anaesthesia), a reduction in the quantity of anaesthetic required to anesthetise the patient and an increase in the effectiveness of the anaesthetic.[2] The most common vasoconstrictors used in combination with local anaesthetics belong to the group of sympathomimetic amines, which includes adrenaline, noradrenaline, levonordefrin, phenylephrine and felypressin.[2]

Genotoxic agents negatively affect the integrity of a cell's genetic material and are defined as any substance or chemical that damages DNA. Although the ability of a substance to damage DNA does not automatically render it as a health hazard, it does raise concerns that the substance may be a potential mutagen and/or carcinogen.[4]

Some local anaesthetics have not been tested for carcinogenicity or genotoxicity. Prilocaine is a local anaesthetic that has been under review by the National Toxicology Program (NTP, USA) since October 2007.[5]

The micronucleus test is widely used to evaluate the ability of a substance to break chromosomes (referred to as its clastogenicity) or affect the formation of the mitotic metaphase plate and/or spindle, both of which can lead to inequitable distribution of chromosomes during cellular division.[6] The micronucleus test generates results with strong statistical support; therefore, it is widely used as a screening tool to determine the safety of many substances and to classify agents as carcinogenic or non-carcinogenic.[7] The ease of implementation of the micronucleus test has led to widespread adoption worldwide as a standard genotoxicity test to monitor the safety of agents for use in the human population.[8]

To the best of our knowledge, there are no studies in the literature addressing the genotoxic potential of the repetitive use of local anaesthetics. Local anaesthetics are widely used in dentistry and medicine, and studies that evaluate the risk of repetitive exposure to these substances may contribute to a better understanding of their potentially toxic effects on genetic material and their potential risk to exposed patients.

The objective of this study is to investigate the genotoxic potential of the repetitive use of local anaesthetics using the micronucleus test.