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Investigation of Gadobutrol-Induced Sister Chromatid Exchange in G_0 Phase and Circulating Human Lymphocytes

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Abstract

Gadobutrol (Gadovist®) is a macrocyclic, extracellular gadolinium-based contrast agent widely used in magnetic resonance imaging. This study aims to assess the genotoxic and cytotoxic potential of gadobutrol in human G_0 phase lymphocytes and circulating lymphocytes. The Sister Chromatid Exchange (SCE) assay, a fast, sensitive, and reliable method for evaluating genotoxicity, was employed. Genotoxic effects were assessed by measuring SCE frequency, while cytotoxicity was determined using the mitotic index (MI). Peripheral blood samples from two healthy donors were treated *in vitro* with three different concentrations of gadobutrol for 24 hours in G_0 phase lymphocytes and 72 hours in circulating lymphocytes. The results indicated that gadobutrol did not exhibit cytotoxic effects in either cell type. However, at the highest concentration (25 mM), gadobutrol significantly increased the formation of SCE in circulating lymphocytes ($p < 0.05$), while no significant genotoxic effect was observed in G_0 phase lymphocytes ($p > 0.05$). These findings suggest that gadobutrol, although not cytotoxic, may induce genotoxic effects in a concentration-dependent manner in circulating lymphocytes. Further studies are needed to explore the clinical implications of these findings.

Key words: gadobutrol, genotoxicity, Sister Chromatid Exchange, G_0 phase, cell cycle

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Introduction

Gadolinium-based contrast agents (Gd-CAs) are widely used in magnetic resonance imaging (MRI) to enhance image quality and improve diagnostic accuracy. However, they cause safety concerns due to their toxicity (1). Recent studies have shown that after the administration of Gd-CAs, Gd ions separated from the molecule to which they were chelated accumulate in various tissues such as the brain, bone, and liver (2–4). Growing concerns regarding the potentially toxic effects of Gd-CAs have prompted investigations into their impact on human cells, particularly about DNA damage and chromosomal alterations (5–8). Since DNA damage can lead to mutations in critical genomic regions associated with various cancers, cardiovascular diseases, and neurodegeneration, genotoxicity testing is particularly important (9). It has been reported that exposure of mammalian cells to Gd causes a decrease in cell viability, an increase in MN frequency, DNA breakage and ROS production, and stimulates apoptosis (10, 11). Similarly, there are studies reporting that exposure of mammalian cells to Gd-CAs causes an increase in MN frequency (10, 12, 13), SCE frequency (8, 14) and Comet (5, 8, 10) parameters.

Among Gd-CAs, gadobutrol is a macrocyclic, non-ionic contrast agent (15) with high stability and rapid renal elimination, establishing it as a leading option for clinical use (16). In recent years, some studies have investigated gadobutrol's genotoxic and cytotoxic effects in different cell types. Some of these studies have reported that gadobutrol has a genotoxic potential (7, 8, 12, 17), while others did not report (18). Similarly, there are conflicting results on the cytotoxic effects of gadobutrol (7, 8). Thus, this study was designed to improve the understanding of the genotoxic and cytotoxic potential of gadobutrol in human peripheral lymphocytes at different stages of the cell cycle, including both circulating and G_0-phase cells. G_0-phase lymphocytes are quiescent cells that constitute the majority of peripheral blood lymphocytes and play a crucial role in immune function. It has been suggested that chromosomal damage in these long-lived, metabolically inactive G_0-phase lymphocytes can persist for many years (19). While circulating lymphocytes are commonly used in genotoxicity and cytotoxicity assessments, G_0-phase lymphocytes have also been recommended for evaluating the genotoxic potential of xenobiotics (20). However, to the best of the authors' knowledge, there are no published data regarding the genotoxic and cytotoxic effects of gadobutol on G_0 phase human lymphocytes.

Sister chromatid exchange (SCE) serves as a sensitive indicator of genotoxicity and has been extensively studied in response to various chemical and environmental exposures (7, 21, 22). It is frequently used for biomonitoring and genotoxicity testing, especially for chemicals with mutagenic and carcinogenic potential (23). It has been reported that the molecules targeted by xenobiotics in the formation of SCE may be DNA replication enzyme, DNA topoisomerase II, and DNA repair enzymes (24, 25). The SCE assay uses human peripheral lymphocytes, more than 95% of which are naturally in the G_0 phase of the cell cycle (26). In this study, we aim to investigate the potential of gadobutrol to induce SCE in human lymphocytes, with a specific focus on its effects during the G_0-phase and in circulating human lymphocytes. By evaluating the frequency

of SCE as a marker of genotoxicity, we seek to provide insights into the biological impact of gadobutrol. The novelty of our study was to reveal the effects of gadobutrol G_0 exposure on SCE, MI and PI parameters. Our findings may contribute to a better understanding of the genomic safety of this widely used contrast agent and its implications for long-term health risks.

Materials and Methods

Peripheral whole blood samples obtained from two volunteer donors were used in the study (two females aged 22 years). Donors gave consent by signing a voluntary consent form before sampling and the study was approved by the Çanakkale Onsekiz Mart University Clinical Research Ethics Committee (Decision no: 2021-08).

Chemicals

Gadobutrol was obtained from 1.0 mmol/mL Gadovist (Bayer, Germany). Mitomycin-C (Sigma, USA) was used as a positive control and no addition to negative controls. The other chemicals purchased from following suppliers: methanol, acetic acid, potassium chloride, entellan, and Giemsa (Merck, Germany), Phytohaemagglutinin (PHA, Biological Industries, Israel), bromodeoxyuridine (BrdU), colcemide, RPMI 1640, fetal calf serum (Sigma, USA).

Assessment of Concentration Ranges and Cytotoxicity of Gadobutrol

Kirsch-Volders suggests that the concentration of the test substance that causes approximately 60% cytotoxicity is the highest concentration that can be studied and that at least 3 different concentrations should be studied below this concentration (26). In this study, concentrations of gadobutrol causing less than 60% cytotoxicity (1, 5, 25 mM) were used. These concentrations were obtained by Çobanoğlu (7) by calculating the cell proliferation index by the cytokinesis-blocked micronucleus (CBMN) assay in human peripheral lymphocytes. The parameters SCE, Proliferation Index (PI), and mitotic Index (MI) were used for genotoxic, cytostatic, and cytotoxic effects, respectively (27).

Treatment Protocols Used for SCE Induction by Gadobutrol

To treat the lymphocytes in the G_0 stage, we set up a culture containing only RPMI 1640 and fetal calf serum without adding PHA as a mitogen. Whole blood samples and gadobutrol were added to the medium. The cultures were kept at 37°C for 24 hours. After 24 hours, the test substance was removed by washing three times with RPMI 1640. The cells treated for 24 hours were re-established, terminated, and stained for circulating lymphocytes as summarized below (Figure 1).

Figure 1. Experimental design for human G0 phase lymphocytes
Slika 1. Eksperimentalni prikaz limfocita u G_0 fazi

In Vitro SCE Assay

The method was performed according to Moorhead with minor modifications (29). Two parallel lymphocyte cultures were set up and each parallel contains five culture tubes: one for the negative control, one for the positive control, and three for different concentrations (1, 5, 25 mM) of gadobutrol (2 parallels, 10 cultures in total). As an initial step, we prepared lymphocyte culture medium mixture consisting of RPMI 1640, fetal calf serum and PHA as a mitogen. Negative and positive control agents, as well as whole blood, were added to the culture medium. The samples were maintained at 37°C during the culture period (72 hours). At the 24th hour of culture, BrdU (10 µg/ml**)** and test substance (Gadobutrol) were added to each culture. After BrdU was added to the culture tubes, the cultures were kept in the dark. Colcemide (0.2 µg/ml) was added to each culture at the 70th hour of the culture to obtain metaphase chromosomes, and the cultures were terminated at the 72nd hour. After the cell culture was terminated, the harvest stage was performed (Figure 2). At this stage, the cells were first treated once with KCl (0.075M) and then washed three times with methanol/acetic acid (3/1). It was centrifuged after each treatment with KCl and methanol/acetic acid, and the supernatant was discarded. After the last wash, the samples were dropped onto cold microscopy slides. The dried-slides were subjected to fluorescent plus Giemsa (FPG) staining according to Perry and Wollf (30) and covered with entellan for further scoring.

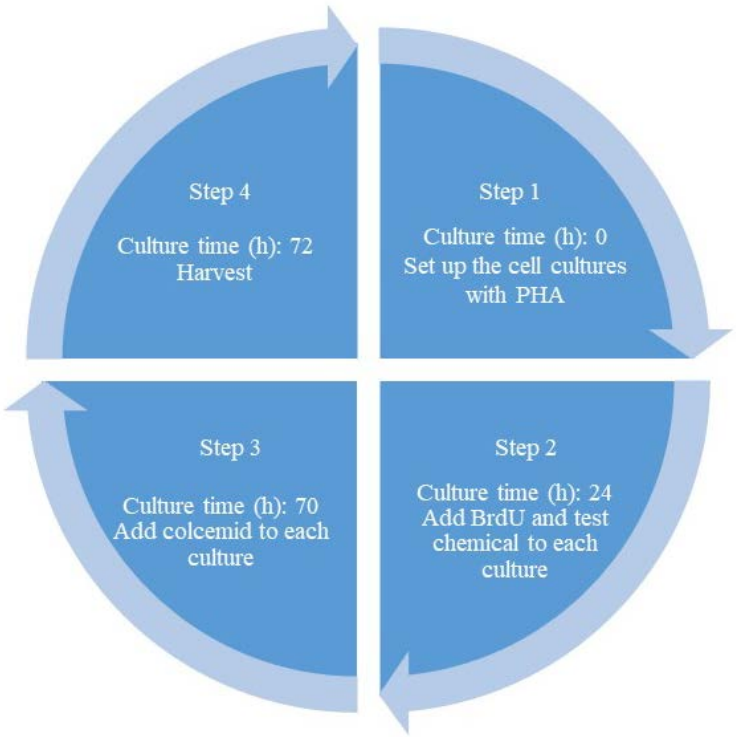

Figure 2. Experimental design for human circulating lymphocytes
Slika 2. Eksperimentalni prikaz cirkulišućih limfocita

Microscopic Evaluation

To determine SCE frequencies in response to gadobutrol, negative and positive controls, 25 well-dispersed (contain 46 chromosomes) metaphases (consisting of one arm dark and one arm light-stained chromosomes) from each slide were evaluated under a light microscope at 100× magnification (Figure 1) (30–32). A total of 100 metaphases (2 parallels and 2 donors) were evaluated for each concentration. In the evaluation, dark fragments in the light-stained arm and light fragments in the dark-stained arm were counted (20). For MI calculation, 1000 cells were evaluated for each slide. The number of cells in the metaphase stage was determined, and the following formula was used for the calculation:

$$MI = (100 \times \text{metaphase number}) / 1000$$

For PI calculation, 100 metaphases were evaluated for each slide. It was determined how many of these metaphases were the first metaphase (M1), how many were the second metaphase (M2), and how many were the third metaphase (M3), and the following formula was used for calculation:

$$PI = ((M1 \times 1) + (M2 \times 2) + (M3 \times 3)) / 100$$

In this formula, M1 represents metaphases in which both arms are stained dark, M2 represents metaphases in which one arm is light, and one arm is dark (Figure 3), and M3 represents metaphases in which both arms are light, and one arm is light, and one arm is dark (27).

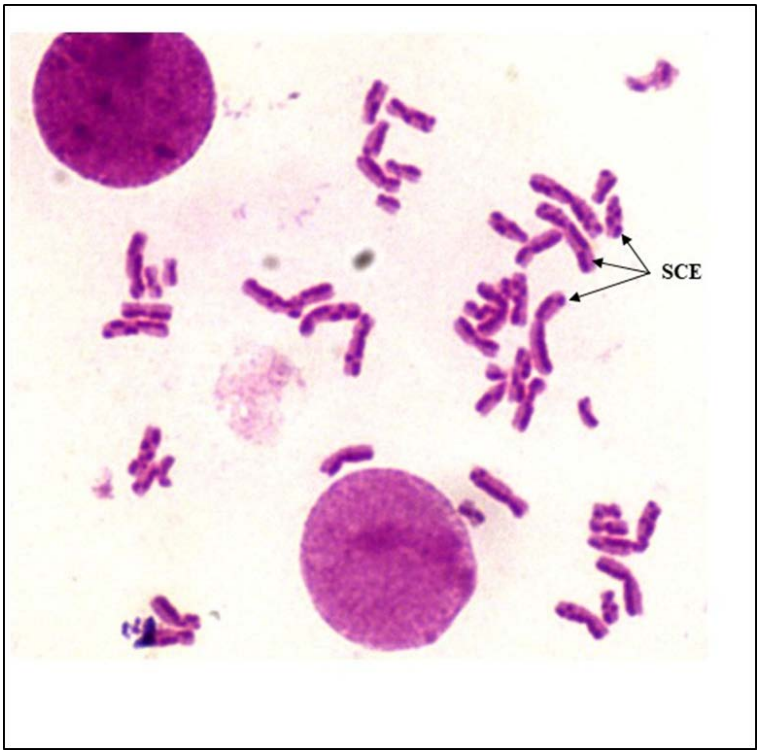

Figure 3. SCE formation in the metaphase of the second division (M2)
Slika 3. Formiranje SCE u metafazi druge deobe (M2)

Statistical Analysis

Statistical analyses of the data were performed with GraphPad Prism 10 software. The SCE frequency at each concentration of Gadobutrol was compared to that of the negative control by applying the Kruskal-Wallis H test, followed by Dunn's post hoc test for the SCE, MI, and PI data.

Results

This study examined the genotoxic, cytotoxic, and cytostatic effects of gadobutrol *in vitro* in both G_0 phase lymphocytes and circulating lymphocytes actively progressing through the cell cycle. In general, the results indicate a slight increase in SCE frequencies in response to gadobutrol exposure in both lymphocyte types. When compared to the negative control, this increase was not statistically significant in G_0 cells. Notably, at the highest gadobutrol concentration (25 mM), a significant increase in SCE formation was observed in circulating peripheral lymphocytes compared to the negative control

($p < 0.05$). Additionally, SCE frequency in circulating cells showed a linear dose-dependent increase with gadobutrol concentration, whereas no such association was found in G_0 phase lymphocytes (Table I and Table II). Finally, the analysis of MI and PI showed that gadobutrol did not cause any significant changes in either G_0 phase or circulating lymphocytes at the tested concentrations ($p > 0.05$; Table III).

Table I SCE frequency in response to gadobutrol exposure in G_0 phase lymphocytes

Tabela I Frekvencija SCE u limfocitima u G_0 fazi nakon izlaganja gadobutrolu

	Metaphases	SCE/cell
Negative Control	100	4.86 ± 0.52
MMC (Positive control)	100	19.5 ± 0.70
Gadobutrol		
1 mM	100	5.56 ± 0.48
5 mM	100	5.76 ± 0.13
25 mM	100	5.93 ± 0.68

SCE; sister chromatid exchange, MMC; mitomycin-C

Table II Genotoxic effect of gadobutrol in circulating human peripheral lymphocytes

Tabela II Genotoksični efekat gadobutrola u cirkulišućim perifernim limfocitima

	Metaphases	SCE/cell
Negative Control	100	4.58 ± 0.49
MMC (Positive control)	100	21 ± 1.41
Gadobutrol		
1 mM	100	5.21 ± 0.23
5 mM	100	5.47 ± 0.40
25 mM	100	5.79* ± 0.38

SCE; sister chromatid exchange, MMC; mitomycin-C

Table III Cytotoxic and cytostatic effects of gadobutrol in G_0 phase and circulating human peripheral lymphocytes

Tabela III Citotoksični i citostatski efekti gadobutrola u limfocitima u G_0 fazi i u cirkulišućim perifernim limfocitima

	Cells in G_0 phase		Circulating cells	
	MI	PI	MI	PI
Negative Control	2.5	1.6	2.8	1.7
Gadobutrol				
1 mM	2.6	1.5	2.8	1.8
5 mM	2.6	1.5	2.6	1.7
25 mM	2.5	1.4	2.5	1.6

MI: mitotic index; PI: proliferation index

Discussion

In the present study, we investigated gadobutrol's genotoxic and cytotoxic potential in both circulating cells and cells in the G_0 phase using the SCE assay. The results showed that gadobutrol increased SCE formation significantly in circulating human peripheral lymphocytes only at the highest concentration. Furthermore, in these cells, we found that the frequency of SCE showed a positive linear correlation with gadobutrol concentrations. The results indicate that a genotoxic response may also occur at lower concentrations with long-term exposure to gadobutrol or higher concentration may exert more DNA damage. Another *in vitro* study in circulating human peripheral lymphocytes on gadobutrol's genotoxicity reported a significant increase in SCE frequency (8). Furthermore, a previous study reported a statistically significant increase in micronucleus (MN) formation at 5 and 25 mM concentrations of gadobutrol in circulating lymphocytes using the cytokinesis-block micronucleus (CBMN) assay (7). The findings of this current study is in the line with those of Çobanoğlu (7) and Akbaş (8), indicating that gadobutrol has genotoxic potential with different mode of actions such as SCE and MN formation (7, 8). It is known that SCE occurs through the breakage of two sister chromatids and the subsequent physical displacement of homologous loci (24). On the other hand, one of the molecular mechanisms underlying MN formation is chromosome breakage (20). The *in vitro* studies summarized above suggest that gadobutrol stimulates both MN and SCE formation. Given that chromosomal breaks are a shared molecular mechanism in both methods, it can be inferred from that the genotoxic potential of gadobutrol may stem from its clastogenic effects.

To our knowledge, there is no *in vitro* study on the genotoxic effects of gadobutrol on G_0-phase lymphocytes. Although the SCE levels in response to *in vitro* gadobutrol exposure increased versus the control at all tested concentrations, these increases were not statistically significant. This result suggests several possibilities. Firstly, a significant increase in SCE frequency can be expected at higher concentrations or in response to longer exposure duration. Secondly, gadobutrol may be more genotoxic on lymphocytes progressing through the cell cycle, which would not be surprising. This is because the DNA of cells moving through the cell cycle is more susceptible to damage (20, 33). Finally, after G_0 exposure, cells were advanced through the cell cycle with PHA. Theoretically, cells must pass through S phase for the damage caused by G_0 exposure to be visible as SCE. Some of the damage formed in the G_0 phase may have been repaired before entering the S phase (34). It is thought that the glutathione content of cells may be the factor involved in this mechanism. Glutathione has many important roles in cell physiology such as scavenging ROS and protecting important molecules such as DNA (35). In some cell lines, different amounts of gulutathione were found in different cell stages. It has been found that the content of gulutathione increases in the lag phase of the cell, reaches the highest amount in the log phase and decreases in the logarithmic phase (36–38). However, as we have not investigated glutathione level in this study, further study will be warranted to investigate how glutathione is involved in this mechanism.

There are several studies investigating the cytotoxic effect of gadobutrol on circulating lymphocytes. For example, Akbaş showed that gadobutrol significantly decreased the MI value, representing the cytotoxic effect, at the 2 highest concentrations (56,000 and 112,000 µg/ml) (8). This result contradicts our result. This contradiction is thought to be due to the fact that the studied concentration was higher than the concentration we tested. In another study, investigating the cytotoxic effects of gadobutrol using the CBMN assay, no cytotoxic effect was reported (7). In the present study, it was found that gadobutrol had no cytotoxic effect on either G_0-phase lymphocytes or circulating lymphocytes. The findings align with those of Çobanoğlu regarding the cytotoxic potential of gadobutrol (7). The fact that gadobutrol was not cytotoxic at the same concentrations by two different methods strengthens the hypothesis that gadobutrol may not have a cytotoxic effect.

The observed increase in SCE formation was restricted to the highest concentration of gadobutrol, a level far exceeding those typically reached in clinical practice (8, 39). Under standard medical conditions, gadobutrol is administered at well-defined diagnostic doses, characterized by the low likelihood of repeated use, short systemic exposure, and rapid elimination (40). Moreover, human cells are equipped with highly efficient DNA repair and surveillance systems that effectively counteract transient genotoxic insults (41). Thus, while the *in vitro* findings suggest a potential effect at supraphysiological concentrations, the clinical relevance under routine exposure scenarios appears minimal. Nonetheless, the possibility of concern cannot be excluded in cases of chronic or repeated exposure. To further clarify this, more sensitive assays such as the comet assay, which detects single- and double-strand DNA breaks, could be employed to determine whether lower, clinically relevant concentrations also induce damage. Combining such approaches with DNA repair activity assays would additionally help assess the proportion of induced DNA lesions that can be efficiently repaired following gadobutrol exposure.

In conclusion, our results indicate that *in vitro* gadobutrol exposure does not produce a cytotoxic effect on G_0 or circulating lymphocytes in concentrations between 1–25 mM. The SCE findings indicated that gadobutrol might have a genotoxic effect when patients are treated by gadobutrol. Furthermore, the significant increase in SCE formation suggests that gadobutrol may have a clastogenic effect. Therefore, we suggest that contrast-enhanced MRI be employed with caution. On the other hand, our observations should be validated by future studies designed with different methods. In this context, we recommend designing *in vitro* cytogenetic studies using the fluorescence in situ hybridization (FISH) staining technique to clarify whether gadobutrol has a calstogenic potential. In addition, investigation of the effects of gadobutrol on oxidative stress parameters in future studies will be useful in understanding the underlying cause of its genotoxic potential. Finally, moving beyond *in vitro* systems, human population studies would provide more meaningful insights into the potential genotoxic risk of gadobutrol in real-world contexts.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

H.Ç.: Conceptualization, Investigation, Project administration, and Writing – original draft; **A.Ç**.: Conceptualization, Investigation, Formal analysis, and Supervision.

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Istraživanje razmene sestrinskih hromatida izazvane gadobutrolom u limfocitima u G_0 fazi i u cirkulišućim limfocitima

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Kratak sadržaj

Gadobutrol (Gadovist®) je makrociklični, ekstracelularni kontrastni agens na bazi gadolinijuma koji se često koristi u magnetnoj rezonanci. Cilj ove studije je da se proceni genotoksični i citotoksični potencijal gadobutrola u limfocitima u G_0 fazi i u cirkulišućim limfocitima. Za procenu genotoksičnosti korišćen je test razmene sestrinskih hromatida (SCE), koji je brza, osetljiva i pouzdana metoda za evaluaciju genotoksičnosti. Genotoksični efekti su procenjivani merenjem frekvencije SCE, dok je citotoksičnost određivana pomoću mitotskog indeksa (MI). Uzorci periferne krvi od dva zdrava davaoca tretirani su *in vitro* sa tri različite koncentracije gadobutrola tokom 24 sata u limfocitima u G_0 fazi i 72 sata u cirkulišućim limfocitima. Rezultati su pokazali da gadobutrol nije imao citotoksične efekte ni u jednom tipu ćelija. Međutim, pri najvišoj koncentraciji (25 mM), gadobutrol je značajno povećao formiranje SCE u cirkulišućim limfocitima ($p < 0,05$), dok kod limfocita u G_0 fazi nije uočena značajna genotoksičnost ($p > 0,05$). Ovi nalazi ukazuju da gadobutrol, iako nije citotoksičan, može indukovati genotoksične efekte u zavisnosti od koncentracije u cirkulišućim limfocitima. Potrebna su dalja istraživanja kako bi se razjasnile kliničke implikacije ovih nalaza.

Ključne reči: gadobutrol, genotoksičnost, razmena sestrinskih hromatida, G_0 faza, ćelijski ciklus