

## Research Article

# Association of Genetic Polymorphisms of Multidrug Resistance Protein (MDR) with Clinical Outcomes in Colchicine Intoxication

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## Abstract

**Objectives:** The current study aimed to investigate the question that if the genetic polymorphisms of MDR1 could be a contributing factor in prognosis of colchicine poisoned patients. For this purpose, we examined clinically significant MDR1 genetic polymorphisms in patients with colchicine intoxication and their relationship with treatment outcomes.

**Methods:** MDR1 polymorphisms were studied in the blood samples collected from patients with intake of subtoxic-toxic-lethal doses of colchicine before plasma or whole blood exchange between years 2013- 2018.

**Results:** A total of 17 patients were included in the study. Median age was 15 years (min:1-max:17). Mean dose of colchicine was  $0.52 \pm 0.2$  mg/kg. Activated charcoal and gastric lavage was performed to all of the patients and granulocyte colony stimulating factor was given to 8 (47.1 %) patients. Two (11.8 %) of the 17 patients died. Whole blood exchange was performed in 11 (64.7%) patients. Extracorporeal membrane oxygenation was performed to 2 (11.8%) patients. For 1236C>T genotypes, wild type, heterozygous (CT) and homozygous mutant genotypes were demonstrated in 1 (5.9%), 11 (64.7%) and 5 (29.4%) patients, respectively. For 2677G>T/A genotype heterozygous (GT) and homozygous mutant (TT) genotypes were demonstrated in 10 (58.8 %) and 7 (41.2%) patients respectively. For 3435C>T polymorphism, wild type, heterozygous (CT) and homozygous genotypes were demonstrated in 1 (0.9 %), 10 (58.8%) and 6 (35.3%) patients, respectively. Five (29.4%) out of 17 patients had combined TT-TT-TT homozygous genotypes for the polymorphisms of MDR1 1236C>T, 2677G>T/A, 3435C>T and two of these five patients died. The rate (40%) of died two patients carrying homozygous (TT-TT-TT) mutant haplotypes compared with rate (0%) of none of died twelve patients having heterozygous (CT or GT) mutant haplotypes was borderline significant (40% vs 0%,  $p=0.07$ ).

**Conclusion:** Two patients who died due to colchicine intoxication were homozygous carriers of the variant alleles with TT-TT-TT haplotype. Colchicine toxicity might lead to worse consequences including increased mortality in patients who are homozygous carriers of MDR1 polymorphic alleles.

**Keywords:** Colchicine intoxication, multidrug resistance-1 protein (MDR1), genetic polymorphism

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Colchicine is a potent inhibitor of the formation and function of microtubules.<sup>[1]</sup> Cellular mitosis, intracellular transport mechanism, and the continuity of cellular

structure and shape are disrupted through this pathway. Colchicine is an oil-soluble alkaloid obtained from a plant and rapidly absorbed from the gastrointestinal tract. It

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reaches peak plasma concentration in 30 minutes to two hours. Colchicine is mainly used for the treatment of Familial Mediterranean Fever, Behçet's Disease, acute gouty arthritis and additionally in the treatment of various autoimmune diseases.<sup>[2]</sup> Colchicine is primarily metabolized through hepatic deacetylation and demethylation mediated by cytochrome P450 3A4 (CYP3A4), and eliminated by bile, while the urinary system excretes 20% of the dose as unchanged.<sup>[3]</sup> Colchicine and most of its metabolites enter the enterohepatic circulation.<sup>[4]</sup> Colchicine is a substrate for P-glycoprotein (MDR1, ABCB1), a drug efflux transporter. This transporter is responsible for the excretion of colchicine from the body. Acute colchicine toxicity is a condition associated with a high mortality rate. Toxic effects are not usually seen at doses below 3 ng/mL. Colchicine binds to plasma proteins by 50%. The distribution volume is 2.2 liters/kg, which is greater than the total body fluid.<sup>[5]</sup> As a result, colchicine is rapidly absorbed in the body, but it remains in the bone marrow, skin, heart, spleen, kidney, lungs, and brain for a long time. Its terminal elimination phase is between 1.7 and 30 hours. In the case of colchicine intoxication, the elimination half-life can be prolonged up to 11 to 32 hours. There is no delay in the absorption even in the case of high-dose intake.<sup>[6]</sup> After absorption, colchicine spreads rapidly into all tissues and attaches to the intracellular components. It has been reported that colchicine can be detected in neutrophils and urine for up to 9 days, even after using a single dose.<sup>[7]</sup> The elimination half-life can raise up to 10fold in patients with severe renal insufficiency and liver cirrhosis. Postmortem tissue studies have shown high amounts of colchicine in the bone marrow, testis, spleen, kidneys, liver, gastrointestinal tract, lungs, and brain.<sup>[6]</sup>

Colchicine intoxication is a life-threatening condition and is dose-dependent. Colchicine-related deaths are usually due to hypovolemic shock and cardiovascular failure, which depends on rapidly developing organ failure.<sup>[8]</sup> Hemodialysis and hemoperfusion is not beneficial in the treatment of colchicine intoxication because colchicine has a very wide tissue distribution and binds to plasma proteins at a high rate. In the first hours of high dose colchicine intake, it is taken in the white and red blood cells as 5 to 10 times more concentrated than in serum. Therefore leukopenia and thrombocytopenia are observed in the case of colchicine intoxication. Colchicine affects neutrophil functions by influencing inflammatory pathways and mediators. Colchicine inhibits neutrophil accumulation and attachment by decreasing the expression of L-selectin in endothelial cells.<sup>[9]</sup>

In the pathophysiology of colchicine toxicity; after drug in-

gestion, microtubule polymerization is inhibited by binding to intracellular tubulin protein. Impairment of the microtubule network leads to the disruption of cell shape, reduces cellular motility, and as a result, mitosis stops. Toxic doses of colchicine stop mitosis in the metaphase phase, thus cell division is inhibited. This effect occurs in all cells throughout the body, which results in multiple organ failures in colchicine intoxication. Bone marrow, gastrointestinal tract, and hair follicles, which have a fast cell division cycle, are the most vulnerable areas.

Multidrug resistance-1 glycoprotein (MDR1, ABCB1) is a protein of the MDR1 gene and belongs to the ATP-binding cell membrane transport superfamily.<sup>[10]</sup> MDR1 was first isolated from chemotherapy-resistant cancer cells and is responsible for multidrug resistance through drug efflux.<sup>[11]</sup> In a study, Ozen and colleagues examined DNA samples of 52 patients refractory to colchicine therapy and demonstrated a significant correlation between 3435C>T polymorphism in the MDR1 gene and resistance to colchicine.<sup>[12]</sup> In other words, in vivo expression and activity of MDR1 increase in patients with MDR13435TC>T functional polymorphism, MDR1 protein is synthesized twice more than those without polymorphism. Increased MDR1 protein leads to the efflux of colchicine out of the cell, resulting in unresponsiveness to colchicine. In another study, the relationship of MDR1 gene 3435C>T polymorphism and colchicine resistance was investigated in 22 patients with FMF (Familial Mediterranean Fever) who were unresponsive to colchicine and 98 patients who responded to colchicine. It was shown in this study that homozygous mutant patients were associated with a better colchicine response.<sup>[7]</sup> Mean colchicine dose required for remission was significantly lower in TT subjects.<sup>[13]</sup>

When the question of why some patients die despite similar treatments in patients with toxic-lethal dose colchicine intoxication combined with knowledge of treatment due to MDR1 polymorphisms; the hypothesis of MDR1 homozygote patients for the polymorphic alleles with lower functionality being the responsible factor has emerged.<sup>[7]</sup> To investigate this hypothesis, MDR1 genetic polymorphisms in patients with colchicine intoxication were examined.

## Methods

MDR1 polymorphisms were studied in the blood samples collected from patients with subtoxic-toxic-lethal dose of colchicine intoxication before plasma exchange and whole blood exchange in between 2012 and 2016. Ethical approval was obtained from the Hacettepe University Ethics Committee.

### Determination of MDR1(ABCB1) Genotypes: C1236T, G2677T/A, and C3435T

In order to determine MDR1 genotypes, blood samples were collected and taken into EDTA-containing tubes. The samples were stored at -20 °C until the analysis. Before the study, blood samples were lysed at room temperature for one hour, and about 4-12 µg of DNA was isolated in 200 µl from the blood samples using a kit.

To identify the MDR1 rs1128503 (C1236T) genotype; a polymerase chain reaction (PCR) was performed using 5'-TGGACTGTTGTGCTCTCCCC-3' and 5'-TGTCACCTTATC-CAGCTCTCCA-3' primers at a concentration of 20 µM. PCR conditions were as follows: 15 minutes at 95°C, 30 seconds at 95°C, 30 seconds at 60°C, 30 seconds at 72°C (30 times), and 10 minutes at 72°C. A mixture of 200 µM dATP, 200 µM dCTP, 200 µM dGTP, 200 µM dTTP, and 12.5 mM MgCl<sub>2</sub> were used in PCR. The product of 412 base length obtained from PCR was left to cut using a HaeIII cutting enzyme at 37°C for 16 hours. The cutting enzyme breaks the PCR product into pieces of 377 + 43 + 35 base length in the presence of C allele, and into pieces of 412+43 base length in the presence of T allele. Cutting products were run in 3% agarose gel and then visualized under UV light.

To detect MDR1rs2032582(G2677T/A) genotype; the 5'-TGCAGGCTATAGGTTCCAGG-3' and 5'-TTTAGTTTGACT-CACCTTCCCCG-3' primers were used. PCR was performed under the conditions used to detect MDR1 rs1128503 genotype. The product of 224 base length obtained from PCR was left to cut using BanI cutting enzyme at 37°C for 16 hours. BanI enzyme cleaves the PCR products into pieces of 198+26 base length in the presence of G allele, while it does not make cutting in the presence of T allele. Detection of cutting products was carried out in the same way as MDR1 rs1128503 cutting products were detected. In order to determine A allele, a further PCR was performed under the same conditions using 5'-TGCAGGCTATAGGTTCCAGG-3' and 5'-GTTTGACTCACCTTCCCCAGG-3' primers. The product of 220 base length obtained from the PCR was left to cut using BsrI cutting enzyme 65°C for 16 hours. While BsrI enzyme does not make cutting in the presence of G allele, it breaks the PCR product into pieces of 206+14 base length in the presence of A allele. Unlike the previous method, the cut products were run using 3.5% agarose gel.

To detect MDR1rs1045642 (C3435T) genotype, 5'-TGTTTTCAGCTGCTTGATGG-3' and 5'-AAGGCATGTAT-GTTGGCCTC-3' primers were used. MboI enzyme was used for the cut of the PCR product of 197 base length. PCR and cutting conditions were the same as MDR1rs1128503 genotype. While MboI enzyme breaks the PCR product into pieces of 158+39 base length in the presence of C allele, it does not

make cutting in the presence of T allele. Visualization of the cutting products is the same as MDR1rs1128503 genotype.

### Statistical Analysis

Descriptive statistics of data were analyzed using software; Statistical Package For Social Sciences for Windows 20.

### Results

In between 2012 and 2016, total 17 patients who had received a subtoxic-toxic-lethal dose of colchicine were included in study population. Median age was 15 years (min:1- max:17) and most of them were female (n=15, 88.2%). Mean dose of received colchicine was 0.52±0.2 mg/kg. Twelve (70.6%) of the patients received colchicine for suicide attempt. Activated charcoal and gastric lavage was performed to all (n=17) of the patients and granulocyte colony-stimulating factor was given to 8 (47%) patients. Two (11.7 %) of the 17 patients died. Whole blood exchange was performed to 11 (65 %) patients. Extracorporeal membran oxygenation was performed to 2 patients. In C1236T genotype wild type<sup>[14]</sup>, hetero (CT) and homozygote<sup>[7]</sup> mutant polymorphism locus were demonstrated in 1 ( 5.9 %), 11 (64.7%) and 5 (29.4 %) patients , respectively. In G2677T/A genotype hetero (GT) and homozygot<sup>[7]</sup> mutant polymorphism locus were demonstrated in 10 ( 58.8 %), 7 (41.2%) patients , respectively. In C3435T genotype wild type<sup>[14]</sup>, hetero (CT) and homozygot<sup>[7]</sup> mutant polymorphism locus were demonstrated in 1 (5.9 %), 10 (58.8%) and 6 (35.3 %) patients, respectively. Mean P-MODS of patients was 4±1.1. The details of all patient characteristics and the received dose of colchicines and performed therapy modalities were demonstrated in Table 1.

### Discussion

The current study was demonstrated that 5 out of 17 patients who received a subtoxic-toxic-lethal dose of colchicine had TT homozygote allele polymorphism in C1236T, G2677T/A, C3435T gene loci. Two of these five patients with homozygote polymorphism of MDR-1 gene were died although they have intensive treatment including whole blood exchange.

There is an overlap between the therapeutic and the toxic doses because of the narrow therapeutic index of colchicine. When its dose exceeds 0.5 mg/kg, colchicine may lead to intoxication with high rates of mortality. Whereas, minor toxicities such as gastrointestinal abnormalities and impairment in the coagulation system may be detected in cases of colchicine intakes <0.5 mg/kg. Major toxicities such as bone marrow aplasia are observed in colchicine intake in between 0.5 to 0.8 mg/kg with a mortality rate

| Table 1. Clinical and MDR-1 gene polymorphism characteristics of the patients with colchicine intoxication  |             |        |            |                  |   |        |   |               |                      |                        |                      |  |
|---|-------------|--------|------------|------------------|---|--------|---|---------------|----------------------|------------------------|----------------------|--|
| Case  | Age (years) | Gender | Dose mg/kg | Reason           | Treatment   | P-MODS | End Organ Damage  | Final Status  | 1236C>T Polymorphism | 2677G>T/A Polymorphism | 3435C>T Polymorphism |  |
| 1   | 16          | female | 0.4        | Suicide Inotrope | AC, GL, PE, G-CSF   | 3      | Cardiac, hematologic, hepatic                                 | Full recovery | CT                   | TT                     | CT                   |  |
| 2   | 14          | female | 0.6        | Suicide          | AC, GL, Whole Blood Exchange, inotrope, G-CSF               | 4      | Cardiac, neurologic, respiratory, hematologic                 | Full recovery | CT                   | GT                     | CC                   |  |
| 3   | 1           | female | 0.4        | Accidentally     | AC, GL, PE  | 4      | Respiratory, neurologic cardiac, hematologic,                 | Full recovery | CT                   | GT                     | CT                   |  |
| 4   | 16          | female | 0.8        | Suicide          | AC, GL, PE, G-CSF, Whole Blood Exchange,                    | 5      | Respiratory, cardiac, hematologic, neurologic, hepatic        | Full recovery | CT                   | GT                     | CT                   |  |
| 5   | 5           | male   | 1.2        | Accidentally     | AC, GL, PE, G-CSF, HFO, CVVHDF, ECMO, Whole Blood Exchange, | 6      | Respiratory, cardiac, hematologic, neurologic, renal          | Died          | TT                   | TT                     | TT                   |  |
| 6   | 16          | female | 0.5        | Suicide          | AC, GL, MV, PE, Whole Blood Exchange, Inotrope, ECMO        | 6      | Respiratory, cardiac, hematologic, neurologic, hepatic, renal | Died          | TT                   | TT                     | TT                   |  |
| 7   | 16          | female | 0.5        | Suicide          | AC, GL, PE, Whole Blood Exchange,                           | 3      | Hematologic, hepatic, cardiac                                 | Full recovery | CT                   | GT                     | CT                   |  |
| 8   | 14          | female | 0.4        | Suicide          | AC, GL, PE, G-CSF   | 3      | Hematologic, neurologic, respiratory                          | Full recovery | CT                   | GT                     | CT                   |  |
| 9   | 16          | female | 0.5        | Suicide          | AC, GL, HD, PE, Whole Blood Exchange, G-CSF, Inotrope       | 5      | Respiratory, cardiac, hematologic, hepatic, renal             | Full recovery | CC                   | GT                     | CT                   |  |
| 10  | 15          | female | 0.4        | Suicide          | AC, GL, PE, Whole Blood Exchange,                           | 5      | Respiratory, cardiac, hematologic, hepatic, neurologic        | Full recovery | CT                   | GT                     | CT                   |  |
| 11  | 3           | male   | 0.8        | Accidentally     | AC, GL, PE, G-CSF, whole Blood Exchange,                    | 4      | Cardiac, hematologic, hepatic, respiratory                    | Full recovery | CT                   | GT                     | CT                   |  |
| 12  | 2           | female | 0.4        | Accidentally     | AC, GL, PE  | 3      | Hematologic, hepatic, respiratory                             | Full recovery | CT                   | GT                     | CT                   |  |
| 13  | 16          | female | 0.4        | Suicide          | AC, GL, PE, Whole Blood Exchange, G-CSF                     | 4      | Respiratory, hematologic, hepatic, neurologic                 | Full recovery | TT                   | TT                     | TT                   |  |
| 14  | 15          | female | 0.4        | Suicide          | AC, GL, PE  | 3      | Hematologic, hepatic, neurologic                              | Full recovery | CT                   | TT                     | TT                   |  |
| 15  | 14          | female | 0.4        | Suicide          | AC, GL,   | 3      | Hepatic, neurologic hematologic                               | Full recovery | CT                   | GT                     | CT                   |  |
| 16  | 3           | female | 0.6        | Accidentally     | AC, GL, PE, Whole Blood Exchange,                           | 4      | Respiratory, hematologic, hepatic, renal                      | Full recovery | TT                   | TT                     | TT                   |  |
| 17  | 17          | female | 0.5        | Suicide          | AC, GL, PE, Whole Blood Exchange,                           | 4      | Respiratory, hepatic, neurologic hematologic                  | Full recovery | TT                   | TT                     | TT                   |  |
| AC: Activated Charcoal; GL: Gastric Lavage; PE: plasma exchange; HFO: High-frequency oscillation; CVVHDF: Continuous venovenous hemodiafiltration; ECMO: Extracorporeal membrane oxygenation; MV: Mechanical Ventilation; HD: Hemodialysis; MDR: Multiple drug resistance; P-MODS: Pediatric multi-organ dysfunction score. |             |        |            |                  |   |        |   |               |                      |                        |                      |  |

AC: Activated Charcoal; GL: Gastric Lavage; PE: plasma exchange; HFO: High-frequency oscillation; CVVHDF: Continuous venovenous hemodiafiltration; ECMO: Extracorporeal membrane oxygenation; MV: Mechanical Ventilation; HD: Hemodialysis; MDR: Multiple drug resistance; P-MODS: Pediatric multi-organ dysfunction score.



of 10%. Lethal dose has been reported as  $> 0.8$  mg/kg.<sup>[15]</sup> Despite these facts, there is a lot of variability between the doses leading to colchicine intoxication and clinical findings, and the prognosis is not exactly correlated with ingested dose of colchicine. There is no clear limit between non-toxic, toxic and lethal doses. The lowest dose of oral colchicine has been reported in between 7 and 26 mg.<sup>[16]</sup>

The main signs of colchicine intoxication can be summarized in three phases. In first phase 1 which was observed in first 24 hours, nausea-vomiting, diarrhea, dehydration, and leukocytosis can be detected. This phase is also called the gastrointestinal phase.<sup>[17]</sup> In second phase (1-7 days); Multi-organ failure and metabolic changes are detected. Sudden cardiac death, pancytopenia, renal insufficiency, sepsis, acute respiratory distress syndrome (ARDS), electrolyte imbalance, and rhabdomyolysis may be seen at this phase. In colchicine intoxication, death usually occurs due to hemodynamic collapse or cardiac arrhythmias, infectious and hemorrhagic complications. Death occurs 24-36 hours after colchicine intake, although sudden deaths have also been reported.<sup>[8, 18]</sup> In third phase ( $>7$  days and later); patients who survive enter the recovery period. In this period, rebound leukocytosis is usually observed and organ failures are improved. In addition, alopecia, myopathy, neuropathy, and myoneuropathy may be detected in survivors of acute colchicine intoxication.<sup>[19]</sup> Signs of axonal neuropathy may occur due to impaired neuronal conduction.

At admission to hospital firstly we attempt eliminate the ingested colchicine from the gastrointestinal tract by gastric lavage followed by activated charcoal.<sup>[19]</sup> Due to large volume distribution capacity of colchicine hemodialysis and hemoperfusion is ineffective. Therefore in routine daily practice main treatment strategy against colchicine intoxication is supportive therapy. Fluid replacement, inotropes if necessary, and respiratory support (intubation and positive pressure ventilation, when needed) are administered, and antibiotics are given in the case of a suspected secondary infection. Gastric lavage and repeating doses of activated charcoal are given within the first 1-2 hours since colchicine enter the enterohepatic circulation. G-CSF (Granulocyte colony-stimulating factor) can be administered if leucopenia develops.

In literature there are preliminary studies to overcome colchicine toxicity. There were some attempts to develop anti-colchicine polyclonal antibodies. In animal models anti- anti-colchicine antibodies reversed the anti-mitotic effect of colchicine.<sup>[20]</sup> However, these antibodies were in earlier phases of development. Anti-colchicine antibody increased the clearance of rat urinary colchicine in a rat model of colchicine intoxication.<sup>[14]</sup> In literature there was

one case of 25 year old woman who was ingested 60 mg colchicine and successfully treated with administration of goat colchicine-specific Fab fragments.<sup>[21]</sup> Specific antibodies against colchicine are promising. Unfortunately, in current clinical practice until now these antibodies has not been commercially available. There has been no specific therapy previously established. There was lack of data and new treatment approaches are urgently needed. Although there is lack of strong evidence, early initiation of either whole blood or plasma exchange may be considered in patients presenting with administered 0.5 mg/kg or more colchicine. In a study published from our center in 2011, benefits of urgent plasma exchange and whole blood exchange were investigated in pediatric age group patients who had received potentially lethal doses of colchicine.<sup>[22]</sup> Twenty-three patients who had received potentially lethal doses of colchicine between 1985 and 2011 were included in that study. Colchicine intake was found at sub-toxic doses ( $<0.5$  mg/kg) in 16 patients, toxic doses (0.5 - 0.8 mg/kg) in three patients, and lethal doses ( $>0.8$  mg/kg) in four patients. All the 16 patients who had received sub-toxic doses of colchicine were administered active charcoal and/or gastric lavage, while only one patient underwent plasma exchange. This whole group was discharged with full recovery. Seven patients who had received colchicine in toxic and lethal doses were administered whole blood exchange, plasma exchange, and vasopressor support treatments. Three (13%) of these patients died, despite these treatment combinations. In this study four patients exposed to lethal ( $>0.8$  mg/kg) dose of colchicine. Two of the died patients had been exposed to lethal doses of colchicine. Thus, of the patients who had received lethal doses of colchicine, only 50% died. There are publications in the literature reporting mortality by 100% in the intoxication of lethal dose colchicine.<sup>[8]</sup> This rate was 50% in the publication from our center. The fact that despite receiving similar treatments, some patients die, while the others are discharged with full recovery suggests that there might be underlying causes, which we decided to investigate.

In the current study, it was found that two patient who died was a homozygous carrier of the variant alleles for all three loci examined a subject with TT-TT-TT haplotype. In patients exposed to colchicine intoxication at a toxic or lethal dose, efflux of colchicine out of the cell might possibly be less effective in patients with polymorphic alleles in the MDR1 gene (patients homozygous for the variant alleles) as compared with patients carrying heterozygote type alleles. Therefore, colchicine toxicity may lead to worse consequences including mortality in patients who are homozygous mutant carriers. Colchicine rather remains in tissues in patients with homozygous variant alleles. Therefore, plasma exchange

and removing colchicine from plasma may be insufficient for treatment. We assume that adding erythropheresis and leukapheresis to treatment to remove colchicine in tissues may contribute to the treatment of these patients. On the other hand case 13, 16 and 17 had also homozygous mutant carriers of alleles (TT-TT-TT), however, these three cases were benefited from treatment which was also include whole blood exchange. They were discharged from pediatric intensive care unit with full recovery. It needs to emphasize that why the two of patients with homozygous mutant carriers of alleles (TT-TT-TT) was died and the other three did not died. Recent porcine model study evaluating the role of anti-colchicine Fab fragments to prevent lethal colchicine toxicity was published. In that study animal model of colchicine toxicity was created and when the researchers administer a full-neutralising equimolar Fab dose given 6 h after colchicine infusion they observe that all free plasma colchicine was removed. However, colchicine toxicity did not prevented in these animals who received antibody 6 hours from colchicine infusion. In the same study earlier administration over 1 h of the full neutralising dose, 1 or 3 h after the colchicine, all of the free plasma colchicine removed until 20 h, and porcine models of colchicine toxicity survive until the end of the study without marked cardiotoxicity.<sup>[23]</sup> As we realize from that study the early intervention after colchicine toxicity is lifesaving. First hours after poisoning is very important. In the current study as we reported 3 out of 5 patients with homozygous mutant carriers of alleles (TT-TT-TT) did not died and benefited from therapy. We retrospectively checked the patients hospital file data to learn the admission time interval of these patients after colchicine administration. We realize that the three patients with homozygous mutant carriers of alleles (TT-TT-TT) and discharged with full recovery admitted to hospital within first 6 hours after ingestion. On contrary the two patients with homozygous mutant carriers of alleles (TT-TT-TT) who were died, admitted to hospital 72 hours after ingestion of colchicine. We thought that in early time period after ingestion of toxic doses of colchicine, although the patients having homozygote alleles polymorphism of MDR-1 gene colchicine can be removed from body by performing whole blood exchange.

## Conclusion

In conclusion, evaluation of MDR1 genetic polymorphisms may be suggested as a prognostic parameter in patients with colchicine intoxication at toxic and lethal doses. Presented results might suggest a protective role for MDR1 gene polymorphisms in patients with toxic dose of colchicine intake. This knowledge leads us to novel therapies targeting intracellular colchicine clearance for the selected patients with certain genotypes.

## Disclosures

**Ethics Committee Approval:** The study was approved by the Ethical Committee of the Hacettepe University Hospital.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

**Authorship Contributions:** Concept – M.U.Y., B.B.; Design – M.U.Y., M.B.; Supervision – M.B., A.M., M.U.Y.; Materials – M.U.Y., A.M., M.B.; Data collection &/or processing – M.U.Y., A.M.; Analysis and/or interpretation – M.U.Y., B.B., A.M., M.B.; Literature search – M.U.Y., A.M.; Writing – M.U.Y., A.M.; Critical review- M.U.Y., A.M., M.B., B.B.

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