

39. Colchicine-Induced Pancytopenia During Therapeutic Dose Administration. French Pharmacovigilance Database Survey and Literature Review

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Background: Colchicine is an antimitotic agent, highly effective in the treatment of microcrystalline arthritis, Behcet's disease and familial Mediterranean fever. Pancytopenia by bone-marrow depression is common after colchicine overdose and intoxication. It is less common at therapeutic dose and it may be fatal. Colchicine has a low narrow therapeutic range.

Aims: The purpose of this work is to determine the seriousness, the risk factors and the outcome of pancytopenia in patients treated with low dosage of colchicine ($\leq 2\text{mg/d}$).

Methods: All case-reports of pancytopenia and marrow depression were collected in French Pharmacovigilance database between 1984 and May 2006, and from literature, and were analysed.

Results: 42 case-reports were retained: 33 from database and 9 from literature (see table I).

Table I. Case reports

	Database n = 33	Literature n = 9
Average age	63.8 (33-93 years old)	61.9 (29-96 years old)
Renal/liver impairment	n = 27	n = 4
Drug-drug Interaction ^a	n = 3	n = 2
P-gp inhibitors ^b	n = 6	-
Hematotoxic drugs comb ^c	n = 18	-
Onset delay ≤ 1 month	n = 19	n = 7
> 1 month	n = 9	n = 2
unknown	n = 5	-
Outcome Favourable	n = 13	n = 4
Sequelae	n = 2	-
Death	n = 14	n = 5
Unknown	n = 4	-

a Drug-drug interaction: macrolides.

b P-gp inhibitors: amiodarone (2), metronidazole (1), simvastatin (1), nicardipine (1), spironolactone (1), acebutolol (1).

c Hematotoxic drugs combination: allopurinol (11), azathioprine (2), methotrexate (1), chemotherapy (1), others (3).

Discussion: Colchicine is primarily eliminated through biliary excretion. Renal excretion play a less significant role. Case reports suggest that pancytopenia often occurred during colchicine administration with combined liver and/or renal impairment (database: 81.8%, literature: 44.4%), and with hematotoxic drugs (database: 54.5%). CYP3A4 is responsible for colchicine demethylation. Colchicine may interact with other drugs (macrolides) by interfering with metabolism by CYP3A4. Colchicine is also a substrate of the P-gp, a transporter involved in cellular efflux and elimination of numerous drugs. Co-administration of colchicine and CYP3A4 and/or P-gp inhibitors may impair colchicine elimination, resulting in excess drug exposure and toxicity, and explaining severe adverse effects and deaths.

Conclusion: Colchicine can be toxic even at therapeutic dose. It should be used with extreme caution in patients receiving CYP3A4 and/or P-gp inhibitors and hematotoxic drugs, particularly if they are elderly with renal and/or liver impairment. We propose modifications of the French summary of product characteristics concerning adverse drug reactions section.

References

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