



**HAL**  
open science

## **Risk of hospitalisation for serious colchicine intoxication after concomitant exposure to pristinamycin: A nationwide healthcare database study**

Cécile Souty, Ana-Maria Vilcu, Cécile Conte, Béatrice Saint-Salvi, Marianne Sarazin, Louise Rossignol, Thierry Blanchon, Thomas Hanslik, Maryse Lapeyre-Mestre, Olivier Steichen

### ► To cite this version:

Cécile Souty, Ana-Maria Vilcu, Cécile Conte, Béatrice Saint-Salvi, Marianne Sarazin, et al.. Risk of hospitalisation for serious colchicine intoxication after concomitant exposure to pristinamycin: A nationwide healthcare database study. *Therapies*, 2022, 10.1016/j.therap.2022.12.012 . hal-04070806

**HAL Id: hal-04070806**

**<https://hal.science/hal-04070806>**

Submitted on 16 Apr 2023

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# Risk of hospitalisation for serious colchicine intoxication after concomitant exposure to pristinamycin: a nationwide healthcare database study

Titre court: Risk of colchicine-pristinamycin interaction

Cécile Souty <sup>1</sup>, Ana-Maria Vilcu <sup>1</sup>, Cécile Conte <sup>2</sup>, Béatrice Saint-Salvi <sup>3</sup>, Marianne Sarazin <sup>1</sup>, Louise Rossignol <sup>1,4</sup>, Thierry Blanchon<sup>1</sup>, Thomas Hanslik <sup>1,5,6</sup>, Maryse Lapeyre-Mestre <sup>2</sup>, Olivier Steichen<sup>1,7</sup>

1. Sorbonne Université, INSERM, Institut Pierre Louis d'épidémiologie et de Santé Publique, Paris, France
2. Université de Toulouse 3, Service de Pharmacologie médicale et clinique, CIC 1436, Toulouse, France
3. Agence Nationale de Sécurité du Médicament et des produits de santé, Saint-Denis, France
4. Université de Paris, Département de Médecine Générale, Paris, France
5. Université de Versailles Saint-Quentin-en-Yvelines, UVSQ, UFR de Médecine, Versailles, France
6. Assistance Publique - Hôpitaux de Paris (APHP), Hôpital Ambroise Paré, Service de Médecine Interne, Boulogne Billancourt, France
7. Assistance Publique-Hôpitaux de Paris (AP-HP), Hôpital Tenon, Service de médecine interne, Paris, France

Auteur correspondant : Pr Olivier Steichen  
Service de médecine interne, hôpital Tenon  
4 rue de la Chine, 75020 Paris, France  
Tel 01 56 01 78 31 ; Fax 01 56 01 71 46  
Email [olivier.steichen@aphp.fr](mailto:olivier.steichen@aphp.fr)

Keywords: colchicine; pristinamycin; drug interactions; adverse drug reactions; pharmacoepidemiology

## Introduction

The therapeutic margin of colchicine is narrow, with serious intoxication involving the digestive tract, the bone marrow, the neuromuscular system, eventually leading to multi-organ failure and death. The risk of intoxication increases with high doses or reduced clearance of colchicine (renal or hepatic insufficiency).

Colchicine concentration may also be increased by CYP3A4 or P-glycoprotein inhibitors such as pristnamycin, a mixture of streptogramins A and B approved in France for the treatment of bacterial sinusitis or pneumonia, and skin infections. Cases of colchicine poisoning with concomitant exposure to pristnamycin have been reported (1,2). Based on this rationale, co-administration of pristnamycin and colchicine is contraindicated by the French National Drug Safety Agency (*Agence nationale de sécurité du médicament et des produits de santé* [ANSM]) (3). French dispensing data show that they are nonetheless frequently codelivered (4). However, pharmaco-epidemiological evidence of the associated risk is lacking (5).

We aimed to estimate the risk of hospitalisation for presumed serious intoxication in patients using colchicine and exposed to pristnamycin, based on drug dispensing and hospital data concerning all beneficiaries of the French healthcare insurance system.

## Methods

### Data sources

This study was based on the French national health data system (*Système national des données de santé* [SNDS]) (6). This system covers about 99% of the population living in France (about 67 million people). The SNDS contains information on individuals (age, sex) and medical claims – including drugs dispensed by community pharmacies and reimbursed by the French Insurance system (date of dispensing, drug identification number, number of boxes), and hospital stays (dates, diagnoses).

### Study population

All adults ( $\geq 18$  years old) hospitalized for a diagnosis compatible with colchicine intoxication or a known serious adverse reaction to colchicine between 2010 and 2018 while exposed to colchicine during the 15 days before the admission were included in the study.

### Hospitalisation for presumed serious intoxication

Hospitalizations for presumed serious colchicine intoxication were identified using the ICD-10 codes registered as primary or related diagnosis referring to anaemia, thrombocytopenia, agranulocytosis, polyneuropathy, myopathy, toxic liver disease, agranulocytosis, toxic nephropathy, shock and drug poisoning.

## Study design

The association between concomitant exposure to colchicine and pristinamycin and presumed colchicine intoxication was estimated using a case-crossover design, a self-matched case-control design in which each case serves as its own control according to periods well suited for evaluating outcomes of drug–drug interactions (7).

To account for the increased risk of colchicine intoxication possibly associated with the underlying infection (indication bias), we also considered exposure to amoxicillin-clavulanic acid (co-amoxiclav) as a negative control precipitant (antibiotic used to treat similar infections but without CYP3A4 and P-glycoprotein inhibiting properties).

For each patient, we compared the concomitant exposure to pristinamycin or co-amoxiclav and colchicine during the 15-day period preceding the hospitalization (hazard period), with the exposure during the control periods, which were defined as all 15-day periods of exposure to colchicine over the year preceding the hazard period (Figure 1). Thus, the number of control periods varied among individuals included in the analysis. We set a 15-day washout period just prior to the hazard period in order to avoid autocorrelation in exposure between periods and carryover effects (7).

## Exposure to colchicine and pristinamycin or amoxicillin-clavulanic acid

Exposure to colchicine was assumed to begin from the day of drug dispensing. The duration of exposure was estimated using the defined daily dose (1 mg per day) and dispensed volume (number of units per box and unit dosage) (8). Concomitant exposure to pristinamycin or co-amoxiclav and colchicine was defined by a dispensing of the drug during the 15-day period of colchicine exposure.

## Statistical analysis

We first assessed the number of patients hospitalised for presumed colchicine intoxication over the study period, including those concomitantly exposed to pristinamycin. We then used conditional logistic regression to estimate the odds ratios (ORs) of the association between hospitalisation for presumed colchicine intoxication and concomitant exposure to colchicine and pristinamycin or colchicine and co-amoxiclav, compared to colchicine alone.

Patients were informative for this analysis and included in the regression model if (i) they had at least one control period with exposure to colchicine within the year preceding the hospitalisation and (ii) they had a discordant exposure to pristinamycin during the hazard period and at least one of their control periods.

Analyses were adjusted for exposure to other drugs that could interfere with the risk of colchicine intoxication: macrolides (except spiramycin), ciclosporin, fluconazole, strong inhibitors of CYP3A4 (cobicistat, itraconazole, ketoconazole, posaconazole, ritonavir, voriconazole), ombitasvir and paritaprevir, verapamil (3).

## Results

From 2010 to 2018, in France, 2 951 075 individuals were exposed to colchicine and 128 859 (4.4%) were concomitantly exposed to pristinamycin. Among those exposed to colchicine, 2 945 (0.1%) were hospitalised for a presumed serious adverse reaction to colchicine and 1 568 (53.2%) presented at least one other period of exposure to colchicine within the year preceding the hospitalization, which could be used as control period.

We included 233 individuals with discordant exposures to pristinamycin or co-amoxiclav between the hazard period and at least one control period in the conditional logistic regression model. Their median age was 71 years old (inter-quartile range 62-80), and 161 (69%) were men. The two most frequent hospitalization diagnosis were "Drug-induced aplastic anaemia" (n=76, 33%) and "Other specified disorders of muscle" (n=50, 21%). The median duration of hospital stay was 7 days (IQR 2-12) and 18 individuals (8%) died during their stay. The median number of control windows per patient was 8 [interquartile range from 3 to 13]. Compared to exposure to colchicine alone, the OR of hospitalization for colchicine intoxication was 1.37 [95%CI: 0.71, 2.64] after concomitant exposure to pristinamycin and 1.54 [95%CI: 1.08, 2.20] after concomitant exposure to co-amoxiclav. These risks did not differ significantly (Wald p=0.76).

## Discussion

Although the concomitant administration of colchicine and pristinamycin is contraindicated in France, we found that 4.4% of patients who had been taking colchicine during the study period were concomitantly exposed to pristinamycin at least once. However, using this nationwide real-world data collected over 9 years, we did not evidence an increased risk of hospitalisation for presumed colchicine intoxication after concomitant exposure to colchicine and pristinamycin compared to colchicine alone. The trend toward a slightly higher risk may be related to the underlying acute health condition, as suggested by the similar figure observed after concomitant exposure to co-amoxiclav. Indeed, co-amoxiclav does not interact with colchicine and the increased risk of intoxication must therefore be attributed to the infections for which it was prescribed. Since pristinamycin and co-amoxiclav share a large part of their indications, a similarly increased risk can be attributed to the infections for which pristinamycin was prescribed.

CYP3A4 and P-glycoprotein inhibiting properties have been reported for pristinamycin and its prodrug quinupristin/dalfopristin (9). These drugs could therefore increase the risk of colchicine intoxication. Two case reports of colchicine intoxication following pristinamycin exposure have been published. However, both involved elderly patients with chronic kidney disease who received high doses of

colchicine (6 or 7 mg within the first 3 days) (1,2). These patients had at therefore least three risk factors of colchicine intoxication apart from pristinamycin, whose contribution is therefore uncertain. Our study has several strengths. We analysed nationwide real-world data using a case-crossover design, which estimates the short-term risk of an acute outcome associated with transient exposure, time-invariant confounding being accounted for by design (7,10). We adjusted the estimates on exposure to other drugs that may interact with colchicine. We accounted for the pristinamycin-related indication bias by comparison to co-amoxiclav as a negative control.

However, our study has some limitations related to the use of claims data. First, drug use was implied from drug dispensing and periods of exposure to colchicine were defined using the DDD, which could differ from the actually prescribed or taken dose. Delayed self-medication with left over pills and partial intake of purchased drugs are both likely. Exposure misclassification is therefore possible. For the same reason, we were unable to explore a relationship between dose of colchicine or pristinamycin and the risk of hospitalisation. Second, we presumed that hospitalisation for a possible complication of colchicine in patients taking colchicine was indeed due to colchicine but it may have been due to another cause. Third, data on comorbidities available in the SNDS are incomplete, indirect, and imprecise. The self-controlled study design controls for chronic comorbidities, which are stable over time, but not for acute comorbidities, such as acute kidney or liver insufficiency. Fourth, our study design accounts for serious colchicine intoxication only. Mild or moderate intoxication managed at home (mild diarrhoea) or in the emergency department without hospitalisation cannot be studied with the SNDS. Lastly, the negative control drug should ideally have the same exact indications as the investigated drug. Although pristinamycin and co-amoxiclav share most of their indications (acute bacterial sinusitis, acute otitis media in adults, acute bacterial exacerbations of chronic bronchitis, community-acquired pneumonia, and skin and soft tissue infections), co-amoxiclav has a few other ones (acute urinary tract infections due to susceptible bacteria, and bone and joint infections).

In conclusion, we found no evidence of a higher risk of serious colchicine intoxication after concomitant use of pristinamycin than after concomitant use of co-amoxiclav among patient using colchicine retrieved over 9 years in the nationwide French health data system. The contra-indication of pristinamycin in colchicine users should be reassessed in the light of all available evidence.

### **Conflict of Interest**

The authors declared no competing interests for this work.

### **Data availability**

The data that support the findings of this study are available from third party (data owner). Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of third party.

### **Funding information**

This project has received funding from the French National Agency for Medicines and Health Products Safety (ANSM) in the framework of the Scientific Interest Group EPI-PHARE. This publication represents the views of the authors and does not necessarily represent the position of the relevant health authorities.

### **Acknowledgement**

We thank the French National Agency for Medicines and Health Products Safety (ANSM) and the Scientific Interest Group EPI-PHARE for their financial support.

### Ethics

This study was approved by the French Data Protection Supervisory Authority (Commission Nationale de l'Informatique et des Libertés, #DR-2020-184), and the Expert Committee for Health Research, Studies and Evaluations (Comité d'Expertise pour les Recherches, les Études et les Évaluations dans le domaine de la Santé, #891321)

which did not require informed consent because data are anonymized.

### References

1. Nisse P, Arab T, Garat A, Descamps IM, Canevet C, Gressier B. Décès après co-prescription de pristinamycine et de colchicine. *La Presse Médicale*. 2012 Apr 1;41(4):441–2.
2. Cremades S, Leroux G, Dumas G, Dutasta F, Drugeault B, Malterre G. La co-prescription colchicine-pristinamycine est dangereuse. *La Revue de Médecine Interne*. 2010 Jun 1;31:S141.
3. Thésaurus des interactions médicamenteuses - ANSM [Internet]. [cited 2022 Jun 6]. Available from: <https://ansm.sante.fr/documents/referance/thesaurus-des-interactions-medicamenteuses-1>

4. Girard de Courtilles M, Balusson F, Queric C, Bouric S, Carlhant-Kowalski D, Scailteux LM, et al. Interactions médicamenteuses avec la colchicine, les contre-indications sont-elles bien respectées ? Étude descriptive des prescriptions en Bretagne à partir des données de l'Assurance maladie. *Therapies*. 2020 Nov 1;75(6):675–9.
5. Montastruc JL, Benevent J, Montastruc F, Bagheri H, Despas F, Lapeyre-Mestre M, et al. What is pharmacoepidemiology? Definition, methods, interest and clinical applications. *Thérapie*. 2019 Apr;74(2):169–74.
6. Tuppin P, Rudant J, Constantinou P, Gastaldi-Ménager C, Rachas A, de Roquefeuil L, et al. Value of a national administrative database to guide public decisions: From the système national d'information interrégimes de l'Assurance Maladie (SNIIRAM) to the système national des données de santé (SNDS) in France. *Rev Epidemiol Sante Publique*. 2017 Oct;65 Suppl 4:S149–67.
7. Bykov K, Mittleman MA, Glynn RJ, Schneeweiss S, Gagne JJ. The Case–Crossover Design for Drug–Drug Interactions: Considerations for Implementation. *Epidemiology*. 2019 Mar;30(2):204–11.
8. Souty C, Launay T, Steichen O, Conte C, Turbelin C, Sarazin M, et al. Use of the French healthcare insurance database to estimate the prevalence of exposure to potential drug-drug interactions. *Eur J Clin Pharmacol*. 2020 Dec;76(12):1675–82.
9. Rubinstein E, Prokocimer P, Talbot GH. Safety and tolerability of quinupristin/dalfopristin: administration guidelines. *J Antimicrob Chemother*. 1999 Sep;44 Suppl A:37–46.
10. Maclure M. The Case-Crossover Design: A Method for Studying Transient Effects on the Risk of Acute Events. *American Journal of Epidemiology*. 1991 Jan 15;133(2):144–53.



Figure captions.

Figure 1. Hazard and control periods of patients included in the risk analysis.