Electronic monitoring of potential adverse drug events related to lopinavir/ritonavir and hydroxychloroquine during the first wave of COVID-19

Christian Skalafouris [1,2] Caroline Samer,[3] Jerome Stirnemann,[4] Olivier Grosgurin,[4] François Eggimann,[5] Damien Grauser,[5] Jean-Luc Reny,[4] Pascal Bonnabry [1,2] Bertrand Guignard[1]

[1]Pharmacy, Geneva University Hospitals, Geneva, Switzerland
[2]Institute of Pharmaceutical Sciences of Western Switzerland (ISPSO), School of pharmaceutical sciences, University of Geneva, Geneva, Switzerland
[3]Clinical Pharmacology and Toxicology Division, Geneva University Hospitals, Geneva, Switzerland
[4]General Internal Medicine Division, Geneva University Hospitals, Geneve, Switzerland
[5]Information Systems Department, Geneva University Hospitals, Geneva, Switzerland

Correspondence to
Christian Skalafouris, Pharmacy, Geneva University Hospitals, 1205 Geneva, Switzerland; christian.skalafouris@hcuge.ch

Received 23 December 2020
Revised 2 March 2021
Accepted 9 March 2021
Published Online First 8 April 2021

EAHP Statement 4: Clinical Pharmacy Services. EAHP Statement 5: Patient Safety and Quality Assurance.

To cite: Skalafouris C, Samer C, Stirnemann J, *et al*. *Eur J Hosp Pharm* 2023;**30**:113–116.

ABSTRACT

During Switzerland's first wave of COVID-19, clinical pharmacy activities during medical rounds in Geneva University Hospitals were replaced by targeted remote interventions. We describe using the electronic PharmaCheck system to screen high-risk situations of adverse drug events (ADEs), particularly targeting prescriptions of lopinavir/ritonavir (LPVr) and hydroxychloroquine (HCQ) in the presence of contraindications or prescriptions outside institutional guidelines. Of 416 patients receiving LPVr and/or HCQ, 182 alerts were triggered for 164 (39.4%) patients. The main associated risk factors of ADEs were drug–drug interactions, QTc interval prolongation, electrolyte disorder and inadequate LPVr dosage. Therapeutic optimisation recommended by a pharmacist or proposals for additional monitoring were accepted in 80% (n=36) of cases. Combined with pharmacist contextualisation to the clinical context, PharmaCheck made it possible to successfully adapt clinical pharmacist activities by switching from a global to a targeted analysis mode in an emergency context.

INTRODUCTION

The SARS-CoV-2 pandemic hit Switzerland in March 2020, and many hospitals had to reorganise rapidly to cope with the influx of COVID-19 patients.[1] The 2000-bed Geneva University Hospitals (HUG) were designated as the unique point of care for COVID-19 patients requiring hospitalisation in the canton of Geneva; non-COVID-19 patients were admitted to private clinics.[2] Over 11 weeks, more than 1200 COVID-19 patients were admitted, occupying the equivalent of up to 20 acute care wards in the Department of General Medicine (four times normal admissions). Intensive care unit capacity was increased from 30 to 80. The main treatments prescribed were restricted to a few therapeutic classes for managing symptoms and complications (eg, antipyretics, anticoagulants, antibiotics) or supportive care (resuscitation measures with oxygen therapy).

During the pandemic's initial phase, certain drugs were identified as potential treatments specifically for SARS-CoV-2. Expectations were high. Although there were very limited preliminary data regarding their potential efficacy, these drugs were known for their potential adverse effects or propensity for drug–drug interactions (DDIs). An in-house multidisciplinary expert group regularly redefined institutional guidelines in the light of new data. The compounds considered in HUG's institutional guidelines were: lopinavir/ritonavir (LPVr) 400 mg/100 mg twice daily for 5 days (for patients >75 years old, dose reduced to 400 mg/100 mg before noon, 200 mg/50 mg at bedtime) and hydroxychloroquine (HCQ) 800 mg as a single dose (weak grade 2C recommendations). Off-label dosages were justified using pharmacokinetic data and expert opinions and were motivated by the fear of drug shortages.[3 4]

Patients on the HUG's internal medicine wards are screened daily by a pharmacist using the in-house PharmaCheck electronic screening tool to detect 20 high-risk situations that could lead to adverse drug events (ADEs). PharmaCheck screens electronic health records by aggregating information from the hospital's data lake in near real-time (eg, drug prescriptions, laboratory values, vital signs, medical problems). The pharmacist analyses the detected situations and alerts the prescriber if a risk of ADE is clinically relevant, recommending a treatment adjustment. PharmaCheck was deployed in the hospital information system in February 2020. Since then a pilot study began to assess PharmaCheck's impact on clinical pharmacist efficiency.

As soon as our hospital became a COVID-19 centre (March 2020), the massive increase in patients made traditional medication reviews during medical rounds no longer efficient. They were replaced exclusively by centralised pharmaceutical screening using PharmaCheck, and the tool was extended to monitor prescriptions of LPVr and HCQ.

Except for the pharmacist who had developed and tested the PharmaCheck software before its deployment, experience in its use was short. During this first wave, PharmaCheck was also used for the detection of 20 high-risk situations as it was intended in addition to the version dedicated to patients treated with LPVr and/or HCQ.

The present study assessed how many high-risk situations PharmaCheck detected regarding LPVr and HCQ prescriptions during the first wave of COVID-19, the proportion of these situations for which clinical pharmacists recommended treatment

adjustments or additional monitoring, and whether prescribers accepted these recommendations.

METHODS

Settings

Two types of alerts are provided by the institutional clinical decision support system associated with computerised provider order entry (CPOE): active alerts (ie, providing a warning with a disruptive pop-up) are triggered on the exclusive basis of drug data (maximum dosage exceeded, double drug alert) without any possible contextualisation (automated correlation with biological or vital signs); passive alerts (ie, providing warning to the prescriber when consulting the integrated alerting system) are used to identify drug interactions in accordance with a single third-party database (Thériaque, CHNIM).[5]

Study design

PharmaCheck was evaluated during a 7 week prospective observational study (24 March to 12 May 2020). All patients admitted to internal medicine wards with current LPVr prescriptions and/or a history of HCQ prescription (even if discontinued due to the drug's long half-life) were included.

Alerts and triggers

Different triggers were set up to isolate high-risk situations: co-prescription of at least one drug that can interact with LPVr and/or HCQ as per the 'do not co-administer' category in the University of Liverpool's list of DDIs[6]; QT interval corrected using the Bazett formula (QTc) ≥500 ms or QTc increase of ≥50 ms after initiation of LPVr and/or HCQ; hypokalaemia (<3.6 mmol/L) or hypomagnesaemia (<0.59 mmol/L); and lopinavir dose not adapted to age (dose reduction required for patients >75 years old). When a current LPVr prescription or a history of HCQ prescription was detected in the presence of one or more triggers, the clinical pharmacist was sent an alert.

Alert processing

Two decisional algorithms were built to standardise alert analysis (figure 1). PharmaCheck ran twice daily to identify patients with high-risk situations related to LPVr and/or HCQ prescriptions. As per the decisional algorithm, the most relevant alerts led to telephoned recommendations to prescribers for therapeutic adjustments or additional monitoring. For alerts associated with QTc increase, attributability to LPVr and/or HCQ was retrospectively assessed by the regional pharmacovigilance centre in order to report possible, probable or certain adverse drug reactions to the Uppsala Monitoring Centre (UMC).

Four pharmacists took turns using the tool and were following up situations requiring closer monitoring. An electronic tracking file shared among the pharmacists made it possible to document their attitude when the alert was analysed and to transmit information in a targeted way to the rest of the pharmaceutical team.

We measured the distribution of alerts and triggers, each trigger's positive predictive value (PPV) (ratio of triggers associated with an intervention divided by total interventions), the proportion of alerts resulting in a recommendation for treatment adjustment or additional monitoring, and whether prescribers accepted the recommendations.

Statistics

Descriptive statistics were calculated and the different variables measured were represented by means±SD. Comparative analyses of the proportions were performed using χ^2 tests with Monte Carlo correction (10 000 draws) (R software version 3.3.0). A p value <0.05 was considered statistically significant.

RESULTS

Alerts and triggers

Over 7 weeks, 1208 patients were admitted and 416 (34.4%) received at least one of the two experimental treatments (LPVr +HCQ, n=77; LPVr alone, n=109; HCQ alone, n=230). PharmaCheck triggered 182 alerts for 164 patients taking these treatments (39.4%): 77 alerts for LPVr and 105 alerts for HCQ. Mean alert generation delays were 1.2±1.0 days after LPVr treatment initiation and 7.3±9.4 days after HCQ treatment initiation. Mean daily new alert generation was 5.4±6.4 (2.3±4.2 LPVr alerts and 3.1±3.2 HCQ alerts). In total, 218 triggers were linked to these alerts: 149 alerts (81.9%) with one trigger, 30 (16.5%) with two triggers, and three (1.6%) with three triggers; 136 alerts were triggered by at least one DDI (204 different DDIs involved 50 different compounds, with 1.3±1.1 DDIs for LPVr alerts and 1.0±1.0 DDIs for HCQ alerts); 107 alerts triggered by a DDI (79.0%) were linked to a risk

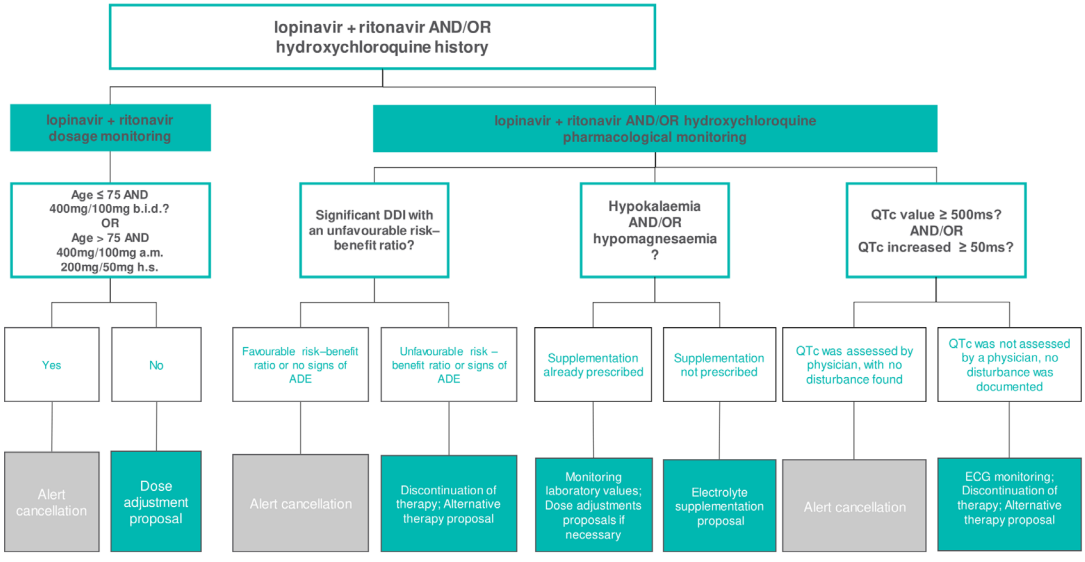

Figure 1 ADE, adverse drug event; a.m., every morning; b.i.d., two times a day; DDI, drug-drug interactions; ECG, electrocardiogram; h.s., at bedtime.

Table 1 Descriptions of patients and triggers

Patients characteristics				
Description	**Mean±SD**			
Sex ratio	1:0.45 (127 male, 57 female)			
Age	66.5±13.2 years			
Length of stay	8.4±5.9 days			
Trigger distribution and PPV				
Trigger	**LPVr**	**HCQ**	**P value**	**PPV**
At least one drug–drug interaction	59 (67.0%)	77 (59.2%)	0.26	12.5% (17/136)
QTc interval >499 ms or QT interval prolongation >49 ms	19 (21.6%)	30 (23.1%)	1.0	32.6% (16/49)
Hypokalaemia	2 (2.3%)	21 (16.2%)	10^{-3}	8.3% (2/24)
Hypomagnesaemia	0 (0.0%)	2 (1.5%)	0.5	100% (2/2)
LPVr wrong dose	8 (9.1%)	0 (0%)	10^{-4}	100% (8/8)
Total	*88*	*130*	–	*20.6%*
Therapeutic classes involved in drug-drug interactions distribution				
Therapeutic classes involved in drug–drug interactions	**% (n)**			
Antipsychotics (haloperidol, quetiapine, etc)	20.5% (42)			
Antibacterials for systemic use (azithromycin, levofloxacin, etc)	14.6% (30)			
Calcium channel blockers (amlodipine, felodipine)	11.7% (24)			
β-blocking agents (metoprolol, atenolol, propranolol)	11.7% (24)			
Antithrombotic agents (acenocoumarol, clopidogrel, edoxaban, etc)	10.7% (22)			
Psychoanaleptics (citalopram, escitalopram, etc)	7.3% (15)			
Cardiac therapies (amiodarone, isosorbide dinitrate)	3.9% (8)			
Analgesics (tramadol, morphine, etc)	3.4% (7)			
Others	16.2% (33)			

HCQ, hydroxychloroquine; LPVr, lopinavir/ritonavir; PPV, predictive positive value (ratio of triggers associated with an intervention divided by total interventions).

of arrhythmia and 29 (21.0%) to another risk. Patients' characteristics, triggers' PPVs, and the therapeutic classes involved in DDIs are shown in table 1.

Alert processing

Overall, 20.9% (n=38) of the alerts (LPVr 23.4% (n=18); HCQ 19.0% (n=20); p=0.48) resulted in 45 recommendations for therapeutic optimisation or additional monitoring, 80% (n=36) of which were accepted by physicians (LPVr 84.2% (n=16); HCQ 77% (n=20); p=0.71). The acceptance of one intervention (2.2%) could not be evaluated. Recommendation refusals were linked to physicians estimating a favourable risk–benefit ratio (n=7) or to an unknown reason (n=1). For 42 patients with a QTc prolongation potentially attributable to LPVr and/or HCQ, 16 situations (38%) were assessed as probable and were reported to the UMC.

DISCUSSION

Our in-house PharmaCheck electronic screening tool enabled us to automatically check electronic health records to identify potentially high-risk situations linked to LPVr and/or HCQ prescriptions. By contextualising these alerts, the clinical pharmacist recommended the most relevant ones for treatment adjustments, which were mainly accepted by the prescribers.

More alerts were associated with HCQ than with LPVr because although patients only received a single dose of HCQ, its long half-life (7–50 days) exposed them to delayed ADEs.[4] As CPOE no longer displayed discontinued HCQ prescriptions, physicians had more difficulty identifying potentially risky situations, including DDIs. In contrast, LPVr's short half-life (5–6 hours) creates exposure to immediate ADEs; therefore, only patients with an active prescription were targeted, as their risk factors for ADEs were probably more easily identifiable on the CPOE during the 5 day treatment period.

The presence of at least one DDI was the most frequent trigger, with most DDIs involving the risk of arrhythmia (79.0%). However, clinical pharmacists only recognised a few of these situations as at risk of ADEs and PPVs were low; some DDIs were only theoretical or associated with very low evidence with no effects on an electrocardiogram (ECG) in the literature (eg, HCQ and calcium channel blockers, β-blockers, diuretics).[7] Some DDIs were relevant but inconsequential, involving low-dose oral therapies for which the risk of ADEs was lower than at high doses (eg, haloperidol, quetiapine, risperidone).[8]

Pharmacists intervened in about a quarter of the alerts involving a QTc interval increase. In our electronic patient records, ECGs are computerised and associated parametric measurements, such as QTc interval, are provided automatically by the manufacturer's algorithms.[9] Despite recent improvements to these algorithms, interpretation errors remain possible and reduce the specificity of these techniques, meaning that traditional interpretation remains necessary (ie, visual inspection of the traces).[10–12] Nevertheless, QTc value was a trigger of choice as it was easily accessible and queryable, even though physicians, in most cases, assessed prolonged intervals as normal and not requiring intervention. Hypomagnesaemia and hypokalaemia are two well-known risk factors for QT interval prolongation, and are frequently involved in heart rhythm disorders.[13] Most cases of hypokalaemia in our study were already in correction and required no intervention other than daily monitoring. However, hypomagnesaemia alerts led to more pharmaceutical recommendations for supplementation, as this electrolyte disorder can be under-interpreted or under-detected.[14] Finally, dose adjustments were recommended for over- or under-dosed LPVr prescriptions regarding patient age, as called for in our institutional guidelines.

Pharmacists estimated 20.6% of alerts to be specific enough to merit intervention. To the best of our knowledge, no published studies have evaluated a rule-based system targeting experimental LPVr and/or HCQ treatments against SARS-CoV-2. However, the PPVs of such alerts have previously been described as varying between 7.6% and 11% using similar tools targeting more common high-risk situations.[15–17] The slightly greater specificity of our study's

alerts can be explained by the potentially higher incidence of factors contributing to drug-related problems, especially in a healthcare emergency context: prescription of uncommon treatments, heavy workloads, rapid reorganisation of care units, influxes of patients, stress and fatigue.[18] Isolating the most relevant alerts according to patients' clinical contexts and transmitting recommendations to physicians in a telephone call enabled an 80% acceptance rate to be achieved—close to rates observed when pharmacists go on medical rounds with face-to-face interventions (80–87%). Acceptance rates would probably have been lower if interventions had merely been written in patient files (53–56%).[17 19–21]

Active alert systems are associated with an alert fatigue phenomenon (due to lack of specificity).[22] Regarding DDIs, passive alert systems are likely to be less well taken into account and dependent on the content of the third-party database.[23] We assumed that contextualised alerts would be more considered by prescribers, particularly if they are pre-filtered by pharmacists. PharmaCheck's major interest was to target, on the one hand, medical orders correlated with discriminating biological and vital signs and, on the other hand, drug interactions specifically involving LPVr and HCQ (the list of which was regularly updated according to Liverpool publications).

Our study had certain limitations. Without a control group, it is unknown whether fewer ADEs occurred as a result of our interventions. Our system's sensitivity was not established and only alerts associated with at least one trigger were detected and analysed. Again, a control group using a standard practice medication review would have made this possible, and testing PharmaCheck outside a healthcare crisis would measure its sensitivity. Concerning alert specificity, a thorough, often lengthy analysis of electronic health records was carried out despite low PPVs of certain triggers (undetermined daily durations estimated from 1 to 3 hours). Our system's performance could be improved by weighting each alert using a risk score to sort out patients' electronic records to be analysed as a priority. A weighting system has already been proposed that would only display alerts for prescriptions with the highest risk of prolonging the QTc interval.[24]

CONCLUSION

PharmaCheck helped to quickly adapt our clinical pharmacy activities during the first wave of COVID-19 hospitalisations, moving from a thorough drug therapy analysis mode (limited patient numbers during medical rounds in selected care units) to a targeted analysis mode (high patient numbers analysed remotely for numerous wards). High-risk situations were selected from among the triggers characterising the main risks associated with LPVr and HCQ and for which analysis by the clinical pharmacist led to recommendations for therapeutic optimisation in the most relevant situations, which increased acceptance by prescribers. PharmaCheck can be adapted rapidly, and a new set of rules has been developed for the second wave of COVID-19, triggering potential ADEs related to remdesivir, dexamethasone and anticoagulants.

Twitter Christian Skalafouris @ckalafouris and Pascal Bonnabry @bonnabry

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

ORCID iDs
Christian Skalafouris http://orcid.org/0000-0002-1648-1422
Pascal Bonnabry http://orcid.org/0000-0002-8690-649X

REFERENCES

1 Cc 818.101.24 ordinance 3 of 19 June 2020 on measures to combat the coronavirus (COVID-19) (COVID-19 ordinance 3). Available: https://www.admin.ch/opc/en/classified-compilation/20201773/index.html [Accessed 10 Aug 2020].
2 Carballo S, Agoritsas T, Darbellay Farhoumand P. COVID-19: réorganisation sous toutes Ses formes dans un hôpital universitaire. *Forum Médical Suisse* 2020;20:390–5.
3 Crawford KW, Spritzler J, Kalayjian RC, *et al*. Age-related changes in plasma concentrations of the HIV protease inhibitor lopinavir. *AIDS Res Hum Retroviruses* 2010;26:635–43.
4 Lim H-S, Im J-S, Cho J-Y, *et al*. Pharmacokinetics of hydroxychloroquine and its clinical implications in chemoprophylaxis against malaria caused by Plasmodium vivax. *Antimicrob Agents Chemother* 2009;53:1468–75.
5 Thériaque. Available: https://www.theriaque.org/apps/contenu/accueil.php [Accessed 11 Feb 2021].
6 Liverpool COVID-19 interactions. Available: https://www.covid19-druginteractions.org/checker [Accessed 31 Jul 2020].
7 CredibleMeds. CredibleMeds : QTDrugs lists (registration required). Available: https://crediblemeds.org/index.php/?cID=328 [Accessed 31 Jul 2020].
8 Ray WA, Chung CP, Murray KT, *et al*. Atypical antipsychotic drugs and the risk of sudden cardiac death. *N Engl J Med Overseas Ed* 2009;360:225–35.
9 Tyl B, Azzam S, Blanco N, *et al*. Improvement and limitation of the reliability of automated QT measurement by recent algorithms. *J Electrocardiol* 2011;44:320–5.
10 Garg A, Lehmann MH, Mh L. Prolonged QT interval diagnosis suppression by a widely used computerized ECG analysis system. *Circ Arrhythm Electrophysiol* 2013;6:76–83.
11 Schläpfer J, Wellens HJ, Hj W. Computer-interpreted electrocardiograms: benefits and limitations. *J Am Coll Cardiol* 2017;70:1183–92.
12 Smulyan H. The computerized ECG: friend and foe. *Am J Med* 2019;132:153–60.
13 Pasquier M, Pantet O, Hugli O, *et al*. Prevalence and determinants of QT interval prolongation in medical inpatients. *Intern Med J* 2012;42:933–40.
14 Whang R, Ryder KW. Frequency of hypomagnesemia and hypermagnesemia. requested vs routine. *JAMA* 1990;263:3063–4.
15 Jha AK, Laguette J, Seger A, *et al*. Can surveillance systems identify and avert adverse drug events? A prospective evaluation of a commercial application. *J Am Med Inform Assoc* 2008;15:647–53.
16 Rommers MK, Zwaveling J, Guchelaar H-J, *et al*. Evaluation of rule effectiveness and positive predictive value of clinical rules in a Dutch clinical decision support system in daily hospital pharmacy practice. *Artif Intell Med* 2013;59:15–21.
17 Quintens C, De Rijdt T, Van Nieuwenhuyse T, *et al*. Development and implementation of "Check of Medication Appropriateness" (CMA): advanced pharmacotherapy-related clinical rules to support medication surveillance. *BMC Med Inform Decis Mak* 2019;19:29.
18 McDowell SE, Ferner HS, Ferner RE. The pathophysiology of medication errors: how and where they arise. *Br J Clin Pharmacol* 2009;67:605–13.
19 Falcão F, Viegas E, Lopes C, *et al*. Hospital pharmacist interventions in a central hospital. *Eur J Hosp Pharm* 2015;22:94–7.
20 Guignard B, Bonnabry P, Perrier A, *et al*. Drug-related problems identification in general internal medicine: the impact and role of the clinical pharmacist and pharmacologist. *Eur J Intern Med* 2015;26:399–406.
21 Johansen ET, Haustreis SM, Mowinckel AS, *et al*. Effects of implementing a clinical pharmacist service in a mixed Norwegian ICU. *Eur J Hosp Pharm* 2016;23:197–202.
22 Carli D, Fahrni G, Bonnabry P, *et al*. Quality of decision support in computerized provider order entry: systematic literature review. *JMIR Med Inform* 2018;6:e7170:e3.
23 Revue Médicale Suisse. Quel programme informatique de détection des interactions médicamenteuses néfastes ? Available: https://www.revmed.ch/RMS/2012/RMS-358/Quel-programme-informatique-de-detection-des-interactions-medicamenteuses-nefastes [Accessed 11 Feb 2021].
24 Tisdale JE, Jaynes HA, Kingery JR, *et al*. Effectiveness of a clinical decision support system for reducing the risk of QT interval prolongation in hospitalized patients. *Circ Cardiovasc Qual Outcomes* 2014;7:381–90.