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Utility of drug provocation tests in the evaluation of quinolone hypersensitivity reactions

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Clinical implications:

We confirmed the diagnosis of DHR to quinolones in a quarter of patients, mainly by DPT.

We showed an over 90% match between the semiology and chronology of index reactions and those elicited by DPT. We suggest a DPT protocol of 5 doses, with 2 supplementary low doses in case of anaphylactic index reactions.

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51 Currently, quinolones are the second-most used antibiotic line in human medicine in Europe,
52 after betalactams (1). Drug hypersensitivity reactions (DHR) to this group of medication are
53 mostly immediate and moxifloxacin singles out as a trigger of life-threatening anaphylaxis
54 (2,3).

55

56 In this study, we retrospectively describe our experience with quinolone allergy work up,
57 including skin tests (ST) and drug provocation test (DPT). The patients (children and adults at
58 the time of the allergy work-up) were retrieved from the Drug Allergy and Hypersensitivity
59 Database (DAHD) (2004-2019) and from the database of the Allergy Unit of the Metz
60 Hospital since 2015. ST were performed according to the concentrations presented in **Table**
61 **E1** in both centers.

62 We performed a descriptive analysis of the cases then used logistic regression to search for
63 risk factors of confirmed DHR. Variables with $p < 0.15$ in univariate analysis were included in
64 the multivariate model. Odds ratios were expressed with 95% confidence interval (95% CI).
65 A p value < 0.05 was considered statistically significant. The R software (R 3.4.1) was used
66 for the analysis.

67

68 To analyze DPT, we performed survival analysis to detect reactive doses (RD, expressed as a
69 ratio between the cumulative reactive dose and the total DPT dose for a given patient; *i.e.*, the
70 dose reached if DPT was to be completed). RD was expressed as a percentage. The studied
71 event was occurrence of a reaction during DPT.

72 Quinolone DPT performed in the two centers were conducted according to an open empirical
73 protocol, with 30-minute incremental doses, followed by a compulsory surveillance period of
74 1 hour 30 minutes after the last administered dose. In the Allergy Unit in Montpellier, the
75 protocols (4) described in **Table E1** were used for an adult with no need of dose adjustment.
76 In cases of anaphylaxis, the first dose was 1/10 of the initial dose (e.g., 0.1 mg instead of 1
77 mg).

78

79 The same protocol was used for immediate (4) and mild-to-moderate nonimmediate reactions,
80 and general DPT contraindications (namely severe cutaneous adverse reactions) were
81 observed (5). The patients (or their parents, in case of children) gave their written informed
82 consent to take part in this study for which approval from the local ethical committee was

83 granted (IRB-MTP-2020-01-202000334). In all the patients in Metz, a basophil activation test
84 (BAT) was also performed.

85 One hundred fifty-nine patients (139 from Montpellier and 20 from Metz) were analyzed in
86 this study (20 other patients, 19 from Montpellier and one from Metz were excluded due to
87 inconclusive data). They were mostly adults (mean age: 50.6 ± 16.4 years; two children were
88 tested, aged six and ten). Three quarters (117, 73.6%) were female patients. The most
89 frequently involved quinolone in the index reaction was ofloxacin (50 cases, 31.4%),
90 followed by ciprofloxacin (42 cases, 26.4%), levofloxacin (30 cases, 18.9%) and
91 moxifloxacin (14 cases, 8.8%). Almost half of the index reactions (71 cases, 44.4%) were
92 immediate. Thirty-nine patients could provide precise data on chronology (range: 1-240
93 minutes), and in half of these cases, the reaction occurred within 20 minutes after the intake
94 (IQR25-75: 10-30 min). The index reactions were elicited on Day 1 of exposure for most
95 patients (median: 1, IQR25-75: 1-2). They were mainly urticarial (40.5%) or anaphylactic
96 (20%). Only a minority of patients (15%) recalled a previous course of quinolone. Patients
97 were tested within a median time of 48 months (IQR25-75: 8-144) after their last episode.

98
99 ST were performed in two thirds of patients (100 cases, 62.9%), and they were positive in
100 nine of them (9% of the tested patients) (**Table E2**). Two of these patients had a DPT for an
101 alternative quinolone (and they tolerated it). All nine had presented immediate reactions,
102 seven with a history of anaphylaxis (five shocks) and two with urticaria/angioedema. In 31
103 patients, 40 DPTs were positive for different quinolones. Of note, the majority of patients
104 were initially tested (in ST and DPT) for their culprit quinolone (91.8% match). Patients who
105 were skin tested prior to DPT had more immediate reactions ($p=0.01$) than those who did not
106 undergo ST, but there were no other differences between these groups in terms of type of
107 initial reaction ($p=0.2$), type of culprit quinolone ($p=0.5$), previous use of quinolone ($p=0.10$),
108 or confirmed hypersensitivity ($p=0.5$).

109
110 All in all, DHR to quinolones was confirmed in a quarter of the tested patients (40, 25.1%).
111 **Table 1** describes in detail the characteristics of these patients. As demonstrated by
112 multivariate analysis, several clinical predictors were independently associated with a
113 confirmed DHR. Thus, having an immediate index reaction significantly increased the risk by
114 3-fold (OR=3.1, 95% CI: 1.0-9.7), anaphylaxis by 8-fold (OR=8.3, 95% CI: 1.7-38.9), but
115 urticaria/angioedema did not (OR=3.1, 95% CI: 0.8-12.1), and neither did the delay between
116 the reaction and tests. Moxifloxacin exposure was the strongest risk factor, associated with a

117 13-fold increased risk of confirmed DHR (OR=13.5, 95% CI:2.8-63.9). Of all the patients
118 with anaphylaxis in their index history, 21.2% were diagnosed by positive ST (7 cases),
119 36.3% by DPT (12 cases) and in 42.4%, the diagnosis of DHR was ruled out and patients
120 tolerated the DPT with the culprit drug.

121 The reactions elicited during the 40 positive DPT were anaphylactic (8 DPT, 20%) or
122 cutaneous (32 DPT, 80%). In 27 cases, the index reactions had been cutaneous, in 12
123 anaphylactic and in one, the patient had presented an isolated bronchospasm. Of the 12 index
124 anaphylactic reactions who underwent a DPT, they were all captured either during DPT or
125 during the compulsory surveillance period after DPT completion (7 anaphylaxis, 5 milder
126 reactions) and they were treated with antihistamines H1 and corticosteroids (none received
127 epinephrine), with no sequelae. The reactions elicited during DPT were of similar or lesser
128 severity compared to the index reaction in all but one patient (2.5%). Indeed, although his
129 index reaction was described as cutaneous and of delayed chronology, i.e., 6-24h after the last
130 intake, he presented anaphylaxis at 17.1% of ofloxacin daily therapeutic dose). The global
131 match between the chronology of the index reaction and that of the DPT was 81% (30 of the
132 37 DPT with both chronologies available: 26 for immediate reactions and 4 for delayed
133 reactions). In 6 cases, there was a miss-match, with 5 non-immediate index reactions eliciting
134 an immediate symptomatology and one presumably immediate reaction occurring late (4
135 hours after the last intake during DPT; this reaction turned out to be a fixed drug eruption).
136 Thus, for immediate and non-immediate index reactions, in 96.3% and 100% of cases
137 respectively, the patients reacted either within the same delay after the last dose, or earlier.

138

139 **Figure 1** and **Table 2** shows the distribution of the events and in particular of the
140 anaphylactic events on the Kaplan Meier curve. Visually, there were several steep drops,
141 evocative of the occurrence of several events at close doses, namely before: RD=1%,
142 RD=20%, RD=50% and at RD=100%. Considering this distribution, we then focused on the
143 severity of the reactions and we could observe that in our series, anaphylaxis in DPT started at
144 RD=0.1%. Moreover, in 75% of the cases, anaphylaxis in DPT had already occurred before
145 RD=20%, the following thresholds for anaphylaxis being at RD=41% and RD=96.6%,
146 respectively.

147

148 For the 20 patients explored in the Metz hospital (6 immediate and 14 non-immediate
149 reactions), a BAT was systematically performed. It was negative in all the patients, as were
150 ST and DPT.

151

152 Exploring quinolone DHR suspicions has become increasingly important in the last decade,
153 with the increased use of these antibiotics. In France, and according to the National Medicine
154 Agency surveys, fluoroquinolones are the second most used antibiotics, following beta-
155 lactams. Our data confirm (3,5,8) that moxifloxacin is the quinolone most frequently
156 associated with a confirmed diagnosis of DHR. The large 95% CI, however, are evocative of
157 a small sample size.

158

159 Although non-immediate DHR to quinolones have been described and confirmed, immediate
160 DHR are more frequent and mostly attributable to 2 mechanisms: IgE-mediated (with
161 evidence of sIgE to quinolones (6) and via the MGRPX2 activation pathway, which would
162 not need a previous sensitizing contact (3,9). Indeed, in our cohort, up to 45% of patients who
163 did not recall a previous use of quinolone had a confirmed DHR following allergy work-up.
164 However, unknown previous contact cannot be ruled out without having access to the full
165 lifelong patient's previous health records. Moreover, quinolones are widely used in the food
166 industry (poultry, rabbit, veal) and in fish farming (1).

167

168 ST for immediate reactions are controversial because they are considered irritant (beyond
169 1/100 dilutions of the IV products) (2) or having low sensitivity for non-immediate reactions,
170 and *in vitro* tests are neither sufficiently sensitive, nor easily accessible (2,3). Therefore, DPT
171 seems the method of choice to explore quinolone DHR. It has been suggested to perform DPT
172 directly to an alternative quinolone and not to the culprit one, due to the potential anaphylactic
173 risk, which materialized in 20% of DPT in our series. Nevertheless, of all the patients who
174 had initially described anaphylaxis, the diagnosis was ruled out in up to 42.4%, proving the
175 utility of DPT.

176

177 The DPT to quinolones used in our Units were empirical (but similar over the past 20 years)
178 and included 5 to 7 doses, depending on the drug (preceded by a supplementary low dose in
179 case of anaphylactic index history).

180 As advocated by the European Network on Drug Allergy, we initially designed our empirical
181 DPT protocols to reach a daily therapeutic dose, instead of a single dose. The clinical
182 relevance of the MGRPX2 activation pathway for quinolones is not known, but it could be
183 argued that some of the positive DPT were due to too high a dose, administered in a short

184 time interval. While this might be true for some patients, 65% of those reacting by DPT did so
185 at RD < 50%, which would be the equivalent of a single dose.

186 The dose increments usually consisted of a 2 or 3-fold increase between successive steps,
187 allowing us to explore and detect reactions we could not have otherwise detected, had our
188 empiric DPT been shorter. The two patients who reacted with anaphylaxis at RD=0.1% and
189 RD=0.6% had clinical histories of anaphylaxis. We therefore consider that small doses should
190 not be overlooked in patients with severe index reactions. Ideally, a data-driven protocol
191 would attempt to reach at each step cumulative doses lower than those causing anaphylaxis,
192 with the hypothesis that the reaction would thus be less severe (e.g., anaphylaxis elicited at
193 RD=27% might be captured as urticaria at RD= 20%). Several episodes of anaphylaxis
194 occurred within a close range of doses before RD=20%. Taking into account all these
195 considerations, we propose the following DPT protocol: 5%-10%-15%-20%-50%, preceded
196 by 0.1% and 0.5% in case of anaphylactic index reactions.

197

198 In a cohort of patients with a suspicion of quinolone DHR, we: (i) confirmed the diagnosis in
199 25.1% of cases, mainly by means of DPT; (ii) showed the good match (over 90%) between
200 the semiology and the chronology of the index reactions and those elicited by DPT; (iii)
201 proved the utility of the one-day DPT for both immediate and non-immediate reactions.
202 Having analyzed the details of the reaction patterns during DPT, we suggest a DPT protocol
203 of 5 doses, with 2 supplementary low doses in case of anaphylactic index reactions.

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References

- (1) Joint interagency antimicrobial consumption and resistance analysis report. Available at https://www.ema.europa.eu/en/documents/report/ecdc/efsa/ema-second-joint-report-integrated-analysis-consumption-antimicrobial-agents-occurrence_en.pdf. Last accessed 12th of June, 2020.
- (2) Doña I, Moreno E, Pérez-Sánchez N, Andreu I, Hernández Fernandez de Rojas D, Torres MJ. Update on Quinolone Allergy. *Curr Allergy Asthma Rep.* 2017;17:56.
- (3) Van Gasse AL, Sabato V, Uyttebroek AP, Elst J, Faber MA, Hagendorens MM et al. Immediate moxifloxacin hypersensitivity: Is there more than currently meets the eye? *Allergy.* 2017;72:2039–2043.
- (4) Messaad D, Sahla H, Benahmed S, Godard P, Bousquet J, Demoly P. Drug provocation tests in patients with a history suggesting an immediate drug hypersensitivity reaction. *Ann Intern Med.* 2004;140:1001–1006.
- (5) Demoly P, Adkinson NF, Brockow K, Castells M, Chiriac AM, Greenberger PA et al. International Consensus on drug allergy. *Allergy.* 2014;69:420–437.
- (6) Blanca-López N, Ariza A, Doña I, Mayorga C, Montañez MI, Garcia-Campos J et al. Hypersensitivity reactions to fluoroquinolones: analysis of the factors involved. *Clin Exp Allergy.* 2013;43:560–567.
- (7) Manfredi M, Severino M, Testi S, Macchia D, Ermini G, Pichler WJ et al. Detection of specific IgE to quinolones. *J Allergy Clin Immunol.* 2004;113:155–60.
- (8) Demir S, Gelincik A, Akdeniz N, Aktas-Cetin E, Olgac M, Unal D et al. Usefulness of In Vivo and In Vitro Diagnostic Tests in the Diagnosis of Hypersensitivity Reactions to Quinolones and in the Evaluation of Cross-Reactivity: A Comprehensive Study Including the Latest Quinolone Gemifloxacin. *Allergy Asthma Immunol Res.* 2017;9:347–359.
- (9) Porebski G, Kwiecien K, Pawica M, Kwitniewski M. Mas-Related G Protein-Coupled Receptor-X2 (MRGPRX2) in Drug Hypersensitivity Reactions. *Front Immunol.* 2018;9:3027.

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257 **Legends**

258

259 **Figure 1.** Kaplan–Meier curve (and 95% CI in dotted lines) for the whole set of drug
260 provocation test events.

261 **Table 1.** Characteristics of the studied population.

262 **Table 2. Distribution of the events (and in particular the anaphylactic events on the**
263 **Kaplan Meier curve).** By RD=10%, two patients had reacted with anaphylaxis during DPT,
264 one at RD=0.1% and another one at RD=0.6%; between RD=10% and RD=20%, four more
265 cases had occurred, all at RD=17%-18%; finally, the last two cases occurred at RD=41% and
266 RD=96%, respectively.

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Figure 1. Kaplan–Meier curve (and 95% CI in dotted lines) for the whole set of drug provocation test (DPT) events. The Reactive Doses (RD) are mentioned on the X axis in percentage.

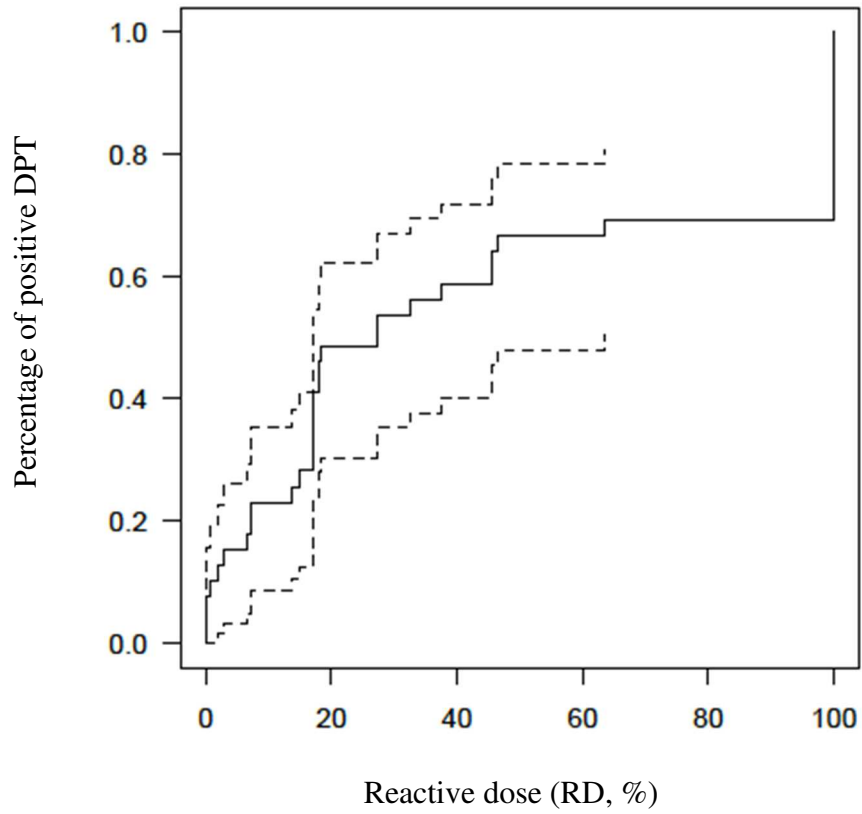


Table 1. Characteristics of the studied population.

	Total number of patients	Patients with no DHR	Patients with confirmed DHR	p value
	N=159	N=119 (%)	N=40 (%)	
Female patients	117	88 (75.2)	29 (72.5)	0.85
Symptoms and signs of index reaction^o				< 0.0001
Urticaria and/or Angioedema	64	49 (41.5)	15 (37.5)	
Anaphylaxis	33	14 (11.8)	19 (47.5)	
w/o shock	21	9 (7.5)	12 (30)	
with shock	12	5 (4.2)	7 (17.5)	
Maculopapular exanthema	49	44 (37.2)	5 (12.5)	
Other	11	11 (9.3)	0 (0)	
Isolated	1	0 (0)	1 (2.5)	
bronchospasm				
Chronology of index reaction after the last ingested dose				< 0.0001
≤1h	57	33 (27.7)	24 (60)	
1-6h*	14	7 (5.8)	7 (17.5)	
> 6h (6-24h, >24h)	59	53 (44.5)	6 (15)	
Unknown	29	26 (21.8)	3 (7.5)	
Culprit quinolone (index reaction)				< 0.0001
Ciprofloxacin	42	36 (30.2)	6 (15)	
Levofloxacin	30	22 (18.5)	8 (20)	
Moxifloxacin	14	3 (2.5)	11 (27.5)	
Ofloxacin	50	38 (31.9)	12 (30)	
Other quinolone**	23	20 (16.8)	3 (7.5)	
Previous use of quinolone				0.0015
Yes	24	17 (14.2)	7 (17.5)	
No	40	22 (18.4)	18 (45)	
Unknown	95	80 (67.2)	15 (37.5)	
Age* (years): mean±SD	50.6±16.4	51.1±16.7	49.2±15.5	0.5
Delay# (months) between reaction and tests: median (IQR25-75)	86.8±99.5	30 (7-120)	90 (13-150)	0.09

* normally distributed variable; # not normally distributed variable; ^ocontains one missing variable (therefore 158 patients)
DHR, drug hypersensitivity reaction; DPT, drug provocation test; IQR, interquartile range; SD, standard deviation; ST, skin tests

p-value of comparison between the group with confirmed quinolone hypersensitivity (either by ST or by DPT) and the one whose hypersensitivity suspicion was ruled out

*For further analysis, these patients were considered in the immediate group (this choice made sense clinically and statistically).

** This group included: norfloxacin, lomefloxacin, pefloxacin, pipemidic acid.

Table 2. Distribution of the events (and in particular the anaphylactic events on the Kaplan Meier curve). By RD=10%, two patients had reacted with anaphylaxis during DPT, one at RD=0.1% and another one at RD=0.6%; between RD=10% and RD=20%, four more cases had occurred, all at RD=17%-18%; finally, the last two cases occurred at RD=41% and RD=96%, respectively.

<u>% Positive DPT</u>	5	27.5	47.5%	65%	100%
Data-driven steps (RD %)	0.1	10	20	50	100
New DPT reactions since previous steps (cumulative cases)	2	7 (9)	10(19)	7 (26)	14 (40)
New DPT reactions with anaphylaxis since previous steps (cumulative cases)	1	1 (2)	4 (6)	1 (7)	1 (8)