Cardio-vascular vital sign measurements could be reduced in number during the drug allergy work-up

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To the Editor,

Drug provocation test (DPT) is considered the gold standard test to diagnose drug hypersensitivity reactions (DHR), in absence of contraindications. However, it may be very time consuming. The procedure usually consists in the administration of a medication with cautious incremental doses under close medical observation.[1-4]Vital sign measurements (e.g., blood pressure (BP), pulse) and surveillance of the patient' symptoms and signs are usually performed several times during the entire procedure to capture and prevent as soon as possible any severe reaction. However, learned societies only set a frame for DPT performance and do not make specific recommendations about the type and rhythm of these measurements.[1, 3, 4] In our center, data-driven DPT (i.e., based on patterns of reactions detected through Kaplan Meier curves) is performed in 4-7 step dosing for beta-lactams (BL),[5] 2-6 steps for nonsteroidal anti-inflammatory drugs (NSAID),[6] 3-4 steps for paracetamol,[7] and 5-7 steps for fluoroquinolones (article in press), with time increments of 30 or 60 minutes (up to 3h for certain NSAID). The BL pattern is generally applied to DPTs for other drugs. Empirically, we considered the measurement of BP and pulse as mandatory and required before starting the DPT, before every incremental dose and at any time during the DPT if symptoms of a DHR occurred. We presumed this would ensure the best safety for patients undergoing DPT, particularly for those with immediate severe reactions, namely anaphylaxis with or without shock. However, the benefit of such an attitude in patients with non-immediate reactions or immediate non-severe reactions could be questioned and to the best of our knowledge, no study has been published on this issue. In addition, measurement of BP during ST is not common practice.

During the past two decades of our center experience, based on clinical observation and previous analyses,[8, 9] we observed that isolated symptoms and signs evocative of shock during drug allergy work-up are very rare. Patients usually presented those signs in conjunction with symptoms and signs from other systems, including mucocutaneous (CU), respiratory (RS), and gastrointestinal (GI). Therefore, we hypothesized that BP measurement could be reduced in number in some circumstances, according to risk stratification (that we presumed related to the patient's individual situation and involved drug class). This retrospective analysis was then carried out in order to identify cases with symptoms and signs evocative of shock during drug allergy investigation in our center. The patients (or their parents, in case of children) gave their written informed consent at the time of the allergy work-up for their anonymous data to be used for research purposes.

We conducted a retrospective analysis using data retrieved from the Drug Allergy and Hypersensitivity Database (DAHD) between January 1996 and June 2019 in the Allergy Unit of the University Hospital of Montpellier, France. Patients with suspicions of DHR who underwent drug allergy work-up and presented with symptoms and signs evocative of shock during the tests were included in the analysis. The search terms included: "malaise", "hypotension", "collapse", "loss of consciousness", and "unspecified cardiovascular problem". Drug allergy work-up including skin test (ST) and DPT was performed according to the European

Network of Drug Allergy (ENDA) recommendations.

During the study period, 10 198 patients were tested with 53 059 single tests (a single test is defined as ST or DPT for an allergen). A total of 32 patients (0.3%) (9 males, mean age at tests of 37.0 ± 14.9 years) with 36 reactions (0.06%) who presented with the above mentioned cardiovascular (CV) signs/symptoms were identified (31 during DPT, 5 during ST). Antibiotics were the most frequent drug classes involved (47.2%), followed by NSAIDs (13.9%), and paracetamol (13.9%) (**Supplementary Table 1**). Among these reactions, 4 were found to be isolated CV signs/symptoms (3/11000 DPT (0.03%), and 1/42059 ST (0.002%), while CV with other systemic signs/symptoms were present in 32 reactions (88.9%). **(Table 1 and Supplementary Text 1)**

Using retrospective analysis from the DAHD during the past 25 years, we have demonstrated that patients with CV symptoms and signs evocative of a severe immediate DHR (shock) during the drug allergy investigation are rare, namely 0.3% of all tested patients and 0.06% of all single tests. Amongst them, only 4 patients (0.04%) with 4 reactions (0.007%) were found to have isolated CV signs/symptoms. Whether these signs were markers of true DHR could be debatable for patients no. 1 (considering her multiple similar episodes, ruled out by further investigations) and no. 3 , while patient no. 4 developed anaphylactic shock during positive ST to BL drugs (meaning that the systemic symptoms were associated to positivity at the injection site). Therefore, only one case (patient no. 2) could be classified as having isolated CV signs/symptoms as an allergic reaction.

Based on this analysis and previous analyses of patterns of reactivity and severity during DPT for different drug classes (e.g., BL, NSAIDs, paracetamol, quinolones), we propose criteria to reduce the frequency of BP measurements during DPT, according to risk stratification based on patient clinical history and drug class. Clinical history could be classified into three categories: immediate severe (high risk), immediate non-severe (low risk), and non-immediate non-severe (low risk) reactions (i.e., severe non-immediate reactions being classical contraindications to DPT).[3] Regarding drug class, we based our risk stratification on previous studies tackling patterns of DPT reactions to BL, NSAIDs, paracetamol and quinolones showing that the frequency of anaphylaxis elicited by DPT was 15%, 10%, 25% and 20% respectively.[5-7] For NSAIDs, the immediate non-severe reaction (e.g., urticaria, angioedema, rhino-conjunctivitis) is a typical clinical presentation and for such an index reaction, 90% of the positive DPT are benign cutaneous reactions (6). Thus, NSAIDs could be classified as low risk drug class. Therefore, the criteria of BP measurement could be categorized as in **Table 2.** Regarding our 4 patients with isolated CV symptoms, all of them would've been classified in the high-risk groups (patient no. 1 and no. 3 because of index history of immediate severe reaction, patient no. 2 and no. 4 because of the drug class).

It could be argued that by reducing the number of CV vital signs measurements, the professional performing the DPT could be distracted from the very core of the allergy work-up, which is ensuring patient safety during the procedures. However, our study shows that isolated CV signs/symptoms are extremely rare during the drug allergy work-up performed according to safety recommendations (i.e., step-wise exposure to allergen). In contrast, the decrease in this technical workload could be beneficial to patients because physicians/nurses would then have more time to concentrate on patient questioning and reassurance during the tests. In addition, the reduction of this measurement could reduce the uncomfortable, or painful feeling of the BP measurement, particularly for young children.

To the best of our knowledge, this is the first study specifically addressing the outcome of the BP measurement during drug allergy work-up in an evidence-based manner. Reporting and analyzing the rarity of cases with isolated CV signs/symptoms enabled us to propose 4 frames for BP measurement. In a prospective trial for 1 month, BP frequency could be reduced by 14.3% (range 10.3-26.5), alleviating the technical task and favoring the medical one instead. The prospective evaluation is ongoing in our center.

In conclusion, patients with symptoms and signs evocative of shock are extremely rare during drug allergy work-up, therefore BP measurement could be reduced in number according to patient clinical history of DHR and drug class risk stratification.

References

1. Aberer W, Bircher A, Romano A, Blanca M, Campi P, Fernandez J, et al. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. Allergy. 2003;58:854-863.

2. Demoly P, Adkinson NF, Brockow K, Castells M, Chiriac AM, Greenberger PA, et al. International Consensus on drug allergy. Allergy. 2014;69:420-437.

3. Romano A, Atanaskovic-Markovic M, Barbaud A, Bircher AJ, Brockow K, Caubet JC, et al. Towards a more precise diagnosis of hypersensitivity to beta-lactams - an EAACI position paper. Allergy. 2020;75:1300-1315.

4. Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Drug allergy: an updated practice parameter. Ann Allergy Asthma Immunol. 2010;105:259-273.

5. Chiriac AM, Rerkpattanapipat T, Bousquet PJ, Molinari N, Demoly P. Optimal step doses for drug provocation tests to prove beta-lactam hypersensitivity. Allergy. 2017;72:552-561.

6. Nohra D, Molinari N, Demoly P, Chiriac AM. Data-driven step doses for drug provocation tests to nonsteroidal anti-inflammatory drugs. Allergy. 2020;75:1423-1434.

7. Nohra D, Schrijvers R, Touati N, Nahas O, Ben Fadhel N, Ferrando L, et al. Risk factors for positive paracetamol drug provocation testing and procedure optimization. J Allergy Clin Immunol Pract. 2019;7:2045-2048.e2042.

8. 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.

9. Rubio M, Bousquet PJ, Gomes E, Romano A, Demoly P. Results of drug hypersensitivity evaluations in a large group of children and adults. Clin Exp Allergy. 2012;42:123-130.

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WS, AG, MM, PD, and AMC designed the study. WS and AMC collected and analyzed the data. WS, AG, and AMC wrote the first draft of the manuscript. All authors participated in a critical review and revision of the manuscript. All authors have read and approved the final version of the manuscript.

Table 1. Characteristics of the patients with cardio-vascular symptoms and signs evocative of shock and their drug allergy work-up results

Patient No.	Sex	Age at tests (Yr)	Year (Yr)	Drug tested	Type of test	Chronology of the reaction^{+}	Symptoms and signs during drug allergy work-up	Symptoms and signs during drug allergy work-up	Symptoms and signs during drug allergy work-up
							CV	**CU**	**RS**
1	**F**	**29**	**1998**	**Aspartame**	**DPT**	**1-6h**	**malaise without hypotension**	**-**	**-**
2	**F**	**17**	**2013**	**Cefuroxime**	**DPT**	**<1h**	**malaise hypotension**	**-**	**-**
3	**F**	**24**	**2011**	**Dexamethasone**	**DPT**	**<1h**	**hypotension**	**-**	**-**
4	**F**	**32**	**2000**	**Amoxicillin PPL, MDM**	**ST**	**<1h**	**hypotension, collapse, loss of consciousness**	**-**	**-**
5	F	34	2002	Lidocaine chlorhydrate/ Benzalkonium chlorure	DPT	1-6h	malaise	urticaria	-
		34	2002	Pholcodine	DPT	1-6h	malaise	isolated pruritus	-
6	F	30	2002	Paracetamol/ codeine	DPT	1-6h	malaise	urticaria	dyspnea

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7	F	29	1999	Cefatrizine	DPT	<1h	malaise	urticaria, conjunctivitis	dyspnea
		29	1998	Dihydroergotamine	DPT	1-6h	hypotension	urticaria, angioedema	-
		28	1997	Amoxicillin/clavulanic acid	DPT	<1h	hypotension	urticaria, pruritus, angioedema, conjunctivitis	-
8	M	27	2004	Prystinamycine	DPT	6-24h	malaise	isolated pruritus	-
9	M	67	2006	Diclofenac	DPT	<1h	malaise	macular rash	-
10	M	28	2006	Amoxicillin	DPT	1-6h	malaise	urticaria	dyspnea
11	F	31	2009	Adalimumab	DPT	<1h	malaise	-	dyspnea
		30	2008	Etanercept	ST	unknown	malaise	-	dyspnea
12	F	15	2010	Amoxicillin	DPT	1-6h	malaise hypotension	urticaria	-
13	F	38	2010	Prednisolone	DPT	<1h	malaise	conjunctivitis	-
14	F	46	2015	Cefuroxime	DPT	<1h	malaise	urticaria	-
15	F	80	2019	Amoxicillin/clavulanic acid	DPT	<1h	malaise	urticaria	-
16	M	33	1997	Diclofenac	DPT	<1h	hypotension, collapse, loss of consciousness	urticaria	-
17	M	46	2002	Diclofenac	DPT	1-6h	hypotension	urticaria	dyspnea
18	F	32	1997	Spiramycin	DPT	1-6h	hypotension, collapse, loss of consciousness	angioedema	-
19	M	44	1997	Paracetamol	DPT	1-6h	hypotension	urticaria, angioedema	-

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20	M	30	2004	Cefatrizine	DPT	1-6h	hypotension	macular rash, conjunctivitis	dyspnea, cough
21	F	57	2005	Paracetamol	DPT	1-6h	hypotension	maculopapular rash, pruritus	-
22	M	33	2006	Ceftriaxone	DPT	1-6h	hypotension	isolated pruritus	-
23	F	30	2008	Ketoprofen	DPT	1-6h	hypotension	urticaria, angioedema, conjunctivitis	-
24	F	51	2009	Paracetamol	DPT	1-6h	hypotension	urticaria	-
25	F	38	2012	Rifampicin	DPT	<1h	hypotension	urticaria	-
26	F	22	2012	Paracetamol	DPT	1-6h	hypotension	urticaria	dyspnea
27	F	8	2000	Cefatrizine	DPT	<1h	hypotension	macular rash, pruritus	-
28	F	61	2001	Pholcodine	DPT	1-6h	hypotension	urticaria, angioedema, conjunctivitis	-
29	M	45	2019	Ibuprofen	DPT	1-6h	hypotension	urticaria conjunctivitis	dyspnea
30	F	51	2000	BL	ST	<1h	hypotension	pruritus, conjunctivitis	-
31	F	54	2002	Cefradine	ST	<1h	hypotension	angioedema	bronchospas
32	F	49	2017	BL	ST	<1h	hypotension	urticaria, conjunctivitis	dyspnea

Patient No.	Sex	Age at tests (Yr)	Year (Yr)	Drug tested	Type of test	Chronology of the reaction+	Symptoms and signs during drug allergy work-up	Symptoms and signs during drug allergy work-up	Symptoms and signs during drug allergy work-up
+ After the last ingested dose ++ From the antibiotic class of streptogramins Abbreviations: BL, Beta-lactam drugs; CU, Mucocutaneous; CV, Cardiovascular; DPT, Drug provocation test; F, Female; GI, Gastrointestinal; H, hours; M, Male; MDM, minor determinant mixture; PPL, benzylpenicilloyl poly-L-	+ After the last ingested dose ++ From the antibiotic class of streptogramins Abbreviations: BL, Beta-lactam drugs; CU, Mucocutaneous; CV, Cardiovascular; DPT, Drug provocation test; F, Female; GI, Gastrointestinal; H, hours; M, Male; MDM, minor determinant mixture; PPL, benzylpenicilloyl poly-L-	+ After the last ingested dose ++ From the antibiotic class of streptogramins Abbreviations: BL, Beta-lactam drugs; CU, Mucocutaneous; CV, Cardiovascular; DPT, Drug provocation test; F, Female; GI, Gastrointestinal; H, hours; M, Male; MDM, minor determinant mixture; PPL, benzylpenicilloyl poly-L-	+ After the last ingested dose ++ From the antibiotic class of streptogramins Abbreviations: BL, Beta-lactam drugs; CU, Mucocutaneous; CV, Cardiovascular; DPT, Drug provocation test; F, Female; GI, Gastrointestinal; H, hours; M, Male; MDM, minor determinant mixture; PPL, benzylpenicilloyl poly-L-	+ After the last ingested dose ++ From the antibiotic class of streptogramins Abbreviations: BL, Beta-lactam drugs; CU, Mucocutaneous; CV, Cardiovascular; DPT, Drug provocation test; F, Female; GI, Gastrointestinal; H, hours; M, Male; MDM, minor determinant mixture; PPL, benzylpenicilloyl poly-L-	+ After the last ingested dose ++ From the antibiotic class of streptogramins Abbreviations: BL, Beta-lactam drugs; CU, Mucocutaneous; CV, Cardiovascular; DPT, Drug provocation test; F, Female; GI, Gastrointestinal; H, hours; M, Male; MDM, minor determinant mixture; PPL, benzylpenicilloyl poly-L-	+ After the last ingested dose ++ From the antibiotic class of streptogramins Abbreviations: BL, Beta-lactam drugs; CU, Mucocutaneous; CV, Cardiovascular; DPT, Drug provocation test; F, Female; GI, Gastrointestinal; H, hours; M, Male; MDM, minor determinant mixture; PPL, benzylpenicilloyl poly-L-	+ After the last ingested dose ++ From the antibiotic class of streptogramins Abbreviations: BL, Beta-lactam drugs; CU, Mucocutaneous; CV, Cardiovascular; DPT, Drug provocation test; F, Female; GI, Gastrointestinal; H, hours; M, Male; MDM, minor determinant mixture; PPL, benzylpenicilloyl poly-L-	+ After the last ingested dose ++ From the antibiotic class of streptogramins Abbreviations: BL, Beta-lactam drugs; CU, Mucocutaneous; CV, Cardiovascular; DPT, Drug provocation test; F, Female; GI, Gastrointestinal; H, hours; M, Male; MDM, minor determinant mixture; PPL, benzylpenicilloyl poly-L-	+ After the last ingested dose ++ From the antibiotic class of streptogramins Abbreviations: BL, Beta-lactam drugs; CU, Mucocutaneous; CV, Cardiovascular; DPT, Drug provocation test; F, Female; GI, Gastrointestinal; H, hours; M, Male; MDM, minor determinant mixture; PPL, benzylpenicilloyl poly-L-

Patient No.	Sex	Age at tests (Yr)	Year (Yr)	Drug tested	Type of test	Chronology of the reaction^{+}	Symptoms and signs during drug allergy work-up	Symptoms and signs during drug allergy work-up	Symptoms and signs during drug allergy work-up

Table 2. Proposed criteria of BP measurement according to risk stratification based on patient clinical history and drug class.

Clinical history of patients	Drug class	Criteria of BP measurement
Patients with clinical history of immediate severe reaction	Any drug	Perform BP measurement before every step dose
Patients with clinical history of immediate non-severe reaction	Any drug^{+} (except NSAIDs)	Perform BP measurement before every step dose
	NSAIDs	Perform BP measurement before the first and the last dose
Patients with clinical history of non-immediate reaction	Any drug	Perform BP measurement before the first and the last dose
Abbreviations: BP, blood pressure; NSAIDs, nonsteroidal anti-inflammatory drugs +By default, because of lack of substantial data for most drug classes, we consider that any immediate reaction, even the non-severe ones, could be immune-mediated	Abbreviations: BP, blood pressure; NSAIDs, nonsteroidal anti-inflammatory drugs +By default, because of lack of substantial data for most drug classes, we consider that any immediate reaction, even the non-severe ones, could be immune-mediated	Abbreviations: BP, blood pressure; NSAIDs, nonsteroidal anti-inflammatory drugs +By default, because of lack of substantial data for most drug classes, we consider that any immediate reaction, even the non-severe ones, could be immune-mediated

Supplementary Text 1: Detailed description of the four reactions of four patients who presented isolated cardio-vascular symptoms and signs evocative of shock during drug allergy work-up.

Patient no. 1 was a 29-year-old female who reported a history of discomfort, edema of the neck, difficulty breathing, paresthesia of the lower limbs, hands, and face, and mild erythematous eruption on the chest and neck, 3-4h after taking aspartame in coffee. After the third DTP dose of 1 mg (cumulative dose of 1.22 mg aspartame), she developed the same feeling of discomfort, malaise, without hypotension. The symptoms persisted for 1h and disappeared spontaneously. The patient then refused to continue the test. She had been previously considered allergic to clavulanic acid and dihydro-ergotamine, based on objective symptoms occurring during DPT with these drugs. Years after her initial allergy work-up, she reported similar episodes to misoprostol, cefuroxime, and pristinamycin (a synergistin antibiotic). However, after DPT, no other DHR could be confirmed. She was also investigated for endocrine abnormalities, without any abnormal test result.

Patient no. 2 was a 17-year-old female, with a history of urticaria developed 1h after ceftriaxone injection. ST were positive to penicillin G, amoxicillin, ampicillin, and ceftriaxone, but negative to cefuroxime. DPT to cefuroxime was performed and 5 minutes after the fourth dose (cumulative dose of 42.5 mg), she had a sensation of malaise, BP dropped to 90/60 mmHg (previous BP was 125/80 mmHg). Antihistamine H1 and systemic corticosteroids were given, with improvement of signs/symptoms within 2h.

Patient no. 3 was a 24-year-old female, with a history of perioperative reaction, labelled as potentially allergic. She presented CV arrest and pulmonary edema during surgery for teeth removal. During DPT

to dexamethasone, 5 minutes after the fourth dose (cumulative dose of 16.2 mg), this patient developed hypotension (70/40 mmHg) that persisted for 1.5h. BP control was achieved after intravenous isotonic normal saline. The patient was lost to follow up.

Patient no. 4 was a 32-year-old female, with a history of generalized urticaria developed 2h after voluntary tasting cefatrizine (powder mixed in milk for her son). During ST to BL, positive intradermal reaction to the BL-ring was observed, followed by collapse, loss of consciousness, and hypotension.

Supplementary Table 1. Summary table of the patients who presented cardio-vascular symptoms and signs evocative of shock during drug allergy work-up.

Clinical characteristic (n=32 patients)
Male, N (%)
Mean age at tests ± SD
Drug allergy work-up (n=36 reactions) N (%)
Tested medication
ATB
Beta-lactams
Others ATB
NSAIDs
Paracetamol^{+}
Corticosteroids
Biological agents
Others^{++}
Type of test
DPT
ST
Chronology of the reaction during the test (after last ingested dose)
<1h
1-6h
6-24h
Unknown
Categories of symptoms
Cardiovascular (CV)
Mucocutaneous (CU)
Respiratory (RS)
Gastrointestinal (GI)
Systemic (e.g., fever)
Symptom associations
Isolated CVS
CV+CU
CV+CU+RS
CV+CU+GI
CV+CU+RS+GI
CV+RS+GI
CV+CU+GI+fever
+Paracetamol; 4 with paracetamol, 1 with paracetamol/codeine ++Other; Aspartame, Dihydroergotamine, Lidocaine chlor