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Data-driven step doses for drug provocation tests to non-steroidal anti-inflammatory drugs

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Abstract

Introduction: Hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs) are of great concern because they are frequently encountered in daily clinical practice. Drug provocation tests (DPT) are particularly needed for NSAIDs.

Methods: The aim of this retrospective study was to detect eliciting dose thresholds during NSAIDs DPT in order to suggest optimal step doses, using the survival analysis method. Our secondary objective was to describe subgroups at higher risk during DPT and evaluate the safety of our 30 min incremental 1 day protocol. The study comprised all the patients attended the Allergy of the University Hospital of Montpellier (France), between 1997 and 2017 for a suspicion of drug hypersensitivity reaction to NSAIDs.

Results: Throughout the study period 311 positive DPT were analyzed (accounting for 285 hypersensitive patients). We identified eliciting thresholds (dose and time) and we suggest the following steps for future DPT. for the rapid absorption group (Acetylsalicylic acid, ibuprofen, ketoprofen, tiaprofenic acid), every 30 min: 20%-30%-50% of daily therapeutic dose, for the moderate absorption group, every 30 min: for diclofenac 5%-15%-30%-50% and for celecoxib,

20%-80%. For the slow absorption group, piroxicam, 25%-75% separated by a 3h interval. A surveillance period of 3h after the last dose is mandatory for patients.

Conclusion: DPT protocols for NSAID are empirical, driven by the knowledge on patterns of DHR, cross-reactivity between NSAID and pharmacological effects of these all drugs. This is the second experience in improving DPT protocols, after BL (B-Lactam) antibiotics.

Keywords: Absorption, COX selectivity, Drug allergy, Drug provocation test, Non-steroidal anti-inflammatory drugs.

INTRODUCTION

Drug provocation test (DPT) is generally accepted as the “gold standard” investigation for the diagnosis of non-steroidal anti-inflammatory drugs (NSAID)- induced drug hypersensitivity reactions (DHR) (1,2). Most DHR to NSAID are immediate (or accelerated, occurring within 6h after the last ingested dose (2)) and appear in the absence of immunological recognition, rendering skin tests of no practical relevance (except for a few specific NSAID (2)). They are mediated by cyclooxygenase (COX) inhibition resulting in low production of prostaglandin E2 and an

associated increase in the synthesis, release and/or sensitivity of cysteinyl leukotrienes, responsible for the clinical manifestations. As for other frequent elicitors of DHR, namely beta-lactams (BL), there is no formal consensus on the DPT protocol to NSAID (2). The ENDA/DAIG position paper on practical approach to NSAID DHR suggests with a grade D recommendation that “*it would be possible to start with 1/10 of the single dose and increase doses in two to three steps every 2h till inducing symptoms or reaching the single therapeutic dose of the culprit drug*”. Protocols of NSAID DPT greatly vary between centers (3-9).

More than 10 years ago, our group published several hypothesis-driven DPT protocols, including DPT for NSAID. Our protocol was based on 30-min incremental doses for both immediate and nonimmediate mild/moderate DHR (10).

The aim of this retrospective analysis was to detect eliciting doses during NSAID DPT, using the survival analysis method, in order to suggest data-driven doses, as we recently did for BL antibiotics (11). Our secondary objective was to describe subgroups at higher risk during DPT and to evaluate the safety in our DPT protocol.

METHODS

Study population

Patients were selected from the *Drug Allergy and Hypersensitivity Database* (DAHD®). We retrieved from this historico-prospective cohort all patients who attended the Allergy Unit of the University Hospital of Montpellier from 1997 until 2017 with one or more suspicions of NSAID DHR and who were explored by a DPT that turned out positive. Patients who had experienced severe nonimmediate life-threatening skin reactions, drug-induced autoimmune diseases or severe organ involvement were excluded due to the fact that DPTs are contraindicated in these cases (2,12). The *Institutional Review Board* of the University Hospital of Montpellier approved the design of the study (2018_IRB-MTP_11-19; NCT03743220).

DPT Protocol

Protocols of DPT used in our center were heterogeneous. The precise dose escalation for the most frequently used NSAID during DPT is shown in **Table 1** (and in **Appendix Table 1**, for the other NSAID). Hypothesis-driven protocols were based on previous experience and general recommendations for DPT performance (10,12).

For children, the dose was calculated according to their weight, in order to reach a total dose corresponding to their therapeutic (total) daily dose (TDD). Time intervals between doses were set at 30 min. The same protocols were used for clinical histories of immediate and nonimmediate reactions.

Technical aspects (miscellaneous)

We followed the general ENDA/DAIG recommendations for DPT indications, contraindications, prohibited co-medication and enhanced safety measures (e.g. intravenous catheter) in case of anaphylaxis during clinical history (12). Uniformed capsules/preparations, delivered in specified doses prepared by the hospital pharmacy, were used for DPT. The oral route was chosen systematically. All DPT were performed during one-day hospitalization. DPT were mostly performed as open challenges, and rarely, as single-blind or double-blind placebo-controlled DPT since we were looking for objective reactions.

Definitions used in the study

NSAID classification

Based on existing data on pharmacology as well as on clinical experience with NSAID DPT, we took into consideration three possibilities to classify the NSAID: according to their (i) structure, (ii) pharmacokinetics/pharmacodynamics and (iii) COX-inhibition selectivity according to the summary of the characteristics of each product. These classifications are presented in **Appendix Table 2**. We ultimately decided to divide the NSAID into three groups according to their absorption (according to the Summaries of Product Characteristics) and their COX selectivity, which were highly matched. Thus, acetylsalicylic acid (ASA), tiaprofenic acid, ketoprofen and ibuprofen belonged to the *rapid absorption group* (plasma peak levels up to 2h after intake); celecoxib and diclofenac to the *moderate absorption group* (plasma peak levels 2-3h after intake); piroxicam was considered on its own in the *slow absorption group* (2-4h). We excluded flurbiprofen, nimesulide, fenamic acid, nabumetone, meloxicam, tenoxicam and naproxen from our DPT study analysis because of their low frequency in our population (6% in total).

Collected data

Demographic characteristics, clinical history and the results of allergy work-up were retrieved and analyzed. Children were defined as patients younger than 18 years at the time of the DPT. *Immediate reactors* were patients with the onset of index clinical reaction within 1 h after the last drug intake. Otherwise, patients were considered *nonimmediate reactors*. However, since there is no consensus regarding the cut-off between immediate and nonimmediate reactions for NSAID (2), we worked throughout our analyses with several time cut-off points, namely 1, 3, and 6h. Urticaria and angioedema (U/AO) were considered as a single entity. Isolated rhino-conjunctivitis was considered as a cutaneous/mucosal (C/M) sign. Anaphylaxis was defined according to Sampson et al (14). Chronic spontaneous urticaria (CSU) was defined according to current guidelines (16).

Positive DPT

The DPT was considered positive if objective signs occurred during NSAID administration. The objective signs were (isolated or associated) C/M eruptions or angioedema, rhinoconjunctivitis, respiratory symptoms (bronchospasm, wheezing, cough with at least 15% reduction in the forced expiratory volume in one second), systolic blood pressure drop of at least 30 mmHg.

In case of occurrence of subjective symptoms during DPT, the supervising physician could decide either to repeat the last step, divide the next step into two doses, or proceed as planned. When subjective symptoms occurred but the patient could complete the DPT without further objective signs or symptoms, the DPT was considered negative. When a reaction considered positive occurred at any time during DPT, the DPT was stopped and the reaction was immediately treated accordingly.

DPT event

Because the purpose of the study was to define dose steps for DPT, we analyzed the DPT events, rather than the patients. Thus, each DPT event was considered as a distinct entity. One DPT event ('case') was composed of one index reaction and the corresponding positive DPT result for one tested NSAID. The index reaction was defined as the history of DHR associated with the intake of NSAID. When a patient reported several histories of DHR to NSAID, the last clinical history was considered for the index reaction clinical presentation, assuming that the last reaction was at least as severe as the previous ones. Otherwise, the most recent severe reaction was chosen. When a patient had a positive DPT for the NSAID involved in the index reaction and during a DPT for the

identification of an alternative NSAID (mostly piroxicam or celecoxib), the same index reaction was attached to each DPT event, separately. The hypersensitivity reaction elicited during the DPT event was classified as *similar to, less or more severe* than the index reaction according to clinical criteria. The DPT events with different semiology from index reaction/history were also noted. Isolated benign C/M reactions, such as U/AO and maculopapular exanthema (MPE), were considered less severe than anaphylactic shock or isolated respiratory symptoms involving bronchospasm.

Survival analysis: reactive doses and reactive time points (11)

The reactive dose (RD) was calculated from the total cumulative dose (mg) reached when the DPT was considered positive. Due to the complexity and multitude of DPT protocols (TDD varying according to the tested NSAID and the age of the patient), we chose to define the RD as a ratio between the cumulative RD (mg) and the total DPT dose (i.e., the dose reached if DPT was to be completed; see **Table 1**). The RD was expressed in percentage.

The reactive time point (R_{time}) was the delay between the DHR elicited by DPT and the last administered dose during DPT. It was analyzed according to the delay after the last administered dose (considering within 1h an immediate reaction, between 1-6h an accelerate reaction and $> 6h$ a nonimmediate reaction). Censoring time (or dose) corresponds to the total observational time if $R_{\text{time}} > \text{total observational time}$ (or if $RD > \text{total cumulative dose}$).

In exploring the Kaplan Meier curves for RD and R_{time} , we first searched for visually-detectable steps that cumulated most of the events. If no such steps were noticed, we worked with decile of reactive patients. After the steps were established, we evaluated their input in terms of number of events and safety, and we proposed a data-driven protocol.

Surveillance period

Patients were kept under medical surveillance for 3h after the last administered dose. If no reaction occurred, they were discharged with a corticosteroid and H1 antihistamine prescription, a result, a telephone number and an email contact. Patients were educated to observe their reaction after discharge (in case of index clinical/history of nonimmediate reaction), contact the staff immediately and treat accordingly if the reaction occurred. If an immediate reaction occurred

during the DPT, the patient was properly treated and released only when all symptoms had disappeared (typically 2–3h after the reaction).

Statistical methods

Qualitative variables were expressed as numbers and percentages. Quantitative data were expressed as medians with interquartile range (IQR) with 25th and 75th percentiles (Q25–Q75 IQR, not normally distributed data assessed with a Shapiro–Wilk test). The chi-square test was used to analyze differences in nominal variables between groups or Fisher's exact test for small samples. Comparisons of quantitative variables were made using the Student-Anova test and the Pearson correlation test. Clinical predictors of RD (quantitative variable) were searched using univariate and multivariate linear regression. Clinical risk factors of anaphylaxis were searched using univariate and multivariate binary logistic regression, and odds ratio (ORs) were expressed with 95% confidence intervals (CIs). RD and R_{time} were considered as time-dependent data and were analyzed with survival data analysis methods. *P* values were based on two-tailed tests, with values <0.05 considered statistically significant.

RESULTS

Patient characteristics and DPT events

Throughout the study period, 296 patients had 460 index reactions, accounting for 311 positive DPT. These 311 DPT events were further analyzed. Median age at DPT was 37 years (21–51.2). There were 60 (19.3%) children.

The culprit NSAID in the index reaction were: ASA (131, 42.7%), ketoprofen (27, 8.8%), ibuprofen (69, 22.5%), diclofenac (20, 6.5%), piroxicam (16, 5.2%), tiaprofenic acid (20, 6.5%), celecoxib (three, 1%) and others (25, 6.8%). There were 113 (36.3%) cases with multiple episodes, in most cases two episodes were described (71, 23.4%).

Forty-one patients (13.8%) had a clinical history of CSU.

Two hundred sixty-five (85.2%) DPT events were performed for an index reaction for immediate (43.9%) and accelerate (41%) reactions. The majority (82.4 %) of index reactions had occurred within day 1 (D1) of drug intake. The delay between index reaction and DPT was ranging from 1

and up to 378 months with a median of 7.5 months (3-33). The median DPT duration was 2h (1.5-2.5). The median delay of DPT reaction after the last dose was 0.9 h (0.5-2.9).

In hundred sixty-nine (54.3%) cases, the culprit drug was chosen for challenge. If an alternative drug was preferred, it was mostly piroxicam or celecoxib (**Appendix Table 3**).

Considering the clinical presentations of DHRs, the most frequent index reaction was C/M (190, 61.1%), followed by anaphylaxis (115 cases, 37%, including 25 episodes of anaphylactic shock), and isolated respiratory symptoms (6, 1.9%). When we cross-matched the symptoms of the index reaction with those of the reactions elicited at DPT, we observed that in most cases, but not in all, the elicited reactions during DPT reproduced the DHR of the initial episode (just as (35.4%) or less (54%) severe, in terms of signs and symptoms) regardless of the drug being tested (alternative or the culprit drug). Indeed, when the symptoms in the index reaction were C/M, we noticed that 88.5% vs 10.4% vs 1.1% were C/M vs anaphylaxis vs respiratory symptoms, respectively, during DPT. Similarly, when the index reaction was described as anaphylaxis, 73.6% DPTs elicited C/M signs and 22% resulted in anaphylaxis. Interestingly, in case of an isolated respiratory index reaction, 62.5% DPTs were respiratory, but a quarter were more severe, i.e., anaphylactic.

Reactive doses and times

Figure 1 shows the reactive patterns for doses.

Rapid absorption group

We could notice sharp drops on the RD curve (**Figure 2A**), corresponding to RD= 6.8%, 10.3%, 23.2%, 50% and 100%. Before RD= 10.3%, there were 9 DPT with anaphylaxis (6 cases) or respiratory compromise (i.e., bronchospasm, three cases) (**Table 3A**). In 7 cases (77.7%), the clinical history was either anaphylactic or bronchospasm. We therefore decided that these low doses, 1%, 5%, 10%, would be kept for patients with a clinical history of anaphylaxis or bronchospasm. Between 43% and 50%, there were 8 episodes of anaphylaxis during DPT, but only three of 8 actually had had a clinical history of anaphylaxis. Of the 12 DPT with anaphylaxis between RD=50% and 100%, 8 (66%) occurred at RD= 100%; of the 12 episodes, only five had anaphylaxis as an index event. When combining safety and practical approach, we decided for future DPTs a DPT with 20-30-50% (and therefore RD= 20%, 50% and 100%), and 1-5-10% for patients with clinical history of anaphylaxis or bronchospasm. Tiaprofenic acid had a slightly

different curve. We only had 12 positive DPTs to this NSAID. The majority (10 of 12, 83.3%) were positive after RD=63.5% (including two anaphylactic DPTs).

Moderate absorption group

Diclofenac

Following the reasoning above, we could see sharp drops on the RD curve (**Figure 2B**), corresponding to RD= 1.2%, 6.9%, 18.7%, 47.6% and 100%. Diclofenac was the NSAID with the most anaphylaxis as index event (73.6%), and with four anaphylactic DPT (all of them with an anaphylactic index reaction). Three of them occurred before RD=10% (one at RD=1.3%, and two at RD=7%). After RD=20%, there were no more anaphylactic events. Therefore, combining safety and practical approach, we decided for future DPTs a DPT (**Table 3B**) of 5%-15%-30%-50%, preceded by 0.1 and 1% for index reactions of anaphylaxis.

Celecoxib

This group had the smallest sample size (nine cases; in three cases, DPT was performed for a clinical history of DHR to celecoxib, and for the remaining six, as an alternative). Visually, the drops on the RD curve were at RD between 15-20% and RD=100%. Sixty percent of the patients were positive by RD= 20%. There was a single anaphylactic shock (with an identical history for this NSAID) in DPT at RD=15.2%. We decided for future DPTs a two-step DPT: 20% followed by 80% (cumulative RD=20% and then 100%). An adapted protocol (e.g., starting at 10%) could be used when testing celecoxib for an index history of anaphylaxis to this very drug.

Slow absorption group

Visually, the most contributive steps for piroxicam (**Figure 2C**), were at RD=29.9%, 80% and 100%. There was a single episode of anaphylaxis (clinical history of anaphylaxis with a different NSAID), at RD=29.9%. Taking into account the peculiar curve of piroxicam in R_{time} (see paragraph below), we decided for future DPTs a DPT of two doses, 25% followed by 75% (so cumulative dose of 25% followed by 100%, **Table 3C**), but with a longer time step (see reactive time points). Most of the times (89.6%), piroxicam was tested as an alternative NSAID, but in 9 of 87 cases, it was tested for a clinical history of DHR to piroxicam itself (one and two cases of anaphylaxis w/o and with shock, respectively, and five of C/M reactions). This latter group had no remarkable specificities, all RD were $\geq 80\%$, regardless of the clinical history.

Reactive time points

Figure 3A shows the patterns of R_{time} .

Rapid absorption group

The median R_{time} was 35 min (30-120). In our study population, 122 (68.9%), 147 (83%) and 154 (87%) cases reacted within 1h, 3h and 6h respectively, after the last dose. We calculated that the difference between $< 3h$ and $< 6h$ was not clinically significant, considering the non-severe elicited symptoms (C/M). We noticed 29 cases (16.4%) reacting after the surveillance period, the elicited symptoms where in majority C/M (93.1%). There were two presumably anaphylactic episodes (6.9%) with ASA and tiaprofenic acid, described at 18h and 24h, respectively, after the last dose (**Appendix Table 4**).

Moreover, ASA, ibuprofen and ketoprofen followed similar trends (**Figure 3B**), with 80%, 95% and 83% of cases reacting within 3h after the last dose. Tiaprofenic acid had slightly slower reaction times, with 25% of cases (three of 12) reacting more than 3h after the last dose.

Concerning the concordance between chronology of the index reaction and that of the symptoms elicited during DPT, we observed that the immediate and accelerate groups followed a similar trend for up to 80% of cases (**Figure 3C**). We noted that in the immediate group, 60 cases (81.1%), 69 cases (93.2%) and 71 cases (96%) reacted within 1h, 3h and 6h respectively. Therefore, 8% percent of cases with immediate index reactions reacted after the surveillance period. In the accelerate group (1h-6h), 51 cases (69%%) reacted faster than the chronology of their index reaction (within 1h), 65 (87.8%) reacted within 3h and 69 patients (95%) reacted within 6h. For the nonimmediate group, the chronology matched (i.e., $>6h$) in only 44% of cases; whereas a third (8 cases, 32%) reacted within 1h, 40% reacted within 3h, 56 % reacted within 6h.

Globally, in more than 80% of cases, the chronology of the DPT reaction was either similar or faster, compared to the index reaction.

Moderate absorption group

Twenty-two cases (78.6%) reacted within 1h (median R_{time} for diclofenac= 30 min, (5-60); median R_{time} for celecoxib = 30 min (20-354)). This group mostly included patients with immediate (17 cases, 60%) and accelerated index reactions (26 cases, 32.1%), that followed similar trends, with

82.4% and 77.8% of reactions respectively occurring within 1h during DPT. The other R_{time} (six cases) were heterogeneous (< 3h, up to 6h, > 6h). We noticed similar trends between the two molecules (**Appendix Figure 1**), diclofenac and celecoxib for the reactions elicited up to 1h after the last dose (17 cases, 89.4% and five cases, 62.5%, respectively). Reactions elicited beyond 3h where C/M (four cases, 14.2%).

Slow absorption group

The median R_{time} was 120 min (53-224). For piroxicam (**Figure 3D**), the agreement between the chronology of the index reaction and that of DPT was only 41% (16 cases) for immediate index reactions. Additional 41% of cases reacted up to 3h. All in all, 95% of cases reacted within 6h after the last dose. For nonimmediate index reactions, the match was 50%.

DPT safety and risk factor analysis

The DPT elicited benign C/M reactions in 268 cases (86.1%), 36 anaphylactic episodes (11.5%) including five anaphylactic shocks) and seven cases of respiratory isolated symptoms with bronchospasm (2.3%).

In 247 DPT events (79.4%), the reaction occurred while the patient was either during DPT or during the 3h surveillance period following DPT completion. In all the other cases (64, 20.4%), the reactions occurred after day hospital dismissal, they were handled properly with full recovery in all cases. **Appendix Table 4** presents the two cases with potential severe reaction after hospital dismissal.

There were only 42 (16.7%) and two (6.4%) cases of nonimmediate C/M symptoms and anaphylaxis, respectively. We noted that 100% of isolated respiratory symptoms were of immediate or accelerate occurrence, always within 3h after the last administered dose (i.e., during the prolonged medical surveillance after the last dose). Overall, the reactions elicited by DPT were of similar severity to the index reaction in 110 cases (35.4%). While the reaction was estimated to be more severe in 33 cases (10.6%), it was in most cases less severe (168 DPT, 54%). The DPT events with more severe reactions than the index reaction comprised 17 anaphylaxis, 14 U/AO and two respiratory isolated symptoms.

Virtually all (89.4%) but two cases (10.5%) reacted within 1h for diclofenac and this NSAID was the most frequently involved in anaphylactic index reactions (nine of all anaphylaxis cases, i.e., 33.3%) and anaphylactic shock during DPT (two of five cases, 40%).

The patients with confirmed NSAID hypersensitivity were challenged to find safe alternative drugs, which were most of the times, piroxicam and celecoxib (60% of cases).

We found several clinical predictors for RD: female gender, asthma, an immediate index reaction, a generalized index reaction and anaphylaxis were significantly associated with a lower reactive dose ($p < 0.05$). Atopy had no independent association with RD ($p = 0.16$) and neither did CSU ($p = 0.18$).

In multivariate analysis the independent variables that remained significantly associated with RD were: (i) a generalized index reaction, it reduced the median RD by 13.3%, $p = 0.001$); (ii) asthma, reducing the mean RD by 13.7%, $p = 0.005$); (iii) a nonimmediate index reaction, increasing the RD by 14.9%, $p = 0.003$); (iv) testing an alternative NSAID, increasing the RD by 11.6% ($p = 0.005$). The most significant factor affecting the RD was the type of the initial reaction (generalized versus localized) with the highest standardized coefficient.

The three variables that independently predicted anaphylaxis during DPT were having anaphylaxis symptoms during index reaction (OR=2.5, CI [1.2-5.8], $p = 0.009$), having a DHR during childhood (OR=0.8, CI [0.7-0.9], $p = 0.005$) and not having asthma (OR=0.2, CI [0.1-0.6], $p = 0.002$).

In our study, the cross-intolerant status of the patients was not specifically confirmed by ASA challenge. However, in thirty-one cases (amongst the 169 tested for the NSAID involved in the clinical history) two or more episodes to two different NSAIDs had occurred. We can therefore presume that these patients were cross-intolerant, as well as all the cases tested for an alternative that turned out positive (142). When Kaplan Meier curves were broken down by cross-intolerant status ("yes" or "unknown"), there was no difference in patterns of reactive doses (*data not shown*).

DPT in children

The median age at DPT was 12 years (8.2-14) and half of children were female patients. The DPT elicited benign C/M reactions in 46 cases (76.7%), 13 cases of anaphylaxis (21.7%, all without shock) and one case of isolated respiratory symptoms (1.7%). Median RD and R_{time} were 100% (46.2-100) and 30 min (20-90). When comparing the Kaplan Meier curves between adults and children, we did not find any difference in the rapid or slow absorption group (**Appendix Figure 2**). In our study population, there were no positive DPT for diclofenac or coxibs.

DISCUSSION

Performing DPT is particularly crucial for the diagnosis of NSAID DHR because of the insufficiency of diagnostic skin and *in vitro* tests (1,2). DPT protocols for NSAID are empirical (a priori), driven by the knowledge on patterns of DHR (cutaneous/respiratory/anaphylactic), cross-reactivity between NSAID and pharmacological effects of these drugs.

Following our experience with BL DPT (11) we applied a similar methodology to a population with positive DPT to NSAID, in an attempt to suggest data-driven protocols. Up to present, we have used the same empirical protocols (10) for NSAID DPT, and this consistency allowed data comparison and analysis over a 20-year time period.

Dealing with NSAID DPT raises special challenges related to the pharmacology of the drug and the mechanism of NSAID DHR via COX-inhibition. Our choice to regroup NSAID from different structural families in three distinct classes relies on both pharmacokinetics and pharmacodynamics of these drugs.

The sharp drops on the Kaplan Meier curves, suggestive of the most contributive RD for each class differed quite clearly, showing different behaviors during DPT. For frequently used NSAID (i.e., the rapid absorption group), the cumulative doses responsible for the majority of events were rounded up to 20%, followed by 50% and 100%, suggesting that a three-step dose (as proposed by others (4,5,9)) could be considered for future DPTs. Nevertheless, severe events (anaphylactic) did occur at RD < 20%, making lower doses compulsory when testing patients with anaphylactic index reactions, in order to ensure their safety. Diclofenac (i.e., moderate absorption group) was the most frequent culprit of anaphylaxis during the index reaction in our series, as for others (13). Compared to the previous NSAID group, where anaphylactic episodes were scattered throughout

the Kaplan Meier RD curve, 75% of anaphylactic events elicited by diclofenac DPT occurred at low doses (i.e., $RD < 10\%$, starting with $RD = 1.3\%$). This pattern of reaction was strikingly similar to what we observed for BL DPT (11) both in terms of most contributive RD (5-15-30-50%) and of low-dose induced anaphylaxis. Therefore, although our diclofenac DPT could not identify lower doses than 1.3%, we decided to follow the BL pattern and include an extra 0.1% step (before the 1% step) in case of an index reaction of anaphylaxis with diclofenac.

Whilst providing a more secure DPT in patients with index reactions of anaphylaxis, this extra 1-16% (e.g., the total cumulative dose would then be 101-116% for the rapid absorption group or 106% for the moderate absorption group) still complies with maximal daily dose for these NSAIDs.

Piroxicam is usually regarded as a safe alternative in patients with cross-intolerance, due to its COX-inhibition profile (3,4). Our study confirms the good safety profile of DPT with piroxicam (two cases of anaphylaxis for 87 positive DPT, i.e., 2.2%). Additionally, piroxicam had the longest median R_{time} , and the poorest match between the chronology of the initial reaction (which was in 89% of cases with a NSAID distinct from piroxicam) and the one elicited by DPT. This mismatch confirms our clinical experience with this NSAID and is probably due to its slow absorption profile. Therefore, in the case of piroxicam DPT, increasing the time between the doses might be more important than working on the doses themselves. Furthermore, the RD analysis showed fewer steps than for the other groups, prompting us to imagine a two-dose DPT (25%-75%) but with larger intervals between doses, namely 3h, even when testing piroxicam as an alternative for immediate DH. This protocol could also be applied when performing a DPT for a clinical history to piroxicam itself, since our data suggests its safety profile in this subpopulation as well. Nevertheless, considering the small size of this subgroup (nine cases), we could imagine adding a supplementary dose (e.g., of 10%), when performing DPT in patients with anaphylaxis to piroxicam. The analysis performed on DPT to celecoxib is hampered by the small sample size (nine cases) but suggests a two-step protocol can be considered, with the same precautions as described above for piroxicam (e.g. 10% supplementary dose at the beginning of DPT, in case of anaphylactic index reaction to celecoxib). That being said, we believe that skin testing is highly advisable in cases of an anaphylactic reaction with a single NSAID, and should be performed prior to DPT, whatever the protocol.

By observing a 3h compulsory surveillance period after the last ingested dose during DPT we were able to capture 80% of positive tests, and all the severe ones (the diagnosis of anaphylaxis in the two patients reacting after dismissal is doubtful, **Appendix Table 4**). As for BL (11), we observed a good match between the chronology of the index reaction and the one elicited by DPT, in the immediate and accelerate group (>80%), and a poor one in case of nonimmediate reactors. Our choice to work throughout the analysis with subgroups of <1h, 1-6h (sometimes splitting this interval at 3h), >6h was motivated by: (i) the recognized peculiarity of the clinical manifestations of DHR to NSAID, that can have an immediate appearance (i.e., U/AO) but with a delayed onset (i.e., >1h) and (ii) our intention to capture potential miss-match in terms of R_{time} , if a single classification, i.e., <1h, >1h had been chosen.

Learned societies create a frame for DPT protocol, advising to start 'low' and reach a therapeutic daily dose, but no dose or interval steps are mentioned between the first and the last dose, leaving an open choice. All groups use empirical protocols, with variations in dose (starting at 1%, 10% or 25% in most cases) (3,7,9), various time interval between doses (30 to 180 min) (3,7,9) and even duration of DPT (3,9). Sometimes the same group uses different DPTs to address distinct populations, e.g., cross-intolerant patients versus selective responders (4). Although they are rooted in clinical experience and knowledge about NSAID specificities (both pharmacological and in terms of DHR), these protocols remain empirical. Only responses to ASA DPT in NSAID-exacerbated respiratory disease (NERD) patients have already been modeled using logistic regression, with a model that correctly classified 86% of all cases and 99.5% of cases with positive DPT (6). However, this is a very specific population of NSAID DHR.

By providing data-driven patterns of response to DPT in a large population with various characteristics, our analysis brings further insight into DHR to NSAID. At present, in the era of precision medicine, the drug allergy work-up for NSAID remains mainly clinical and based on DPT. Working on clinical variables is therefore mandatory, and we have shown that it can further tailor this intervention (i.e., DPT) according to patient's history. Our initial DPT protocols (10), with very gradual incremental steps allowed us to capture reactions at low doses, take them into account and then propose a data-driven protocol for future DPTs. These new shortened protocols are meant to increase patients' comfort (shorter hospital stay), gain time for the medical team, while maintaining patient's safety. Contrary to BL DPT (11), anaphylaxis during DPT to NSAID is rare but such protocols are designed to capture it. Our new data-driven protocols have a similar

dose profile (3-4 step protocol for propionic acid derivate NSAID (3-5) or even identical (e.g., piroxicam (9)) to those of other groups, and a time profile tailored to R_{time} for different groups of NSAID (3).

In this analysis, we chose to work with a classification based on pharmacokinetics/pharmacodynamics and COX inhibition selectivity of NSAID rather than to put forward a DHR classification (1) because our purpose was to focus on the characteristics and outcome of DPT event itself (i.e., a clinical history, leading to the choice of a DPT, eliciting a reaction to a certain RD and R_{time}).

Our study has several limitations. We analyzed data from one center, but this limitation will be overcome in a prospective phase involving several centers in France, that will further evaluate the safety and benefits of the new data-driven protocols. Because our aim was to work on DPT protocols, this study excluded some patients with a high probability of (too severe) NSAID DHR from the database, i.e., those with negative DPT for an alternative NSAID. We must also pinpoint the fact that we did not specifically diagnosed the status of cross-intolerance and selective response by ASA challenge (1). In more than half of the cases the cross-intolerant status was extrapolated as explained above in the text. When Kaplan Meier curves were broken down by cross-intolerant status (“yes” or “unknown”), there was no difference in patterns of reactive doses in our cohort. Another limit concerns the small samples for certain clinical histories (e.g., NERD) or for certain rarely-tested (**Appendix Table 1**) or rarely positive NSAID (celecoxib). In our study, few patients (i.e., 6) had isolated respiratory symptoms at index reaction or during DPT (i.e., 7). Therefore, we cannot analyze this small sample to detail patients with NERD. This is a selection bias since we have long ago considered in our daily practice (in concordance with literature data) that the positive predictive value of a clinical history of NERD is high enough to avoid elective DPT in these patients (6); it has become over the years a non-indication for DPT for us. For patients with asthma and/or nasal polyposis and a clinical history suggestive of NSAIDs-induced bronchospasm, but with a clear differential diagnosis (i.e., bronchospasm occurring after NSAID intake during an upper tract respiratory infection), we would use a protocol similar to the one for anaphylaxis (i.e., high risk patients).

For our initial empirical protocols, the 30-min interval had been set in accordance to general recommendations on DPT performance. Therefore, this could not be changed retrospectively. Whilst we acknowledge that certain patients may react beyond 30-min, our results show that an at

least 30-min profile is fairly safe for most clinical entities, namely the ones included in our cohort. A clear pattern of delayed reaction (within 3h) was seen both clinically and by statistical modelling for drugs like oxicams.

Pyrazolones, that are known to be elicitors of IgE-dependent reactions, are not marketed in France. Other NSAIDs (largely used in other countries, e.g., flurbiprofen, nimesulide, fenamic acid, nabumetone, meloxicam, tenoxicam) were rarely tested in our experience. Kaplan Meier curves were performed for each of these NSAIDs and no peculiarities were noticed (data not shown).

A high proportion of patients in our study are atopic. Atopy, and particularly sensitization to mites has been associated with NSAID DHR (17), and the hypothesis of a co-localization on the same gene of loci regulating leukotriene synthesis and IgE-mediated immune responses has been put forward. Our study was not designed to capture the association between atopy and NSAID DHR, and atopy was not an independent factor influencing RD.

Our DPTs were performed as open challenges, raising the hypothesis that some results may be false positive. Patients reacting to placebo usually present subjective symptoms of nausea, headache, or itch and only rarely objective symptoms (15). In our study these subjective symptoms were not used as stop signs or interpreted as a positive DPT.

In conclusion, we retrospectively analyzed our experience with positive DPT to NSAID using the Kaplan Meier analysis method. The appearance of the Kaplan Meier curves actually showed that NSAIDs belonging to a similar pattern of absorption followed a similar pattern of reactivity. This would imply that imagining a DPT for a newly tested peculiar NSAID (with lower degree of evidence in DPT), by following its absorption pattern would be feasible. We identified eliciting thresholds (dose and time) and we suggest the following steps for future DPT to NSAID, for immediate and nonimmediate reactors (except for NERD and whilst observing contraindications of DPT), for both children and adults: (i) rapid absorption group (ASA, ibuprofen, ketoprofen, tiaprofenic acid), every 30 min: 20%-30%-50% of daily therapeutic dose, preceded by 1%-5%-10% in patients with a history of anaphylaxis; (ii) moderate absorption group, every 30 min: for diclofenac 5%-15%-30%-50% (preceded by 0.1-1% for patients with anaphylaxis) and for celecoxib, 20%-80% (and an additional step of 10% in case of anaphylaxis); (iii) slow absorption group, piroxicam, 25%-75% separated by a 3h interval (preceded by 10% in patients with anaphylaxis separated by a 30min-1h interval). A surveillance period of 3h after the last dose is mandatory for all patients, to guarantee that severe reactions be captured under medical

surveillance. These protocols are currently undergoing a prospective validation process (to evaluate their safety and benefits), in a multicenter French study.

Author contributions

DN, AMC and PD initiated the study. DN and AMC contributed to data collection. DN, AMC and NM performed the statistical analysis. DN and AMC wrote the initial manuscript. PD and NM revised the manuscript. All authors participated in the design of the study and interpretation of the results and approved the final version.

NSAID	Dose escalation (mg)	Total DPT dose (mg)	Unit dose/Tablet (mg)	Therapeutic daily dose (<i>TDD</i>)	
				Adults	Children
Acetylsalicylic acid	(1)-10-20-50-(100)- 200-500	780 (880)	250mg- 500mg- 1000mg	3000mg	50mg/kg
Tiaprofenic acid	1-10-100-150-150	411	100 -200mg	200-600mg	>15kg 10mg/kg
Celecoxib	0.1-1-10-25-50-150	236.1	150mg		not recommended*
Diclofenac	1 -5 -10 -20 -50	86	25 -50 -75 - 100mg	75-150mg	>6yrs 2-3 mg/kg
Ibuprofen	2 -10 -40 -100 -200 - 400	752	200-400mg / Syrup 20mg/ml	200-1200mg	20-30mg/kg
Ketoprofen	1-5-10-20-50-100	186	50-100-150- 200	100-200mg	0.5 -2 mg/kg
Piroxicam	1-5-5-10	21	10-20mg	20mg	not recommended**

**Table 1:
Protocols
used
at
present
for
DPT.**

DPT, drug provocation test; NSAID, non-steroidal anti-inflammatory drug; TDD: therapeutic daily dose

*Coxibs are not recommended for children (although they have been successfully and uneventfully used in children with true DHR to other NSAIDs). In our data, we had no positive DPT to coxibs in children.

** Oxicams are not recommended for children under 15 years of age but similarly to coxibs, they may be used as an alternative in children with proven DHR. In our study, 2 children (3.3%) having a clinical history to piroxicam and 13 (21.7%) DPT with piroxicam.

At DPT, we used 20 mg (100%) as a therapeutic daily dose for children > 15 years and for children < 15 years, we used 10 mg.

Table 2. Descriptive statistics of the DPT events.

Clinical Characteristics			Number (%)
DPT Reaction	Gender	Female	192 (38.1)
	NSAIDs family at DPT	Acetylsalicylic acid	87 (28)
		Arylcarboxylic derivatives	116 (37.3)
		Oxicam derivatives	90 (28.9)
		Indolic derivatives	1 (0.3)
		Selective COX-2 Inhibitors	9 (2.9)
		Nimesulide	5 (1.6)
		Fenamic acid	3 (1)
	NSAIDs drugs at DPT	Acetylsalicylic Acid	87 (28)

	Tiaprofenic Acid	12 (3.9)
	Ketprofen	41 (13.2)
	Ibuprofen	37 (11.9)
	Diclofenac	19 (6.1)
	Celecoxib	9 (2.9)
	Piroxicam	87 (28)
	Others	19 (6)
Asthma	Yes	70 (22.5)
Atopy	Yes	232 (74.6)
DPT tested NSAIDs	Culprit NSAIDs	169 (54.3)
	Alternative NSAIDs	142 (45.7)
Chronology of the DPT reaction after the last NSAID intake	< 1 h	158 (50.8)
	1h-6h	108 (34.7)
	6h-24h	34 (10.9)
	> 24 h	11 (3.5)
Age at DPT	Child < 18 Years	60 (19.4)
	Adult ≥ 18 Years	251 (80.6)
Occurrence of DPT reaction	During DPT procedure	121 (38.9)
	During surveillance period (3h)	126 (40.5)
	After surveillance period (>3h)	64 (20.6)
Semiology of DPT	Cutaneo-mucosal	270 (86.8)
	Anaphylaxis	34 (10.9)
	Isolated respiratory symptoms	7 (2.3)
Type of DPT reaction	Generalized	103 (33.1)
	Localized	208 (66.9)
Severity of DPT reaction compared to index reaction	Less	168 (54)
	Same	110 (35.4)
	Worse	33 (10.6)

COX, cyclooxygenase; DPT, drug provocation test; NSAID, nonsteroidal anti-inflammatory drug

Table 3. Detail of the data-driven protocol for: A) Rapid absorption group; B) Moderate absorption group; C) Slow absorption group. For all subgroups, the steps are presented in terms of

RD according to visually-identified significant drops on the corresponding Kaplan Meier curves. The number of positive DPT since the previous step in the protocol (and more specifically, the number of anaphylactic shocks and anaphylaxis w/o shock) is noted for each RD.

3A)

% Positive DPT in the rapid absorption group	10%	15.8%	22%	45%	100%
Data-driven steps (RD %)	6.94	10.3	23.2	50	100
New DPT reactions since previous steps (cumulative cases)	18	10 (28)	17 (45)	30 (75)	102 (177)
New DPT reactions with shock since previous steps (cumulative cases)	1	1 (2)	0 (2)	0 (2)	0 (2)
New DPT reactions with anaphylaxis since previous steps (cumulative cases)	4	0 (4)	2 (6)	8 (14)	12 (26)

3B)

% Positive DPT in the moderate absorption group: Diclofenac	5%	15%	50%	60%	100%
Data-driven steps (RD %)	1.2%	6.9%	18.7%	47.6%	100%
New DPT reactions since previous steps (cumulative cases)	1	2 (3)	6 (9)	3 (12)	7(19)
New DPT reactions with shock since previous steps (cumulative cases)	0	1	1 (2)	0 (2)	0 (2)
New DPT reactions with anaphylaxis since previous steps (cumulative cases)	1	1 (2)	2 (4)	0 (4)	0 (4)

3C)

% Positive DPT in the slow absorption group	1%	7%	12.9%	100%
Data-driven steps (RD %)	5	29.9	80	100
New DPT reactions since previous steps (cumulative cases)	1	5 (6)	6 (12)	75 (87)

New DPT reactions with shock since previous steps (cumulative cases)	0	0	0	0
New DPT reactions with anaphylaxis since previous steps (cumulative cases)	0	1	0 (1)	1 (2)

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Figures:

Figure 1: Reactive doses for the *rapid, moderate and slow absorption* groups.

Figure 2: Reactive doses for the: A) rapid absorption group (tiaprofenic acid, ASA, ibuprofen, ketoprofen); B) moderate absorption group (diclofenac, celecoxib); C) piroxicam.

Figure 3: Reactive time points after the last dose administered during DPT for: A) the whole population; B) the rapid absorption group by drug; C) the rapid absorption group, according to the chronology of the index reaction; D) piroxicam, according to the chronology of the index reaction.

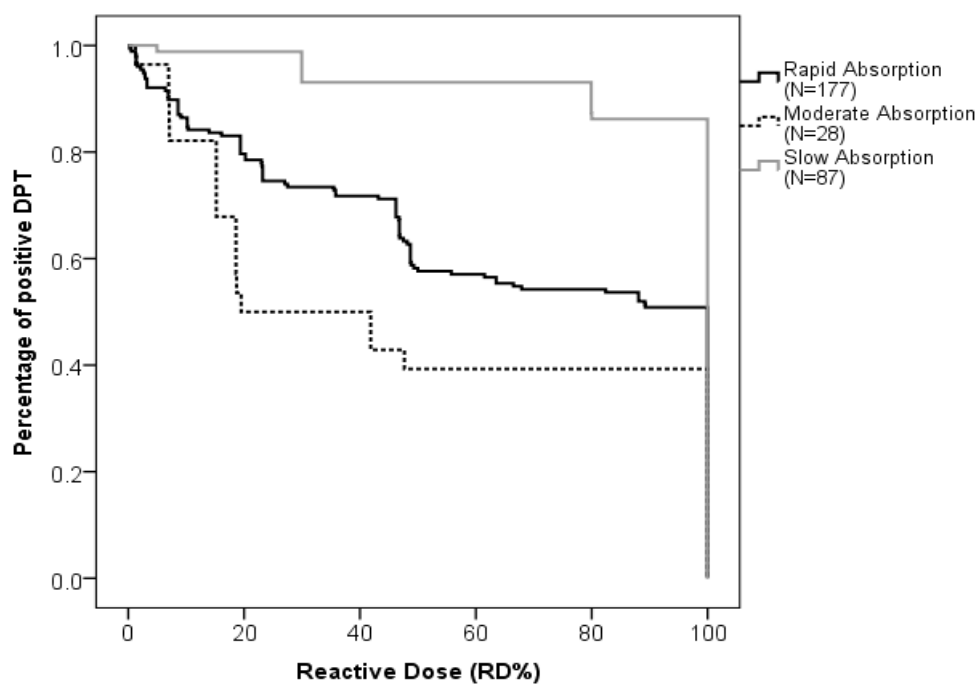


Figure 1: Reactive doses for the the *rapid*, *moderate* and *slow absorption* groups.

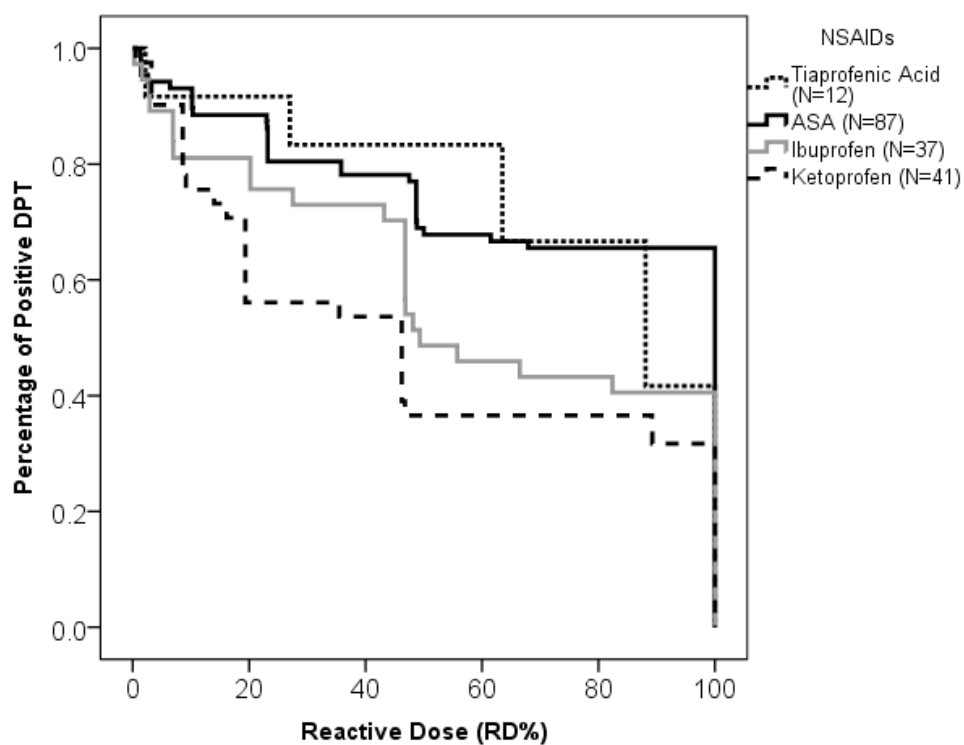


Figure 2: Reactive doses for the: A) rapid absorption group (tiaprofenic acid, ASA, ibuprofen, ketoprofen).

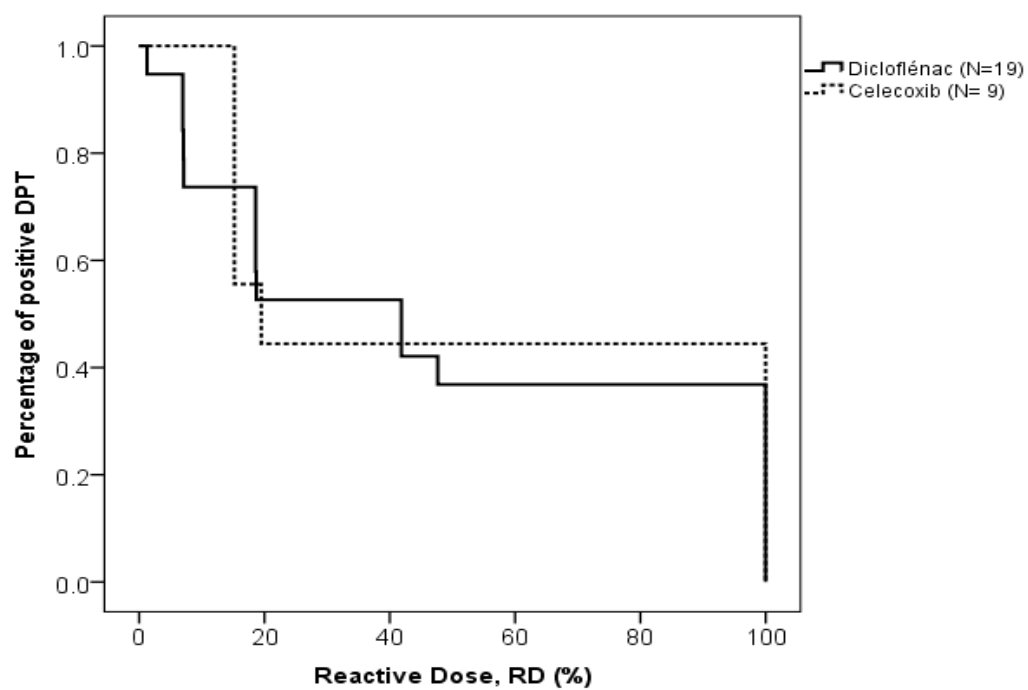


Figure 2: B) Reactive doses for the: moderate absorption group (diclofenac, celecoxib).

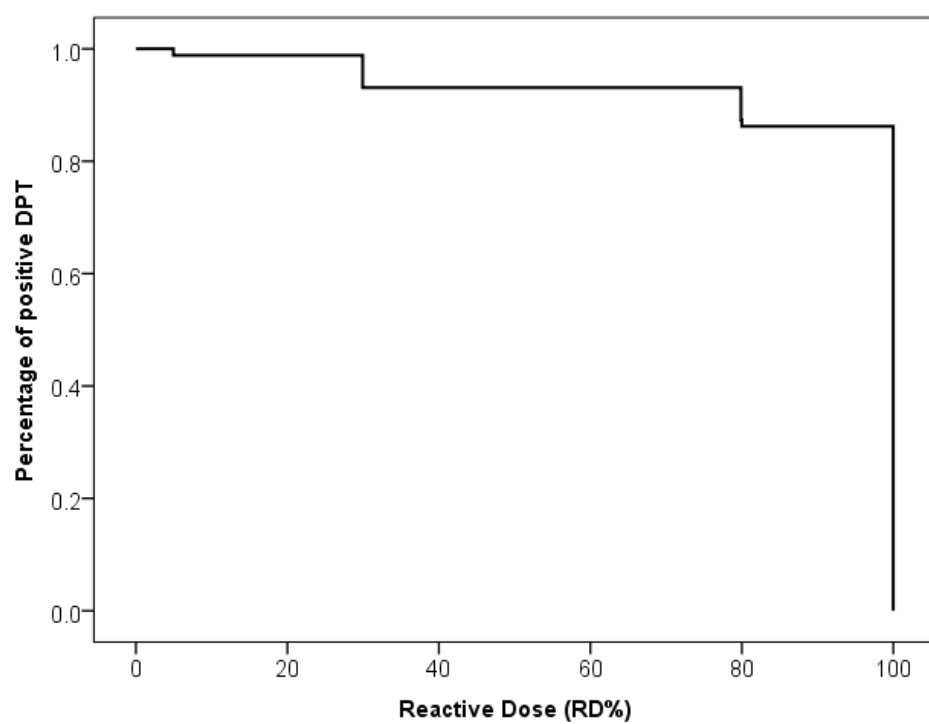


Figure 2: C) Reactive doses for the: piroxicam.

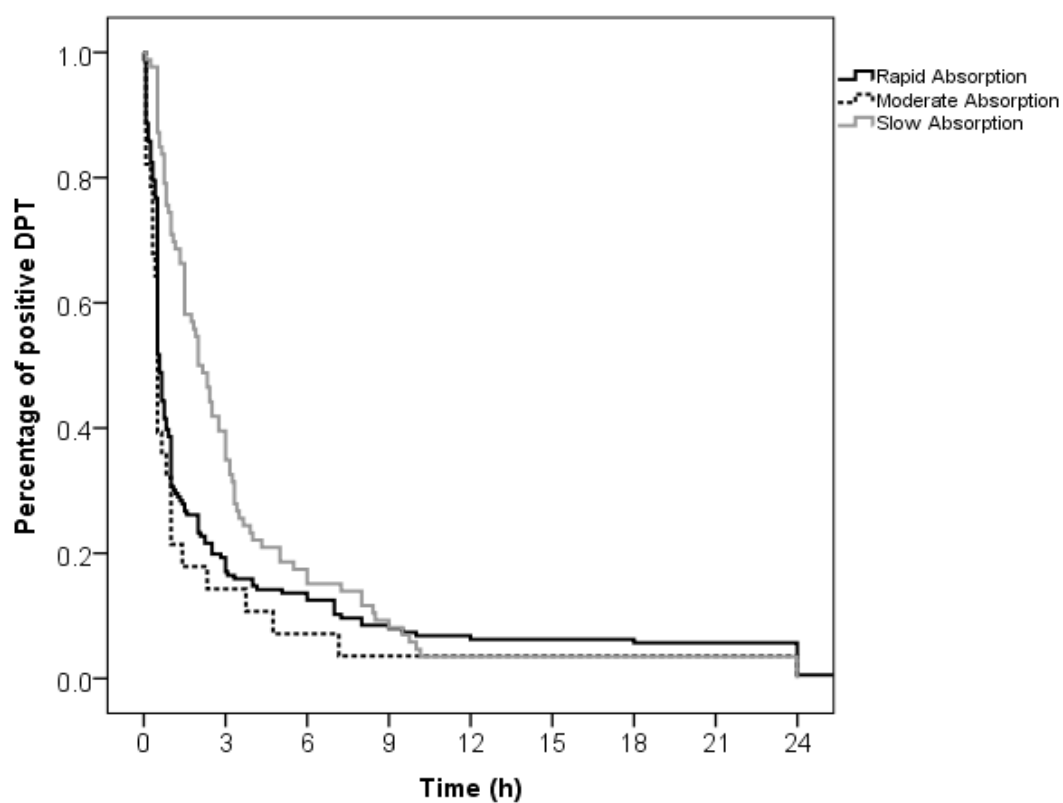


Figure 3: A) Reactive time points after the last dose administered during DPT for: the whole population;

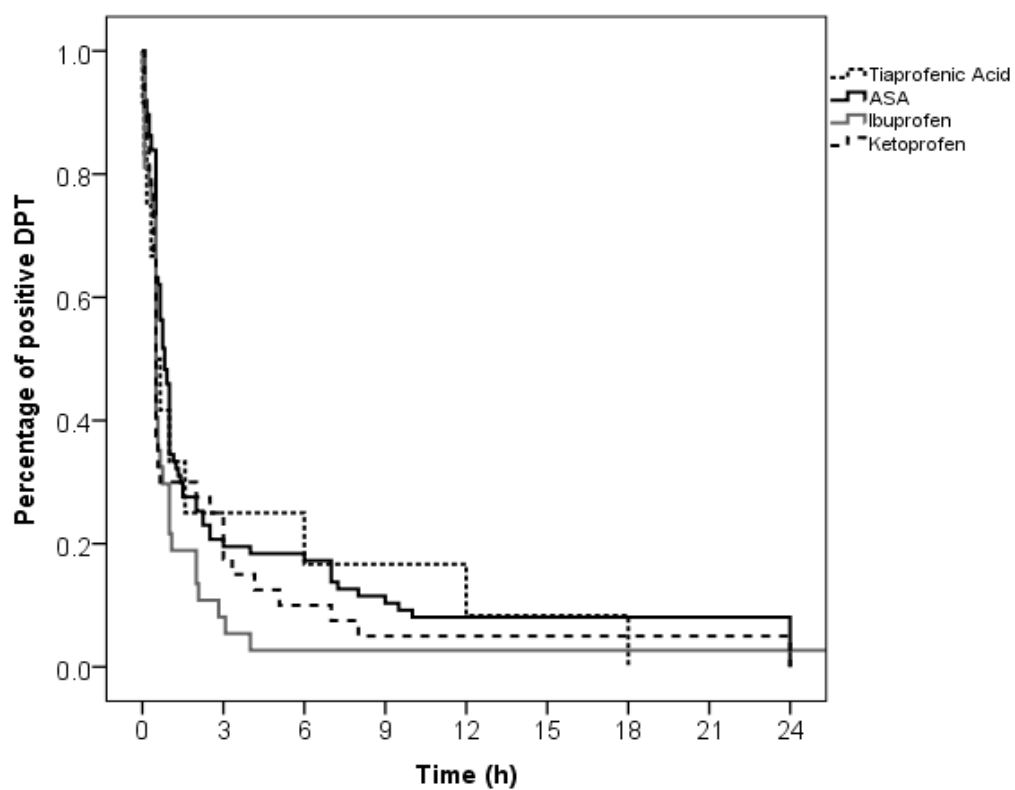


Figure 3: B) Reactive time points after the last dose administered during DPT for: the rapid absorption group by drug;

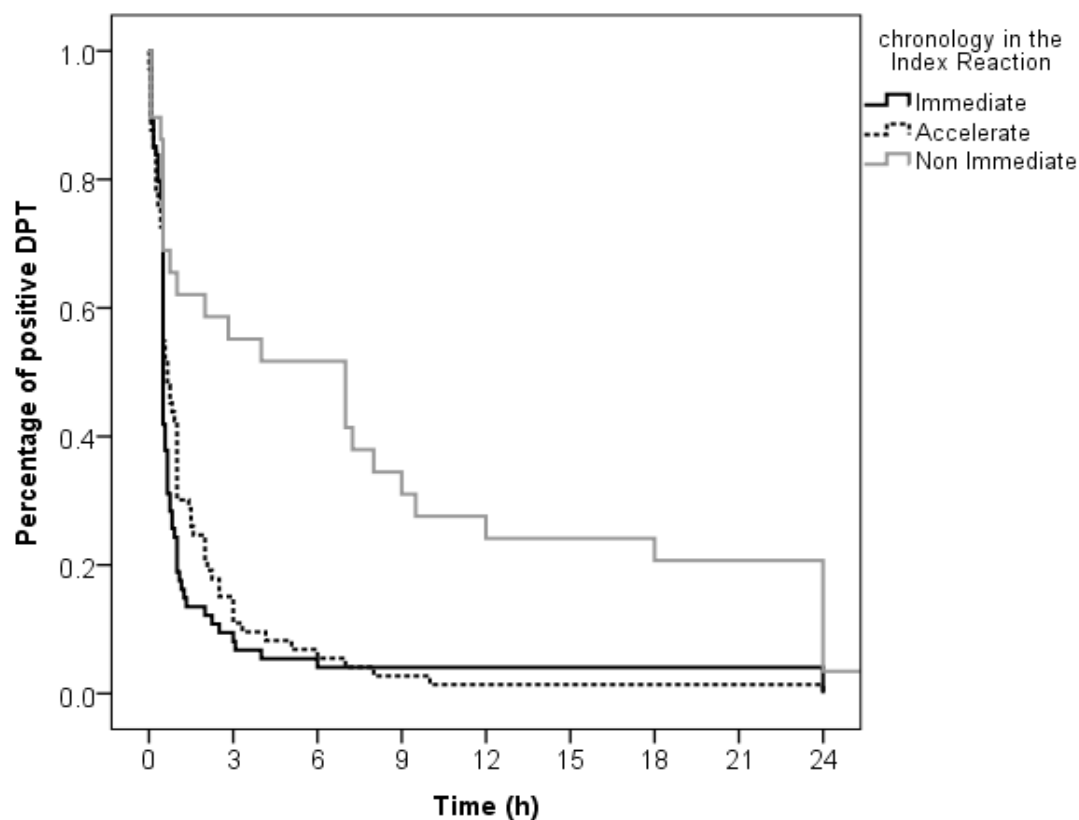


Figure 3: C) Reactive time points after the last dose administered during DPT for: the rapid absorption group, according to the chronology of the index reaction;

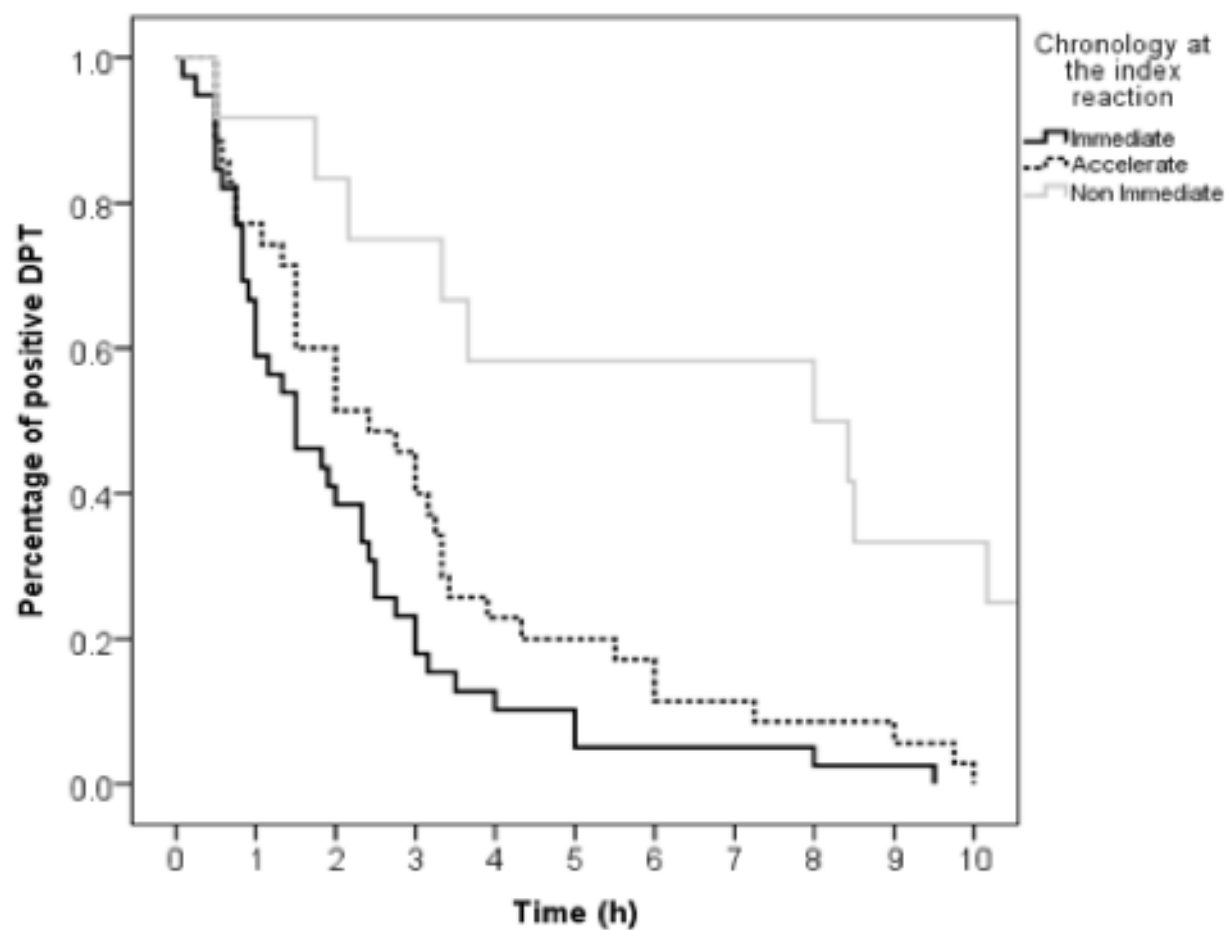


Figure 3: D) Reactive time points after the last dose administered during DPT for: piroxicam, according to the chronology of the index reaction.

Appendix Tables:

Appendix Table 1. Protocols used at present for DPT.

NSAID	Dose escalation	Total DPT dose (mg)	Unit dose/Tablet (mg)	Therapeutic daily dose (TDD)	
				Adults	Children
mefenamic acid	2.5 -7.5 -25 -125- 250-250	660	250mg	750-1000mg	>12 yrs 500-750mg
niflumic acid	2.5 -7.5 -25 -125- 250-250	660	250mg	750-1000mg	>12 yrs 500-750mg
alminoprofen	(0.3) - 3 - 30- 90 -150 -300 -300	873.3	300mg	600-900mg	
fenoprofen	0.3 -3 -30 -90 -150 -300 - (300)	873.3	300mg	300-1200mg	
flurbiprofen	1 -5 -10 -50 -100 -100	266	100mg	100-300mg	
meloxicam	1/100- 1/20 -1/10 -1/2 -1/2	8.7	7.5-15mg	7.5-15mg	
nabumethon	(1)-10-20-50-(100)-200-500-1000	1881	1000mg	1-2g	
naproxen	5-10-25-50-150-250-500	990	250-275-500-550-750	500-1100mg	>25Kg: 10mg/kg
nimesulid	1/200 - 1/20 -1/10 -1/4 -1/2 -1	191	100mg	200mg	
tenoxicam	(0.1) -1 -5 -10 -20	36.1	20mg	20mg	

NSAID, non-steroidal anti-inflammatory drug; TDD, therapeutic daily dose; yrs, years

Doses in brackets were optional (administered according to the responsible physician's prescription).

19 **Appendix Table 2: Pharmacokinetics of NSAIDs.**

NSAIDs	Absorption		Distribution		Metabolism	Elimination	Half-life time	Anti-COX effect
	Absorption in the human body	Plasma peak levels	Distribution in the human body	Binding				
Acetylsalicylic Acid								
Acetylsalicylic acid	Fast in the small bowel and stomach	2h (25 to 60 min)	Extracellular tissues and fluids	80 to 90% to plasma proteins	Hepatic (3 major metabolites)	Urinary	15 to 20 min	COX 1
Arylcarboxylic								
Tiaprofenic acid	Fast in the duodenum	40 to 120 min (1 to 2h)	Throughout the body	98% related to plasma proteins		Renal	1.5 to 2.5 h	COX 1
Diclofenac		2 to 3 h	Accumulation in the synovial fluid	99% related to plasma proteins	Hepatic	65% Urinary 35% Biliary	1 to 2 h	COX 1
Ibuprofen	Taking with food delays absorption	1 to 2h	Easily crosses the plasma	98% related to plasma proteins	Hydroxyl Metabolites and Carbonyls (inactive metabolites)	90 % urinary	2 h	COX 1
Ketoprofen	Taking with food delays absorption	1 to 2h	Crosses the placental and the haematoencephalic barrier	98% related to plasma proteins	Hepatic	Urinary	2 h	COX 1
Oxicams								
Piroxicam		2 to 4h	Crosses the placental barrier	98% related to plasma proteins	Hepatic hydroxylation	Urinary and fecal	50 h	COX 1 COX 2

Coxibs								
Celecoxib	Taking with food delays absorption	2 to 3 h		97% related to plasma proteins	5 metabolites	Renal (by metabolism)	22 h	COX 2

Appendix Table 3: Cross-match between the NSAID involved in the index reaction and NSAID at DPT

NSAIDs at index reaction	NSAIDs at DPT						
	Tiaprofenic acid	ASA	Ibuprofen	Ketoprofen	Diclofenac	Piroxicam	Celecoxib
Tiaprofenic acid	10 (90.9%)	2 (2.4%)	-	1 (2.6%)	-	7 (8.6%)	-
ASA	1 (9.1%)	74 (89.2%)	3 (8.1%)	19 (50%)	1 (5.3%)	26 (32.1%)	3 (37.5%)
Ibuprofen	-	6 (7.2%)	34 (91.9%)	1 (2.6%)	2 (10.5%)	23 (28.4%)	1 (12.5%)
Ketoprofen	-	1 (1.2%)	-	16 (42.1%)	1 (5.3%)	8 (9.9%)	1 (12.5%)
Diclofenac	-	-	-	1 (2.6%)	15 (78.9%)	3 (3.7%)	-
Piroxicam	-	-	-	-	-	14 (17.3%)	-
Celecoxib	-	-	-	-	-	-	3 (37.5%)

ASA, acetylsalicylic acid; DPT, drug provocation test; NSAID, nonsteroidal anti-inflammatory drug

Appendix Table 4: Cases with potential severe reaction after hospital dismissal.

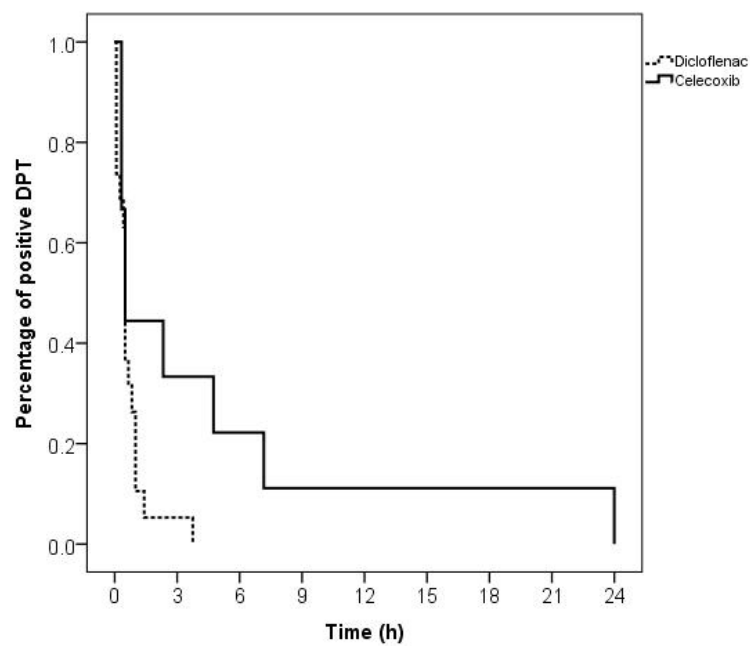
Number patient	Sex, age at DPT (yrs)	Culprit NSAID	Semiology of IxR	Chronology of IxR	Tested NSAID	Time between IxR and DPT (months)	RD (%)	DPT Reaction	Adrenaline use	Time of reaction onset
29305	F, 55	ASA	Angioedema eyes and hands	Non-Immediate (6h-24h)	ASA	22	100	Angioedema of the lips and eyelids, dyspnoea (Anaphylaxis)	No	After surveillance time
28610	M, 34	ASA	Urticaria on the arm	Non-Immediate (6h-24h)	Nimesulid	33	100	AO of upper lip and chest tightness (Anaphylaxis)	No	30h after dismissal

ASA, acetylsalicylic acid; NSAID, non-steroidal anti-inflammatory drug; DPT, drug provocation test; F, female; IxR, index reaction; M, male; RD, reactive dose; yrs, years

Appendix figures:

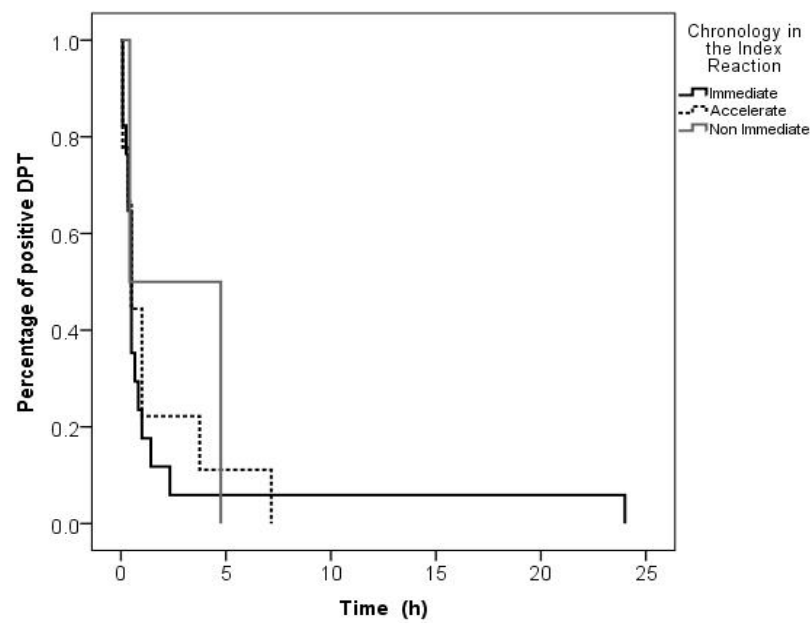
Appendix Figure 1: Reactive time points for patients in the moderate absorption group according to: A) each drug; B) chronology of the index reaction.

63 A)



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65 B)



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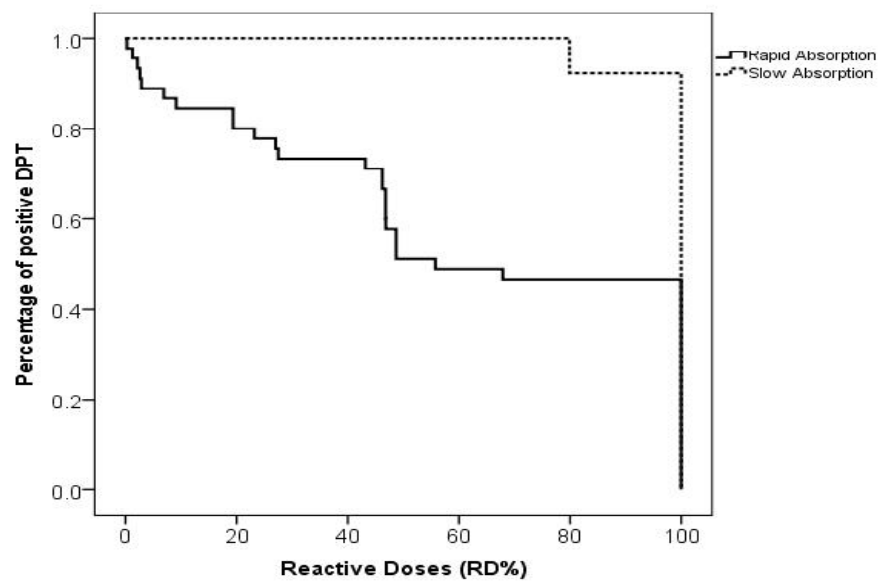
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69 **Appendix Figure 2:** Reactive doses (2A) and times (2B) for the in the rapid and slow
70 absorption groups, in children.

71 A)

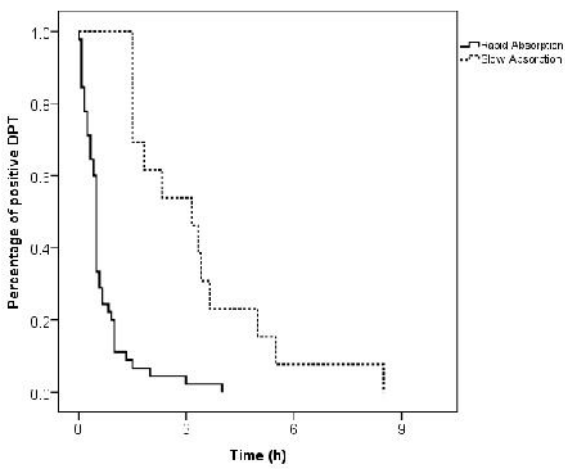
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75 **B)**



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