Cutaneous adverse drug reactions in children. A series of 90 cases

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Les toxidermies chez l'enfant. Une série de 90 cas

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RÉSUMÉ

Prérequis : Les toxidermies sont fréquentes chez l'enfant. Elles ont des aspects cliniques variables et peuvent être dues à plusieurs médicaments.

But: Evaluer les caractéristiques épidémiologiques des toxidermies ainsi que les médicaments en cause dans une population pédiatrique tunisienne.

Méthodes: Nous avons rétrospectivement inclus 90 patients (<16 ans) présentant une toxidermie confirmée et consultant au service de Dermatologie de l'hôpital Charles Nicolle de Tunis durant une période de 18 ans (1991-2008). Ces données ont été précisées : l'âge, le sexe, la durée des lésions, le type de lésions cutanées, les médicaments responsables, la durée entre la prise médicamenteuse et l'apparition de l'éruption, la validation par le centre de pharmacovigilance, le traitement et l'évolution.

Résultats: Les patients avaient un âge moyen de 6.9 ans (sex-ratio M/F 1.19). Il avaient une éruption maculo-papuleuse (EMP) (57.7%), une urticaire aigue (16.6%), un érythème pigmenté fixe (14.4%), un érythème polymorphe (2.2%), une photosensibilisation (1.1%) ou une toxidermie sévère (10%). Les médicaments incriminés étaient : les antibiotiques (55.5%),
les anti-inflammatoires non stéroïdiens (18.8%), les antiépileptiques (11.1%) et les antalgiques (5.5%). Les ßétalactamines étaient les antibiotiques les plus incriminés (32 sur 50 patients; 64%). Les barbituriques étaient les antiépileptiques les plus incriminés (7/90 cases, 7.7%). Tous les patients ont favorablement évolué, y compris ceux présentant des toxidermies sévères.

Conclusion: Les EMP dues aux antibiotiques étaient les toxidermies prédominantes chez l'enfant. L'imputabilité médicamenteuse doit être basée sur des arguments solides, vu la fréquence des EMP d'origine infectieuse et la prescription fréquentes des antibiotiques en pédiatrie.

Mots-clés
Toxidermie - Enfant

SUMMARY

Background: Cutaneous adverse drug reactions (CADR) are frequent in children. They have different clinical presentations and may be caused by several drugs.

Aim: To evaluate the epidemioclinical features of cutaneous adverse drug reactions (CADR) and the different causative drugs in a Tunisian paediatric series.

Methods: We have retrospectively included 90 children (under 16 years old) with a well documented cutaneous drug reaction, seen in the Department of Dermatology of Charles Nicolle hospital of Tunis over 18 years (1991-2008). Age, gender, duration of skin disorders, type of cutaneous lesions, incriminated drugs, delay between drug consumption and eruption, validation by the national pharmacovigilance centre, treatment and outcome were recorded.

Results: Our patients were 6.9 year-aged (sex-ratio M/F 1.19). They had maculopapular eruption (MPE) (57.7%), acute urticaria (16.6%), fixed drug eruption (14.4%), erythema multiform (2.2%), photosensitization (1.1%) or severe cutaneous drug reactions (10%). Incriminated drugs were: Antibiotics (55.5%), non-steroidal anti-inflammatory drugs (18.8%), antiepileptics (11.1%), and analgesics (5.5%). Betalactamins were the most commonly incriminated antibiotics (32 out of 50 patients; 64%). Barbiturates were the most commonly incriminated anti-epileptics (7/90 cases, 7.7%). Favourable outcome was noted in all patients, even those with severe drug reactions.

Conclusion: MPE to antibiotics were the most common kinds of CADR in children. Drug responsibility should be based on solid criteria given the frequency of MPE of infectious origin and the frequent prescription of antibiotics in paediatric population.

Key-words
Drug eruptions - Child

Adverse drug reactions (ADR) constitute a significant public health issue. Their overall incidence in outpatient children is estimated at 1.46% [1, 2]. The factors that predispose children to ADR include polypharmacy, a lack in paediatric clinical trials and in drugs adapted to children, infections and the possibility of a genetic variation leading to altered metabolism of a drug, with a partially or fully immunologic consequence [3].

CADR are the most common kinds of ADR and account for the majority (67.12%) of ADR in hospitalized children reported by Kushwaha et al [4]. Outpatient studies of CADR estimate that 2.5% of children who are treated with a drug, and up to 12% of children treated with an antibiotic, will experience a CADR [5-8]. The aim of this study is to evaluate the epidemiological features of cutaneous drug reactions (CADR), the different clinical aspects, and the different causative drugs, through a retrospective Tunisian paediatric series.

METHODS

We have retrospectively included all children (under 16-years old), seen in the Department of Dermatology of Charles Nicolle hospital of Tunis over 18 years (1991-2008), with the diagnosis of cutaneous drug reaction. Drug responsibility was confirmed based on the Tunisian national pharmacovigilance validation, semiology of lesions and/or positive drug rechallenge for non-severe CADR.

Ninety patients were analysed. For each patient, we have indicated the following data: age, gender, duration of skin disorders, type of cutaneous lesions, incriminated drugs, delay between drug consumption and eruption, treatment and outcome.

For statistical analysis, data were compiled electronically into Excel programme and analysed by means of SPSS version 11.

RESULTS

During the analysed period, the total paediatric population seen was of 28700 patients. The hospital prevalence of CADR was 0.3%. Our patients were 49 males and 41 females (sex-ratio M/F 1.19), aged between 40 days old and 16 years old (mean: 6.9 years). Seventeen point seven percent (17.7%) of our patients were less than one year old. Various types of cutaneous lesions were observed: maculopapular eruption in 52 cases (57.7%) (Figure 1), acute urticaria in 15 cases (16.6%), fixed drug eruption in 13 cases (14.4%) (Figure 2), erythema multiform in 2 cases (2.2%) (Figure 3) and photosensitization in one case (1.1%). Severe forms of cutaneous drug reactions were observed in 9 patients (10%): one case of anaphylaxis, one case of angioedema, 2 cases of Stevens Johnson syndrome, 2 cases of vasculitis, one case of toxic epidermal necrolysis (TEN) (Figure 4), one case of erythroderma and one case of Sweet's syndrome (1%). The incriminated drugs were: Antibiotics in 50 cases (55.5%), non-steroidal anti-inflammatory drugs in 17 cases (18.8%) (Aspirin: 16 cases and ibuprofen: one case), antiepileptics in 10 cases (11.1%), and analgesics in 5 cases (5.5%). Betalactamins were the most commonly incriminated antibiotics (32 out of 50 patients (64%), penicillin: 27 cases, cephalosporin: 5 cases), followed by sulfamides (7/50 patients; 14%) and macrolids (5/50 patients; 10%). Barbiturates were the most commonly incriminated anti-epileptics (7/90 cases, 7.7%), followed by valproic acid (2/90 cases, 2.2%) and carbamazepin (1/90 cases, 1.1 %). The delay between drug consumption and the eruption, indicated in 61 patients, amounted to 9 days [extremes: 12 hours-180 days]. The pharmacological inquiry, carried-out in all patients, concluded to drug responsibility in 97% of the cases (n=87) and was non conclusive in 3 cases of MPE (2.9%). In these latter cases, drug rechallenge led to the recurrence of the rash, confirming the drug reaction. In addition to drug cessation, therapeutic attitude was specified in 83 cases: an ambulatory symptomatic treatment (antihistamine and/or topical steroids) in 74 cases (89.1%) and hospital care was necessary for the remaining patients (10.8%).

Figure 1 : Maculo-papular eruption

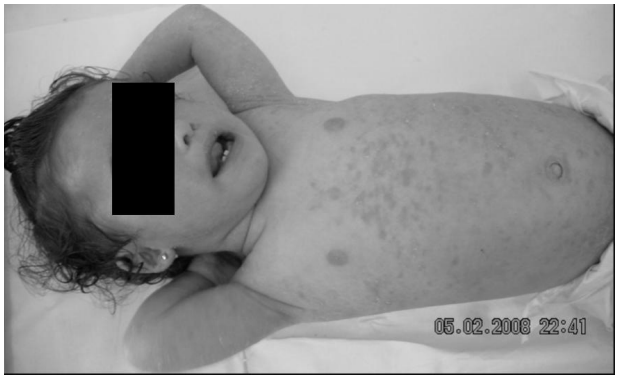


Figure 2 : Fixed drug eruption

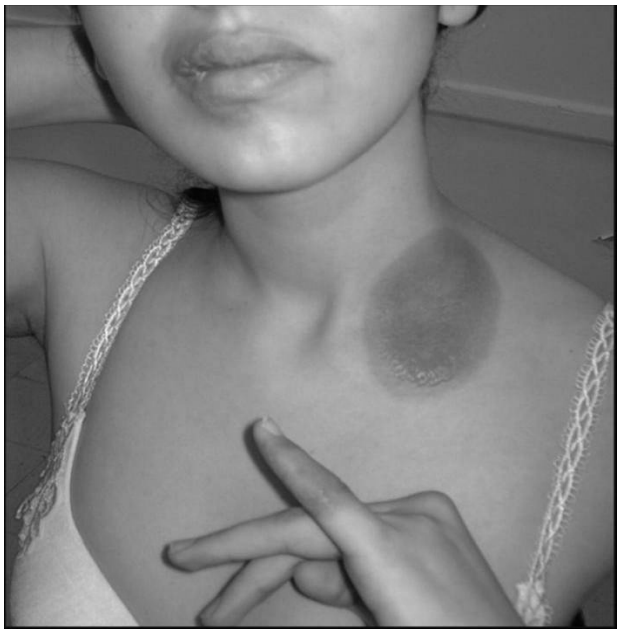


Figure 3 : Erythema multiform

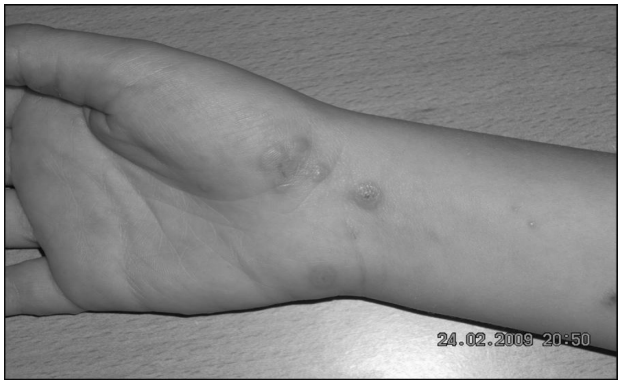
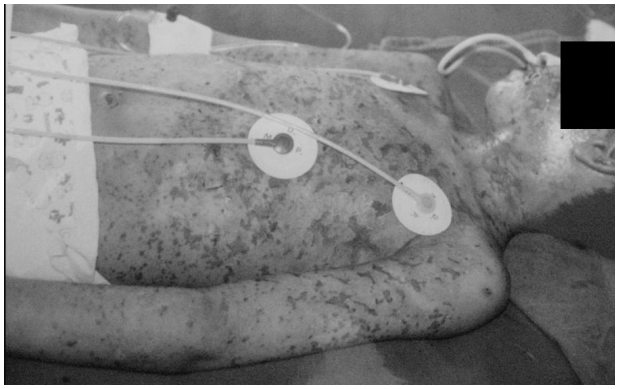


Figure 4 : Toxic epidermal necrolysis



A favourable outcome was noted in all patients, even those with severe drug reactions. The patient who had had TEN developed corneal opacities with visual loss. Table 1 summarises results relating to the 90 children and table 2 CADR to antibiotics.

Table 1 : Epidemiological and clinical characteristics of cutaneous drug reactions with incriminated drugs in 90 children

Type of lesions	Number (%)	Mean age ; range	Sex	Duration of skin disorders (days)	Incriminated drug	de1ay between drug consumption and eruption	Pharmacological inquiry	Severity	Treatment	Hospitali zation	outcome
					*** Antibiotics (ATB): 33/52cases (80.7%)** - ß lactamins: 23 cases (44.2%) (penicillin :19 cases, cephalosporin: 4 cases) -Macrolides: 5 cases (9.6%)		- Probable: 31 cases				
MPE	52 cases (57.7%)	6.1 years [40 days- 16 years] ≤ 1: 16 cases 17.7%)	30M/22F SR=1.4	5.5 days	-Sulfamethoxazole trimetoprim : 1 case - Lincocin: 1 case -Anti tuberculosis : 1 case - Ofloxacin: 1 case -Doxycycline: 1 case *** Aspirin (6 cases (11.5%)** ***Phenobarbital: 5 cases (9.6%)** *** Paracetamol: 3 case (5.7 %)** *** Depakin: 2 cases (3.8%)** *** Hepatitis B vaccine: 1 case (1.9)** ***Salazopyrin: 1 case (1.9%)** ***Bethamethsone: 1 case (1.9%)**	10 days [12 hours-180 days]	- doubtful: 21 cases	No	Withdrawal of the incriminated drug with antiH1	3 cases with severity	Favourable
Urticaria	15 cases (16.6%)	8.3 years [8 mths-15y]	6M/9F	NP	***ATB: 8 cases** - ß lactamins: 7 cases -Vancomycin: 1 case *** Aspirin: 5 cases** ***Ibuprofen: 1 case** ***Paracetamol: 1case**	5 days [20minutes-15 days]	probable	Yes in 2 cases: angioedema (1 case, penicillin), anaphylaxis (1 case, penicillin)	- Drug withdrawal -Anti H1: 15 cases -short course of parenteral corticosteroids: 5 cases - intensive care in anaphylaxis	Yes : the 2 severe cases	Favourable
FDE	13 cases (14.4%)	8.9 years [3-16 years]	5M/8F	5 months	*** ATB: 6 cases** - Sulfamethoxazole trimetoprim : 4 cases - ß lactamins: 1 case - Not precised : 1 case ***Aspirin: 3 cases** ***Phenobarbital: 2 cases** ***Paracetamol: 1 case** ***Drug not precised: 1 case**	NP	Probable (positive drug rechallenge in 3 cases)	No	Drug withdrawal	No	Residual pigmentation : 1 case
EMF	2 cases (2.2%)	2 years /13 years	1F/1M	2 days (F)	NP	NP	Not performed	No	Drug withdrawal	No	favourable
Vasculitis	2 cases	4 years /6 years	2M	NP	***ß lactamin (cefotaxim)** ***Sulfamethoxazole trimetoprim**	NP	Probable (accidental drug	yes	Drug withdrawal	No	favourable

Table 2 : Drug reactions to antibiotics

Antibiotics	Number of cases	Cutaneous lesions
ß lactamins	32 cases (64%)	- MPE : 23 cases
- Penicillin	27 cases	- Urticaria: 7 cases
- Cephalosporins	5 cases	- FDE: one case
		- Vasculitis: one case
Sulfamethoxazole trimetoprim	7 cases (14%)	- MPE: one case
		- FDE: 4 cases
		-Vasculitis: one case
		- Sweet's syndrome: one case
Macrolides	5 cases (10%)	MPE: 5 cases
Antituberculosis	One case (2%)	MPE
Doxycyclin	One case (2%)	MPE
Lincocin	One case (2%)	MPE
Ofloxacin	One case (2%)	MPE
Vancomycin	One case (2%)	Urticaria
Not precised	One case (2%)	FDE
Total	50 cases (55.5%)	-

DISCUSSION

As in the literature, maculopapular eruption (MPE) (57.7%), especially due to antibiotics (80.7%) was the most common CADR described in our paediatric study [5, 9-11]. Incriminated drugs in MPE are mainly nonsteroidal anti-inflammatory drugs (NSAIDs), anticonvulsivant agents and antibiotics. MPE is usually a minor and transient, but frequent condition and may be mistaken for viral exanthema. On the other hand, viral exanthemas are very common in children and we are often faced with a diagnostic challenge between viral rash and drug-induced MPE. In such a condition, physicians usually withdraw, some times unnecessarily, the suspected drug and contraindicate it, so as all drugs of the same class [10]. Consequently, this will unnecessarily limit therapeutic options and may result in the administration of alternative drugs that may be more expensive and less effective [5]. Therefore, diagnosis of CADR, especially when it is a drug exanthema, requires an efficient method based on anamnestic, semiological and pharmacological criteria in order to estimate the probability of a drug association and to determine the likelihood of a relapse with a drug rechallenge. Three of our patients had positive rechallenge test. Patch tests and intradermal reaction test with the suspected drug are useful tools to confirm drug responsibility when they are positive and for later reintroduction of the drug when they become negative due to the loss of immunologic memory [12]. A recent study by Stur et al. Showed that elevated levels of soluble fatty acid synthetase ligand (sFASL) serum concentration may represent a discriminating tool between drug rashes and viral exanthemas [13].

Among drug allergies due to antibiotics of our series (50/90, 55.5%), betalactamins (n=32, 64%), sulfamethoxazole trimetoprim (n=7, 14%) and macrolids (n=5, 10%) were the most frequently incriminated drugs. Among CADR to betalactamins, there were 27 cases due to penicillin and 5 cases due to cephalosporin. Cephalosporins especially first-generation cephalosporins may cause allergic reaction, independent of the crossed reaction, since they present specific epitopes and others in common with penicillin [5, 14-19].

Allergy to penicillin is often over diagnosed and is the consequence of the pressing concerns of a child's family, who motivate the physician to discontinue the use of the presumed drug. Pilzer JD et al., by assessing the accuracy of drug allergies in a university hospital and clinic, found that 80% of allergies to betalactamins and sulfonamides antibiotics were found to be true or probable adverse drug reactions [20]. A study of paediatric patients who were referred to an allergy clinic for antibiotic induced skin rashes, found that the reactions (erythematous rash or urticaria) were reproducible with a drug rechallenge in only 8 of 62 patients [21].

Acute urticaria represented respectively 16.6% and 6% of CADR in our series and in the series by Sharma et al [9]. Inversely, only 5.4% of the 54 cases of acute urticaria, reported by Sackesen et al., were due to drugs [22]. As in MPE, infections are frequent causes of acute urticaria in children. Drug attribution in a child should always take into account the possibility of infectious origin. Positive prick tests confirm IgE-mediated urticaria and then implicated drug must be definitively discontinued. In front of recent onset urticaria with negative prick tests, pharmacological urticaria is more likely and drug reintroduction is possible with no risk for the child.

Fixed drug eruption (FDE) represented 14.4% of all CADR of our series. As in the literature, sulfamethoxazole trimethoprim is frequently implicated in our series (4 out of 13 cases) [23]. Other drugs have been associated with FDE such as tetracycline, nonsteroidal anti-inflammatory drugs (NSAIDs) (2/13 in our series) and anticonvulsivants (Phenobarbital in 2 of our cases). Rechallenge remains the gold standard for FDE diagnosis and is usually safe to perform at a later date, pending on the severity of the initial reaction [24]. Three of our patients with FDE had positive drug rechallenge test.

Only one case of photosensitization due to Dexchlorpheniramine was recorded in our series. According to Selvaag, 8% of cutaneous drug eruptions are photosensitivity reactions including phototoxic and photoallergic reactions. Implicated drugs in children are antibacterials (tetracycline, fluoroquinolones and sulfonamides) and NSAIDs [25-27].

In some instances, CADR may be severe. In our series, nine cases (10%) of severe drug-induced cutaneous reaction were observed. The risk of severe CADR ranges between 1 in 1000

and 1 in 10 000 [10, 24, 28-30]. They include anaphylaxis (one of our patients), drug hypersensitivity syndrome also referred to as drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, [31] Stevens-Johnson syndrome (SJS) (two of our patients), and toxic epidermal necrolysis (TEN) or Lyell syndrome (one of our patients). We have also observed one case of a previously reported severe Sweet's syndrome, due to sulfamethoxazole trimetoprim [32] and two cases of drug-induced vasculitis. These reactions are rare but may be life threatening. In children SJS, TEN and SJS/TEN-overlap represent 10% of all cases reported by the severe cutaneous adverse reaction (SCAR) study and the multinational severe cutaneous adverse reaction (EuroSCAR) study. In children, SJS and TEN seem to cause lower mortality rate (7.5%) than in adults (25%), but a significant morbidity [33, 34]. The drugs most commonly identified as aetiological agents were anti-infective sulfonamides, phenobarbital, carbamazepine, and lamotrigine. They are even identified to be strongly associated with the risk of SJS or TEN [34]. In our series, SJS and Lyell syndrome were attributed to aspirin with no recorded death.

Anaphylactic reactions to penicillin are rare. In our series, one of our patients developed anaphylaxis to penicillin. In the literature, 3.2% of patients taking benzathine penicillin for prophylaxis of rheumatic disease had developed reactions to penicillin after a 3-year clinical follow-up. Among them, anaphylaxis was recorded in 1.23 per 10.000 injections [35, 36]. The only case of erythroderma recorded in our series was due to carbamazepin. Erythroderma can be associated with DRESS syndrome. In children, the latter is most commonly attributed to aromatic anticonvulsant agents, including phenytoin, carbamazepine, and phenobarbitol with cross reactivity, and antibiotics, mainly minocycline and sulfamethoxazole.

The early detection of these reactions, as well as the identification of the causative drug and its prompt discontinuation, are essential in order to prevent complications and to reduce mortality in severe CADR [37].

Our study indicates that CADR in paediatric populations are predominantly benign and transient eruptions. Antibiotic, NSADs and anticonvulsivant agents are most frequently implicated since they are frequently prescribed in children. The differential diagnosis with an infection, especially in MPE and acute urticaria is challenging in children. Accurate diagnosis, based upon semiological, chronological and bibliographical criteria, avoids CADR over diagnosis.

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