Drug Eruptions in Children: A Review of 111 Cases Seen in a Tertiary Skin Referral Centre

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ABSTRACT

A common dilemma faced by the clinician in the outpatient clinic is in distinguishing a drug eruption from a viral exanthem in a child. This is further confounded by multiple drugs frequently prescribed for common childhood ailment. Therefore many children are wrongly labelled as having drug allergy or mistakenly sent for allergy testing. This retrospective study seeks to address this common problem.

Method: The case records of children aged 12 and below clinically diagnosed as having drug eruptions, seen from January 1995 to December 1997 in the National Skin Centre, were reviewed.

Results: One hundred and eleven children were seen. The indications for drug prescribed were upper respiratory tract infection (47%), fever (18%) and chest infection (10%). The common discriminating drugs prescribed were amoxycillin/ampicillin in 59%, paracetamol in 36% and cotrimoxazole in 19% of patients. In general, the drug eruption took place within 1 day in 39%, by the 2nd day in 10% and by the 3rd to the 7th day in 13% of patients. Drug eruption patterns seen were urticaria/angioedema (45%), maculopapular rash (32%) and fixed drug eruption (12%). Drug allergy was confirmed in 8 patients (7%), while it was deemed probable in 22%, possible in 31% and unlikely in 41% of patients.

Conclusion: A detailed drug history, knowledge of the various drug eruption patterns and drug specific reaction rates, and appropriate oral rechallenge test, are essential factors to the successful management of a child with drug eruption. Radio-allergosorbent test (RAST) and patch test may be useful in some cases.

Keywords: children, drug history, drug eruption patterns, oral rechallenge, drug-specific reaction rates

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INTRODUCTION

A drug eruption is any adverse skin reaction caused by a drug used in its normal doses. It poses as a frequent diagnostic problem in the outpatient setting, and easily confused with viral exanthem in children. This problem is further confounded by the habitual practice of prescribing multiple drugs for common childhood ailments. Moreover information on drugs and their adverse reactions may not always be reliable because of under-reporting, despite attempts by governmental and pharmaceutical bodies in monitoring the situation.

This retrospective study aims to describe the clinical pattern of drug eruptions seen among children in Singapore and to suggest an approach to this problem.

MATERIALS AND METHOD

The case records of children aged 12 and below clinically diagnosed as having drug eruption, seen between January 1995 and December 1997 in the National Skin Centre, were reviewed. The following data were gathered: age at diagnosis, sex, race, the incriminating drugs, indication of use, time of onset, morphology, distribution site, associated features, investigations and assessment of probability. Excluded from the study were cases which the onset of rash were prior to the consumption of medication, and also cases which were consistent with the diagnosis of viral exanthem. In this study, urticarial drug eruption is defined as an eruptions of transient, well demarcated, intensely pruritic wheels, but with individual lesions lasting less than 24 hours. Angioedema is defined as subcutaneous extension of urticarial lesions that appear as large swellings with indistinct borders. Maculopapular eruption is defined as red macules and papules that become confluent, and usually erupt on the trunk with subsequent spread to the extremities. Fixed drug eruption (FDE) is defined as a solitary or multiple, sharply demarcated, erythematous patch that evolve into an intense macular hyperpigmentation. Erythema multiforme (EM) is defined as an eruption of a symmetrically distributed, dusky red macules that take on a target appearance. Stevens Johnson syndrome, toxic epidermal necrolysis and anaphylactic

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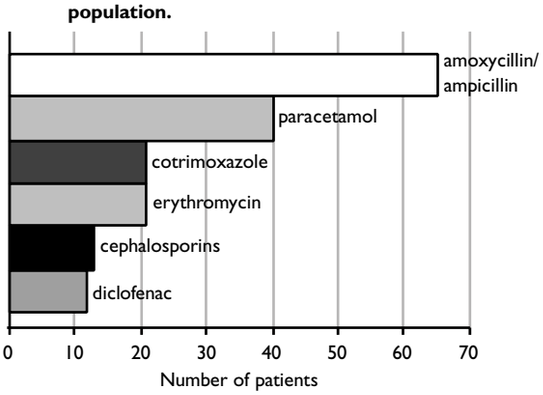
Table I. Main variables in the assessment of drug aetiology in skin eruptions.

Previous experience with the drug in the general population
Alternative explanation for the eruption
Timing of the drug exposure
Drug levels or evidence of overdose or long-acting drug
Patient reaction to dechallenge
Patient reaction to rechallenge

Table II. The various types of drug eruption in our study population.

Types of drug eruption	Percentage
Urticaria/angioedema	52%
Maculopapular eruption	23%
Fixed drug eruption	12%
Erythema multiforme	3%
Others	7%

Fig. 1 The common incriminating drugs in our study population.



drug reactions were excluded from this study as these were usually seen in the acute hospitals. Using the 6 variables in Table I as a guide[1], each case seen in our Drug Eruption Clinic was assessed with regards to indications for drug usage, type of drug or drugs ingested, alternative explanation for the drug eruption, timing between drug ingestion and eruption, subsequent progression of the eruption and reactions to dechallenge and rechallenge. Investigations, if indicated, would then facilitate in concluding the case as an unlikely, possible, probable or definitive drug allergy.

RESULTS

There were 111 children seen during this period, 74 males and 37 females (male to female ratio of 2:1). Eighty six were Chinese (77%), 18 were Malays (16%), 5 were Indians (5%) and 2 were of other races (2%). The age at diagnosis ranged from 2 months to 11 years, with a mean age of 5.7 years. Drugs were prescribed for 52 patients (47%) with upper respiratory tract infection, 20 (18%) with fever, 11 (10%) with chest infection, 3 (3%) with asthma and 25 (23%) with other miscellaneous illnesses.

One suspected incriminating drug was prescribed in 43 patients (39%), 2 drugs in 29 patients (26%) and 3 or more drugs in 39 patients (35%). In general, the common suspected incriminating drugs prescribed were amoxycillin/ampicillin in 65 patients (59%), paracetamol in 40 (36%), cotrimoxazole in 21 (19%) and erythromycin in 21 (19%) (Fig. 1). Other drugs included cephalosporins in 13 patients (12%), diclofenac in 12 (11%), ibuprofen in 6 (5%) and cloxacillin in 4 (4%).

Drug eruption patterns observed were urticaria/angioedema in 50 patients (45%), maculopapular rash in 26 (23%) and fixed drug eruption in 13 (12%). Three patients with erythema multiforme, 2 with vesiculopapular eruptions and 1 with an eczematous eruption made up the rest (Table II).

Urticaria/angioedema

Amoxycillin/ampicillin (31 patients), paracetamol (23), diclofenac (11) and erythromycin (10) were some of the common incriminating drugs. The onset of rash occurred within 1 day of drug ingestion for 31 out of 50 patients, 2 days for 2 patients, more than 3 days for 4 patients while 13 patients had difficulty in recalling drug event. In 23 patients, the rash appeared on the face presenting either as urticarial wheels or periorbital or perioral swellings. The remaining 27 patients had scattered urticarial lesions elsewhere on the body.

Twenty-five patients were tested to radio-allergosorbent test (RAST), of which 2 gave positive results to amoxycillin, and 1 positive to cephalosporin. Due to the unlikely account of the drug event, one of the RAST-amoxycillin positive patient was subsequently rechallenged with oral amoxycillin, which showed negative result. The role of drug rechallenge (oral provocation test) in urticaria angioedema is mainly to rule out unlikely drugs (negative rechallenge) as positive rechallenge is hazardous. Of the 21 patients that underwent drug rechallenge, 2 patients gave unexpected positive results to paracetamol and they were labelled as having definitive drug allergy to paracetamol.

In the final assessment, 2 patients had definitive drug allergy, 8 probable, 25 possible and 15 unlikely drug allergy.

Maculopapular eruption

The common incriminating drugs were amoxycillin/ampicillin in 19 out of 26 patients, cephalosporin in 6, paracetamol in 5 and cotrimoxazole in 5 patients respectively. The onset of rash occurred within 1 day in 8 patients, 2 days in 7, and 3 to 7 days in 4 patients. The rash was generalized in 21 patients, while 3 had eruptions on the face and 2 had eruptions on the trunk.

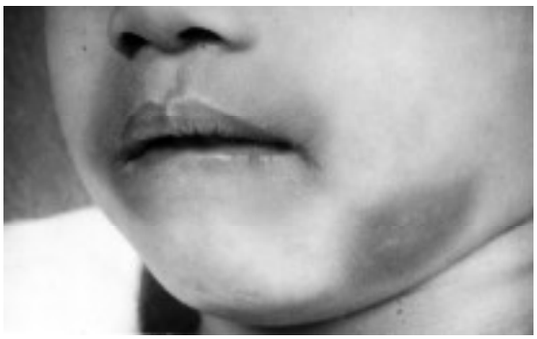


Fig. 2 Dusky, bruise-like lesions of fixed drug eruption in a 6-year-old boy.

Twelve RAST were done of which 1 was positive to amoxycillin and another to cephalosporin. The former was only 4 months of age while the latter declined oral rechallenge test. Both these patients were labeled as having probable drug allergy. Nine other patients had drug rechallenge, of which 1 was positive to amoxycillin. She was labeled as having definitive drug allergy to amoxycillin. One patient was assessed as having definitive chug allergy, 9 probable, 7 possible and 9 unlikely drug allergy.

Fixed drug eruption

Topping the list of suspected incriminating drugs were paracetamol which were used in 9 out of 13 patients (70%), cotrimoxazole in 6 and amoxycillin/ampicillin in 4 patients. Ten patients (77%) were unable to recall the onset of the rash eruption, 1 occurred within the first day, 1 on the second day, and 1 in the second week. The rash appeared on the trunk in 8 patients and on the face or lips in 5 patients.

RAST was not indicated for these patients. Six were rechallenged of which 2 were positive to cotrimoxazole, 1 to paracetamol and 1 to erythromycin.

There were therefore 5 definitive cases of drug allergy, 4 probable, 2 possible and 2 unlikely drug allergy.

Erythema multiforme

Three patients had erythema multiforme lesions over the upper limbs, with truncal involvement in 2 of them. The incriminating drugs were amoxycillin, cotrimoxazole and paracetamol in each case respectively.

RAST and oral drug rechallenge were not indicated. The 3 patients were assessed as having probable drug allergy.

Miscellaneous

One case of eczematous eruption, 1 pustular drug eruption and 2 vesicopapular eruptions made up other pattern of drug eruptions seen.

Fifteen other patients had no more skin lesions by the time of consultation and were also unable to describe the rash. Nevertheless, their accounts were suggestive of drug eruptions.

DISCUSSION

One of the most perplexing problem encountered by the clinician is to distinguish drug eruption from viral exanthem in an ill child. This is further complicated by prior medications prescribed for illness. Spontaneous reports on drug eruption in children were few and certainly underestimate the true incidence in the population. Moreover the reports in the literature tends to be bias because only the more severe reactions were reported.

The initial task is to establish the diagnosis of a drug eruption in a child with a rash. In our weekly Drug Eruption Clinic, history taking from the caregiver of the child and physical examination remain the most important tools in the assessment process. A good evaluation would include the following details: (1) indication of drug used, (2) the drug(s) consumed and this often entail calling up the prescribing physician for more details, (3) the route, dosage and frequency, (4) the time taken between drug ingestion and onset of rash, (5) the clinical pattern of the eruption and (6) previous encounter and problem with the incriminating drug (7) concomitant traditional medications and home remedies used. Investigations such as oral drug rechallenge, RAST and patch test are done if indicated.

In this study, the 111 patients made up 0.3% of all paediatric cases seen over the 3 year period. There was a male preponderance, as similarly observed in a few other reports[2-4], but this gender difference was of doubtful clinical significance. The racial distribution was in proportion with that of the general population. As expected, upper respiratory tract infection, fever and chest infection were the common indications for the drugs prescribed as these were common childhood ailments seen at primary care level. Therefore these prescriptions contributed substantially to the list of incriminating drugs such as amoxycillin/ampicillin, paracetamol, cotrimoxazole and erythromycin.

Earlier work has shown that drug-specific reaction rate is a better index in indicating the frequency of drug reactions attributed to that specific drug. For example, amoxycillin (51.4 cases/1000 exposed), cotrimoxazole (33.8 cases/1000 exposed) and ampicillin (33.2 cases/1000 exposed) are the commonest drugs causing drug eruptions[5]. So knowing both the frequency of prescription and specific drug reaction rate will alert the clinician when prescribing these drugs.

Urticaria langioedema was the most common type of drug eruption seen, accounting for 45% of cases but admittedly some might be due to viral infection[6]. In fact there is great difficulty in dissociating viral infection

from drug ingestion as a cause for eruption, as drug challenge test is often not possible due to ethical and safety considerations[7]. Our observation differs from 6% reported in children[2] and 20% in adults[8] perhaps due to the bias recall of the drug event and bias incrimination of drug rather than viral infection as the cause of eruption. Amoxycillin/ampicillin and diclofenac were the common incriminating drugs, similar to amoxycillin and aspirin reported both in infants[9] and adults[8] with the exception that aspirin was rarely prescribed for children in Singapore for fear of Reye's syndrome. IgE-mediated hypersensitivity reaction is involved in amoxycillin/ampicillin allergy whereas a variety of mechanisms of action including non-immunological pathway are responsible for non-steroidal anti-inflammatory drugs (NSAIDs) allergy. Most urticarial eruptions presented acutely within 1 day of exposure to the drug and a few others within the next several days; however it was difficult to ascertain from the history whether patients had any prior exposure, which sometime could be asymptomatic. Urticaria frequently involved the face with the majority having an angioedema component presenting as periorbital or perioral swellings, but there was no laryngeal involvement. The yield of RAST was low for 2 main reasons. Firstly, not all urticarial drug reactions were IgE mediated and for such RAST would be negative. Secondly, circulating IgE antibodies would begin to disappear within 10 to 30 days of initial reaction. On the other hand, a positive RAST test does not conclusively prove an allergy except to indicate that drug allergy is probable. Therefore RAST results have to be interpreted with great caution. The role of negative drug rechallenge in urticaria/angioedema was strictly to rule out unlikely drugs, especially in patients prescribed with multiple drugs, so that they would not be unnecessarily deprived of some common and useful drugs in future. There is no role for positive drug rechallenge as it is hazardous.

The second most common reaction pattern seen was maculopapular eruptions in our study, although this was the most common pattern reported in the Boston Collaborative Drug Surveillance Program[5]. Once again amoxycillin/ampicillin was the most common incriminating drug, as similarly observed by Sharma[2] and Porter[10], followed by cephalosporin and cotrimoxazole. The eruptions involved the trunk and limbs symmetrically in most of our patients. The onset of rash occurred within the first 2 days of drug ingestion for most patients but it can appear anytime between the first day and 3 weeks. Most exanthematous eruptions are due to delayed hypersensitivity reaction although other allergic mechanisms may be possible. Therefore the 12 RAST performed were not very helpful. A positive oral rechallenge is generally accepted as strong evidence for drug causality. Half of our patients were rechallenged but only 1 had positive reaction to amoxycillin. Negative result to rechallenge may mean that the drug eruption was due to drug-drug interaction or virus-drug interaction (as in ampicillin rash in infectious mononucleosis). It may also mean that there was a refractory period following the initial eruption and therefore a lack of response to rechallenge. Sometimes the dose in rechallenge test is too small to elicit a true positive response. All these possibilities must be borne in mind when interpreting rechallenge results. Patch testing has its advocates in diagnosing maculopapular eruptions[11]. A positive patch test, which in effect is an allergic contact dermatitis reaction, implies drug allergy to the tested drug. However the parent drug used in patch testing on the skin may not be the same as the circulating drug metabolite that caused the allergic reaction. Other technical problems include the appropriate concentration, vehicle and reading time with respect to patch testing.

In this study, the suspected incriminating drugs in FDE were paracetamol, cotrimoxazole and amoxycillin ampicillin. One patient was confirmed to have FDE to paracetamol and 2 to cotrimoxazole, by means of oral rechallenge, whereas none was positive to amoxycillin. This is in agreement with earlier studies in which paracetamol positive to amoxycillin. This is in agreement with earlier studies in which paracetamol and cotrimoxazole were listed as frequent causes of FDE whereas there were only 3 isolated cases of FDE reported with amoxycillin/ampicillin thus far[12]. Tetracycline is another frequently implicated drug but this is rarely prescribed for children. Cell mediated hypersensitivity reaction is responsible in the pathogenesis of FDE, and oral rechallenge is the most dependable test in identifying the causative agent. This method is generally safe except in cases of extensive FDE lesions. Another method includes patch testing the inactive sites of previous FDE to suspected agent[13]. A positive patch test result is conclusive but a negative one is not diagnostic.

The majority of EM cases are precipitated by various infections and only 10% are possibly drug related[14]. Since the prodromal symptoms of respiratory tract infection are often treated with antibiotics, it becomes difficult to ascertain which is responsible for EM eruption. There is no role for oral rechallenge because of the risk of developing Stevens Johnson syndrome/toxic epidermal necrolysis. The pathogenesis of this reaction is poorly understood and no test is available to establish a causal relationship with any drug. Some of the common incriminating drugs listed in the literature include the sulphonamides, phenytoin and carbamazepine.

Patients who came after the resolution of the drug eruption posed another diagnostic problem. The

patient's caretaker often had both recall and description problems. There is no "standard battery" test that can screen for drug allergy and very often, the history had to be retaken in greater detail, the family physician contacted, in order to reconstruct the events that led up to the drug eruption.

CONCLUSION

Drug eruption proves to be a challenging problem faced by many children presenting with a rash. On one hand approaching this issue with a dismissive stance may invite disaster, on the other hand wrongly labeling drug allergy in a child would deprive him of a useful medication in future.

The solution lies in taking a detail drug history, coupled with a good grasp of the common drug eruption patterns and drug-specific reaction rates, and finally confirming any drug allergy with the appropriate tests as mentioned above. Restrain in prescribing unnecessary antibiotics for viral illnesses in children should be exercised, especially those drugs with known high drug-specific reaction rates.

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