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Ultra-rapid desensitization with rifampicin syrup

Accoutumance orale ultra-rapide à la rifampicine

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ABSTRACT

Hypersensitivity (HS) reactions to antituberculosis drugs are difficult to manage, notably since the advent of multiresistant tuberculosis. In patients with immediate HS to antituberculosis drugs, a rapid desensitization (DS) procedure may represent an interesting alternative.

Study objectives. – Describe the procedure for rapid oral DS with rifampicin syrup/suspension and demonstrate its contribution to the management of tuberculosis (TB).

Methods. – A cross sectional study including patients followed-up for tuberculosis in pulmonology C department of Abderrahman Mami Ariana hospital between 2003–2020. Patients with confirmed immediate HS were desensitized with a suspension of Rifampicin (100 mg/5 ml). Informed consent of patients or guardian was required.

Results. – Ultrarapid DS with rifampicin syrup/suspension was performed in 14 patients (8 men, 6 women, mean age 32 ± 12.5 years). The mean times between initiation of the treatment, the last administration of the drug and onset of the reactions were 16.5 days (range: 3–47 days) and 204 minutes (20–420 min) respectively. Most reactions were urticaria, pruritus and erythema. Severe anaphylaxis was reported in 2 cases and Quincke edema in 1 case. Nine patients (64.3%) were successfully desensitized. In 5 patients (35.7%), ultrarapid desensitization failed.

Conclusion. – Reactions to rifampicin are diverse and unpredictable. The severity of the allergic reaction and the absence of other effective therapeutic alternatives are arguments in favor of drug desensitization. Despite the diversity of protocols reported in the literature, the results of desensitization are generally favorable, with a significant success rate.

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R É S U M É

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Les réactions d'hypersensibilité (HS) aux antituberculeux sont difficiles à gérer, notamment depuis l'avènement de la tuberculose (TB) multirésistante. Chez les patients allergiques aux antituberculeux, une accoutumance ultrarapide peut représenter une alternative intéressante.

Objectifs de l'étude. – Décrire une procédure d'accoutumance orale ultrarapide avec la rifampicine-suspension et démontrer sa contribution à la prise en charge de la tuberculose.

Méthodes. – Étude transversale des patients suivis pour tuberculose dans le service de pneumologie C de l'hôpital Abderrahman Mami Ariana entre 2003–2020. Des accoutumances à la Rifampicine-suspension ont été réalisées chez les patients atteints d'une HS immédiate confirmée à cet antituberculeux.

Résultats. – Une désensibilisation (DS) ultrarapide à la rifampicine a ainsi été réalisée chez 14 patients (8 hommes, 6 femmes, âge moyen : $32 \pm 12,5$ ans). Les délais moyens d'apparition des réactions entre le début du traitement antituberculeux, la dernière administration du médicament et la survenue des réactions étaient respectivement de 16,5 jours (3–47 j), et 204 minutes (20–420 mn). La majorité des réactions étaient des urticaires/prurits/érythèmes, 2 patients rapportaient des anaphylaxies sévères et un patient un œdème de Quincke. La DS a été couronnée de succès chez 9 patients (64,3 %) et a échoué chez les 5 autres patients.

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Conclusion. – Les réactions à la rifampicine sont diverses et imprévisibles. La sévérité de la réaction allergique et l'absence d'autres alternatives thérapeutiques efficaces sont des arguments en faveur de la désensibilisation médicamenteuse. Malgré la diversité des protocoles rapportés dans la littérature, les résultats de l'accoutumance sont globalement favorables, avec un taux de réussite significatif.

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1. Introduction

Hypersensitivity (HS) reactions to anti-tuberculosis (TB) drugs are rare (4–5% of all tuberculosis patients) [1,2]. Their occurrence is unpredictable and poses both a diagnostic and therapeutic challenge, especially for major anti-TB drugs (Isoniazid and Rifampicin). Drug desensitization (DS) is defined as an induction of temporary tolerance towards drugs and represents a therapeutic alternative in patients allergic to drugs [3]. Only a few protocols of desensitization to rifampicin have been reported in the literature [1,3].

2. Patients and methods

A cross-sectional study of patients followed-up for tuberculosis in pulmonology C department of Abderrahman Mami Ariana hospital between January 2003–December 2020. Fourteen patients with a confirmed HS reaction to rifampicin were included and desensitized with a suspension of Rifampicin (100 mg/5 ml). Hypersensitivity to rifampicin has been confirmed based on a highly suggestive clinical history (immune allergic manifestations as urticaria, severe anaphylaxis, quincke edema, palmoplantar pruritus...) in all cases, associated to a positive oral challenge test performed in 12 cases. Informed consent of patient or guardian was obtained for all patients.

Desensitization was performed in the hospital in a day hospitalization unit in allergology. Premedication with antihistamines or corticosteroids was not used (prednisone was discontinued for 7 days before the procedure) because these drugs may mask initial symptoms of anaphylaxis during DS and the patients were not treated with betablockers or angiotensin-converting enzyme inhibitors. Emergency kits containing the necessary equipment for the management of a vital emergency were prepared (adrenaline, oxygen mask, fluids, corticosteroids, antihistamines, bronchodilators).

Desensitization was performed as follows: solution A contained 5 ml (100 mg) of rifampicin syrup (Rifadine® drinkable suspension 2% bottle 120 ml, Sanofi) diluted in 95 ml of water, and solution B contained non-diluted rifampicin syrup (100 mg/5 ml). The first dose administered was 10^{-6} of the daily dose (600 mg) and was doubled every 15 minutes until reaching the therapeutic dose (Table 1). Desensitization was stopped if an allergic reaction (urticaria, rash, angioedema, wheezing, respiratory acute failure, bronchospasm, nausea, vomiting, diarrhea...) occurred.

3. Results

3.1. Rifampicin ultrarapid oral desensitization

Ultra-rapid DS was performed in 14 patients (8 men, 6 women). The mean age of patients was $32 \text{ years} \pm 12$. Nine patients had pulmonary tuberculosis. The other sites were pleural in 2 patients, lymph nodes in 2 patients, and disseminated in 1 patient.

These patients had presented urticaria (13 cases), pruritus (11 cases), erythema (11 cases), severe anaphylaxis (2 cases), and

Table 1

Rifampicin oral desensitization procedure.

Time	Rifampicin (mg)	Rifampicin (ml)
Solution A "sol A": 100 mg rifampicin + 100 ml of tap water		
T0 mn	0.1	0.1 ml sol A
T15 mn	0.5	0.5 ml sol A
T30 mn	1	1 ml sol A
T45 mn	2	2 ml sol A
T60 mn	4	4 ml sol A
T75 mn	8	8 ml sol A
T90 mn	16	16 ml sol A
T105 mn	32	32 ml sol A
Pure rifampicin syrup: Solution B		
T120 mn	50	1 spoon measure (s.m) de 2,5 ml
T135 mn	75	1 s.m + ½ s.m of 2,5 ml
T150 mn	100	1 s.m of 5 ml
T165 n	150	1 s.m. à 5 ml + 1 s.m à 2,5 ml
T180 mn	300	3 s.m à 5 ml
T24 h	300	3 s.m à 5 ml

Quincke edema (1 case). The mean time between initiation of the treatment and onset of immuno-allergic manifestations was 16.5 days (range: 3–47 days), and the mean time between the last administration of the drug and occurrence of the reactions was 204 minutes (20–420 min).

In those patients, the total duration of ultrarapid DS was 180 minutes. The cumulative dose was 738.6 mg.

3.2. Results of rifampicin ultrarapid oral desensitization

The protocol was completed without any reactions in 9 patients (64.3%) and the patients subsequently tolerated a daily dose of 600 mg. In 5 patients (35.7%), ultrarapid DS failed. Characteristics of these 5 patients are shown in Table 2.

4. Discussion

Drug desensitization may be effective in patients with drug HS (IgE-mediated HS especially) when alternative drugs are not available. Although little is known about the mechanisms involved, desensitization induces a temporary state of tolerance to a medication that has produced an HS reaction by administering incremental doses of the drug until the total cumulative therapeutic dose is achieved [4,10]. This tolerance can be maintained as long as the medication is administered at regular intervals until the end of treatment [11].

Rifampicin is a semisynthetic agent belonging to the group of rifamycin antibiotics. It has a bactericidal action and is primarily used in the treatment of mycobacterial infections. It is well absorbed from the gastrointestinal tract. Peak plasma concentrations are reached within 2–4 h, and the drug is widely distributed in most body tissues and fluids, with a plasma half-life of approximately 3 h. Due to hepatic enzyme induction, the metabolism rate of many other medications is increased [8]. Rifampicin is one of the most potent first-line anti-TB drugs and is rarely associated with hypersensitivity reactions [9].

Table 2
Characteristics of unsuccessful Rifampicin desensitization cases.

Case number	Type and chronology of the index reaction	Type of allergic manifestation to desensitization	Chronology of the desensitization reaction	Cumulative stop dose
Case 1	Urticaria, fever, Quincke edema, Anaphylaxis 35 minutes	Arthralgia, generalized urticaria	3 hours	600 mg
Case 2	Urticaria, generalized pruritus 60 minutes	Fever, urticaria of legs	Immediate	600 mg
Case 3	Urticaria, fever 30 minutes	Fever, generalized urticaria	4 hours 30	600 mg
Case 4	Urticaria, fever 30 minutes	Face edema, pruritus	30 mn after the beginning of protocol	2.6 mg
Case 5	Rush, Urticaria 40 minutes	Rush, urticaria, Arthralgia, nausea	90 mn after the beginning of the protocol	31.6 mg

To our knowledge, we report the first study designed to describe the procedures for rapid oral desensitization with rifampicin in suspension in a relatively important number of patients.

Hypersensitivity reactions to anti-TB treatments are reported in 4 to 5% of patients [5]. The reactions to rifampicin are diverse and unpredictable [6]. They may be immediate (IgE-mediated), or non-immediate (delayed-type, cytotoxic, or mediated by circulating immune complexes) [7]. Whatever the mechanism, the occurrence of an allergic reaction may interfere with the initial regimen and promote the course of the disease.

Rapid desensitization with antituberculosis drugs was applied for first time by Holland et al. [12]. Matz et al. [13] reported rapid desensitization protocols for rifampicin and ethambutol in 10 patients, but the patients were not homogeneous (immediate-type and non-immediate type hypersensitivity), and DS failed in 5 patients (50%). Successful desensitization to rifampicin has been reported in adult patients, based on short (a few hours) to long (≥ 7 days) protocols [4]. Most patients received premedication and DS was performed in an intensive care unit by specialized and experienced physicians.

In our study, premedication with antihistamines or corticosteroids was not used as these drugs do not prevent IgE-mediated reactions and may mask early symptoms to low doses of the drug, thereby increasing the risk of serious reactions at higher doses. The strategy used in our study seemed to be effective and safe. The use of rifampicin syrup was tolerated and efficient in 65% of our patients. Moreover, our protocol is original since it makes possible the avoidance of powdered products, which requires meticulous dosages.

Despite the diversity of the protocols reported in the literature, the results of desensitization to rifampicin are generally favorable, with a success rate of up to 82% [14], and 60% in HIV-infected patients with tuberculosis and rifampicin HS [15]. Rapid desensitization to rifampicin may be safely performed in both adults and pediatric patients [16,17]. Although adverse events (fever, facial flushing, and chest discomfort) were noted in some studies [5,18] these reactions were usually mild and transient, were promptly and effectively controlled, and did not hamper the successful completion of the DS procedure. Fenniche et al. also reported a case of anaphylaxis during desensitization to rifampicin, with a favorable outcome after administration of corticosteroids and antihistamines [7]. Thus, patients who in their studies reacted to the DS, might have been able to tolerate it if it had been resumed on antihistamine $\pm$ corticosteroids or more gradually. In contrast, a Japanese study showed failure of DS to isoniazid and rifampicin in 7 of 30 cases (23%) and 3 of 16 cases (19%), respectively, among a total of 46 patients [19]. Notably, the adverse events leading to failure of desensitization included drug fever and eruption, but not

immediate-type reactions, and a long time between the index reactions and initiation of the DS. The main limit of our study was the lack of previous detailed research on the topic. Further studies are needed for further development in the area of drug hypersensitivity.

5. Conclusion

Rapid oral desensitization enables patients hypersensitive to anti-TB drugs to access appropriate treatments immediately and continuously. The protocol outlined in our study (use of rifampicin syrup/suspension) may be a useful tool for other practitioners, particularly in areas where tuberculosis is endemic and treatment is essential.

Disclosure of interest

The authors declare that they have no competing interest.

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