

Full Length Research Paper

Characteristics of chelation therapy among beta-thalassemia patients in the North of Morocco

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The study aims to give a general idea about the experience of chelating drugs among beta-thalassemia patients in Morocco. It is a declarative survey. It was done in the therapy center of Morocco. Statistics were done in the laboratory of biological essays in Kenitra. All economic and pharmacological data were given by Novartis. Sample size was 108.78% of patients attending the service regularly take deferiprone as treatment while 8% of them combine deferiprone and deferoxamine. Most of the patients take treatments regularly. Chelators have reduced mortality. They have induced skin lightening for 26% of the patients in Rabat. Patients taking deferoxamine experienced injection site reactions. Most of adverse drug reactions (ADR) due to deferiprone were digestive. The main problem with chelators in Morocco is lack of accessibility to drugs, that's why the therapy center of Rabat has worked hard in collaboration with an Italian project to resolve the problem.

Key words: Deferiprone, deferoxamine, prospective study, adverse effects, socio-economic level, behavior.

INTRODUCTION

Thalassemia is a public health problem in Morocco which is part of the Mediterranean countries mostly affected by thalassemia. Beta-thalassemias in Morocco are classified as the tenth in regard to annual conceptions in the Eastern mediterranean region (Model, 2008).

Morocco is classified as the 28th country in regard to the percentage of carriers of beta thalassemia (3%), and number of carriers (445 thousands) and also for annual pregnant carriers (12000s) (Model, 2008).

In fact, thalassemias are spread in small towns in Morocco. Its prevalence in the North of Morocco is 3.8*10⁻³ - 3%. Towns like Aouamra and Mnasra are full of beta-thalassemia major cases in this part of the country (Agouzal et al., 2009).

Treatments of beta-thalassemia major are mainly transfusion and chelation. Most of patients with thalassemia are transfused.

This study has three main objectives:

i. Increase awareness of patients with thalassemia about

iron chelation.

ii. Determine behaviour of patients towards drugs prescribed.

iii. Assess side effects of iron chelators.

MATERIALS AND METHODS

Design

Prospective study

It is a declarative survey done in collaboration with Novartis Morocco.

Setting

The consultation centre of the service of hemato-oncology at the children hospital in Rabat. It is the most important hospital of the kingdom. It treats most of thalassemia patients (Khattab, personal communication). The statistical analysis was done in biological essays laboratory in the Faculty of Kénitra. Chelators data was provided by Novartis department of marketing. Data includes samples from patients that are currently chelated in the main hospital of Tangiers (a city in the North of Morocco).

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Patients

The study was done last June and July 2009. The samples were all β thalassemia patients who undergo monthly transfusion and are also perfused by deferoxamine if it is available by the service.

The sign of chelation treatment is hemochromatosis. In general, patients should start iron chelation after receiving 10 to 20 transfusions, or when their ferritin level exceeds 1000 mg / l.

Treatments prescribed

Deferoxamine (desferal): DFO

Desferal, deferoxamine mesylate, is a dry white powder, available in 500 mg or 2 g units. Each unit is contained in a small glass bottle or vial of dry white powder, which should be diluted to a 10% solution before use. To make up a 10% solution of DFO from a 500 ml vial, for example, 5 ml of distilled water should be added to the powder. DFO is monitored by a pump specially designed to slowly infuse the drug under the skin for 8 to 12 h, at least 6 days a week (Eleftheriou, 2007). Desferal chelates iron by forming a stable complex that prevents the iron from entering into further chemical reactions. The exact dose of each patient is calculated on the basis of age, body iron load and clinical conditions. In the hematology service, desferal powder is freely soluble in salted serum.

Deferiprone (kelfer) DFR

Deferiprone is an oral chelating agent. Each box contains 50 capsules. Each capsule has a dose of 250 or 500 mg. For adults and children, the minimal dose of kelfer to achieve a negative balance is 75 mg/kg/day divided into 2 to 4 doses. Kelfer is manufactured by an Indian laboratory. Properties of both treatments are listed in Table 5 (Novartis, 2009).

Data collection strategies

Data is collected from the transfusion room of the consultation centre of the hospital.

Patients were asked about their behaviour towards treatments, method of administration of deferoxamine and the side effects (if any) they have experienced. For the patients of the hospital of Tangiers, we requested information from their doctor. We also interviewed two secretaries and two nurses from the Moroccan association of thalassemia. The two nurses were taking care of these patients.

The following are the variables analyzed

- * The demographic characteristics (gender, age).
- * Socio-economic level of the patients.
- * The patient's behaviour towards the drug.
- * The side effects experimented by patients.

Analysis

Data was recorded in an Excel file. SPSS software were used for the descriptive and analytical statistics (Agouzal et al., 2009);

- a. Descriptive statistics: First, we defined demographics of the sample. Next, we analysed the availability of chelating molecules in the service, then the behavior of patients and the risks of treatment.
- b. Statistical analysis: This was based on tests of association such as Chi-square test that measures the difference between the

observed and theoretical frequencies. We used chi-square to compare the sexes. We also used analysis of variance (ANOVA), to see if age (dependent variable) is related to the behavior of patients as well as to the occurrence of ADRs (independent variables). If the value of p is less than 0.05, we conclude that there is a relationship between the dependent and independent variables.

On the other hand, the estimation of risk (RR) for sexes allows us to detect the relationship between patients' behaviour and sexes on one hand and between occurrence of EIM and sexes on the other hand. If the value 1 is excluded from the confidence interval (95% CI) of RR, we conclude that there is really an association (relationship) between the two parameters compared.

RESULTS

Description of the sample

The sample consists of 108 cases. The age of patients who receive the treatment ranges mostly between 0 and 15 years with a percentage of 75%. The mean age is 11 ± 7 years. Male are subject to chelation with a rate of 46%. The sex ratio is in favour for a female predominance (0.7). There is no significant difference between males and females in regard to taking chelating treatments ($p = 0.1$).

As far as socio-economic level is concerned, the majority of patients are indigent with a rate of 74% while 26% are ensured. The majority of patients who are chelated were originally from the Tangiers-Tetouan region. This region is in the North part of Morocco (Table 1).

Characteristics of treatments

Deferiprone

Actually, most of the patients take only kelfer with a rate of 52% (Figure 1). Kelfer is taken by patients monitored in the service of Rabat only. 78% take the capsules regularly while 22% do not (Table 2). 71% of patients did not experience any ADR. Nevertheless, 14% ADRs were reported as follows:

- i. 2 neurological ADR: Headache and vertigo.
- ii. 9 digestive ADR: Abdominal pain, vomiting, stomach pains and nausea.
- iii. 1 rheumatologic ADR: Arthralgia.
- iv. 2 general symptoms include loss of appetite.

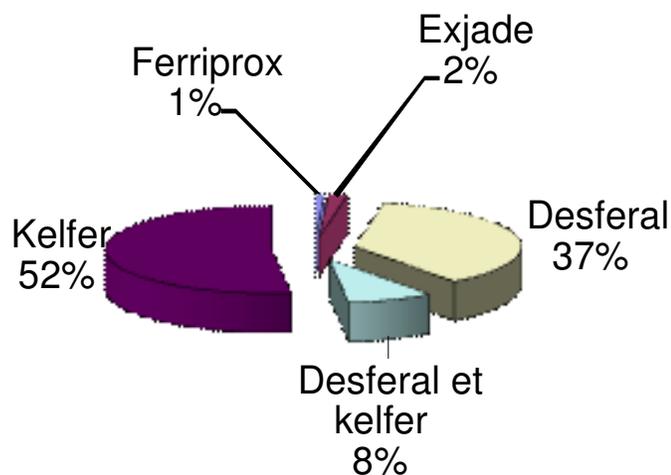
Patients noticed that their urine became red as a result of excretion of deferiprone (Table 5).

Deferoxamine

Actually, 8% of patients take both kelfer and Desferal in the service of Rabat. The 37% who take Desferal alone are patients monitored in Meknes and in the Tangiers-Tetou Northern region (Figure 1).

Table 1. Description of the sample.

Variables	Percentages
Age (n=106)	
[0-15]	75
[15-50]	25
Sex (n=108)	46
Male	62
Female	
Socio-economic level (n=65)	26
Ensured	74
Indigent	
Origin (n=77)	20
Gharb-Chrarda-Bani Hassan	18
Rabat-sale –Zemmour Zaer	41
Tanger-Tetouan	21
Other regions	

**Figure 1.** Treatments taken by transfusion-dependant patients.

In the consultation centre of Rabat, only 12% of patients use the pump for perfusion of desferal. The pump was donated by Italian Government in January 2008. Regarding the behavior, 73% of patients used to take desferal regularly, while 27% do not. 53% of patients reported side effects. Therefore, 26 ADRs were reported as follows:

- i. 3 neurological ADR: Vertigo.
- ii. 1 digestive ADR: Abdominal discomfort, stomach pains, nausea, vomiting.
- iii. 2 dermatological ADR: Allergy.
- iv. 3 general symptoms: Tremble, perspiration, tiredness.
- v. 17 Injection site reactions: Localized irritation, pain,

burning, swelling, indurations, infiltration, pruritus, erythema, wheal formation, eschar, crust, vesicles and local oedema.

Influence of age and sexes on the treatments

Patients monitored in Rabat

Their behavior and side-effects due to taking kelfer do not depend on the age of the patients $p > 0.05$. Side effects due to administration of Desferal depend on the age of the patients because $p < 0.05$ (Table 3).

There is no association between sexes and patients' behavior because 1 is included in the confidence interval (95% CI) of RR. We got same result when we compared sexes with side-effects due kelfer and Desferal (Table 4).

DISCUSSION

Demographics

The Gharb-Chrarda Bani Hassan is the region that is mostly affected by Thalassemia in the North-western part of Morocco as it was shown in a survey taken earlier (Agouzal et al., 2009). According to experts of the regional hospital of Kenitra, most patients from Gharb region get their chelating treatment in the capital (Rabat) hospital.

Most patients who take treatments have an age that ranges between 0 and 15 years, this result is similar to the one from a survey taken by thalassemia patients in the North-western part of Morocco and which shows that the age of affected patients is between 0 and 15 years (Agouzal et al., personal communication). Predominance of sexes is female while it is male in the same survey.

Deferiprone

Most of patients (52%) take kelfer because it is the only drug available so far in the service of Rabat. It is an Italian who donated it to the service. It was available in the service from 09/2008 until 05/2009 and there is still more in the stock.

Two children refused to take the kelfer capsule, their parents have tried different alternatives to help them but in vain. One girl has difficulty ingesting the capsule and the other could not stand its taste. Two patients complained about the posology frequency imposed by hematologists (3 to 4 times a day). The remaining patients did not take the drug regularly because they were not convinced that the treatment would be effective or they were not serious about it.

According to the responsible of the genetic section of are taking Kelfer other are on Deferasirox in India. Results from taking Kelfer are good but there are some side

Table 2. Characteristics of treatments.

	Percentage of patients taking Kelfer %	Percentage of patients taking Desferal %
Behavior (n=55)		
Irregular	22	27
Regular	78	73
ADR (n=48)		
Absent	70	70
Present	30	30

Table 3. Analysis of variance.

Dependant variable : Age	F	P
Independent variables		
Behavior (irregular/regular)	0.2	0.6
ADR due to kelfer (present/absent)	0.9	0.3
ADR due to desferal (present /absent)	6	0.01*

Table 4. Relative risk.

	Sexe (female/male)
Behavior (irregular/regular)	2 (0.5-7)
ADR due to kelfer (present/absent)	3 (0.8-12)
ADR due to desferal (present /absent)	0.8 (0.2-2)

effects like joint pain fall in platelets otherwise it is more effective than any other chelators.

Treatment with deferiprone should be carefully considered for patients unable to use deferoxamine or for patients with an unsatisfactory response to deferoxamine as judged by liver iron and serum ferritin measurements or evidence of cardiac iron overload or iron-induced cardiac dysfunction (Victor et al., 2003). In our study, people do not have this choice; they take deferiprone because it is the only drug available in the service of Rabat.

Deferoxamine

27% of the patients are able to buy desferal; this is because they are insured, the remaining 73% benefited from a donation by Americans from 09/2007 until 05/2008. This is why Novartis sells about 50 boxes monthly (sometimes it sells less than this quantity) in Morocco. Their price is expensive when compared with the purchase power of Moroccan society.

27% of the patients monitored in Rabat do not take desferal regularly because it is chronic and heavy. In France, 20 to 40% of patients were not compliant with Desferal for the same reason (Robert et al., 2006).

The analysis of survival rates according to the age shows that (Figure 2). Patients that are daily perfused with desferal have a survival rate of 100%. Patients who are infused three times a week could die at the age of 32 years, unlike people who may die at the age of 22 years when they are not perfused (Novartis, 2009).

The contrary to a study done in Italy which shows that deferoxamine is a Risk factor for predicting mortality in patients with thalassemia major (Aurelio et al., 2009), in our sample no deaths occurred with the DFO.

DFO and DFP

No deaths occurred with the deferiprone (DFP) alone or when combined with DFO. Previous studies that investigated iron chelation treatments, including retrospective and prospective non-randomised clinical trials, suggested that mortality due mainly to cardiac damage, was reduced or completely absent in patients treated with deferiprone (DFP) alone or when combined with DFO (Maggio et al., 2009).

Nevertheless, deferiprone provides significantly better cardiac protection than deferoxamine (DFO), the current standard treatment (Borgna-Pignati et al., 2004). The trial results from five years showed that sequential treatments with DFP-DFO and DFP alone significantly decreased serum ferritin without major differences in terms of survival, adverse events, or costs (Kolnagou et al., 2008).

ADR characteristics

The ADR experimented by patients are close to those mentioned by Novartis (Table 5). The majority of ADR due to desferal were cutaneous and those due to kelfer are digestive; this is similar to results of literature (Agouzal et al., 2009). A patient aged 21 experienced some neurosensorial trouble with desferal and neutropenia with kelfer. Toxicity of Deferiprone was mild to moderate but acceptable; most commonly, transient arthropathy and nausea/vomiting were observed in a similar study done in Egypt (Beshlawy et al., 2008). Therefore, two rigorous monitoring are required: Hematological for deferiprone and neurosensorial for deferoxamine.

Table 5. Properties of DFO and DFR.

Property	Deferoxamine	Deferiprone
Usual dose(mg/kg/day)	25-60	75.
Route	Subcutaneous, intravenous (8–12 h, 5 days/week)	Oral 3 times daily.
Half-life	20–30 min	3–4 h.
Excretion	Urinary, fecal	Urinary.
Adverse effects	Local reactions, ophthalmologic reactions, auditory reactions, growth retardation, allergic	Gastrointestinal disturbances, agranulocytosis / neutropenia, arthralgia.

Table 6. Descriptive study of national surveys.

Study type	Monitoring	Retrospective	Retrospective
Duration	1992-2000	1982-2000	1980-1998.
Population of hemoglobinopathies	243 cases (40 betathalassemia major)	75 cases (14 BTM)	20 cases of BTM.
Setting	Pediatrics Rabat	Pediatrics Casablanca	Pediatrics Casablanca.
Percentage of chelated patients (%)	28	2	15

Table 7. Estimated reach of treatment for β thalassaemia in each WHO region (Modell and Darlison, 2008).

WHO region	Adequate iron chelation		Inadequate or no iron chelation
	Percentage	Number	
American	58	1604	1146
Eastern Mediterranean	27	10818	28882
European	91	14754	1472
South-east Asian	19	6621	28879
Western Pacific	44	1504	1946
World	39	37866	59764
North-western of Morocco	65	111	59

Deferasirox

Novartis manufactured deferasirox which is as effective as deferoxamine (Delea, 2007). In a randomised trial, a posology of 20 mg/kg/j to 30 mg/kg/j from deferasirox and deferoxamine were compared. Deferasirox gave better results for the intraliver concentration (Rose et al., 2008). Sequential treatment of two patients with deferasirox (Figure 1) showed the following promising results:

- Good compliance because it is dispersible and taken once a day only (Deferasirox showed a plasma elimination half-life of 8 to 16 h (Piga et al., 2006).
- No ADR were experienced.

In fact, Deferasirox is the most recommended chelator by the thalassaemia international federation (TIF, 2007).

In general, treatment was effective because it reduced mortality and morbidity; the proof is that number of chelated patients with age from 15 begins to decrease

significantly. Thalassaemia patients, who are transfused and non-chelated, die before the age of 20 (El Khattab M. University of Souissi, Rabat, personal communication). The efficiency of treatment is proven by the fact that life expectancy is longer because it reaches 25 to 30 years (Giro, 1997).

The first benefit of adequate chelation is skin whitening. This is an immediate clinical consequence. 26% of the patients monitored in Rabat got a clear skin, the rest did not because they may not have taken treatment adequately or they needed time to show results as chelation is new among thalassaemia patients.

In the North-western part of Morocco, only 65% of the patients are chelated. Two studies done in a service that recruits Southern thalassaemia people of Morocco; first study showed that 15% are chelated and second study showed 2% (Table 6).

Table 7 shows that less than 40% of transfused patient obtain adequate iron-chelation therapy. At least 3000 people die yearly in their teens or early 20s from

uncontrolled iron overload (Modell and Darlison, 2008).

The percentage of chelated people in the North-western part of Morocco is 65%, this number is higher than the one from the Eastern Mediterranean region (27%) and also higher than the number from the world (39%) which means that the big part of Morocco is well classified.

Morocco faces the same problem of availability of chelators as Canada: According to the secretary of the Thalassemia Foundation of Canada, the available treatments across Canada are Deferoxamine (Desferal) and also Deferasirox (Exjade) which recently got Health Canada approval and is currently being reviewed by several provinces (it is the provinces that fund drugs for patients, unless it is covered by private insurance) and so is not widely available at the moment. Deferiprone (Ferriprox or L1) is not approved for use in Canada on a wide basis but is available through Health Canada's Emergency Drug Release program (case-by-case when other drugs fail to work).

In Australia, treatments are available for all the 350 beta thalassemia patients. According to the secretary of the Thalassemia Australia Inc. (Formerly Thalassemia Society of Victoria Inc.), chelation therapy in Australia is used by all thalassemia major patients. In particular, there are currently four types being used: Desferal (Deferoxamine), Exjade (Deferasirox), Desferal and L1 combination and L1 (Deferiprone). These can be treated in a variety of ways, depending on which drug is being used. For example Exjade should be taken orally, as is L1, but Desferal is taken using subcutaneous injection. Chelation is determined by the patients haematologist as to which is most appropriate for that particular patient.

In a study done among Australian thalassemia patients (Kidson et al., 2008), despite the availability of effective chelating agents, patients had marked iron overload and a high incidence of complications. This elucidates another problem apart from availability of treatments, is that predictors of complications included increasing number of years of transfusion, coprescription of desferrioxamine and deferiprone for 8% of the patients, and poor adherence to desferrioxamine treatment.

Most children with thalassemia are born in low-income countries. Worldwide, transfusion is available for a small fraction of those who need it, and most transfused patients will die from iron overload unless an available and potentially inexpensive oral iron chelator is licensed more widely (Modell and Darlison, 2008).

The patients' predicament underlines the need for combined treatment and prevention programmes. Wherever combined programmes exist survival is steadily improving, affected births are falling and numbers of patients are stabilizing. The policy is spreading because of its demonstrable cost-effectiveness and thalassemia is gradually becoming contained.

In this sense, in our Country, an Italian project 3H#5-9779 (2007 - 2011) is working through a screening of thalassemia carriers and also its main objective is to offer

chelating for people who need it.

Conclusion

Although the main problem in Morocco is the lack of chelating treatment in the Hospitals (except donations and some parents paying or insured), other developing countries are facing the same problems.

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