Statistical Evaluation

An Observation to the Application of the

Preparation Series

NOTAKEHL

In the Administration Forms of: Capsules, Tablets
Drops, Suppositories, Ointment, Solution for Injection

Pharmaceutical Enterprise:

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Hoya

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1 Introduction

From July 1993 to October 1999 a total of 127 patients were tested by 10 Doctors practices (6 General Practitioners, 3 Internists and 1 Ear, Nose and Throat Specialist) in an observation study with the application of the preparation series Notakehl in the following administration forms: capsules, tablets, drops, suppositories, ointment and solution for injection. The homeopathic test preparation Notakehl comprising of the third to the seventh decimal dilutions of Penicillium chrysogenum, (synonym Penicillium notatum) each according to administration dosage.

-Notakehl drops contain Penicillium chrysogenum (synonym Penicillium notatum) D5 dil. in accordance with Prescription 5a HAB1.

-1 ampoule of Notakehl solution for injection contains 1 ml Penicillium chrysogenum (synonym Penicillium notatum) D5 (Penicillium chrysogenum (synonym Penicillium notatum) D6 and Penicillium chrysogenum (synonym Penicillium notatum) D7 aquos. dil. in accordance with Prescription 5b and 11 HAB 1.

-1 Notakehl capsule contains: 330 mg Penicillium chrysogenum (synonym Penicillium notatum) D4 trit. in accordance with Prescription 6 HAB 1.

-1 Notakehl suppository contains: 0.2 g Penicillium chrysogenum (synonym Penicillium notatum) D3 trit. in accordance with Prescription 6 HAB 1.

-5 ml Notakehl ointment contain: 0.1 g Penicillium chrysogenum (synonym Penicillium notatum) D3 dil. in accordance with Prescription 5a HAB 1.

The aim of the observation was to establish the actual application of the preparations and their tolerance under conditions in every-day practice, moreover that recognition over the acceptance of the preparations on the market should be gained, in particular with children.

In accordance with the structure of the investigation descriptive statistical procedures were drawn. The application of inductive methods were not indicated. An „intention to treat“ assessment was carried out, i.e. all patients were considered who received at least one dose of the medicament.

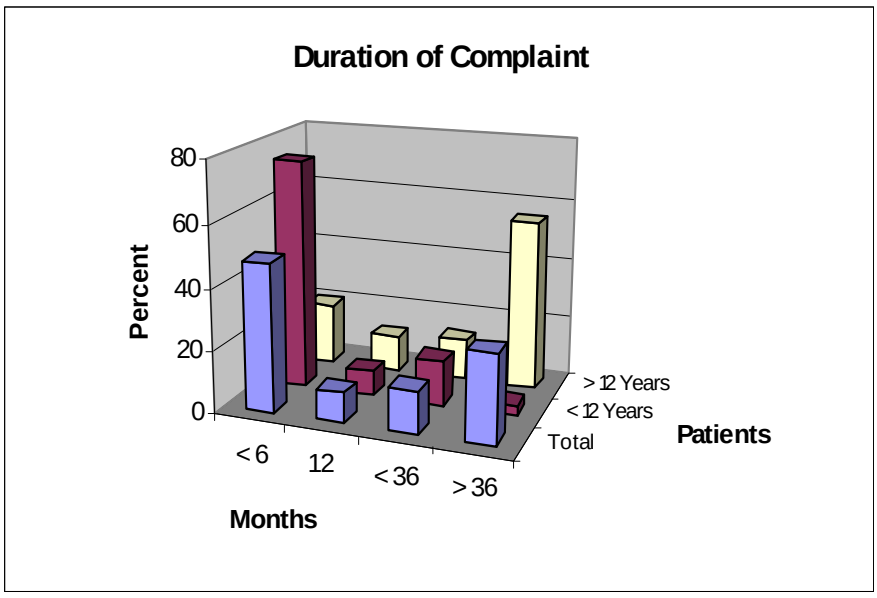
2 Participating Patients

Included in the study were 127 patients which comprised of 49.6% men and 51.4% women. The age of the patients varied between 4 months and 72 years with an average age of 23.4 years and a standard deviation of 20.3 years. Almost half the patients (49.6%) were under 12 years of age. Between the ages of 13 and 20 amounted to 3.9% of the patients, between 21 and 30 years, 11%, 31 and 40, 7.1%, 41 and 50, 15.7%, 51 to 60 years, 9.4%, 61 to 70, 2.4% and finally over 71 years made up 0.8% of the patients. The age structure of the men was classified with an average age of 24.7 ± 21.7 approximately two years older than the women with 22.1 ± 18.7 years.

Height varied between 61 and 193 cm with an average of 140.9 ± 35.4 cm. Body weight lay between 5.5 and 165 kg with an average of 48.2 ± 29.3 kg.

2.1 Diagnosis and Accompanying Diseases

The diagnosis leading to the prescription was to be entered into the Study protocol. It was herewith set out that Notakehl corresponding to Isopathy in a very wide area of



application be applied and the preferred use dependent on the age of the patients.
Whilst Notakehl was mainly applied in the younger patient groups under 12 years with bronchitis, rhinitis, angina and otitis media, patients in the over 12 age group stood in the foreground with illnesses such as candidosis, HWS and LWS syndrome. Collected findings were carried out each before and after completion of the treatment and accompanying therapies were to be documented in a survey form. In order to obtain a measurement of chronic diseases it was asked in the study protocol, how long the disease or discomfort has been in existence. For this a time span of less than 6 months to 1 year, up to 3 years and over 3 years was laid down. The duration of complaints of less than 6 months accounted for half of the patients (48.0%), 12 patients (9.8%) between 6 and 12 months and for 17 patients (13.8%) up to 3 years. 35 patients (28.5%) suffered discomfort for over 36 months.

In comparison to the under and over 12 patient groups, it proves that 74.2% of the children had complaints for less than 6 months whilst 55% of adults had complaints over a time span of 36 months. This concludes that Notakehl was mainly administered to children with acute conditions and adults with chronic conditions

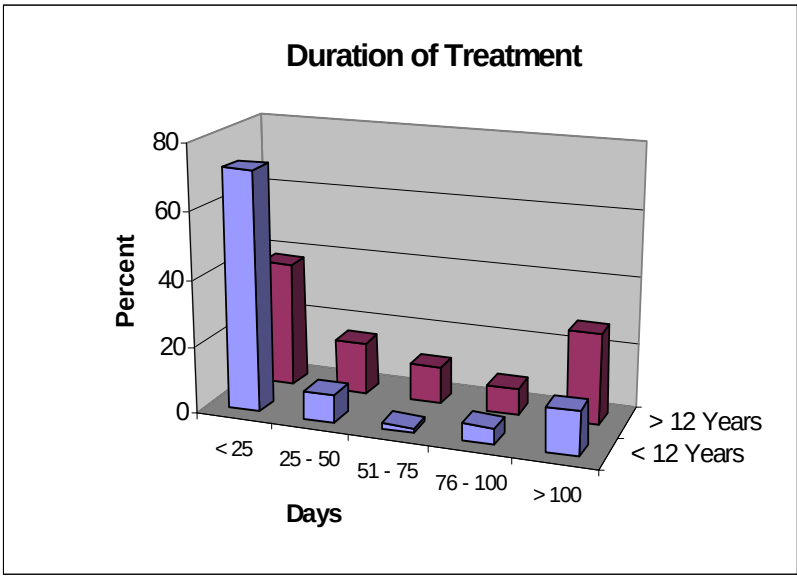
Of the 127 patients included in the study, 46 patients (36 patients < 12 years, 10 patients > 12 years) were previously treated with Notakehl.

3 Dosage and Duration of Treatment

3.1 Time of Consultation and Duration of Treatment

Corresponding to the nature of application observation no rigid time limit was laid down for a final examination which was carried out in a time span between 1 and 795 days with an average of 67.4 ± 122.4 days.
Duration of the therapy in adults (> 12 years) was on average 88.6 ± 145.8 days, almost twice as long as those children (< 12 years) with 46.3 ± 88.3 days. This was to be expected as both groups were distinguished by acute and chronic treatment. The brief therapy period of up to 25 days was predominant with 72.1% of the children, whilst the adults accounted for only 38%, followed by a therapy period of over 100 days with a frequency of 27%.

3.2 Dosage



Duration of Complaint (Months)	Total Patient Population (%)	Patients < 12 Years (%)	Patients > 12 Years (%)
< 6	48.0	74.2	20.0
12	9.8	8.1	11.7
< 36	13.8	14.5	13.3
> 36	28.5	3.2	55.0

The dosage was prescribed for the relevant form of administration according to the package insert with:

Notakehl Drops

For oral intake: 1 x 8 drops daily before mealtimes
For inhalation: 2-3 x daily inhale 20-30 drops
For topical application:
a) 1 x daily 5-10 drops at the location of the complaint or massage into the crease of the elbow.
b) By injection treatment; on injection free days 2 x weekly 5-10 drops

Notakehl Solution for Injection

2 x weekly, inject 1.0 ml either i.m., s.c., i.c., or i.v.

Notakehl Capsules

Daily 1-3 capsules either before breakfast or evenings before bedtime to be taken with some fluid.

Notakehl Suppositories

1 x daily before bedtime 1 suppository to be inserted rectally.

Notakehl Ointment

1-3 x daily apply topically a thin layer onto the affected area. Alternatively apply a thin layer direct onto the dressing and apply on affected area.

With reference to the dosage forms, 16 patients were prescribed capsules, 28 patients with tablets, 55 patients with drops for oral intake, 1 patient with drops for topical application, 4 patient with drops for inhalation, 7 patients with suppositories, 20 patient with ointment and 12 patients with the solution for injection. Multiple entries were necessary if various administration forms were to be combined. The tables below show the medium dosage with respect to the administration form. Injection volumes were administered for one week and the remaining dosage forms were prescribed to the relevant daily dosage.
Nothing else was substantially administered for the under and over 12 age groups.
The dosage of the ointment seems at first glance higher in the childrens group. It is however for this reason that in one case a daily dosage of a 30 cm ribbon of ointment was prescribed. That only 4 patients in this age group were treated with ointment, it does not give a true representation in quantity prescribed.

Besides the mono-therapy with one administration form, two or even three administration forms were also combined into the therapy. Because the injection was applied in weekly

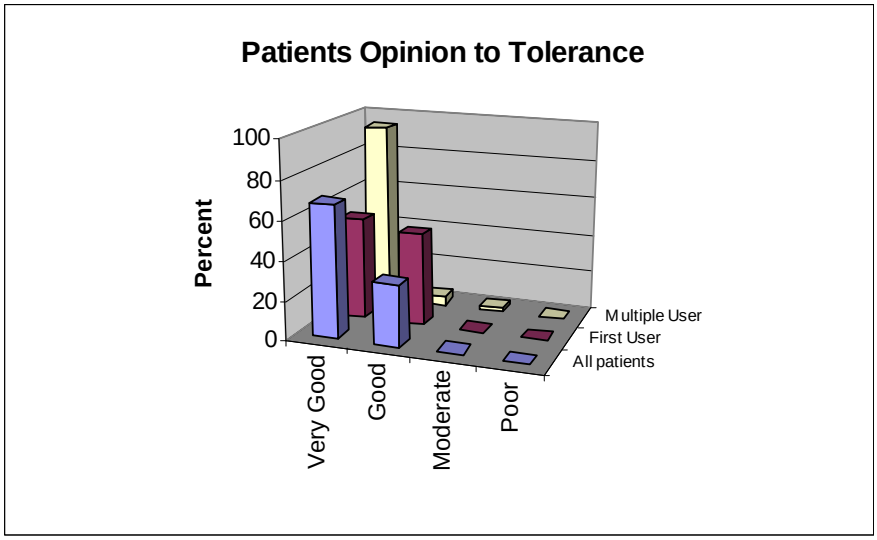
Total Population				
	Medium Dose (%)	Minimum Dose (%)	Maximum Dose (%)	
Capsules	1.4 ± 0.6	1	3	
Tablets	1.4 ± 0.6	1	3	
Drops (oral)	9.4 ± 3.5	4	16	
Drops (topical)	4.0	4	4	
Drops (inhale)	7.2 ± 7.4	2	20	
Suppositories	1.0	1	1	
Ointment (cm)	4.4 ± 6.9	1	30	
Injection (ml)	1.6 ± 0.7	1	3	
All Patients under 12 Years				
	Medium Dose (%)	Minimum Dose (%)	Maximum Dose (%)	No. of Patients (%)
Capsules	1.3 ± 0.5	1	2	3
Tablets	1.0	1	1	2
Drops (oral)	9.4 ± 3.6	4	16	51
Drops (topical)	4.0	4	4	1
Drops (inhale)	3.0	1	4	2
Suppositories	1.0	1	1	5
Ointment (cm)	14.7 ± 10.0	2	30	4
All Patients over 12 Years				
	Medium Dose (%)	Minimum Dose (%)	Maximum Dose (%)	No. of Patients (%)
Capsules	1.4 ± 0.6	1	3	13
Tablets	1.4 ± 0.6	1	3	25
Drops (oral)	9.3 ± 1.9	8	12	3
Drops (inhale)	11.8 ± 8.5	3	20	2
Suppositories	1.0	1	1	2
Injection (ml)	1.6 ± 0.7	1	3	12
Ointment (cm)	1.9 ± 2.3	1	5	16

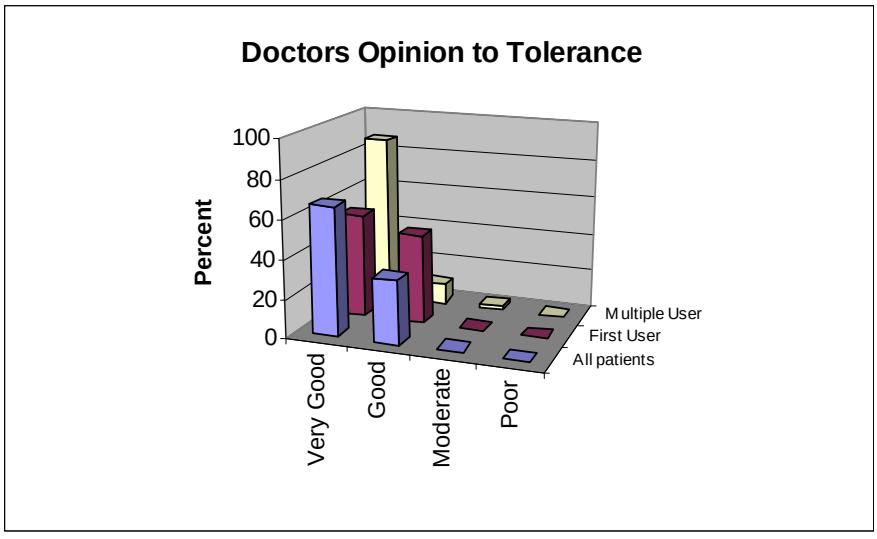
rotation, in addition to the injection free time 4 patients were given capsules, 2 patients, tablets, 1 patient, ointment and 1 patient, ointment and capsules. 1 patient was prescribed drops for oral intake as well as for topical application. Drops for oral intake and for inhalation were used by 3 patients. By 1 patient, drops for oral intake and suppositories were combined. The ointment was combined with tablets for 7 of the patients and capsules for 5 of the patients. There was a clear difference in both age groups in the extent of the combination of the dosage forms. Only 5 patients from the under 12 age group used a combination of different dosage forms. Drops for oral intake and topical application or for inhalation were combined and a combination of drops for oral intake and suppositories as well as capsules with ointment. A combination of solution for injection with the other dosage forms was predominant with the patients in the over 12 age group.

4 Comparison with Former Therapy

47 patients had already received therapy with one or several administration forms of Notakehl within the last five years. Since a third of the patients had already earlier experienced therapy with Notakehl, a comparison was to be established as to effectiveness and tolerance in both patient groups of First and Multiple Users with hints to possible tendencies towards sensitisation from the pharmaceutical effective components.

Opinion to tolerance by multiple application was substantially better than that of a single application usage. Although the doctors and patients in the First Users group gave an assessment of „very good“ and „good“, a designation of „very good“ tolerance was substantially more pronounced with the Mutliple Users group than with the First Users.





Opinion to Tolerance									
Patient Group	Patients Opinion					Doctors Opinion			
	Very Good (%)	Good (%)	Moderate (%)	Poor (%)		Very Good (%)	Good (%)	Moderate (%)	Poor (%)
All patients	68.0	31.3	0.8	0		66.4	32.8	0.8	0
First User	52.5	47.5	0	0		53.8	46.3	0	0
Multiple User	93.8	4.2	2.1	0		87.5	10.4	2.1	0

Opinion to Effectiveness								
Patient Group	Patients Opinion					Doctors Opinion			
	Very Good (%)	Good (%)	Moderate (%)	No Effect (%)		Very Good (%)	Good (%)	Moderate (%)	No Effect (%)
All patients	31.5	51.6	14.5	2.4		28.5	56.9	10.6	4.1
First User	32.5	49.4	15.6	2.6		32.5	54.5	9.1	3.9
Multiple User	29.8	55.3	12.8	2.1		21.7	60.9	13.0	4.3

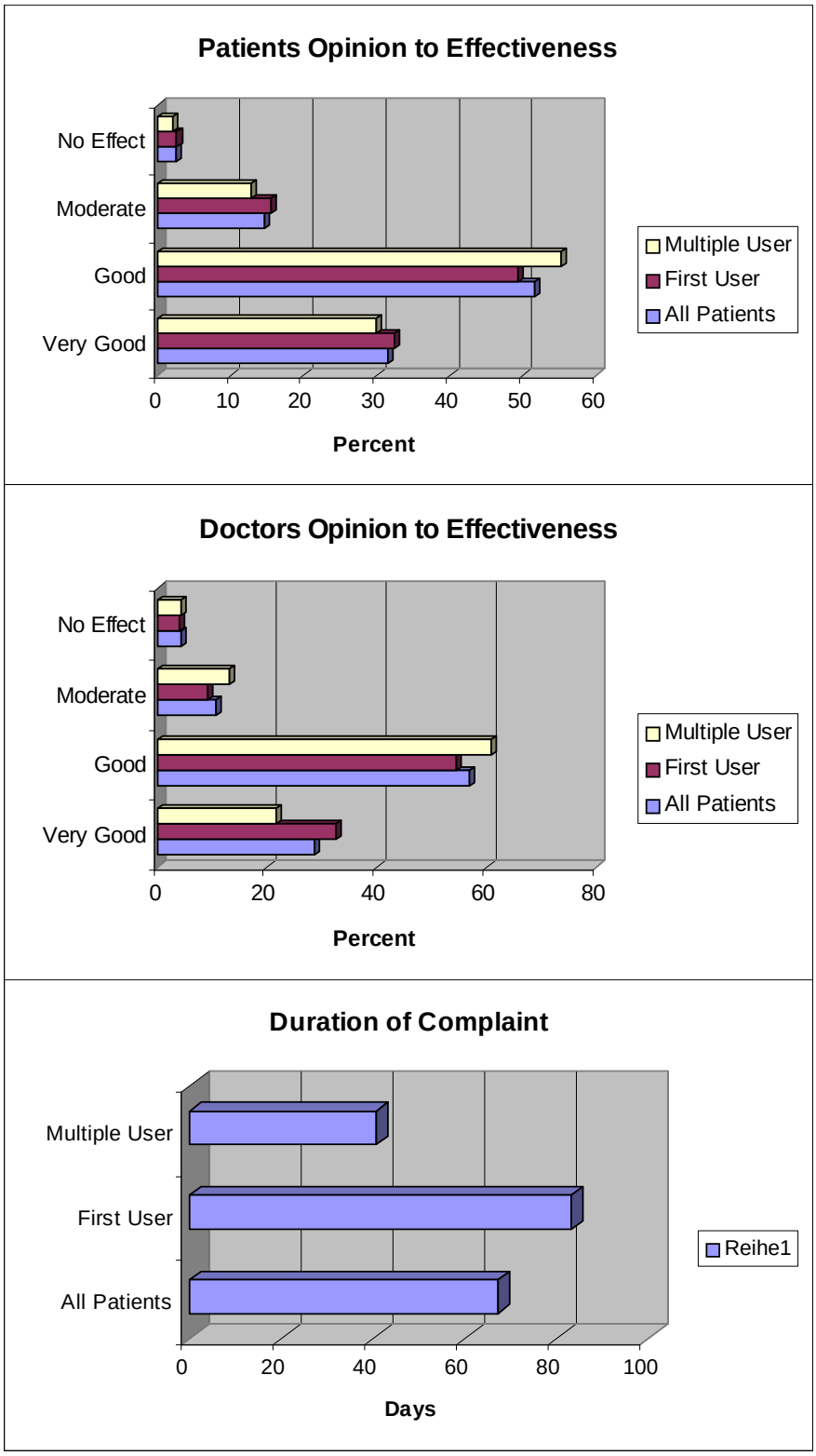
From this data, it shows no potential of an exposure to danger regarding sensitisation of the patients through the pharmaceutical effective component of Penicillium chrysogenum (synonym Penicillium notadum).

It was discovered in the judgement of effectiveness through doctor and patient that there were no differences between the First and Multiple Users. Duration of the therapy was distinguished by the Multiple Users with an average duration of 40.9 ± 77.2 through to one of around 27 days reduced therapy compared with the average. The First Users were treated on average twice as long with 83.4 ± 140.5 days.

5 Effectiveness and Tolerance

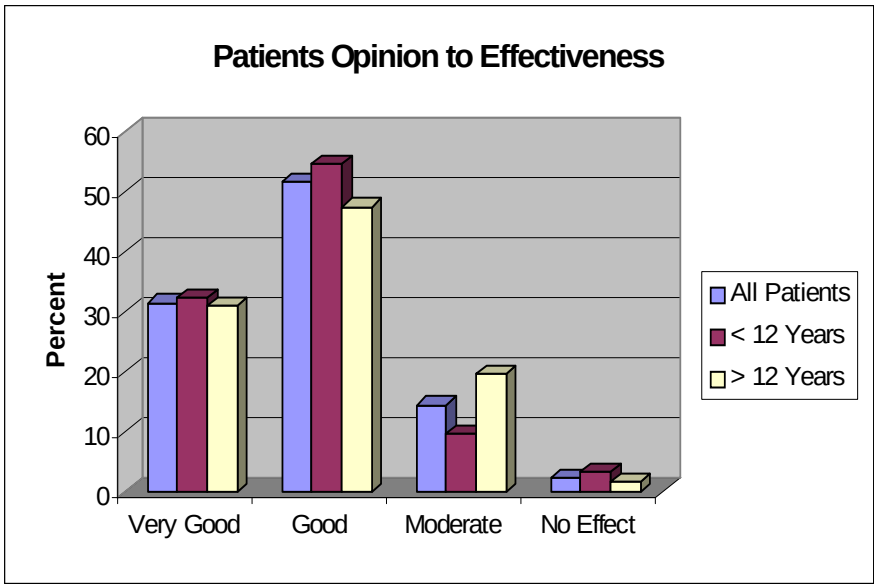
5.1 Assessment of Effectiveness by Doctor and Patient

In a closing assessment, doctors and patients were asked to judge the effectiveness and tolerance. The effectiveness could be assessed with „very good“ „good“ „moderate“ or „no effect“. In addition the doctors were asked according to the patient's compliance to usage, so that it could also be classified with „very good“, „good“, „moderate“

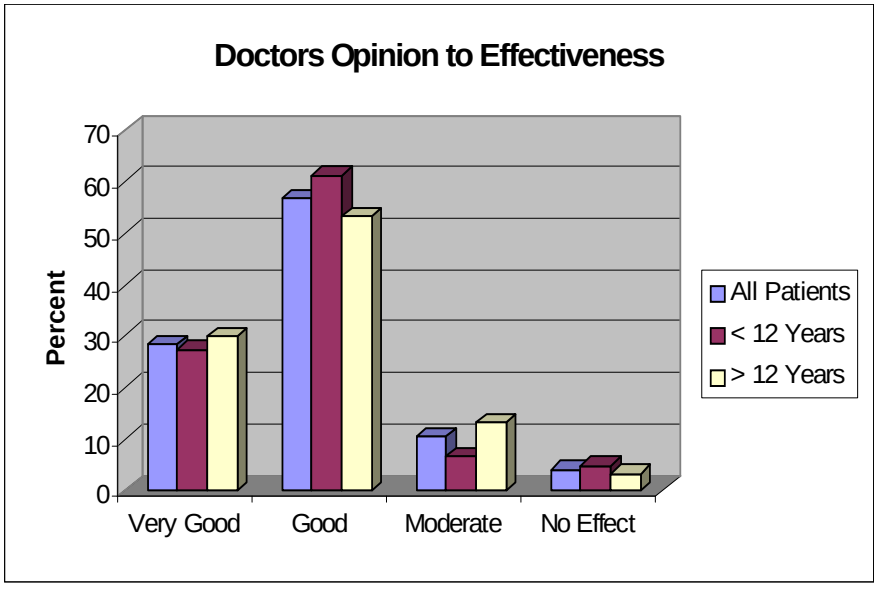


Opinion to Effectiveness									
Patient Group	Patients Opinion					Doctors Opinion			
	Very Good (%)	Good (%)	Moderate (%)	No Effect (%)		Very Good (%)	Good (%)	Moderate (%)	No Effect (%)
All patients	31.5	51.6	14.5	2.4		28.5	56.9	10.6	4.1
< 12 Years	32.3	54.8	9.7	3.2		27.4	61.3	6.5	4.8
> 12 Years	31.1	47.5	19.7	1.6		30.0	53.3	13.3	3.3

or „poor“. 31.5% of patients expressed effectiveness with „very good“, 51.6% with „good“ whilst 14.5% expressed only „moderate“ and 2.4% with „no effect“. The doctors assessment to effectiveness was just as positive as with the patients. 28.5% of patients were classified with „very good“, 59.6% with „good“, 10.6% with „moderate“ and 4.1% with „no effect“.



Application behaviour (N=117) was judged by 82 patients with „very good“ and“good“ by 29 patients through their doctor. With it 87.4% of all those patients involved in the study confirmed very good compliance. For 6 patients, this was only „moderate“ and „poor“ for none of the patients.



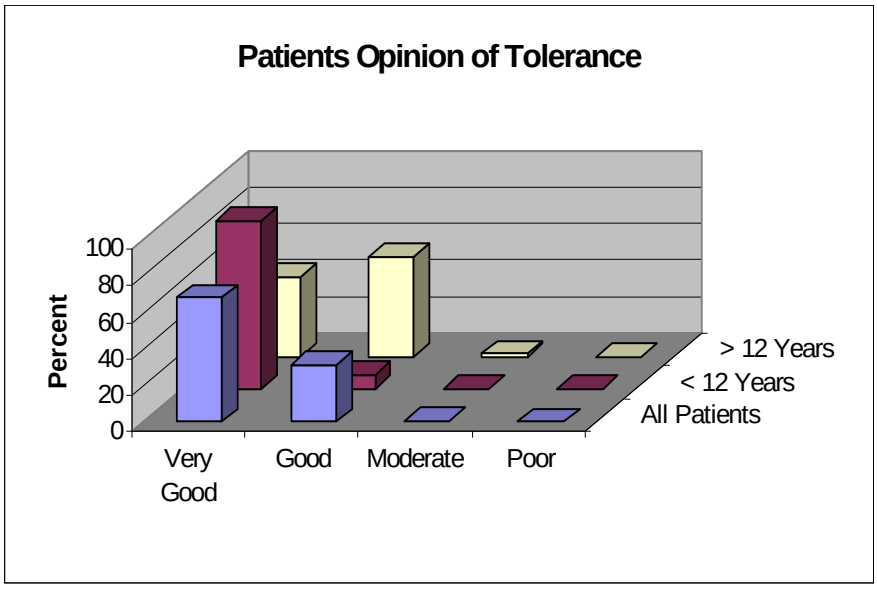
5.2 Opinion of Tolerance by Doctor and Patient

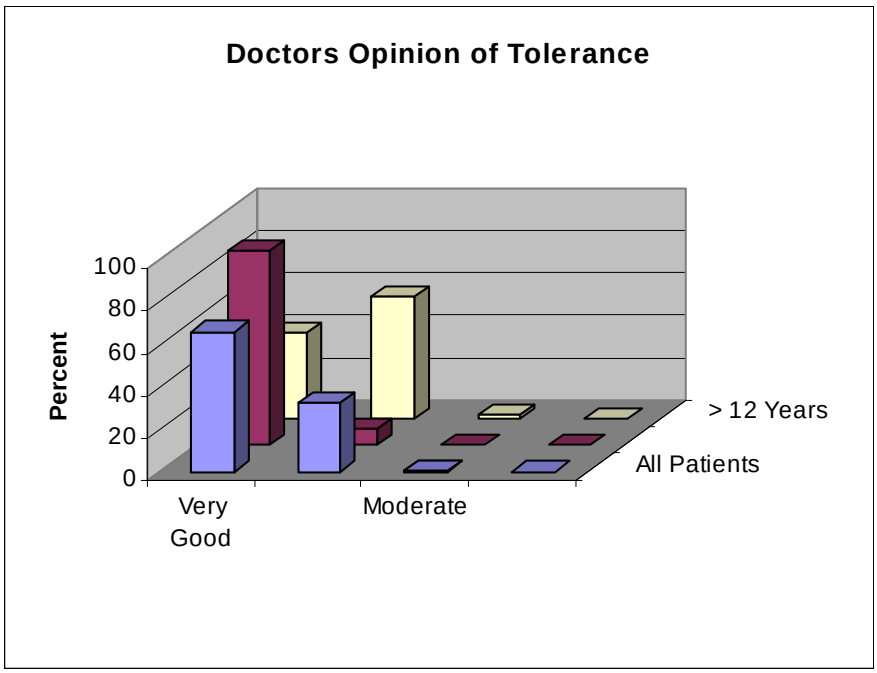
To conclude the examination, an assessment to tolerance was submitted from doctors and patients whereby a judgement of „very good“, „good“, „moderate“ and

Opinion to Tolerance									
Patient Group	Patients Opinion					Doctors Opinion			
	Very Good (%)	Good (%)	Moderate (%)	Poor (%)		Very Good (%)	Good (%)	Moderate (%)	Poor (%)
All patients	68.0	31.3	0.8	0		66.4	32.8	0.8	0
< 12 Years	92.1	7.9	0	0		92.1	7.9	0	0
> 12 Years	43.8	54.7	1.6	0		40.6	57.8	1.6	0

„poor“ could be chosen. 68.0% of patients and 66.4% of doctors classified the tolerance with „very good“ whilst 31.3% of patients and 32.8% of doctors confirmed a good tolerance with Notakehl.
A „moderate“ tolerance was given by 0.8% of patients and doctors. No patient or doctor gave a classification of „poor“.

Tolerance was by far more positively assessed by doctors and patients in the under 12 age group than with the over 12 age group. Whilst in the younger age groups 92.1% of the patients and doctors indicated tolerance with „very good“, this was with the over 12’s only 43.8% of patients and 40.6% of doctors. No assessment of „moderate“ or „poor“ in the under 12 age group was given by the doctors or patients.





5.3 Side Effects and Discontinuation of the Therapy

The therapy with Notakehl was not discontinued by any of the patients. However 4 cases of side effects were reported which are more closely interpreted as follows: A 47 year old patient stated side effects of an influenza infection with coughing, tiredness, sweating and weakness. The doctor however saw no connection of this with the Notakehl therapy. After six days of treatment a Herpes labialis appeared with a 5 year old boy treated with Notakehl drops for oral intake which was then symptomatically treated. A papillary exanthema developed on the neck area of a 5 year old boy also treated with Notakehl drops for oral intake four days after the start of therapy, which without any further therapy remained for three days then disappeared. After three weeks into the therapy with a 60 year old patient ischialgia occurred which showed complete remission after symptomatic treatment. A connection with the therapy with the use of Notakehl could not be determined in any of the cases.
Side effects were listed with the various administration forms. With the Notakehl solution for injection, 1 case of local irritation occurred at the point of needle insertion which disappeared again without further therapy. 3 cases who were administered with a combination of capsules and ointment reported an itching of the skin. One further case of itching of the skin was reported by a patient administered with capsules. These cases were all prescribed from one doctor and was fully reversible. The therapy was not interrupted.

The therapy was interrupted in two cases. After three days of therapy with Notakehl drops for oral intake the therapy was discontinued with a 3 year old girl due to ineffectiveness. The same applied with a 7 year old boy whereby the therapy with Notakehl drops for oral intake was discontinued after four days for the same reason.

In total, no extreme dominant reactions appeared. All those side effects reported were completely reversible.

6 Summary

From July 1993 to October 1999 a total of 127 patients were tested by 10 Doctors practices (6 General Practitioners, 3 Internists and 1 Ear, Nose and Throat Specialist) in an observation study with the application of the preparation series Notakehl in the following administration forms: capsules, tablets, drops, suppositories, ointment and solution for injection.

The age of the patients varied between 4 months and 72 years. Almost half of the patients were under 12 years of age. Notakehl was applied according to isopathy in a very broad area of application, whereby the preferred use was dependent on the age of the patients. In the younger patient groups under 12 years, Notakehl was mainly applied with occurences such as bronchitis, rhinitis, angina and otitis media. In the over 12 age group diseases such as candidosis, HWS and LWS syndrome were predominant. Accompanying therapies were to be documented in the survey form.

The duration of the therapy for children (>12 years) was on average 88.6 ± 145..8 days, around twice as long as with the children (<12 years) of 46.3 ± 88.3 days.

Progress of the treatment was in each case determined at the beginning and end of the therapy.

83.1% of the patients and 85.4% of the doctors described the effects of the treatment as „very good“ and „good“. Tolerance was classified by 99.2% of the patients and doctors each with „very good“ and „good“. Two cases were discontinued due to ineffectiveness, both after 3 and 4 days respectively of therapy start. No serious side effects were observed. Side effects and intolerance was documented and these were mostly all without additional therapy and completely reversible. A connection with the Notakehl therapy could only be made in 1 case where irritation at the point of needle insertion and 4 cases where itching of the skin occurred. Tolerance and effectiveness in the under 12 age group was substantially more positively judged as with the over 12 age group.

Werdorf 16 February 2001

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