

Clinical and Biologic outcomes following the administration of Hydroxyurea to homozygote sickle cell patients in two health facilities of Yaounde.

ABSTRACT

Sickle cell disease is the most frequent genetic disease worldwide with high mortality and morbidity rates. Several therapeutic medications have been put in place amongst which hydroxyurea, an antineoplastic for which the clinical-biologic benefits for the patients have been established in several countries. However in our country few studies have been done on the benefits of this drug.

Our objectives were to determine the clinical and biologic responses upon the administration of hydroxyurea to sickle cell patients followed up at the Yaounde Central Hospital and the Frantz Fanon medical foundation.

We carried out a descriptive cross sectional study with retrospective and prospective components from January 2017 to June 2017. All homozygote sickle cell patients were included in this study (children and adults).

We enrolled 40 patients. The median age was 22 years with extremes of 4 and 50 years. We found a good clinical response marked by a significant reduction by 68% of the number of vaso occlusive crises (VOC) per year. We also found a good biologic response through a statistically significant increase of 7.35% in the level of hemoglobin F (Hb F). However several patients (40%) had poor compliant to the treatment.

Keywords: Hydroxyurea, sickle cell disease, outcome, clinical, biologic, Yaounde.

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26 INTRODUCTION

27 Sickle cell disease also known as sickle cell anemia is a hemoglobinopathy
28 in which hydrophilic glutamic acid is replaced by hydrophobic valin at position 6
29 on the beta globin chain. This leads to modifications in the electrophoretic
30 properties of hemoglobin (1).

31 It the most frequent genetic disorder in the whole world and particularly
32 from people with African origin(2). According to the World Health
33 Organization (WHO) in 2014 there were about 70-120 million careers of the
34 sickle cell trait in the world: we notice a 312 000 annual births of sickle cell
35 patients with 200 000 in Sub Saharan Africa (3) where the strategy of
36 management in order to reduce the morbidity and mortality is not within
37 reach. This is the reason why this figure will rise to 400 0000 by 2025(4).In
38 Cameroon according to *Beyeme et al* in 2004, the frequency of the S trait was
39 22.3%, the frequency of homozytote SS was 1.7% according to regions of the
40 country (5). This is indeed a public health problem which necessitates a
41 multidisciplinary approach.

42
43 The management of this disorder has highly evolved with years. It seems
44 to be that several factors: genetic and environmental influences the
45 physiopathology of the disease. It is these factors that current treatments tend
46 to ameliorate. Thus the treatment of sickle cell disease is not just symptomatic;
47 it is oriented towards fundamental treatment of its complications (6). New
48 therapeutic medications have been put in place especially bone marrow
49 transplants and administration of hydroxyurea.

50 Hydroxyurea (hydroxycarbamide) is a chemotherapeutic drug synthesized
51 for the first time in 1869 for the reduction of the abnormally high white blood
52 cells in patients with myeloproliferative disorders (7). Its efficacy in the

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53 treatment of homozygote sickle cell disease in adults as well as children is
54 known since 1995.

55 Several studies have been carried out in the whole world in order to
56 evaluate the efficacy of hydroxyurea on sickle cell patients. These studies found
57 an improvement in the phenotype of the disease (8,9,10), a reduction of the
58 mortality (11,12,13,14). Hydroxurea is not often used in Africa because it is not
59 accessible (cost, not available in pharmacies), reluctance of health personnel
60 and some parents because of side effects (infertility), meanwhile the clinical
61 and biologic benefits of this drug in severe cases of sickle cell disease have
62 been proven in Africa and Europe.

63 In Cameroon very few studies have been done, those studies carried out
64 does not include pediatric patients. In 2014, *Hassanatou et al* (15) evaluated
65 the efficacy of hydroxyurea in children within 1 year at the Chantal Biya
66 Foundation. They found a clinical and biologic improvement. The introduction
67 of hydroxyurea in the management of sickle cell disease is of recent at the
68 Yaounde Central Hospital but is already a routine at the Frantz Fanon Medical
69 Foundation since 10 years.

70 We proposed in this study to evaluate the clinical and biologic outcomes
71 of sickle cell patients (children and adults) in the short and long term who are
72 taking hydroxyurea.

73

74 METHODOLOGY

75 We carried out a descriptive study with prospective and retrospective
76 components within a 6 months period (January to June 2017). The study site
77 was the hematology service of the Yaounde Central Hospital and the Frantz
78 Fanon Medical foundation of Yaounde.

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79 We enrolled all sickle cell patients without distinction of race or sex that
80 we received at the outpatient consultation and those that were admitted and
81 we treated them with hydroxyurea.

82 We included in our study:

- 83 ❖ Homozygote sickle cell patients
- 84 ❖ Homozygote sickle cell patients treated with hydroxyurea for at
85 least 3 months

86 Were not included in our study:

- 87 ❖ Patients receiving other treatments for sickle cell disease besides folic
88 acid and antibioprophylaxy
- 89 ❖ Patients on vasodilators
- 90 ❖ Patients who refused to participate

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91 We did a consecutive sampling and considered our sample size at the end of
92 sampling. In both the retrospective and prospective components of this study,
93 prior to initiation of HU therapy we collected clinical and biologic information.
94 We entered the information collected in data entry forms and hospital
95 registers.

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96 The retrospective aspect of this study concerned sickle cell patients
97 seen at consultation or admitted or volunteers who were receiving
98 hydroxyurea(HU).

99 The prospective component concerned patients who were freshly put
100 on HU and who had the following criteria for initiation of HU:

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- 101 ▪ High frequency of severe Vaso Occlusive Crises(VOC) or those with
102 at least 3 hospitalizations within 1 year
- 103 ▪ More than 3 blood transfusions for severe anemia within one year
- 104 ▪ At least 2 Acute chest syndrome per year

- Past history of cerebrovascular accident or at risk of a cerebrovascular accident
- Chronic leg ulcer
- Past history of priapism
- Organ failure: heart, lung
- Connective tissue disorder (rheumatoid polyarthritits, systemic lupus)
- Patient aged more than 50.

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We used CSPRO version 6.0 to enter our data and analyzed them with the IBM SPSS software version 23.0

Our results were expressed as frequencies for qualitative variables, means and standard deviations for quantitative variables with a symmetric distribution and medians and quartiles for non-symmetric distributions.

The means were compared with the Student T test and qualitative variables were compared with the Mc Nemar-Bowker test. A $p < 0,05$ was considered to be statistically significant.

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RESULTS

In total, 40 patients were enrolled amongst which 17(42.5%) at the Central Hospital of Yaounde (CHY) and 23(57.5%) at the Frantz Fanon Medical Foundation. The most represented age range was the [10-20] year age group (47,5%).The age of the patients varied from 4 to 50 years with mean of 20,30 ± 10,13 years. We had 22 women (55%) and 18 men (45%) with sex ratio of 1.2 in favor of women. The most represented level of education was the secondary level (35%), then the high level (32.5%). Most of the patients were unemployed (52.5%).Their monthly wages were <100.000 in 50% of cases. Most of the patients had no health insurance (77.5%). Most of the patients originated from

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132 the Center region (45%) and the West region (27.5%).90% of the patients were
133 diagnosed sickle cell before the age of 5; this corresponds to the age of
134 replacement of Fetal Hemoglobin (HbF) by adult hemoglobin. However 3
135 patients (7.5%) were diagnosed after 10 years of age. Before initiating
136 treatment, 27(67.5%) patients affirmed that they were undergoing regular
137 medical followups. After initiating treatment, 39 (97.5%) patients regularly
138 came for consultation. Before initiating treatment, 38 patients(97.5%) were
139 receiving folic acid and after initiation of treatment just one was not taking it.
140 Antibioprophylaxy was used by children aged less than 12 years old. One
141 patient was receiving morphine for a long period for pains. By the end of 6
142 months of treatment, the intensity of his pain had subsided at the point that he
143 did not have to take morphine to calm the pains. Eight patients had brothers or
144 sisters who were sicklers and who were also receiving HU.Three patients
145 voluntarily decided to take HU. The duration of treatment varied from 3 to 168
146 months, with a median of 12 months.40% of patients were treated on a short
147 term (3 to 8 months) and 60% of patients in the long term (more than 8
148 months).

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150 There was a marked reduction of the frequency of crises (from 10.83 to
151 4.31 crises/year); in the duration (4.33 to 2 days) and the intensity (8.2 to
152 5.63/10) of the vaso occlusive crises (VOC); a significant decrease in the
153 frequency (3.33 to 1.95) and the duration (6.97 to 4.80 days) of hospital
154 admissions. In contrast the reduction in the number of blood transfusions
155 (from 1.38 to 0.33) was not statistically significant ($p=0.120$) and in same light
156 as the quantity of blood received ($p=0.795$). There was no statistically
157 significant difference between the clinical response in the short term and the
158 long term as concerns the characteristics of VOC, hospital admissions and

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159 blood transfusions. The occurrence of complications has greatly reduced in
160 patients on treatment. The major acute complication was VOC. 67.5% of
161 patients had VOC before the onset of treatment and after 8 months of
162 treatment; just 50% of patients had VOC. Before the onset of treatment, 6
163 patients had VOC and after the onset of treatment, just one had a VOC. The
164 major chronic complication was leg ulcers that were present in 17.5% of
165 patients. All these leg ulcers were superficial ulcers. After 8 months of
166 treatment these complications disappeared in these patients.

167 The biologic response was marked in the short term by: a decrease in the
168 level of HbF (8.19 to 7.99%), an increase in hemoglobin level (7.38 to 8.03), an
169 increase in Mean Cell Volume (MCV) (88.63 to 88.81 fL), a reduction in the
170 number of leucocytes (14 037 to 11 298/mm³), a reduction in the number of
171 platelets (45 3570 to 44 1500/mm³). The biologic response was marked in the
172 long term by: an increase in HbF (8,19 to 15,54%), an increase in the Hb level
173 (from 7,38 to 8,57g/dL), an increase in MCV (de 88,63 to 94,17fL), a decrease in
174 the number of leucocytes (from 14037 to 10945/mm³), a decrease in the
175 number of platelets (453570 to 364966/mm³). The only statistically significant
176 difference between the biologic response in the long term and in the short
177 term was the variation in the HbF level of 8% with p<0,001. All the other
178 variations were not statistically significant.

179 40% of the patients were not taking their medication every day. 50% of
180 the patients were not taking their medication every day because of the lack of
181 finances and 37.5% because of consequences (fertility, anticancer). Most of the
182 patients did not have any side effects (26%). The blackening of fingers was the
183 most frequent side effect (17.5%).

184

185 DISCUSSIONS

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186 The sample size was 40 patients, more than that of d'Hassanatou et al.

187 [15] in Cameroon that was 30 patients, or of Mellouli in Tunisia [50] that was 27

188 sickle cell homozygotes or of Singh et al in India [48]. This difference can be

189 explained by the fact that we carried out a multi centered study. We found a

190 very low utilization of HU at the CHY (2%) as opposed to 43% found at the

191 Frantz Fanon Medical Foundation. The difference between these two values

192 can be explained by the fact that sicklers at the Frantz Fanon Medical

193 Foundation have been using HU since 10 years meanwhile at the CHY, the

194 introduction of HU in management of sicklers is of recent. The value got from

195 the CHY is different from the 13% obtained by Seungue et al [55] at the

196 Chantal Biya Foundation (CBF) of Yaounde in 2014. This can be explained by the

197 fact that the introduction of HU is recent at the CHY and sensitization of

198 patients is ongoing contrary to the Frantz Fanon Medical Center where it is

199 effective since 10 years. Ademola S et al in March 2017 [51] got a very low

200 percentage use of HU in sicklers in Nigeria. This similarity can be explained by

201 the fact that Nigeria and Cameroon are developing countries where the

202 inhabitants have low income meanwhile treatment with HU is relatively

203 expensive since all these studies were carried out in public hospitals.

204 The median age of our participants was 22 years with extremes of 4 and

205 50 years; this is different from the mean age of the population of Hafiz et al in

206 Yemen [47] that stood at 12 years with the extremes from 5 to 30 years; quite

207 similar to that of Singh et al in India [48] where it was 20 years. These

208 differences can be explained by the fact that Yemen has a more younger

209 population than Cameroon and India. In Cameroon, the median age of the

210 population is 19.4 years. We found a sex ratio of 1.2 in favor of the female sex;

211 contrary to the 1.3 ratio in favor of males that Hassanatou found. In our

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212 context, this finding is probably because of the higher proportion of the female
213 sex in the general population.

214

215 Our patients were treated for a mean period of 35 months with extremes

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216 from 3 to 168 months. Hafiz et al in Yemen [47] found patients who were

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217 treated for a mean period of 18 months ;with extremes of 3 to 48 months.

218 Ademola et al in Nigeria in 2017 [51] had in their series patients who were

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219 treated for a mean period of 26 months with extremes from 1 to 120 months.

220 Our patients were receiving an average dose of 20mg/Kg/dy just like in the

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221 study by Mellouli et al in Tunisia [50],or Hassanatou et al in Cameroun [15]

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222 that stood at 15 to 20mg/Kg/dy or even of singh et al in India that was at

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223 22mg/Kg/dy. This similarities can be explained by the fact that the mean

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224 dosage that induces clinical benefits is 20mg/kg/dy [35].The principal indication

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225 of HU in our study was the presence of more than 3 VOC per year with

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226 hospitalization, followed by increased level of blood transfusions. These results

227 are similar to those of Hassanatou [15] et al in Cameroon or of Mellouli et al in

228 Tunisia,and of Ademola et al in Nigéria [51] and in many other studies [10, 11,

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229 12, 14, 46].This similarity can be explained by the fact that VOC represents the

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230 most frequent manifestation of sickle cell disease. In our study the number of

231 VOC passed from 10.83 to 3.5 per year in the patients. This decrease is similar

232 to the series of Singh et al in which the mean number of crises went from

233 3.63 to 1.67 at the end of one year of treatment. Similarly a significant

234 reduction of the number of crises was observed in Gilmore et al in London

235 [56], in Hassanatou et al. [15] where the number of VOC went from 12 to 3 by

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236 the end of one year. This is because HU enhances the percentage of HbF and it

237 also increases the level of nitric oxide (NO).The increased HbF reduces the

238 polymerization of HbS and the NO produced, being a Powerful vasodilator

239 decreases the frequency of VOC. Our mean number of hospitalization went
240 from 3.33 to 0.88 per year. This is similar to the result obtained by Singh et al in
241 2017 [48], where the mean number of hospitalizations went from 4,75 to 2,25
242 per year. The duration of hospitalization went from 6,97 to 4,80 per year.

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243 Hassanatou et al. [15] found a decrease in the number of days of
244 hospitalizations from 9 to 2 days in the space of one year. The mean number of
245 blood transfusions passed from 1,38 to 0,33 per year. Hassanatou et al. [15]
246 found a decreased mean from 2.56 to 1 by the end of one year; similarly
247 Mellouli et al. in 2013 [50] found that their figure went from 1,6
248 transfusions/patient/year to 0,15 transfusion/patient/year.

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249 We observed a good clinical response in our patients; marked by a reduction in
250 VOC, a reduction in number of hospitalizations and a reduction in the number
251 of blood transfusions. This is because HU enhances the level of HbF which in
252 turn reduces HbS polymerization. Another reason is the production of NO by
253 endothelial cells and the modulation of the inflammatory process and having
254 an amelioration of the major sickle cell syndrome. We did not have a
255 statistically significant difference between patients in long term and those
256 treated in short term. This could be explained by the high percentage of non-
257 compliance. In fact the more the treatment duration increases the more it
258 becomes difficult to support especially in the financial aspect not forgetting
259 discouragements that could occur due to the fact of taking treatment for a long
260 period of time.

261 The level of mean HbF in our study went from 8.19 to 15.54% per year
262 thus a variation of 7.35%. Singh et al. [48] found a variation of 6,34% (from
263 12,83 to 19,17), Hassanatou [15] found 9% (from 12% to 21%), the *Multicenter*
264 *Study Of Hydroxyurea* in United States found 6% [9], Hafiz et al [47] got 4,7%
265 (from 10 to 14,7%), Mellouli et al. [50] had 27% (from 3 to 30%). These

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266 differences can be explained by the difference in duration of treatment or by
267 the genetic variability of populations because we worked in populations with
268 particular differences and the response to the administration of HU varied with
269 respect to genetic variations[38]. Elsewhere the variations we got in our study
270 was equal to those of other studies except that of Mellouli. This is explained by
271 the fact that the response to HU is independent on age [39] because
272 Hassanatou et al worked in a pediatric population and we carried out our study
273 in a mixed population; having children and adults. Singh et al, the *Multienter*
274 *Study of hydroxyurea*, and Hafiz et al all had similar populations.

275 We had an increase in Hb level from the base with a mean that went from 7,38
276 to 8,57g/dL, with variation of 1,19g/dL. This variation is comparable to that of
277 IkeOluwa et al in Nigeria in 2015 (1,18g/dL) [51] or that of Strouse et al in the
278 United States in 2008 (1g/dl) [45]. It is inferior to that of Hafiz et al [47]
279 (variation of 1,9g/dL), of Mellouli et al [50] (1,8g/dL) but superior to that of
280 Singh et al [48] (variation of 0,83g/dL).

281 These differences can be explained by the fact that several factors besides HU
282 influence the level of Hb for example nutrition, infections by *Plasmodium*
283 *falciparum* and the presence or absence of comorbid factors. A significant
284 decrease in the level of leucocytes and platelets was observed like in other
285 studies with means that went respectively from 14037 to 10945 and from
286 453570 to 364966. This decrease can be explained by the fact that HU provokes
287 a decrease in leucocytes via inhibition of ribonucleotide reductase and by
288 medullary cytotoxicity[33] and a decrease in the activation of platelets by
289 induction of NO synthesis[32]. HU provokes macrocytosis and this was verified
290 in our study. Infact the mean Mean Corpuscular Volume(MCV) went from
291 88,63 to 94fL, thus a variation of 5,37fL, comparable to the variation of 7,5fL
292 obtained by Hassanatou [15] et al or of 7,3fL obtained by Singh et al [48].

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293 Our patients had good compliance at 60% level, close to the level of
294 observance of Hassanatou [15] that was 57,5%. Nonetheless this value is
295 inferior to that of Mellouli et al [50] who got a level of compliance of 96.94%
296 but superior to that of Ademola et al. [51] in Nigeria (20%).The most frequent
297 cause of bad compliance was the lack of financial resources. Similar in the
298 series of Ademola et al in Nigeria. [51].In reality the box of treatment costs
299 5600 F CFA, made of 24 capsules. Patients have to take on average 2 per month
300 thus 11200 F everymonth; this is not affordable by all patients since 50% of
301 these patients had monthly revenues less than 100 000 FCFA. Tunisia is a
302 developed country and has enough financial resources to take care of health
303 issues of its population contrary to Nigeria and Cameroon which are both
304 developing countries and patients have to provide for their medical bills. No
305 patient had a lack of medication as found in the series of Hassanatou et al in
306 Cameroon [15] in 2014 where 57% of patients' lacked medications. This
307 illustrates the efforts that have been made by the Ministry of Public Health and
308 pharmacies to make available HU.

309 65% of patients had no side effects, compared to the series of Ademola et al in
310 Nigeria [51], where 83,3% did not have any side effect. This can be explained by
311 the absence of usage of high doses. Infact we did not have in our series
312 patients with dosage above 25mg/kg/dy since the toxicity of HU is high above
313 35mg/kg/jr [35].

314

315

316 CONCLUSION

317 This study has demonstrated the efficacy of HU therapy in reducing Sickle
318 cell diseases complications with few side effects; we thus recommend its use in
319 Sickle cell disease patients in African countries. We also found:

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320 A good clinical response marked by statistically significant decrease of 68%
321 in the number of VOC per year;

322 A good biologic response marked by a statistically significant increase of
323 7.35% on level of HbF.

324 Many patients (40%) had a bad compliance to treatment

325

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TABLES

Table I : Distribution of patients with respect to level of education, profession, monthly income, matrimonial status and region of origin

Variables	Number (N=40)	Percentage (%)
Level of education		
Non	1	2,5
Primary	12	30,0
Secondary	14	35,0
High	13	32,5
Profession		
Un employed	21	52,5
Private sector	19	47,5
Monthly income		
<100000	20	50,0
>100000	7	17,5
Matrimonial status		
Single	31	77,5
Married	9	22,5
Medical insurance		
Yes	9	22,5
No	31	77,5
Region of origine		
Centre	18	45,0
West	11	27,5
Other*	11	27,5

Table II: Distribution of patients with respect to characteristics of VOC, hospitalizations and blood transfusions in the short term and after initiation of treatment

TOTAL : N=40			
caractéristiques	Before (n=40) Mean ± SD	HU After HU (n=16) Mean ± SD	p value
VOC			
Frequency	10,83±8,02	4,31± 4,95	0,019
Duration	4,33±1,99	2,0±1,41	0,005
Intensity	8,2±0,88	5,6±1,99	<0,001
Hospitalisations			
Frequency	3,33±2,14	1,95±0,94	0,018
Duration	6,97±2,69	4,80±3,75	0,029
Blood transfusion			
Frequency	1,38±1,55	0,44±1,09	0,120
Quantity	928,57±522	1333,33±577,35	0,795

Intensity/ 10 at NE= Nominal scale frequency per year, Duration in days,quantity in Millilitres,

Table III: Characteristics of VOC, hospitalizations and blood transfusions before initiation of treatment and in the long term after the initiation of treatment.

TOTAL : N=40

Variables	Before HU (n=40) Mean ± SD	After HU (n=24) Mean ± SD	p value
VOC			
Number	10,83±8,02	3,5±2,64	<0,001
Duration	4,33±1,99	2,08±0,83	<0,001
Intensity	8,2±0,88	5,63±1,41	<0,001
Hospitalisations			
Number	3,33±2,14	0,88±0,85	<0,001
Duration	6,97±2,69	5,09±1,81	<0,001
Blood transfusion			

	Number	1,38±1,55	0,33±0,70	<0,001
	Quantity	928,57±522	900±223,61	<0,001

438 Intensity/ 10 at NE= Nominal scale frequency per year, Duration in days,
439 quantity in Milliliters,

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