Effects of doxycycline in patients with acute cough and purulent sputum: a double blind placebo controlled trial

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SUMMARY

Background. *Acute cough with purulent sputum is a common complaint presented to general practitioners.*

Aim. *A randomized, double blind, placebo controlled clinical trial was undertaken to determine the efficacy of doxycycline in persons aged 18 years and over presenting to 22 general practices in the Netherlands with acute cough and purulent sputum.*

Method. *Patients were excluded if they were pregnant, had an allergy or intolerance to tetracyclines, had severe dyspnoea and fine crackles on auscultation, purulent rhinitis together with maxillary tenderness, chronic airways disease, or had taken antibiotics in the previous two weeks. Patients entered in to the study were given oral doxycycline for 10 days, 200 mg on the first day, followed by 100 mg on the next nine days, or placebo.*

Results. *Duration of frequent daytime cough after entry was a mean of 1.5 days shorter in the group of 71 patients receiving doxycycline than in the group of 69 patients on placebo (4.7 days versus 6.2 days, respectively). In patients aged 55 years and over the mean duration of frequent daytime cough after entry was 4.1 days shorter in the group taking doxycycline than in the placebo group. Patients with a very frequent cough and who also felt ill at entry regained their normal daily activities 2.1 days earlier when using doxycycline than the control group.*

Conclusion. *Doxycycline has small beneficial effects in patients with acute cough and purulent sputum. These beneficial effects are more prominent, and probably clinically relevant, in patients aged 55 years and over and in patients who cough very frequently and who also feel ill.*

Keywords: anti-infective agents; respiratory tract infections; cough; sputum; clinical trials in general practice.

Introduction

ACUTE cough with purulent sputum is a regularly encountered complaint in general practice. Lamberts and colleagues found an incidence of cough of 130 per 1000 patients per year and in 67% of these encounters patients also complained of purulent sputum.[1] When an otherwise healthy patient presents with an acute cough and purulent sputum, more than half of general practitioners will prescribe an antibiotic.[2,3] Whether this policy is the right one is doubtful. Results of trials done in general practice were not conclusive;[4-9] patients with an acute productive cough got better, whether they were receiving antibiotic treatment or placebo. In two studies statistically significant differences in effect were found, but whether these differences were of clinical relevance was not clear.[6,9]

A study was undertaken to assess the effects of a 10 day course of doxycycline in otherwise healthy persons with acute cough and purulent sputum. Doxycycline was chosen because, together with amoxycillin, it is the antibiotic drug of preference in patients with a cough in Dutch general practice.[10] Most of the common bacterial pathogens in lower airway infections seen by general practitioners will be susceptible to doxycycline.[11]

Method

Twenty eight general practitioners in 22 practices participated in the study. Nine practices were located in a city, eight in a small town and five in a village. All participating doctors and their staff were instructed in detail about the protocol by T V.

Patients were included if they met all of the following criteria: coughed purulent sputum; aged 18 years and over; had not had antibiotics in previous two weeks; not allergic to tetracyclines; not pregnant; and not suffering from sinusitis (defined as rhinitis with purulent mucus and maxillary tenderness), pneumonia (defined as severe dyspnoea and fine crackles on auscultation), or chronic airways disease; and did not have impaired resistance against infections.

The pharmacy at Leiden University Hospital prepared 220 drug packages, 110 containing 11 tablets of 100 mg doxycycline and 110 containing 11 placebo tablets. Placebo packages and doxycycline packages were put in randomly permuted blocks of four packages, each block containing two placebo and two doxycycline packages. Each package was numbered. Each practice was initially given two blocks of four packages. Each new patient was assigned to the package with the lowest number. The procedure was blinded for both general practitioner and patient. The randomization list was kept by a pharmacist at Leiden University Hospital.

Thus doxycycline 100 mg, two tablets on day one and one tablet on each of the following nine days or a placebo was allocated at random and double blind to each of the subjects. The only additional medication general practitioners were allowed to prescribe during the trial were 15 ml of promethazine hydrochloride solution before bedtime and paracetamol 500 mg, three tablets a day if necessary.

Informed consent was to be obtained from the patient. The study design had been approved by the medical ethics committee at Leiden University Hospital.

At entry the general practitioner recorded frequency of cough during the day and at night, frequency of productive cough, extent of patient reporting or looking ill, and presence of auscultatory abnormalities. The patient was then instructed to keep a diary for the next 10 days and to return to the practice on day 11. Frequency of cough during the day and night, frequency of productive cough, extent of feeling ill, possible drug side effects and impairment of daily activities were recorded in the diary. General

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practitioners recorded patients' signs and symptoms again on day 11 and stated whether they thought the clinical condition of the patient had improved or not. Both general practitioner and patient recorded signs and symptoms on five-point scales, except in scoring adverse events, where yes/no questions were used. Items scored on five-point scales were afterwards dichotomized. Frequent cough meant that the patient coughed several times throughout the day, very frequent cough meant that the patient coughed several times during each hour of the day. Notes were reviewed three months later to assess persistence or recurrence of complaints.

Progress of the trial was monitored weekly. Patients were included during two winter periods, from December 1989 through to April 1990 and from October 1990 through to May 1991. Practices were allowed to stop participation temporarily during holiday periods. The general practitioners also recorded information on patients who met the inclusion criteria but were not entered in the study. Patient compliance with recording symptoms and taking treatment was assessed by the general practitioner's secretary who telephoned patients three days after entry; the number of tablets in packages returned by patients at day 11 was also counted.

Data analysis

Choosing $\alpha = 0.05$, $\beta = 0.10$ and a minimal relevant difference of two days duration of coughing complaints (with a standard deviation within each group of three days, as was found by Stott and West[5]), it was estimated that a minimum of 76 subjects would need to be included in both the placebo and the doxycycline group.

Differences between dichotomous variables were tested by chi square tests, differences between continuous variables by student *t*-tests for independent samples and Mann Whitney *U* tests. Since the student *t*-tests and Mann Whitney approaches gave virtually identical results, means and 95% confidence intervals of differences in means are presented. For the main outcome variables the effects of several co-variables (for example, age) were studied in a multiple regression analysis. The co-variables that showed a significant increase in R^2 values were considered as prognostic relevant factors.[12] No formal correction was applied for multiple testing. In the results, however, a distinction is made between *P* values below 0.05 and below 0.01 and in the discussion major attention is given to results with $P<0.01$.

Results

A total of 158 patients were included (minimum per practice two, maximum 22), a mean of 1.3 per practice per month. There were no significant differences in characteristics between the patients enrolled by the 28 general practitioners. Apart from the 158 included patients, 51 patients qualified for the trial but did not enter the study. Sixteen patients refused because they wanted an antibiotic, seven because they did not want an antibiotic, four patients refused because they did not wish to participate in a double blind study, and 17 patients did not give their consent because of social circumstances. Four patients were not included because the general practitioner forgot to enter them, or because of lack of time during the consultations. Three patients were not entered because the general practitioner thought an antibiotic was indicated for other reasons. The 51 patients who were not included did not differ significantly from the 158 included patients with regard to sex, age and main symptoms.

Of the 158 patients included, 18 patients (11 placebo, seven doxycycline) did not complete the 10 day treatment. The reasons for withdrawal were: clinical condition worsened (two placebo patients), adverse events (three doxycycline patients), social circumstances (two placebo), quick recovery (three placebo, three doxycycline), and unknown (four placebo, one doxycycline). Except that the mean age of the 18 withdrawals was nine years younger, there were no relevant nor statistically significant differences between the 140 patients who completed the study and those who did not.

Of the 140 patients who completed the trial, 69 received placebo (mean age 41 years, standard deviation 16 years) and 71 doxycycline (mean age 40 years, standard deviation 15 years). The characteristics of the patients at entry to the study as recorded by the general practitioner, are shown in Table 1. Forty four subjects had auscultatory abnormalities: rhonchi or coarse crackles, 11 placebo and 13 doxycycline; wheezes, six placebo and four doxycycline; and other, seven placebo and three doxycycline. There were significantly more subjects feeling ill at entry in to the study in the doxycycline group than there were in the placebo group. In the doxycycline group the mean number of days with productive cough before entry (eight) was two days shorter than in the placebo group (10 days). Although not statistically significant, this difference could be important because the minimum relevant difference in outcome was set at two days.

To estimate the validity of records used in the study the agreement between doctors' records and those of patients were studied. The agreement for coughing complaints during the day at entry to the study was 120/139, 86% (kappa = 0.73), for coughing at night 103/135, 76% (kappa = 0.52) and for feeling ill 123/140, 88% (kappa = 0.74).

Promethazine hydrochloride solution was prescribed for six patients in the placebo group and 12 patients in the doxycycline group. Comparing the 18 patients having promethazine with the 122 who did not revealed no difference in coughing at night. Paracetamol was prescribed to four patients in the placebo group and two in the doxycycline group.

Immediately after the 10 days treatment doctors reported 18% fewer patients with frequent daytime cough and 16% fewer patients feeling ill in the doxycycline group compared with the placebo group (Table 2). No other significant differences were found.

A best–worst case analysis of all 158 subjects including the 18 not completing the study was performed, according to whether the patients' clinical condition had improved or not. Of the 13 patients who withdrew whose outcome was known the three subjects with adverse events, the two subjects who stopped because of social circumstances and the two patients whose worsening

Table 1. Characteristics of patients at entry to the study, as recorded by the general practitioner.[a]

Characteristic	% of patients receiving	
	Doxycycline (*n* = 71)	Placebo (*n* = 69)
Men	*42*	*42*
Smoker	*53*[b]	*52*[c]
Frequent cough:		
Day time	*94*	*91*[b]
Night time	*65*[c]	*60*[c]
Productive	*82*	*78*[b]
Feeling ill	*90*	*77**
Looking ill	*70*	*65*
Auscultatory abnormalities	*28*	*35*[b]
Temperature >37.9 °C	*7*[b]	*7*
Daily activities impaired	*38*	*38*

n = number of patients in group. [a]Temperature measured by GP or patient; activities of daily living impairment reported by patient. [b]Data missing for one patient. [c]Data missing for two patients. Chi square: **P*<0.05.

Table 2. Signs and symptoms of patients on day 11, as recorded by the general practitioner.

	% of patients receiving		
	Doxycycline (*n* = 71)	Placebo (*n* = 69)	Difference (95 CI)
Frequent cough:			
Day time	21[a]	39[b]	18 (2 to 33)*
Night time	12[b]	11[c]	−1 (−12 to 10)
Productive	19[b]	21[b]	2 (−11 to 16)
Feeling ill	19[a]	35[a]	16 (2 to 31)*
Looking ill	14[a]	22[a]	8 (−5 to 21)
Auscultatory abnormalities	7[a]	12[b]	5 (−5 to 15)
Clinical condition improved	87[a]	78[b]	−9 (−22 to 3)

n = number of patients in group. CI = confidence interval. Data missing for: [a]one patient; [b]two patients; [c]three patients. Chi square: *$P<0.05$.

clinical condition made them stop were classified as 'condition not improved'. The six patients who stopped because of quick recovery were classified as 'condition improved'. Of the five who withdrew and whose outcome was unknown (four receiving placebo and one doxycycline), the four subjects who received placebo were first classified as 'condition improved' and the subject with doxycycline as 'condition not improved' (worst case analysis), and then the other way around (best case analysis). In both worst case and best case analyses, trends of more clinical improvement in the doxycycline group were found, similar to the results of the 140 patients on the variable 'clinical condition improved' on Table 2.

The daily records of the 140 patients who completed the trial showed significant differences in effect between placebo and doxycycline in some variables. After four to five days there were fewer patients reporting frequent daytime cough and impairment of daily activities in the doxycycline group than in the placebo group (Table 3). According to patients' records there were only small differences by day 10.

Patients who received doxycycline recorded that their cough resolved a mean of 1.5 days earlier than patients in the placebo group (Table 4). The mean duration of productive cough including the period before entry, and duration of feeling ill were also shorter in the doxycycline group, but here differences with placebo were not significant. Although there were clear differences in impairment of daily activities between the two groups on days five and six (Table 3), the mean duration of impairment of daily activities appeared not to be significantly shorter in the doxycycline group than in the placebo group (Table 4).

Table 3. Patients with frequent day time cough and reporting impaired daily activities during treatment.

	% of patients reporting			
	Frequent day time cough		Impaired daily activities	
Day of treatment	Doxycycline (*n* = 71)	Placebo (*n* = 69)	Doxycycline (*n* = 71)	Placebo (*n* = 69)
1	87	90	38	38
2	84[b]	88	33[a]	35
3	71[a]	77	27	29
4	51[a]	78**	16[b]	29
5	52	72*	9[c]	28**[a]
6	34[a]	53**[a]	7[b]	25**[a]
7	30[a]	50**[a]	7[b]	21*[c]
8	23	49**[a]	7[d]	16[b]
9	23	38[a]	8[e]	13[a]
10	21[d]	30[c]	9[d]	14[d]

n = number of patients in group. Data missing for: [a]one patient; [b]two patients; [c]three patients; [d]four patients; [e]seven patients. Chi square: *$P<0.05$, **$P<0.01$.

Table 4. Duration of complaints, as recorded by patients.

	Mean no. (SD) of days recorded by patients on		
	Doxycycline (*n* = 71)	Placebo (*n* = 69)	Difference (95 CI)
Frequent cough:			
Day time	4.7 (3.1)	6.2 (3.2)	1.5 (0.4 to 2.6)**
Night time	1.9 (2.7)	2.2 (2.7)	0.3 (−0.6 to 1.2)
Productive	2.8 (2.4)	3.3 (3.0)	0.5 (−0.4 to 1.4)
Productive including entry period	11.2 (7.6)	12.7 (11.6)	1.5 (−1.8 to 4.8)
Feeling ill	4.3 (3.0)	5.1 (3.5)	0.8 (−0.3 to 1.9)
Daily activities impaired	1.6 (2.4)	2.5 (3.3)	0.9 (−0.1 to 1.9)

n = number of patients in group. SD = standard deviation. CI = confidence interval. *t*-test: **$P<0.01$.

After multiple regression, age and very frequent cough combined with feeling ill at entry appeared to be prognostic factors for beneficial effects of doxycycline. Other variables such as smoking habits, presence of chest signs, time of entry in the study or duration of complaints before entry did not show a significant increase in R^2 values in stepwise multiple regression. Comparing differences in effect between placebo and doxycycline for different age groups, the effect of doxycycline showed clinically relevant differences in patients aged 55 years and over. Among patients aged 55 years and over, those who received placebo recorded a cough that lasted a mean of 4.1 days longer than those who received doxycycline, and recorded a mean of 2.8 extra days during which they felt ill (Table 5). There were no significant differences between those receiving placebo and doxycycline in the under 55 years age group. In patients who coughed very frequently (several times every hour of the day) and also felt ill at entry, differences between effect of placebo and doxycycline were also prominent, especially in terms of impairment of daily activities (Table 5). There were no significant differences between the placebo and doxycycline group in those who did not feel ill and who had a very frequent cough.

Adverse events were reported by 15 of the 78 subjects in the doxycycline group. Three patients stopped taking their medication because of an adverse effect — two because of nausea and one because of vague complaints attributed by the patient to doxycycline. Eleven other patients reported mild gastrointestinal complaints during treatment and one patient had a mild rash for five days. In the placebo group seven reported gastrointestinal complaints and two others a mild rash.

Follow up after three months showed that 11% of those who received doxycycline and 13% of those who used placebo, had seen their general practitioner again because of respiratory complaints (difference not statistically significant).

Discussion

This study shows doxycycline to have small beneficial effects on patients with an acute cough and purulent sputum. These beneficial effects were more prominent in patients over 54 years of age, and in those who coughed very frequently and felt ill at entry. When drawing conclusions from these findings, the following points should be taken into account.

Table 5. Outcome among those aged 55 years and over; and among those with very frequent cough who also felt ill.

	Patients aged 55+ years on		Difference (95% CI)	Patients with very frequent cough feeling ill on		
	Doxycycline (*n* = 12)	Placebo (*n* = 15)		Doxycycline (*n* = 43)	Placebo (*n* = 34)	Difference (95% CI)
Mean no. of days:						
Frequent daytime cough[a]	2.4	6.5	4.1 (1.6 to 6.6)**	5.3	6.9	1.9 (0.2 to 3.0)*
Feeling ill[a]	2.1	4.9	2.8 (0.5 to 5.1)*	4.9	6.5	1.6 (0.2 to 3.0)*
Daily activities impaired[a]	0.5	1.9	1.4 (–0.9 to 3.7)	1.6	3.7	2.1 (0.7 to 3.5)**
% of pts at day 11:						
With frequent daytime cough[b]	*8*	*53*	*45 (15 to 75)**	*24*[c]	*48*[c]	*25 (3 to 46)**
Clinically improved[b]	*100*	*67*	*–33 (–57 to 10)*	*90*[c]	*85*[c]	*–6 (–21 to 10)*

n = number of patients in group. CI = confidence interval. [a]Reported by patients. [b]Recorded by GP. [c]Data missing for one patient. *t*-test or chi square: *$P<0.05$, **$P<0.01$.

In this study x-rays and bacterial examination of sputum in order to get more information about the cause of the patients' complaints were not performed, because the usefulness of these tests in general practice is doubtful.[13-15] The method used in this study to assess patients' signs and symptoms was consistent with standard clinical practice in general practice. Finding considerable agreement between general practitioner and patient records on the same items, it was concluded that reliability of outcome measurements in this trial was acceptable. The number of patients with an unknown outcome was low, and best–worse case analysis showed that patients who withdrew did not bias the results. Baseline characteristics of the 158 patients were similar to those in other studies.[6,7,9] At entry there were only small differences between the doxycycline group and the placebo group; adjustment for those differences did not alter outcome results.

Patients who received doxycycline had slightly better results compared with placebo in all outcome variables, but differences were only clearly significant on days four to seven of the treatment for day time cough and impairment of daily activities. These results are in accordance with findings of previous studies reporting small differences in favour of antibiotic treatment.[6,9] Interestingly, Dunlay and colleagues saw most beneficial effects of antibiotic treatment from days eight to 10, consequently they suggested that treatment should last more than seven days. However, the results presented here suggest that, when an antibiotic is thought necessary, seven days of treatment is probably sufficient. Stott and West did not see differences in effect between doxycycline and placebo in 207 patients who had purulent sputum.[5] However, comparison with the present trial is difficult because of the use of different inclusion criteria.

The results show that effects of doxycycline were more prominent in patients aged over 54 years. Possibly this could be explained by a higher incidence of bacterial infections of the lower respiratory tract among elderly people, as found by Macfarlane and colleagues.[16] In a previous survey among 800 Dutch general practitioners, respondents were more inclined to give antibiotic treatment to elderly patients with coughing complaints, than to younger patients with the same symptoms.[2] The results further suggest that doxycycline had more prominent effects in patients who coughed very frequently and who also felt ill. In previous trials no subgroups were found who had more benefit from antibiotic treatment; this could be explained by the low numbers of subjects and/or use of different inclusion criteria in those studies.

Before drawing conclusions about doxycycline prescription in patients with purulent sputum, several other possible effects of doxycycline should be considered. This trial showed that adverse events did not occur often and were mostly mild. The rate of recurrent respiratory complaints, found in both groups, did not suggest either treatment or not with doxycycline. However, increasing resistance of bacteria against antibiotics including doxycycline in regions with a high prescription rate should be an incentive for refraining from antibiotic treatment if possible.[17]

We conclude that antibiotics have no clinically relevant effect in all patients who have an acute cough with purulent sputum. In patients aged over 54 years and in patients who cough frequently throughout the day and who also feel ill, the advantages of antibiotic treatment might outweigh the disadvantages. If antibiotic treatment is indicated, a seven day course seems sufficient. More research should be done in this field to confirm the findings.

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