Print ISSN: 2319-2003 | Online ISSN: 2279-0780

IJBCP International Journal of Basic & Clinical Pharmacology

DOI: http://dx.doi.org/10.18203/2319-2003.ijbcp20174776

Original Research Article

Pharmacokinetic study of rational regimen of oral clindamycin in comparison with doxycycline in mild cases of acne vulgaris

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Received: 22 August 2017
Accepted: 21 September 2017

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ABSTRACT

Background: Acne vulgaris is a chronic inflammatory disease of pilosebaceous units. It is a common skin disorder affecting both boys and girls in the adolescent age group and also extends into the post adolescent age group. From time immemorial, various remedies have been suggested and followed by Ayurvedic, Siddha, Unani practitioners and native healers present in various parts of the world. In this study an attempt has been made to evaluate the efficacy of a low dose oral Clindamycin in Acne vulgaris and the results of the study have been presented in ensuing chapters.
Methods: The Prospective, Randomized Controlled, Single blind study was conducted in Out Patient Section, Department of Dermatology, tertiary care teaching hospital September 2016 to May 2017 for Total six weeks. Drug administration - four weeks. Follow up - two weeks mostly drug used Capsule Clindamycin 50mg. Capsule Doxycycline 100 mg. Benzoyl Peroxide 5% topical cream.
Results: The objective of the study is not only to find out the efficacy of a low dose of 50 mg Clindamycin given orally, but also to find out if this efficacy is obtained without producing the adverse effects for which the administration of Clindamycin is hesitated the ant-microbial, Cap. Doxycycline and Cap. Clindamycin act in acne vulgaris by their effect on the Propionibacterium acne. These antibiotics decrease the population of Propionibacterium acne which in turn leads to the inhibition of the bacterial lipases and this is followed by a decrease in concentration of free fatty acids. This produces less tissue inflammation and acne.
Conclusions: This study proves the safety and efficacy of low dose of oral Clindamycin in acne vulgaris, and such low doses can also be tried for other infections where the causative organism responds to Clindamycin.

Keywords: Acne vulgaris, Clindamycin/doxycycline, Topical benzoyl peroxide

INTRODUCTION

Acne vulgaris is a chronic inflammatory disease of pilosebaceous units. It is a common skin disorder affecting both boys and girls in the adolescent age group and also extends into the post adolescent age group. Commonly it is due to formation of obstructing horny plugs in hair follicles, resulting in inflammation around the hair follicles, causing tissue destruction and scar formation. This problem is present universally and affects people of all socio-economic groups. With the improvement in the living status, awareness about acne is more among the affected age group causing psychological problems too.[1] From time immemorial, various remedies have been

suggested and followed by Ayurvedic, Siddha, Unani practitioners and native healers present in various parts of the world. The scientific evidence of improvement has not been documented yet. Modern medicine also prescribes various drugs, which have been found to be useful in controlling this disorder. All of them have been found to be useful to various extents. Topical drug therapy has been the mainstay and some drugs, for example, tetracycline is given orally.[1,2] Since the condition results in scar formation and disfigurement in young boys and girls, it is associated with psychological problems causing great distress.[3] In this study, an attempt has been made to evaluate the efficacy of a low dose oral Clindamycin in Acne vulgaris and the results of the study have been presented in ensuing chapters.

METHODS

The prospective, randomized controlled, single blind study was conducted in Out Patient Section, Department of Dermatology, tertiary care teaching hospital September 2016 to May 2017 for total six weeks. Drug administration - four weeks. Follow up - two weeks mostly drug used Capsule Clindamycin 50mg. Capsule doxycycline 100mg. Benzoyl Peroxide 5% topical cream. Drug was obtained from Capsule Clindamycin, supplied by Indi pharma, Ponda, Goa. Capsule Doxycycline routinely available in the dispensary of tertiary care hospital. When the study was planned, it was first proposed to evaluate the safety and efficacy of oral Clindamycine with oral doxycycline. This study in addition to giving information about the safety and efficacy of oral clindamycin used in low doses, and also give valuable information about the efficacy rate in combination with topical benzoyl peroxide. The Study was started after getting the approval from institutional ethical committee.

Patients were included only after obtaining the informed written consent. In patients who were less than 18 years old, the consent was obtained from parents also. Inclusion criteria include Patients who are Having mild to moderate acne vulgaris with the lesions only on cheek, forehead, chin, nose and neck (above clavicle), Both males and females of 15 years to 25 years, Willing to give written informed consent, suffering from acne vulgaris for three or more months, not under drug therapy for acne vulgaris, not suffering from any systemic illness. exclusion criteria Patients who are having severe acne vulgaris, below 15 years and above 25 years, suffering from systemic illness like cardiac valvular lesions, diabetes mellitus, hypertension and congenital anomalies, not willing to give informed written consent and With the history of hypersensitivity to antimicrobials.

RESULTS

Trial I

The study is conducted as four different trial in each trial totally 60 patients are selected and are randomly divided in to 2 groups, group A and B. In trial-I, 60 patients suffering from mild acne vulgaris are included and are randomly allotted in to group A and B, with 30 patients in each group. Group A patients are treated with oral Doxycycline 100 mg, once daily, in the morning, after food, for four weeks. Group B patients are treated with oral Clindamycin 50 mg once daily in the morning, after food, for four weeks. The patients are assessed before starting drug therapy and after drug administration, at the end of 1st week, 2nd week, 3rd week and at the end of 4th week. The patients are also assessed during the follow up visits at the end of 5th and 6th weeks.

Trial- II

In this study also, 60 patients suffering from mild acne vulgaris are included and are randomly allotted in to group A and B, with 30 patients in each group. But here, Group A patients are treated with 5% topical benzoyl peroxide applied during bed time every day for 4 weeks, in addition to oral doxycycline 100mg given once daily, in the morning, after food, every day for four weeks. Group B patients are treated with 5% topical Benzoyl peroxide applied during bed time every day for 4 weeks, in addition to oral clindamycin 50mg given once daily, in the morning, after food, every day for four weeks. The patients in both the groups are assessed before starting therapy and at the end of every week as done in trial-I.

Assessment criteria

Acne vulgaris is classified into Grade I, II, II and IV depending upon the presence of comedons, papules and pustules.[4,5]

- *Grade I (mild):* Comedons and occasional papules.
- *Grade II (moderate):* Comedons, papules and few pustules.
- *Grade III (severe):* Pustules, nodules and abscesses.
- *Grade IV (cystic):* Very severe form consists of cysts, Abscesses and Scarring.

In this study, only grade I (mild) and grade II (moderate) patients are included and grade III and grade IV patients are not included.[7,8] The effect of drugs in reducing the number of comedons, papules and pustules in all the four trials are recorded before starting treatment and at the end of every week for six weeks.

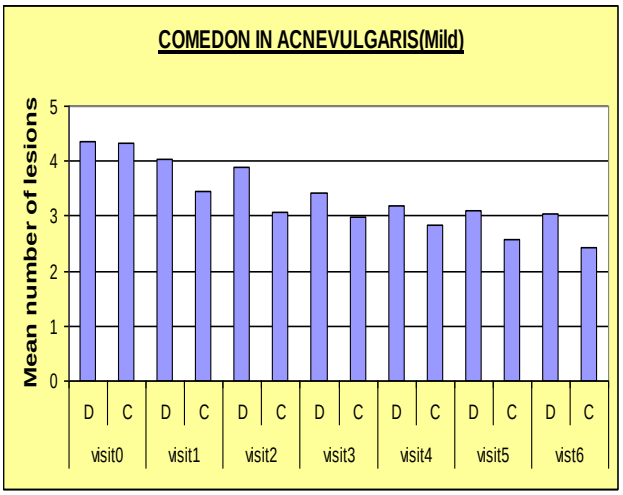
Statistical analysis

Statistical analysis is done by using independent student t-test and the 'P' values are determined.

Trial-I: Comparison of number of comedons between group A and B of trial I

Figure 1 shows Reduction in number of comedons in trial-I. It shows comparison done in relation to number of comedons between group A and B, which received oral

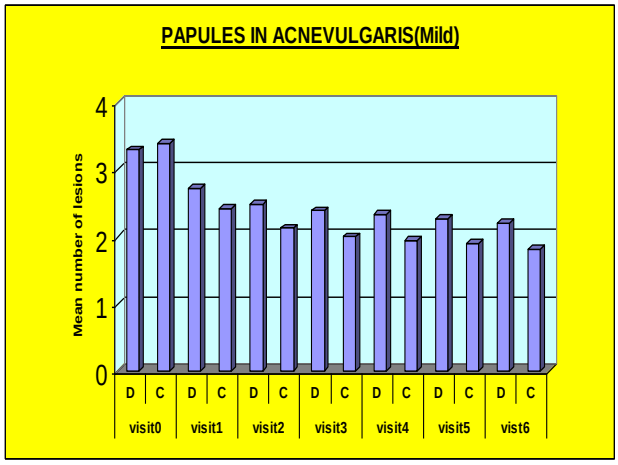
Doxycycline and oral Clindamycin respectively. The 'P' value at the end of sixth week is 0.001 which is significant, its shows the safety of clindamycin is proved, and regarding efficacy clindamycin is more efficacious the doxycycline in the treatment of acnevulgaris.



D = Doxycycline, C = Clindamycin

Figure 1: Reduction in number of comedons in trial-I.

Figure 2 shows comparison between doxycycline and clindamycin orally treated groups in trial I, for papules, the 'P' value at the end of sixth week is 0.05 which is significant.

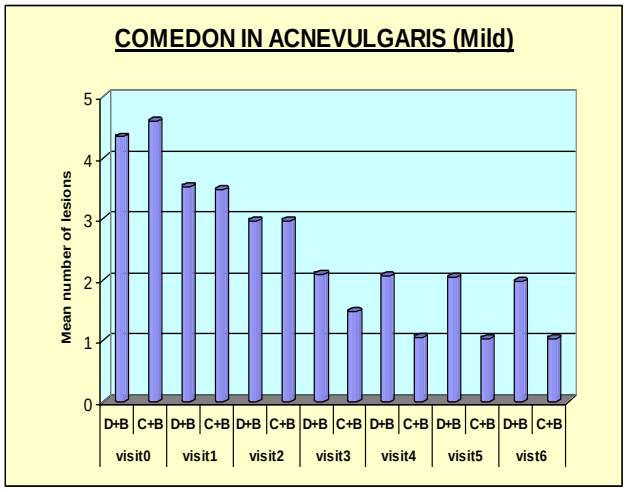


D = Doxycycline, C = Clindamycin

Figure 2: Reduction in number of papules in trial-I.

Trial-II: Comparison of number of comedons between group A and B of trial II

In trial II, that is the group which has been treated oral doxycycline along with topical benzoyl peroxide is compared with the other group treated with oral clindamycin along with topical Benzoyl peroxide. The 'P' value at the end of sixth week in case of Comedon is 0.001, which is significant shown its shows the safety of clindamycin is proved, and regarding efficacy clindamycin is more efficacious the doxycycline in the treatment of acnevulgaris.

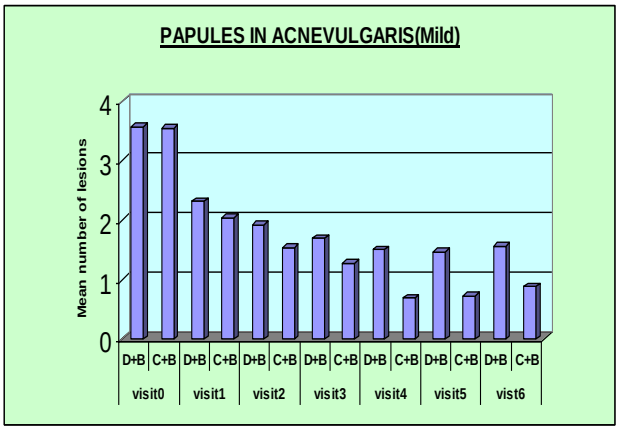


D =Doxycycline, C = Clindamycin, B = Benzoil peroxide

Figure 3: Reduction in number of comedons in trial II.

Comparison of number of papules between group A and B of trial II

In case of papules, the 'P' value determined at the end of sixth week is 0.001, which is also significant shown in Figure 4.



D =Doxycycline, C = Clindamycin, B = Benzoil peroxide

Figure 4: Reduction in number of papules in trial II.

Results of adverse effects

The patients were also followed up for the occurrence of adverse effects. In fact one of the objective of the study is to find out, if clindamycin is producing good results without causing unwanted effects when given in low doses of orally for a period of four weeks.

Table 1 shows the occurrence of adverse effects in the trial treated with clindamycin.

Table 1: Adverse effects with clindamycin.

Adverse effects	No of visit							Total no. of cases
	0	1st	2nd	3rd	4th	5th	6th	
Rashes	0	0	0	0	0	0	0	0
Urticaria	0	0	0	0	0	0	0	0
Nausea	0	1	1	2	1	2	2	9
Vomiting	0	1	2	1	1	1	1	7
Abdominal pain	0	1	1	2	1	2	1	8
Diarrhoea	0	0	1	1	1	1	2	6
Dysentry	0	0	1	1	1	1	1	5
Dizziness	0	0	0	0	0	0	0	0

The table shows the number of cases complaining of adverse effects mentioned during each visit for a period of six weeks. The total number of patients reported with Nausea were 9, Vomiting were 7, Abdominal pain 8, Diarrhoea 6 and Dysentry 5. here was statistically significant reduction in total number of improvement in Group A. Adverse drug reactions during the study showed a better safety profile of Group B which is found to be statistically significant also.

DISCUSSION

The objective of the study is not only to find out the efficacy of a low dose of 50 mg Clindamycin given orally, but also to find out if this efficacy is obtained without producing the adverse effects for which the administration of Clindamycin is hesitated some study 5 percent benzoyl peroxide with 1 percent clindamycin alone found the combination product to be more efficacious, with less P. evidence level B, single blinded RCT acnes resistance.[9]

The worst complication is pseudomembranous enterocolitis it's also with the worst offenders are clindamycin, ampicillin, amoxicillin and the cephalosporins.[10] Clindamycin produces very good effect in acne vulgaris and this is discussed later. These effects are produced without significant adverse effects.

In few cases reported as nausea, vomiting, diarrhoea were clinically insignificant and they were self limiting. The patients revealed the occurrence of such effects only after questioning them specifically for such an effect.

If diarrhoea, abdominal pain had been severe they would have definitely reported to the investigator but no one reported. Doxycycline is the most common tetracycline associated with gastrointestinal upset reported many study. The reported rates of gastrointestinal adverse events in clinical trials for the treatment acne vulgaris.[11] And all of them continued to take the drug without stopping. Here also it should be noted that if nausea and vomiting had been due to *Pseudomembranous* enterocolitis, the condition would have worsened with continuous intake. But the symptoms were self limiting.[11] Only three cases of dysentery were prescribed tablet metronidazole by their own doctor. On analysing the efficacy of oral clindamycin, a low dose that is 50mg administered daily for four weeks has definitely produced better results than doxycycline administered as a single daily dose for 4 weeks.

There is significant reduction in the number of comedons Skidmore R et al, forty patients completed 6 months of treatment. At 6 months, the SD doxycycline group had a significantly greater percent reduction in the number of comedones ($P < 0.01$) and papules in mild cases of acne vulgaris who have received only oral clindamycin when compared to other group who have received only oral Doxycycline.[12] This is evident both in the clinical data which has been presented under the results column and also has been found to be statistically significant. In moderate cases, also the significant improvement is seen in the group which is treated with oral Clindamycin. This is reflected as reduction in the number of comedons, papules and pustules in the Clindamycin treated group, when compared to the other group which is Doxycycline treated control group. The role of Propionibacterium acne in pathogenesis of acne has already been discussed.

The ant-microbial, Cap. Doxycycline and Cap. Clindamycin act in acne vulgaris by their effect on the Propionibacterium acne.[12] These antibiotics decrease the population of Propionibacterium acne which in turn leads to the inhibition of the bacterial lipases and this is followed by a decrease in concentration of free fatty acids. This produces less tissue inflammation and acne.

Since topically applied drugs are widely used in therapy of acne, in the trials in which the oral drug therapy was combined with topical Benzoyl peroxide and the outcome was analysed. Greater efficacy was obtained when oral Clindamycin was combined with topical Benzoyl peroxide. Doxycycline when used alone or in combination with Benzoyl peroxide has retained its efficacy, and the efficacy is greater when combined with topical benzoyl peroxide.[13]

Clindamycin either alone or in combination with topical benzoyl peroxide 5% cream shows greater efficacy than doxycycline either alone or in combination with topical benzoyl peroxide 5% cream. The reason for lesser efficacy of doxycycline could be due to development of resistance by propionibacterium acne in some of the patients included in this trial. The literature tells that there is increase in the resistance of Propionibacterium acne to antibiotics worldwide omparison of efficacy of first-line mild to moderate acne treatments in reducing total acne lesion count. BPO benzoyl peroxide. Clindamycin 1% + BPO 3% gel: Schaller et al, clindamycin, though an anti-microbial, shows greater efficacy in this study.[14] This could be because clindamycin oral therapy has not been used so far for acne vulgaris and probably the bacteria have not developed resistance. The better results obtained in a group which has been treated with topical Benzoyl

peroxide group could be definitely due to its anti-bacterial action and direct anti-inflammatory action.

The study has proved that a low dose of 50mg of oral Clindamycin administered once a day for four weeks produces good results in acne vulgaris. The good results are obtained without unwanted adverse reactions.[15] For many infections 150 to 300 mg are given 3-4 times a day produces many adverse effect.

CONCLUSION

In this trial the low dose of 50mg used is not only highly effective, but also has not produced any significant adverse reactions. So far, the clindamycin has only been used topically for acne vulgaris. This study encourages the use of low dose oral Clindamycin in acne vulgaris. Future study using clindamycin in combination with the other topical agents like tretinoin and adapalene which have different mechanism of actions can be tried. Tretinoin reverses abnormal keratinizing changes in acne vulgaris. Adapalene has got comedolytic property.

This study has been conducted as single study centre and similar multicentric study can promote wider use of oral clindamycin in acne vulgaris.

This study proves the safety and efficacy of low dose of oral clindamycin in acne vulgaris, and such low doses can also be tried for other infections where the causative organism responds to clindamycin.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Arivazhagan N, Kumar RS, Kumar RA. Pharmacokinetic study of rational regimen of oral clindamycin in comparison with doxycycline in mild cases of acne vulgaris. Int J Basic Clin Pharmacol 2017;6:2616-20.