Quality use of medicines: The teenager with moderate acne

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Acne is an oft-encountered presentation in family practice, and while sometimes downplayed as essentially a "cosmetic" and self-limiting problem, it is nonetheless associated with a definite risk of scarring, both physically and emotionally. This paper uses the P-drug approach, as outlined in the WHO Guide to Good Prescribing, to describe a rational approach to the problem of choosing drug therapy for acne, particularly in the teenager presenting with moderate acne. *(SA Fam Pract 2003;45(3):48-50)*

As always, a careful definition of the problem is the first step. Acne vulgaris can be classified into three categories for the purpose of treatment: comedonal, inflammatory and nodulocystic. Comedonal acne is non-inflammatory and consists of open and closed comedones. Erythematous papules or pustules characterize inflammatory or moderate acne. Comedones may also be present. In nodulocystic acne, deeper scarring nodules and cysts occur, possibly together with papulopustular and comedonal lesions.[1] In a recent clinical review, Webster recommends that the most severe lesions present be used to make a diagnosis, as adequate treatment for severe lesions will be effective against lesser lesions.[2] Even a few severe lesions can be disfiguring. Finally, it is important to exclude acne which is not due to acne vulgaris, and which might warrant referral. Unusual causes of acne include drug-induced acne, with drugs such as rifampicin implicated. Muscle hypertrophy should alert the prescriber to the possibility of illegal anabolic steroid-induced acne. Greasy hair straighteners may cause pomade acne.[3]

The therapeutic objective is simply to prevent physical and emotional scarring. This objective appears to be amenable to drug treatment: experts reviewing the subject in three recent articles all stressed that acne is eminently treatable, given the range of treatments available.[1,2,3] The main aim of treatment for all acne vulgaris is reduction of the primary lesion, the comedone. In inflammatory acne, *Propionibacterium acnes*, a non-infective member of the host's normal flora activates the immune system to mount an inflammatory response. Treatment of inflammatory acne is therefore also aimed at reducing *P.acnes*. A number of antibiotics as well as topical agents such as benzoyl peroxide are active against this bacterium. In addition to antibiotics, hormonal agents and isotretinoin are generally considered effective.

Potential agents must now be judged against the criteria of efficacy, safety, suitability and cost. The results of a recent systematic review of acne trials published by the US Agency for Healthcare Research and Quality highlight the difficulties in finding evidence of efficacy and safety for acne.[4] Only 14 of 250 trials screened found reliable evidence of efficacy (level A evidence as defined by this review). Agents found to be more effective than placebo were aluminium chlorhydroxide/sulphur, topical clindamycin, topical erythromycin, benzoyl peroxide, topical isotretinoin, tretinoin, oral tetracycline and norgestimate/ethinyloestradiol. Adapalene was shown to be as effective as tretinoin. Benzoyl peroxide and cyproterone were also shown to be effective, with no difference between the strengths/doses tested in each case.

Evidence that would allow for a clear choice between the various oral antibiotics registered for acne is lacking. A Cochrane review of the safety and efficacy of minocycline was updated in February 2000.[5] As with the US study quoted above, poor methodological quality, including inadequate patient numbers, and the heterogeneity of outcome measures and endpoints used precluded pooling of the results from the 27 randomised controlled trials reviewed. No conclusions could be drawn regarding the safety and efficacy of this drug related to other therapies. There is also a lack of consensus among experts regarding the most efficacious agent. In his review, Webster writes that he uses doxycycline or minocycline first-line because he finds tetracycline insufficient'. He has been criticized by Garner *et al*, who point out that no evidence from randomized-controlled trials supports the use of second-generation tetracyclines over tetracycline for acne[6]

Second generation tetracyclines, such as doxycycline and minocycline, have been promoted as being more

convenient to patients as they are well absorbed even when taken with food and need only be taken once or twice a day.[7] However, Meyer presents data showing that while the newer tetracyclines are less affected, absorption is decreased in all of the tetracyclines and that the interindividual variability of the resulting drug levels is large.[8] He therefore recommends taking each of the tetracyclines with water about one hour before a meal. Cunliffe recommends twice daily doses for erythromycin and daily doses for the second-generation tetracyclines, giving the second-generation tetracyclines the advantage of requiring less frequent dosing.[3] Safety is also of some concern with minocycline. There are more reports of serious adverse events from minocycline use than from the use of other tetracyclines. Rare serious adverse events seen in patients treated with minocycline long-term, and not seen with the other tetracyclines, include drug-induced lupus erythematosus. Common side effects are similar for the tetracycline groups and include epigastric burns, photosensitivity and vaginal candidiasis. Vestibular dysfunction and localized pigment disturbances are common side effects that appear to be noted only with minocycline use.[9]

However, perhaps the most pressing problem for the treatment of inflammatory acne with antibiotics is the emergence in the last 25 years of drug-resistant *P.acnes*. Resistant strains of bacteria have been associated with treatment failure.[10] However, the consequences of antibiotic resistance may be far greater. The danger of spread of antibiotic resistance to other bacterial species such as *Staphylococci* is a community safety concern.[11] The overall incidence of *P. acnes* antibiotic resistance increased from 20% in 1978 to 62% in 1996.[12] Resistance to all commonly used antibiotics, including minocycline, has been reported, with erythromycin the most affected. The long treatment courses that are used in acne treatment exert considerable selective pressure for the development of resistance.[13] Guidelines aimed at minimizing the development of resistance have been developed for the appropriate use of antibiotics in acne, which also emphasise the need for careful consideration of the choice between oral and topical treatment.[13,14,15]

In summary, it is suggested that resistance may be minimized by:

- not using oral antibiotics if a non-antibiotic topical preparation will suffice (e.g. in mild acne);
- continuing oral antibiotic treatment for no longer than is necessary (at least 6 months if there is a treatment effect, but stopping the treatment as soon as the doctor and patient agree that there is no further improvement);
- re-using the same drug wherever possible if further treatment is required;
- using short intervening courses of topical treatment with an antibacterial agent to eliminate any resistant bacteria selected (e.g. 3-5 day washouts with benzoyl peroxide, although it is important to note that the nares are an important site of resistant *P.acnes* and that benzoyl peroxide cannot be used to eliminate this source);
- avoiding the use of oral and topical treatment with different antibiotics to decrease the risk of resistance developing in both;
- using alternatives to antibiotics for maintenance therapy.

If minomycin is eliminated on safety grounds, and erythromycin on the prevalence of resistance, the choice between doxycycline and oxytetracycline can be based largely on suitability and cost. Doxycycline can be given once daily, and the presence of 12 competitor products on the market means lower acquisition costs (the lowest being R77 for 30x100mg capsules). Oxytetracycline has to be given twice a day, and the lowest cost generic is about R98 for a month's supply (at 500mg twice a day).

Evidence is also lacking for the second group of oral agents, the hormonal agents. The Cochrane review of the safety and efficacy of minocycline reports the results of one trial comparing minocycline and cyproterone/ethinyl-oestradiol. No overall difference was found between the treatments. However, the oestrogen concentration of the hormonal preparation was 0.05mg, higher than in the currently available product in South Africa, Diane®.[5] Hormonal agents were evaluated in the US AHRQ systematic review.[4] All the hormonal agents tested demonstrated statistically significant improvement in acne severity from baseline, which suggests that these agents have a role in the treatment of acne in women. However methodological flaws precluded the use of data pooling and no conclusions were reached regarding the comparative efficacy or safety of the hormonal agents or their efficacy and safety relative to other oral alternatives such as the antibiotics. Expert reviews appear to be equivocal, with recommendations ranging from the use only in women who have acne that is resistant to treatment (especially in women with irregular menses), to use in any woman requiring contraception or cycle control.[2,3]

A four-fold greater risk of venous thromboembolism has been shown in users of Diane® compared to levonorgestrel.[16] This has prompted the updating of product information in the UK to reflect new guidelines. These include reminders that cyproterone-containing products are not indicated for use solely as an oral contraceptive, that this agent should be reserved for treatment of women with severe acne that has not responded to oral antibiotics, and that the drug should be withdrawn 3-4 cycles after the treated condition has completely resolved.[17] Suitability is clearly an issue because hormonal agents are only available to women, while the burden of acne disease is greater in men. Cost is considerable, at about R191 per month for Diane®.

Isotretinoin is the agent of choice for patients presenting with severe nodulocystic acne. Side effects are common, with patients complaining of dry skin, lips and eyes. Atopic dermatitis and epistaxis, raised triglyceride levels, thinning of the hair and myalgias have also been reported and depression has also been reported as a rare adverse effect. There may be a flare of acne symptoms on initiation of isotretinoin treatment, requiring the use of other agents at the same time, but not the tetracyclines (as this is associated with increased risk of intracranial hypertension).[1] The most important problem associated with isotretinoin therapy is teratogenicity. These safety concerns have prompted the development of stringent laboratory monitoring

guidelines, including pre-treatment pregnancy tests, weekly or biweekly lipid levels during the first month of use, and both pre-treatment and weekly/biweekly liver function tests in the early stages of treatment. The safety concerns, need for monitoring and cost of this agent make it one that should be reserved for severe recalcitrant cases and experienced prescribers or specialists.

It would therefore appear that, although a range of oral treatments for moderate acne is available, each presents problems, either of unproven efficacy, known safety concerns, suitability or of cost. The mainstay for the treatment of comedonal acne and mild papulopustular acne, and in combination with oral therapy as initial treatment in scarring or nodular acne, remains the topical products. They are also indicated after successful treatment with combination therapy, as maintenance therapy. A range of such products is available in South Africa, some of which are also very expensive. These include the anticomedonal agents adaptalene (R210 per 30g), tretinoin (R111 and R217 for the two strengths, in 20g tubes), azelaic acid (R172 for 30g), and isotretinoin (R92 for 30g). Adaptalene also has anti-inflammatory actions, as have the topical antibiotic lotions, such as clindamycin (R143 for 30ml) and erythromycin (R191 for 50ml). However, given the view that different antibiotics should not be used topically and orally (and the leaning towards the tetracycline group), the topical of choice would seem to be the faithful benzoyl peroxide, available as a lotion (R76 for 30ml) and gel (R67 for 40g). Not only is it effective, but it might also reduce the development of drug resistance – a win all round.❐

Please refer to CPD Questionnaire on page 56.

Acknowledgment:

The assistance of Janet van Maasdyk in sourcing the literature for this paper is gratefully acknowledged.

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